Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan

Title	:	Reporting and Analysis Plan for Study 206215: A randomized, open-label, cross-over, placebo-device study investigating critical and over all errors, training/teaching time, and preference attributes of the ELLIPTA dry powder Inhaler (DPI) as compared to HandiHaler DPI used in combination with either DISKUS DPI or Turbuhaler DPI, in adult patients with Chronic Obstructive Pulmonary Disease (COPD)
Compound Number	:	GSK573719+GW642444+GW685698 (GSK2834425)
Effective Date	:	18-JUL-2017

Description :

- The purpose of this Reporting and Analysis Plan (RAP) is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 2016N292801_01.
- This RAP is intended to describe the planned efficacy and safety analyses required for the study.
- This document will be provided to the study team members to convey the content of the final Statistical Analysis Complete (SAC) deliverable.

Author's Name and Functional Area:

PPD Statistician (Clinical Statistics)	18-JUL-2017

Approved by:

PPD Manager, Statistics (Clinical Statistics)	18-JUL-2017

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• This RAP details all planned analyses and outputs required for the final Clinical Study Report (CSR) of study 206215.
Protocol	• This RAP is based on the original protocol [(Dated: 15-Sep-2016) of study 206215 (GSK Document No. : 2016N292801_01] and eCRF Version 1
Primary Objective	• To compare the number of critical errors made by COPD patients, after a subject has read the respective patient information leaflet(s) (PIL), for each treatment option tested.
Primary Endpoint	• The percentage of subjects making at least one critical error after reading the PIL(s).
Secondary Objectives	• To compare the number of critical errors made by COPD patients after instructions from the Healthcare Professional (HCP) for each treatment option tested. • To compare the number of overall (critical and non-critical) errors made by COPD patients, after a subject has read the PIL(S) or after Instruction from the HCP for each treatment option tested • To compare the number of instructions (maximum of 2) from a HCP which is needed to demonstrate correct inhaler use • To compare the Training/Teaching Time required to demonstrate correct inhaler use • Preference attributes for each treatment option tested

Secondary Endpoints	• The percentage of subjects making at least one critical error after the first instruction from the HCP
	• The percentage of subjects making at least one overall error after reading the PIL(s)
	• The percentage of subjects making at least one overall error after the first instruction from the HCP
	• The number of instructions (0, 1 or 2 times) from the HCP which are needed to demonstrate correct inhaler use
	• The total amount of time taken to demonstrate correct inhaler use (T1+T2).
	• Treatment preference, from questionnaire for:
	  • Number of steps required to take COPD medication
	  • Over all treatment preference

Study Design	• The study will be conducted as a multi-centre, randomised, open-label, placebo-device, cross-over study, with a 2x2 complete block design. The study will comprise of 2 sub studies. Sub study 1 will compare ELLIPTA to DISKUS + HandiHaler and Sub Study 2 will compare ELLIPTA to Turbuhaler + Handihaler.

<table>
<tr><th>Overview</th><th>Key Elements of the RAP</th></tr>
<tr><td></td><td>

Subjects will be randomised 1:1:1:1 to each of the four treatment sequences in both sub study 1 and sub study 2. The randomisation schedules for each sub study will be created independently. 160 participants will be randomised (80 in each sub study), such that approximately 144 are evaluable (72 in each sub study).
The study has three treatment periods. The first two treatment periods are a 2x2 complete block design to test the ELLIPTA against DISKUS + HandiHaler or Turbuhaler + HandiHaler.The third treatment period contains a questionnaire to assess subject preference.
Using 10000 simulations, a total of 72 subjects in each sub-study will provide at least 90% power to show a statistically significant difference between the critical error rate of each of the paired treatment options (Sub-study 1: Treatment option 1 vs. Treatment Option 2; Sub-study 2: Treatment option 1 vs. Treatment Option 3) assuming the following true critical error rates.

<table>
<tr><th>Treatment Option 1:
ELLIPTA Critical Error Rate</th><th>Treatment Option 2:
DISKUS + HandiHaler Critical Error Rate</th><th>Treatment Option 3:
Turbuhaler + HandiHaler Critical Error Rate</th></tr>
<tr><td>11%</td><td>>=37%</td><td>>=37%</td></tr>
<tr><td>10%</td><td>>=35%</td><td>>=35%</td></tr>
<tr><td>9%</td><td>>=34%</td><td>>=34%</td></tr>
<tr><td>8%</td><td>>=32%</td><td>>=32%</td></tr>
<tr><td>7%</td><td>>=31%</td><td>>=31%</td></tr>
<tr><td>6%</td><td>>=29%</td><td>>=29%</td></tr>
</table>
</td></tr>
<tr><td>Planned Analyses</td><td>

No interim analyses are planned for this study.
Sub study 1 and sub study 2 will be reported at the same time.
All decisions regarding final analysis as defined in this RAP document will be made prior to Database Freeze.

</td></tr>
<tr><td>Analysis Populations</td><td>

Subjects Enrolled population (ASE) will consist of all participants who sign the ICF and for whom a record exists in the study database, including screen failures and any subject who was not screened but experienced an SAE between the date of informed consent and the planned date of the Screening visit. All Subjects Enrolled population (ASE) will be used for subject disposition, reason for withdrawal prior to randomisation, inclusion, exclusion and randomisation criteria deviations and SAEs for non randomised subjects.
The Intent-to-Treat population will consist of all randomised subjects, excluding those who were randomised in error and made at least one critical error assessment from one treatment option device. A subject who is recorded as a screen or run-in failure and also randomized will be considered to be randomized in error. Any other subject who receives a randomization number will be considered to have been randomized. The Intent-to-treat population (ITT) will be used for study population, efficacy and safety endpoints.
The Safety population will be the same as the ITT population.

</td></tr>
</table>

Overview	Key Elements of the RAP
Hypothesis	For each sub-study, the null hypotheses are no difference between treatment options: H_0: $p_1=p_i$; i=2, 3 The alternative hypothesis is that there is a difference between treatment options: H_A: $p_1 \neq p_i$; i=2,3 Where treatment p_1 = ELLIPTA, p_2 = DISKUS + HandiHaler and p_3 = Turbuhaler + HandiHaler
Primary Analyses	• The primary endpoint of the percentage of subjects making at least one critical error after reading the PIL(s) for each treatment option tested will be analysed using conditional logistic regression with subject as fixed strata, and treatment option and period as fixed effects.
Secondary Analyses	• The number of critical errors made by COPD patients after instruction from the Healthcare Professional (HCP) for each treatment option tested will be analysed using conditional logistic regression with subject as fixed strata, and treatment option and period as fixed effects. • The number of overall (critical and non-critical) errors made by COPD patients, after a subject has read the PIL(S) or after Instruction from the HCP for each treatment option tested, will be analysed using conditional logistic regression with subject as fixed strata, and treatment option and period as fixed effects. • The number of instructions (maximum of 2) from a HCP which is needed to demonstrate correct inhaler use will be analysed using Wilcoxon sum rank test. • The Training/Teaching Time required to demonstrate correct inhaler use will be analysed using Kaplan-Meier plots and summary statistics. • Preference attributes for each treatment option tested will be analysed using the Cochran-Mantel-Haenszel test.

2. SUMMARY OF KEY PROTOCOL INFORMATION

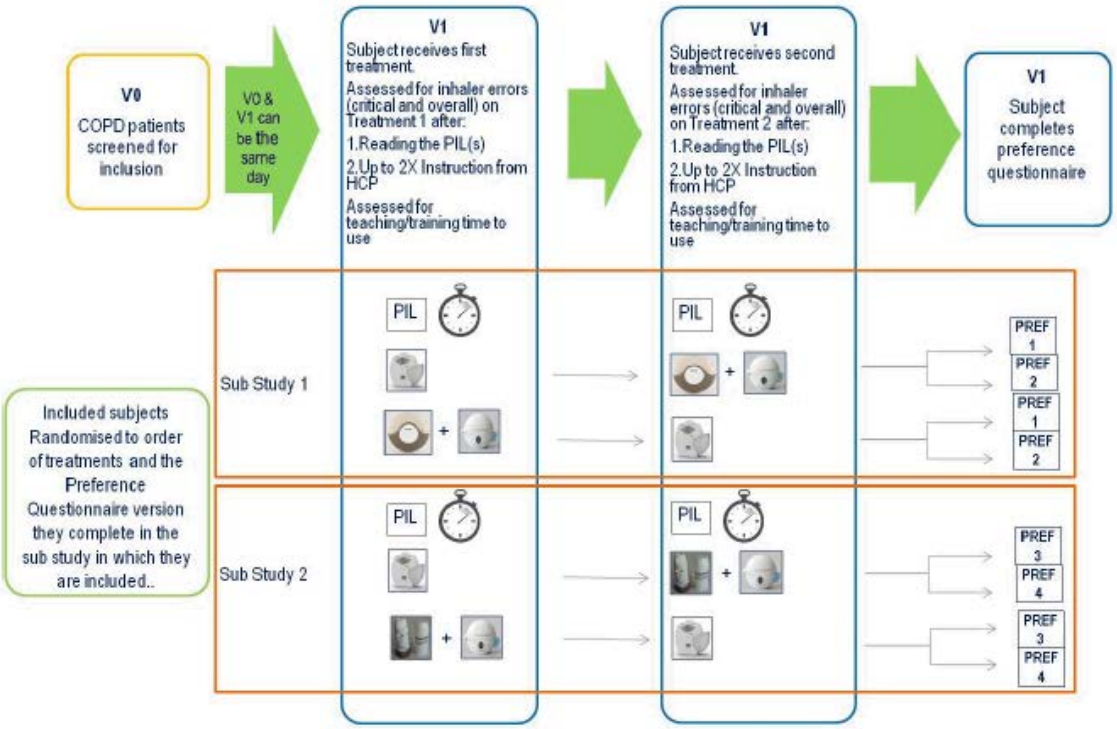
2.1. Changes to the Protocol Defined Statistical Analysis Plan

There is one change to the originally planned statistical analysis specified in the protocol (Dated: 15-Sep-2016). For the secondary endpoint of the number of instructions (0, 1 or 2 times) from the HCP which are needed to demonstrate correct inhaler use, tracked changes were not copied through to the final document. As such the analysis stated in the protocol (logistic regression) is not appropriate and instead the analysis will be performed using Wilcoxon signed rank test as this was the originally planned analysis.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To compare the number of critical errors made by COPD patients, after a subject has read the respective patient information leaflet(s) (PIL), for each treatment option tested	• The percentage of subjects making at least one critical error after reading the PIL(s)
Secondary Objectives	**Secondary Endpoints**
• To compare the number of critical errors made by COPD patients after instruction from the Healthcare Professional (HCP) for each treatment option tested	• The percentage of subjects making at least one critical error after the: • first instruction from the HCP • second instruction from the HCP
• To compare the number of overall (critical and non-critical) errors made by COPD patients, after a subject has read the PIL(S) or after Instruction from the HCP for each treatment option tested	• The percentage of subjects making at least one overall error after reading the PIL(s) • The percentage of subjects making at least one overall error after the first instruction from the HCP • The percentage of subjects making at least one overall error after the second instruction from the HCP
• To compare the number of instructions (maximum of 2) from a HCP which is needed to demonstrate correct inhaler use	• The number of instructions (0, 1 or 2 times) from the HCP which are needed to demonstrate correct inhaler use
• To compare the Training/Teaching Time required to demonstrate correct inhaler use	• The total amount of time taken to demonstrate correct inhaler use (T1+T2). • The amount of time taken to read the patient information leaflet and demonstrate correct inhaler use (T1) The amount of time taken to be given instruction by the HCP (up to 2 times) on use of the inhaler and to demonstrate correct inhaler use (T2)
• Preference attributes for each treatment option tested	• Treatment preference, from questionnaire for: • Number of steps required to take COPD medication • Over all treatment preference

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. It will comprise of two sub studies: • Sub-study 1 will compare ELLIPTA (Treatment option 1) to DISKUS + HandiHaler combination (Treatment option 2) • Sub-study 2 will compare ELLIPTA (Treatment option 1) to Turbuhaler + HandiHaler combination (Treatment option 3). The study has 2 visits (V0 and V1) and both can be completed on the same day. Each sub-study may run independently or in parallel of the other sub study. Each will start dependent on the availability of the placebo DPIs required for that sub-study. The data from the 2 sub studies may be reported independently and as each sub study completes and the data for that sub study have been cleaned. The database will be locked when all of the sub-studies have completed and all data are cleaned.
Dosing	• Not applicable as this is a placebo study.

Overview of Study Design and Key Features

Treatment Assignment

Sub-study 1 Treatment Sequences

Sequence	Period 1	Period 2	Preference Questionnaire
A	ELLIPTA	DISKUS + HandiHaler	1
B	DISKUS + HandiHaler	ELLIPTA	2
C	ELLIPTA	DISKUS + HandiHaler	2
D	DISKUS + HandiHaler	ELLIPTA	1

Sub-study 2 Treatment Sequence

Sequence	Period 1	Period 2	Preference Questionnaire
E	ELLIPTA	Turbuhaler + HandiHaler	3
F	Turbuhaler + HandiHaler	ELLIPTA	4
G	ELLIPTA	Turbuhaler + HandiHaler	4
H	Turbuhaler + HandiHaler	ELLIPTA	3

2.4. Statistical Hypotheses

The primary purpose of this study is to assess the number of critical errors made by COPD patients, after a subject has read the patient information leaflet(s) (PIL) for each treatment option tested. This is a superiority study.

There are two sub-studies and these will be analysed separately. There is no overlap of subjects and so these are considered independent. Hence there will be no adjustment for multiplicity.

The primary endpoint is the percentage of subjects making at least one critical error after reading the PIL(s) on Treatment Option 1 compared with each of Treatment Option 2 (Sub-study 1) and Treatment Option 3 (Sub-study 2).

For each sub-study, the null hypotheses are no difference between treatment options:
H_0: $p_1=p_i$; i=2, 3

The alternative hypothesis is that there is a difference between treatment options.
H_A: $p_1 \neq p_i$; i=2,3

Where treatment p_1 = ELLIPTA, p_2 = DISKUS + HandiHaler and p_3 = Turbuhaler + HandiHaler

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 for both sub-study 1 and sub-study 2.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
3. All criteria for unblinding the randomisation codes have been met.
4. Randomisation code schedules for both sub-studies have been distributed according to RandAll NG procedures.

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 subject who was not screened but experienced an SAE between the date of informed consent and the planned date of the Screening visit.	• Study population • Reason for withdrawal prior to randomisation
Randomised	• All participants who were randomised.	• No formal analysis will be performed on this population
Intent-to-treat (ITT)	• All randomised subjects who made at least one critical error assessment from one treatment option device. A subject who is recorded as a screen or run-in failure and also randomised will be considered to be randomised in error provided they have not performed any error assessments.	• Study population • Efficacy • Subject disposition • Safety • Inclusion, exclusion and randomisation criteria deviations
Safety	This population will be the same as the Intent-to-treat population.	

NOTES :

- Please refer to Appendix 11: 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.
    - Data will be reviewed prior to unblinding and freezing 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

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Component
11.1	Appendix 1: Protocol Deviation Management
11.2	Appendix 2: Time & Events
11.3	Appendix 3: Treatment Phases
11.4	Appendix 4: Data Display Standards & Handling Conventions
11.5	Appendix 5: Derived and Transformed Data
11.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
11.7	Appendix 7: Multicenter Studies
11.8	Appendix 8: Examination of Covariates, Subgroups & Other Strata
11.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses
11.10	Appendix 10: Abbreviations & Trade Marks
11.11	Appendix 11: List of Data Displays
11.12	Appendix 12: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

The study population analyses will be based on the ITT population unless otherwise stated.

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition and Demography			
Study Populations (ASE)	Y		
Attendance at Each Clinic Visit	Y		
Screening Failures	Y		Y
Treatment Status and Reasons for Discontinuation of Study Treatment	Y		Y
End of Study Record by Treatment period	Y		
Subject Disposition at Each Treatment Period	Y		
Reasons for withdrawal	Y		Y(ASE)
Number of Subjects by Country and Centre	Y		
Summary of Age Ranges	Y (ASE)		
Demographic Characteristics	Y		Y
Demographic Characteristics by Country	Y		
Race and Racial Combinations	Y		
Race and Racial Combinations Details	Y		Y
Protocol Deviations			
Important deviations	Y		Y
Inclusion/Exclusion/Randomisation Criteria Deviations	Y		Y
Treatment Misallocations			Y
Medical Condition & Concomitant Medications			
Medical Conditions (Current/Past)	Y		Y
Family History of Cardiovascular Risk Factors	Y		Y
COPD History and COPD Exacerbation History (Only one listing required)	Y		Y
Smoking History and Status	Y		Y
COPD Medications	Y		Y
Non-COPD Medications	Y		Y
Relationship between ATC Level 1, ingredient and verbatim text non-COPD medications only			Y
Devices			
Naivety to Inhaler Devices	Y		Y

6.1. Disposition

The study population summary will 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 in each sub-study and overall who were randomised and who were in the ITT population.

The 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. This will be presented for each sub-study and overall.

6.2. Medical Conditions

The number and percentage of subjects reporting each current medical condition will be presented by sub-study and overall. This table will include a category of 'Cardiovascular Risk Factors'. All medical conditions must be summarised on this table regardless of frequency.

This will be repeated for past medical conditions.

6.3. 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 ATC, 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. These tables will be presented by sub-study and overall.

COPD and non-COPD medications will be listed together.

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

7. PRIMARY STATISTICAL ANALYSES

7.1. Efficacy Analyses

7.1.1. Overview of Planned Efficacy Analyses

The primary efficacy analyses will be based on the ITT population, unless otherwise specified.

Table 3 provides an overview of the planned efficacy analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 3 Overview of Planned Primary Efficacy Analyses

	Absolute			
	Stats Analysis		Summary	
	T	F	T	F
At least one critical error				
Percentage of subjects making at least one critical error after reading the PIL(s)	Y		Y	Y

NOTES :

- T = Table, F = Figure, Y = Yes display generated.
- Stats Analysis = Represents TF related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.

7.1.2. Planned Efficacy Statistical Analyses

Primary Statistical Analyses
Endpoint(s)
• Percentage of subjects making at least one critical error after reading the PIL(s)
Model Specification
• The primary endpoint of the percentage of subjects making at least one critical error after reading the PIL(s) 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. • Country will be included in the model providing there are sufficient subjects distributed to enable the model to run. If the model will not run with country in the model then country will be removed from the model.
Model Checking & Diagnostics
• Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses.
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.
SAS Code

• Logistic regression will be used to calculate the odds ratio with 95% CI and p-value. The following SAS code will be used:
 	
proc logistic data=errors;
class device period country;
strata subject;
model error = country device period / expb;
oddsratio device;
run;
 	
error is derived as shown in Section 11.5.3

Sensitivity and Supportive Statistical 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. • SAS code for the CMH test is provided below: proc freq data=errors (where=(err_ord^=0)); tables seq*err_ord/cmh; run; As with the main analysis, country will be included as a covariate if sufficient data is available as described above. err_ord is derived as shown in Section 11.5.3

8. SECONDARY STATISTICAL ANALYSES

8.1. Efficacy Analyses

8.1.1. Overview of Planned Secondary Efficacy Analyses

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

Table 4 provides an overview of the planned secondary efficacy analyses, with further details of data displays being presented in Appendix 11: List of Data Displays.

Table 4 Overview of Planned Secondary Efficacy Analyses

	Absolute			
	Stats Analysis	Summary		Individual
	T	T	F	L
Number of critical errors made after 1st Healthcare Professional (HCP) instructions				
The percentage of subjects making at least one critical error after the first instruction from the HCP	Y	Y	Y	
Number of overall errors made				
Percentage of subjects making at least one overall error after reading the PIL(s)	Y	Y	Y	
Percentage of subjects making at least one overall error after the first instruction from the HCP	Y	Y	Y	
Number of instructions (maximum of 2) from the HCP				
Number of instructions from the HCP	Y	Y	Y	Y
Total Training/Teaching time required				
Total time taken to demonstrate correct inhaler use (T1+T2)	Y	Y	Y	Y

	Absolute			
	Stats Analysis	Summary		Individual
	T	T	F	L
Preference attributes				
Treatment preference for number of steps required to take medication	Y	Y		Y
Treatment preference for taking COPD medication	Y	Y		Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents TFL related to any displays of individual subject observed raw data.

8.1.2. Planned Secondary Efficacy Statistical Analyses

8.1.2.1. Number of critical errors made after 1st Healthcare Professional (HCP) instructions

Secondary Statistical Analyses
Endpoint(s)
The percentage of subjects making at least one critical error after the: • first instruction from the HCP
Model Specification, Model Checking & Diagnostics, Model Results Presentation
• Same method as percentage of subjects making at least one critical error after reading the PIL(s), see Section 7.1.2 • Note this model will only be fitted if there is sufficient data. If there is insufficient data then only summary statistics will be produced.

8.1.2.2. Number of overall errors made

Secondary Statistical Analyses
Endpoint(s)
• Percentage of subjects making at least one overall error after reading the PIL(s) • Percentage of subjects making at least one overall error after the first instruction from the HCP
Model Specification, Model Checking & Diagnostics, Model Results Presentation
• Same method as percentage of subjects making at least one critical error after reading the PIL(s), see Section 7.1.2 • Sensitivity analysis will also be performed as detailed in Section 7.1.2 • Note this model will only be fitted if there is sufficient data. If there is insufficient data then only summary statistics will be produced.

8.1.2.3. Number of instructions (maximum of 2) from the HCP

Secondary Statistical Analyses
Endpoint(s)
• Number of instructions from the HCP

Secondary Statistical Analyses
Model Specification
• The endpoint of number of instructions from the HCP will be analysed using the Intent-to-treat population. • Those who were unable to demonstrate correct use will not be included in the analysis, but will be summarised in tables • This endpoint will be analysed using the Wilcoxon signed rank test
Model Results Presentation
• Summary statistics on the number of instructions from the HCP will be provided for each device along with the p-value of the Wilcoxon signed rank test.
SAS Code
The following SAS code will be used: proc univariate data=no_error; var diffinst; run; diffinst is derived as shown in Section 11.5.5

8.1.2.4. Training/Teaching time required

Secondary Statistical Analyses
Endpoint(s)
• Total demonstration time (T1+T2)
Model Specification
• The endpoint of training/teaching time will be analysed using the Intent-to-treat population. • This endpoint will be analysed using Kaplan-Meier analysis.
Model Results Presentation
• For DISKUS + HandiHaler or Turbuhaler + HandiHaler the time for each device will be added together to form the total time needed to demonstrate correct use at T1 and T2 respectively. • Median time to correctly use the inhaler after reading the patient information leaflet and HCP's instruction (T1+T2) will be presented for each inhaler group. For subjects who correctly used the inhaler after reading the patient information leaflet set T2=0. T1+T2 is censored for subjects who did not use the inhaler correctly after 3 attempts. Kaplan-Meier survivor functions of T1+T2 will be obtained for each inhaler group and plotted on the same figure. • In the above analysis the median time will be taken from the Kaplan Meier model.
SAS Code

• Kaplan-Meier survivor functions of the proportion of subjects with a time to correctly use the inhaler will be obtained for each inhaler group separately and will be plotted on the same figure. The following SAS code will be used:
ods output ProductLimitEstimates = plest(keep = trtcd timeto failed left)
quartiles=median CensoredSummary=cen;
proc lifetest data=t_device outsurv=survest;
time timeto*event(0);
strata treatment;
run;

8.1.2.5. Preference attributes

Secondary Statistical Analyses
Endpoint(s)
• Treatment preference from questionnaire for number of steps required to take medication • Treatment preference from questionnaire preferred treatment for overall treatment preference.
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
• Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• The percentage of preference for each specific attribute (i.e., preferring ELLIPTA inhaler, preferring the other inhaler, 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.
SAS Code
• SAS code for stratified approximation to Prescott's test for each preference question: ods output CMH = cmhi (where = (upcase(AltHypothesis) =: 'ROW MEAN SCORES') keep = AltHypothesis Prob) ; proc freq data = pref_data ; tables seq * pref_ord country / cmh ; run ; Country will be included in the model providing there are sufficient subjects distributed to enable the model to run. If the model will not run with country in the model then country will be removed from the model. pref_ord is derived as shown in Section 11.5.4

9. OTHER STATISTICAL ANALYSES

9.1. Efficacy Analyses

9.1.1. Overview of Planned Other Efficacy Analyses

The other efficacy analyses will be based on the Intent-to-treat population, unless otherwise specified.

Table 5 provides an overview of the planned other efficacy analyses, with further details of data displays being presented in Appendix 11: List of Data Displays.

Table 5 Overview of Planned Other Efficacy Analyses

	Absolute			
	Stats Analysis	Summary		Individual
	T	T	F	L
Number of critical errors made after Healthcare Professional (HCP) instructions				
The percentage of subjects making at least one critical error after the second instruction from the HCP	Y	Y	Y	
Number of overall errors made				
Percentage of subjects making at least one overall error after the second instruction from the HCP	Y	Y	Y	
Training/Teaching time required				
Time to read PIL(s) (T1)	Y	Y	Y	Y
Instruction time by the HCP (T2)	Y	Y	Y	Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents TFL related to any displays of individual subject observed raw data.

Summary statistics will be generated for the amount of time needed to read the PIL(s) (T1) and the total instruction time by the HCP (T2) separately. These will be presented in the same format as the total amount of time taken to demonstrate correct inhaler use.

9.1.1.1. Number of critical errors/overall errors made after 2nd Healthcare Professional (HCP) instructions

Other Statistical Analyses
Endpoint(s)
• The percentage of subjects making at least one critical error after the second instruction from the HCP • Percentage of subjects making at least one overall error after the second instruction from the HCP
Model Specification, Model Checking & Diagnostics, Model Results Presentation
• Same method as percentage of subjects making at least one critical error after reading the PIL(s), see Section 7.1.2 • Note this model will only be fitted if there is sufficient data. If there is insufficient data then only summary statistics will be produced.

9.1.1.2. Training/Teaching time required

Other Statistical Analyses
Endpoint(s)
• Time to read PIL(s) and demonstrate correct inhaler use (T1) • Instruction time by the HCP (including demonstration of correct inhaler use) (T2)
Model Specification
• The endpoint of training/teaching time will be analysed using the Intent-to-treat population. • This endpoint will be analysed using Kaplan-Meier analysis.
Model Results Presentation
• Median time to correctly use the inhaler after reading the patient information leaflet (T1) will be presented for each inhaler group. Time will be censored for subjects who did not use the inhaler correctly. Kaplan-Meier survivor functions of T1 will be obtained for each inhaler group and plotted together on the same graph. This analysis will then be repeated with no censoring, only allowing subjects who correctly used the inhaler to be included in the model. • Median time to correctly use the inhaler following HCP's instruction (T2) will be presented for each inhaler group. Time will be set to 0 for subjects who correctly used the inhaler after reading the patient information leaflet, and will be censored for subjects who did not use the inhaler correctly after 3 attempts. Kaplan-Meier survivor functions of T2 will be obtained for each inhaler group and plotted on the same figure. • In all of the above analysis the median time will be taken from the Kaplan Meier model.
SAS Code
• See Section 8.1.2.4

9.2. Safety Analyses

9.2.1. Overview of Planned Safety Analyses

These other safety analyses will be based on the ITT populations, unless otherwise specified.

Table 6 provides an overview of the planned safety analyses, with further details of data displays being presented in Appendix 11: List of Data Displays.

Table 6 Overview of Other Planned Safety Analyses

Endpoint	Absolute	
	Summary	Individual
	T	L
Adverse Events		
Overview of AEs	Y	
On-treatment AEs, drug related AE's, fatal/non-fatal SAE's, fatal/non-fatal drug related SAE's	Y	Y
Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Y	
On-treatment serious AEs experienced by 3% (before rounding) or more of subjects in any treatment group	Y	
On-treatment non-serious AEs experienced by 3% (before rounding) or more of subjects in any treatment group	Y	
Subject numbers for individual AEs (ASE)		Y
All AEs including identification of whether each AE occurred pre-treatment or on-treatment (ASE)		Y
Non-fatal SAEs (ASE)		Y
Fatal AEs (ASE)		Y
On-treatment drug related SAEs		Y
AEs leading to discontinuation of study treatment or withdrawal from the study	Y	Y
Cardiovascular Events		Y
Relationship between adverse event system organ class, preferred term and verbatim text (ASE)		Y

NOTES :
- T = Table, L = Listing, Y = Yes display generated.
- Summary = Represents TL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents TL related to any displays of individual subject observed raw data.

9.2.1.1. Adverse Events and Serious Adverse Events

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

- Any AE (pre treatment -, 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 during screening, on treatment or after treatment.

9.2.1.2. Cardiovascular Events

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

9.2.2. 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.

10. REFERENCES

GlaxoSmithKline Document Number 2016N292801_01, Protocol: A randomized, open-label, cross-over, placebo-device study investigating critical and over all errors, training/teaching time, and preference attributes of the ELLIPTA dry powder Inhaler (DPI) as compared to HandiHaler DPI used in combination with either DISKUS DPI or Turbuhaler DPI, in adult patients with Chronic Obstructive Pulmonary Disease (COPD), 15 September 2016

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, 2_{nd} ed. Chichester: John Wiley & Sons, Ltd, 2002. pp 128-131, 202-203.

11. APPENDICES

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 11.1	Appendix 1: Protocol Deviation Management
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 11.2	Appendix 2: Time & Events
Section 11.3	Appendix 3: Treatment Phases
Section 11.4	Appendix 4: Data Display Standards & Handling Conventions
Section 11.5	Appendix 5: Derived and Transformed Data
Section 11.6	Appendix 6: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 11.7	Appendix 7: Multicenter Studies
Section 11.8	Appendix 8: Examination of Covariates, Subgroups & Other Strata
Section 11.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 11.10	Appendix 10: Abbreviations & Trade Marks
Section 11.11	Appendix 11: List of Data Displays
Section 11.12	Appendix 12: Example Mock Shells for Data Displays

11.1. Appendix 1: Protocol Deviation Management

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.

11.2. Appendix 2: Time & Events

11.2.1. Protocol Defined Time & Events

Visit Number	V0	V1	Notes
Study Day	**1**	**1**	V0 can take place on the same day as V1. V1 should be completed no later than 30 days after consent.
Procedure:			
Screening Assessments			Completed prior to randomisation
Written informed consent	X		Informed consent may take place prior to V0 for logistical reasons. Subjects should be included and randomised within 30 days of providing consent.
Subject demography	X		Age, height, weight, year of birth, sex, ethnicity and geographic ancestry will be recorded
Medical/disease history including Chronic Obstructive Pulmonary Disease (COPD)	X		Subject will have a medical history of COPD, previously confirmed by spirometry.
Concomitant medication history including COPD Therapy History	X		Current concomitant medication will be recorded. A minimum COPD therapy history for the preceding 2 years from inclusion will be recorded
Inclusion/exclusion criteria	X		All criteria must be meet prior to randomisation at V1
Study Assessments			Completed once a subject is included on study
Randomisation		X	Randomised to treatment order and preference questionnaire
Assess the number of inhaler errors (critical and overall) on each treatment after reading the Patient information leaflet (PIL) for Inhaler tested		X	No instruction is provided by the Health Care Professional (HCP) for this assessment.
Assess the number of inhaler errors (overall and critical) on each treatment after each of 2 attempts following instruction by HCP		X	If a subject cannot show correct use after reading the PIL, then the HCP has up to 2 attempts to instruct the subject to attain this.

Visit Number	V0	V1	Notes
Teaching-Training Time for each inhaler includes the following: • The amount of time taken to read the patient information leaflet and demonstrate inhaler use • The amount of time taken to be given instruction by the HCP on use of the inhaler and demonstrate inhaler use • The total amount of time taken to demonstrate inhaler use		X	• First assessment is attempt one, including time to read PIL and demonstrate use. • Second assessment will be time for HCP to correct errors and subject to show use for up to 2 more attempts • The Cumulative time for all assessments needed by subject and any HCP instruction to demonstrate no errors will also be captured.
Preference Questionnaire		X	Subject will complete version of Preference Questionnaire they have been randomised to.
SAE/AE assessment		X	Collected until completion of final study assessment at V1.

11.3. Appendix 3: Treatment Phases

11.3.1. Treatment Phases

All data if necessary will be categorised according to the following treatment phases; pre-study, during- study and post- study. These definitions will be defined based on the date of Visit 1, as this is the visit where subjects complete all study assessments. In addition, as date and not time is captured in the eCRF the treatment phase can only be applied if an event spans multiple days.

11.3.2. Treatment Phase Definitions

Definition	Treatment Phase		
	Pre-study	During-study	Post-study
Before Visit 1	Y		
At Visit 1		Y	
After Visit 1			Y

11.4. Appendix 4: Data Display Standards & Handling Conventions

11.4.1. 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
C	Turbuhaler Inhaler + HandiHaler Inhaler	Turbuhaler + HandiHaler	3
Q1	Preference Questionnaire 1	Q1	4
Q2	Preference Questionnaire 2	Q2	5
Q3	Preference Questionnaire 3	Q3	6
Q4	Preference Questionnaire 4	Q4	7

NOTES:

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

11.4.2. Reporting Process & Standards

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/mid206215/final_01
QC Spreadsheet	/arenv/arwork/gsk2834425/mid206215/final_01/documents
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards.	
Generation of RTF Files	
• RTF files will be generated for use in writing the CSR.	

Reporting Standards	
General	
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics	
Formats	
• All data will be reported according to the actual treatment option the subject received unless otherwise stated. • 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. • Numeric data on listings will be reported at the precision collected on the eCRF.	
Planned and Actual Time	
• Reporting for Data Listings: • Unscheduled or unplanned readings will be presented within the subject's listings but not presented in summary tables.	
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.	

11.5. Appendix 5: Derived and Transformed Data

11.5.1. Study Population

Demographics
Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: o Any subject with a missing day will have this imputed as day '15'. o Any subject with a missing date and month will have this imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height (m)]^2

11.5.2. Date of Completion and Withdrawal

This study only has one on-treatment visit. Subjects either complete or withdraw on the day. There is no follow up visit.

11.5.3. Critical and Overall Errors

Critical and Overall errors
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 in the 1st period and DISKUS + HandiHaler or Turbuhaler + HandiHaler in the 2nd period, then for critical error in relation to sequence: • err_ord = -1, if subject had critical error in the 1st period but NOT in the 2nd period • err_ord = 1, if subject had critical error in the 2nd period but NOT in the 1st period • err_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 and DISKUS + HandiHaler or Turbuhaler + HandiHaler in the 1st period and ELLIPTA in the 2nd period, then for each preference question: • err_ord = 1, if subject had critical error in the 1st period but NOT in the 2nd period • err_ord = -1, if subject had critical error in the 2nd period but NOT in the 1st period • err_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.

11.5.4. 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 or Turbuhaler + 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 or Turbuhaler + HandiHaler • pref_ord = 0, if subject has no preference If the sequence of inhaler use is DISKUS + HandiHaler or Turbuhaler + 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 or Turbuhaler + HandiHaler • pref_ord = 0, if subject has no preference

11.5.5. Number of instructions

Number of Instructions
The number of instructions from the HCP which are needed to demonstrate adequate inhalation technique for each inhaler will be summarised. The number of instruction from the HCP will be assigned as follows: • NUMINSTR = 0, if no instruction needed correct after reading leaflet • NUMINSTR = 1, if the participant received 1st instruction and had no error • NUMINSTR = 2, if the participant received the 2nd instruction and had no error • NUMINSTR = 3, if the participant received 2nd instruction and had at least one error From this an ordinal variable (diffinst) will be derived to indicate the difference between the number of instructions required to demonstrate correct use on the ELLIPTA device compared to the DISKUS + HandiHaler or Turbuhaler + HandiHaler devices.

11.6. Appendix 6: Premature Withdrawals & Handling of Missing Data

11.6.1. Premature Withdrawals

Element	Reporting Detail
General	• For reporting purposes, subject study completion will be defined as completion of all three periods (both devices and answered questionnaire) on the day of study visit. • Withdrawn subjects will be defined as those who used at least one device 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 scheduled data will be included in summary tables and figures, unless otherwise specified.

11.6.2. 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 : o 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. o 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 critical errors on both devices in order for the analysis to be performed, if they only complete one period they will not be included in the analysis. Subjects who complete both devices, but do not answer the questionnaire will be included in all analysis excluding those related to preference.
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. Any potential exclusions would be for exploratory purposes only and not for the primary analysis.

11.6.2.1. Handling of Missing/Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 3: Treatment Phases. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.
Concomitant Medications	• Partial dates for any concomitant medications recorded in the eCRF 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.
Adverse Events	• Any partial dates for adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. ○ However, if these results in a date prior to Week 1 Day 1 and the event could possibly have occurred during treatment from the partial information, then the Week 1 Day 1 date will be assumed to be the start date. ○ The AE will then be considered to start on-treatment (worst case). ○ 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.

11.6.2.2. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
Critical Errors	• If any of the critical error assessment elements (sub-questions) have a missing response then, for the purposes of the analysis of the percentage of subjects making at least one critical error, the subject will be defined as having one or more critical errors. All summarised data and listed data at the individual question level will show that response to be missing. Note that if a subject already has a critical error in another question then the missing response will not impact their error status.
Overall Errors	• If any of the error assessment elements have a missing response then, for the purposes of the analysis of the percentage of subjects making at least one error, the subject will be defined as having one or more errors. All summarised data and listed data at the individual question level will show that response to be missing. Note that if a subject already has an error in another question then the missing response will not impact their error status.

11.7. Appendix 7: Multicenter Studies

11.7.1. Methods for Handling Centres

Element	Reporting Detail
Centres	• Central randomisation was used for this study. Data from all participating centres will be pooled prior to analysis.

11.8. Appendix 8: Examination of Covariates, Subgroups & Other Strata

11.8.1. Handling of Covariates

- The following is a list of covariates that may be used in descriptive summaries and statistical analyses. Whilst inhaler sequence will be used throughout, the inclusion of country in the model relies on sufficient data being collected in each country to allow the model to remain statistically valid. If the model is valid the data the analysis will be performed.
- Country will be included as a covariate as part of a sensitivity analysis if enough subjects from each country are recruited, within each of the possible outcomes (critical error/no critical error) by device and randomised sequence, to allow the statistical model to converge without errors.

Category	Covariates and / or Subgroups
Inhaler Sequence	The study inhaler use sequence (ELLIPTA/Other or Other/ELLIPTA) which include information on the treatment and period it was received in will be adjusted for in the statistical analysis. Other refers to either DISKUS + HandiHaler or Turbuhaler + HandiHaler.
Country	This study will be carried out in two countries (the United Kingdom and the Netherlands), summary tables will be provided by country and it may be included in statistical sensitivity analysis if enough subjects from each country are recruited, within each of the possible outcomes (critical error/no critical error) by device and randomised sequence, to allow the statistical model to converge without errors.

11.9. Appendix 9: Model Checking and Diagnostics for Statistical Analyses

Model	Diagnostic Checks
Logistic Regression	Residual vs Fitted plots will be generated to help assess the constant variance assumption. Deviance and Pearson goodness of fit statistics from the model will be examined to help assess the null hypothesis that the model is an adequate fit to the data.
Cochran-Mantel-Haenszel	Homogeneity across groups will be assessed using the Breslow-Day test. SAS Code: proc freq data = pref_data (where = (pref_ord ne **0**)) ; tables country * seq * pref_ord / cmh ; run;

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

11.10. Appendix 10: Abbreviations & Trade Marks

11.10.1. 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

11.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
DISKUS
ELLIPTA

Trademarks not owned by the GlaxoSmithKline Group of Companies
HandiHaler
SAS
Turbuhaler

11.11. Appendix 11: List of Data Displays

If enough subjects are recruited in both the Netherlands and the United Kingdom then the additional analysis tables including country will be included as detailed in the main RAP, and table numbers will be adjusted accordingly.

11.11.1. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
Subject Disposition and Demography					
1.01	ASE	IDSL_SP01	Summary of Subject Populations	Page by sub-study, total column only	SAC
1.02	ASE	IDSL_ES6	Summary of Screening Status and Reasons for Screen Failures	Page by sub-study	SAC
1.03	ASE	IDSL_DM1	Summary of Age Ranges	Page by sub-study	SAC
1.04	ITT	IDSL_SP02	Summary of Attendance at Each Clinic Visit	Page by sub-study, total column only	SAC
1.05	ITT	IDSL_SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	Page by sub-study	SAC
1.06	ITT	IDSL_ES1	Summary of End of Study Record	Page by sub-study	SAC
1.07	ITT	IDSL_DM2	Summary of Demographic Characteristics	Page by sub-study	SAC
1.08	ITT	IDSL_DM2	Summary of Demographic Characteristics by Country	Page by sub-study	SAC
1.09	ITT	IDSL_NS1	Summary of Number of Subjects by Country and Centre	Page by sub-study	SAC
1.10	ITT	IDSL_DM5	Summary of Race and Racial Combinations	Page by sub-study	SAC
1.11	ITT	IDSL_DM6	Summary of Race and Racial Combination Details	Page by sub-study	SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
Protocol Deviations					
1.12	ITT	IDSL_SP04	Summary of Important Protocol Deviations	Page by sub-study	SAC
1.13	ITT	IDSL_IE1	Summary of Inclusion/ Exclusion/ Randomisation Criteria Deviations for Intent-to-treat	Page by sub-study	SAC
Medical Condition & Concomitant Medications					
1.14	ITT	IDSL_MH4	Summary of Current Medical Conditions	Page by sub-study	SAC
1.15	ITT	IDSL_MH4	Summary of Past Medical Conditions	Page by sub-study	SAC
1.16	ITT	IDSL – SP07	Summary of Family History of Cardiovascular Risk Factors	Page by sub-study	SAC
1.17	ITT	IDSL_SP08	Summary of COPD History and COPD Exacerbation History at Screening	Page by sub-study	SAC
1.18	ITT	IDSL_SP10	Summary of Smoking Status	Page by sub-study	SAC
1.19	ITT	IDSL_SP11	Summary of COPD Medications	Page by sub-study	SAC
1.20	ITT	IDSL_CM1	Summary of Non-COPD Medications	Page by sub-study	SAC

11.11.2. 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	Page by sub-study	SAC
2.02	ITT	EFF_T01	Summary of Errors on ELLIPTA by Country	Page by sub-study and country	SAC
2.03	ITT	EFF_T01	Summary of Errors on DISKUS + HandiHaler	Page by DISKUS + HandiHaler Errors, DISKUS Errors and HandiHaler Errors	SAC
2.04	ITT	EFF_T01	Summary of Errors on DISKUS + HandiHaler by Country	Page by DISKUS + HandiHaler Errors, DISKUS Errors, HandiHaler Errors and Country	SAC
2.05	ITT	EFF_T01	Summary of Errors on Turbuhaler + HandiHaler	Page by Turbuhaler + HandiHaler Errors, Turbuhaler Errors and HandiHaler Errors	SAC
2.06	ITT	EFF_T01	Summary of Errors on Turbuhaler + HandiHaler by Country	Page by Turbuhaler + HandiHaler Errors, Turbuhaler Errors, HandiHaler Errors and country	SAC
2.07	ITT	EFF_T06	Summary of Critical Errors	Page by sub-study and assessment	SAC
2.08	ITT	EFF_T06	Summary of Critical Errors by Country.	Page by sub-study, assessment and country	SAC

Overall Summary of Errors					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
Primary Analysis Tables					
2.09	ITT	EFF_T04	Analysis of Percentage of Subjects making at least one Critical Error	Include analysis only if sufficient data is available for models to run. Page by sub-study and assessment	SAC
2.10	ITT	EFF_T07	Sensitivity Analysis of Percentage of Subjects making at least one Error after Reading the PIL(s)	Page by sub-study	SAC
Secondary Analysis Tables					
Number of Overall Errors					
2.11	ITT	EFF_T04	Analysis of Percentage of Subjects making at least one Overall Error	Include analysis only if sufficient data is available for models to run. Page by sub-study and assessment.	SAC
Training/Teaching Time Required					
2.12	ITT	EFF_T02	Summary and Analysis of Time (Minutes) Taken to Demonstrate Correct Inhaler Use	Page by sub-study and assessment.	SAC
Preference Attributes					
2.13	ITT	EFF_T03	Summary of Treatment Preference	Page by sub-study.	SAC
2.14	ITT	EFF_T05	Summary and Analysis of Number of Instructions from the HCP	Only if sufficient data is available. Page by sub-study.	SAC

11.11.3. 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	Page by sub-study.	SAC
3.02	ITT	IDSL_AE1	Summary of On-study Adverse Events	Page by sub-study.	SAC
3.03	ITT	IDSL_AE1	Summary of Post-study Adverse Events	Page by sub-study.	SAC
3.04	ITT	IDSL_AE1	Summary of Serious Adverse Events	Page by sub-study.	SAC
3.05	ITT	IDSL_AE1	On-treatment AEs leading to discontinuation of study treatment or withdrawal from the study	Page by sub-study.	SAC
3.06	ITT	IDSL_AE1	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Page by sub-study.	SAC

11.11.4. Efficacy Figures

Primary Efficacy Analysis					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.01	ITT	EFF_F01	Percentage of Subjects with at Least One Critical Error by Assessment	Page by sub-study.	SAC
Secondary Efficacy Analysis					
2.02	ITT	EFF_F01	Percentage of Subjects with at Least One Error by Assessment	Page by sub-study.	SAC
2.03	ITT	EFF_F02	Number of Instructions required from a HCP	Page by sub-study.	SAC
2.04	ITT	EFF_F03	Kaplan-Meier Plot of Time Taken to Demonstrate Correct Inhaler Use	Page by sub-study and assessment.	SAC

11.11.5. 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	Page by sub-study.	SAC
02	ITT	IDSL_ES2	Listing of Reasons for Study Withdrawal	Page by sub-study.	SAC
Study Population: Protocol Deviations					
03	ITT	IDSL_SP01	Listing of Important Protocol Deviations	Page by sub-study.	SAC
04	ASE	IDSL_IE3	Listing of Inclusion/ Exclusion/ Randomisation Criteria Deviations	Page by sub-study.	SAC
Study Population: Treatment					
05	ITT	IDSL_TA1	Listing of Randomised and Actual Treatment Sequence	Page by sub-study.	SAC
Study Population: Demography					
06	ITT	IDSL_DM2	Listing of Demographic Characteristics	Include BMI as the optional measurement. In addition, include a country column as the first sort variable. Page by sub-study.	SAC
07	ITT	IDSL_DM9	Listing of Race	Include a country column as the first sort variable. Page by sub-study.	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Safety: Adverse Events					
08	ASE	IDSL_AE7	Listing of Subject Numbers for Individual Adverse Events	Page by sub-study.	SAC
09	ASE	IDSL_AE8	Listing of All Adverse Events	Page by sub-study.	SAC
Efficacy: Primary Endpoint					
10	ITT	EFF_L01	Listing of Subject Errors by Assessment	Page by sub-study.	SAC

11.11.6. Non ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population: Subject Disposition					
11	ITT		Listing of Subjects by Country and Centres	Page by sub-study.	SAC
Study Population: Protocol Deviations					
12	ITT	IDSL_TA1	Listing of Treatment Sequence Misallocations	Page by sub-study.	SAC
Study Population: Medical Conditions & Concomitant Medications					
13	ITT	IDSL_MH2	Listing of Medical Conditions	Page by sub-study.	SAC
14	ITT	IDSL_SP05	Listing of Family History of Cardiovascular Risk Factors	Page by sub-study.	SAC
15	ITT	IDSL_SP06	Listing of COPD History and COPD Exacerbation History	Page by sub-study.	SAC
16	ITT	IDSL_SP07	Listing of Smoking History and Smoking Status	Page by sub-study.	SAC
17	ITT	IDSL_CM2	Listing of COPD and non-COPD Medications	Page by sub-study.	SAC
18	ITT	IDSL_CM6	Relationship between ATC Level 1, Ingredient and Verbatim Text	Page by sub-study.	SAC
Study Population: Devices					
19	ITT	IDSL_SP08	Listing of Naivety to Inhaler Devices	Page by sub-study.	SAC
Efficacy: Secondary Efficacy Analysis					
20	ITT	EFF_L02	Listing of Time Taken to Demonstrate Correct Inhaler Use	Page by sub-study.	SAC
21	ITT	EFF_L03	Listing of Preference Questionnaire	Page by sub-study.	SAC

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

11.12. Appendix 12: Example Mock Shells for Data Displays

Example : EFF_T01
Protocol : 206215
Population : Intent to Treat

Table X.X
Summary of errors on ELLIPTA

Sub-study 1: ELLIPTA vs DISKUS + HandiHaler

Inhaler errors test	After Reading Leaflet (N=XXX)	After 1st Instruction from HCP (N=XXX)	After 2nd Instruction from HCP (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. Page by sub-study. For DISKUS + HandiHaler/Turbuhaler + 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 : 206215
Population : Intent to Treat

Table X.X
Summary and Analysis of Time (Minutes) Taken to Demonstrate Correct Inhaler Use

Sub-study 1: ELLIPTA vs DISKUS + HandiHaler
Assessment: Time to read the PIL and Demonstrate Correct Use

	ELLIPTA (N=XXX)	DISKUS + HandiHaler (N=XXX)
n	XXX	XXX
Mean	XX.XX	XX.XX
SD	XX.XXX	XX.XXX
Median	XX.XX	XX.XX
Min	XX.X	XX.X
Max	XX.X	XX.X
Number of Subjects who demonstrated correct use	XXX	XXX
Number of Subjects who failed to demonstrate correct use (censored)	XXX	XXX
Median Time to demonstrate correct inhaler use (minutes) [1]	XXX	XXX

[1] The Median Time to demonstrate correct inhaler use (minutes) is taken from the Kaplan-Meier analysis. If more than 50% of the data is censored then the median is not applicable.
Note: For the Diskus+Handihaler and Turbuhaler +HandiHaler groups, if a subject made an error on one device and not the other the time to demonstrate correct use is censored at the total of time taken for both devices.

Programming notes: Page by sub-study and assessment (Time taken to read the PIL and Demonstrate Correct Use/ Time for HCP Instruction and to Demonstrate Correct Use /Total Time to demonstrate correct use).

Example : EFF_T03
Protocol : 206215
Population : Intent to Treat

Table X.X
Summary and Analysis of Treatment Preference

Sub-study 1: ELLIPTA vs DISKUS + HandiHaler

	Total (N=XXX)	P-Value
Which treatment do you prefer based on the number of the number of steps needed to take your medication?		
n	XXX	X.XXX
ELLIPTA	XXX (XX%)	
DISKUS + HandiHaler	XXX (XX%)	
No Preference	XXX (XX%)	
Which treatment do you prefer for taking your 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: Page by sub-study. %'s calculated out of the small n for each question.

Example : EFF_T04
Protocol : 206215
Population : Intent to Treat

Table X.X
Analysis of Percentage of Subjects making at least one Critical Error

Sub-study 1: ELLIPTA vs DISKUS + HandiHaler
Assessment: After reading the PIL(s)

	ELLIPTA (N=XXX)	DISKUS + HandiHaler (N=XXX)
At least one Critical Error	XXX (XX%)	XXX (XX%)
Zero Critical Errors	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, country and period included as fixed effects.

Programming notes: Page by sub-study and assessment

Example : EFF_T05
Protocol : 206215
Population : Intent to Treat

Table X.X
Summary and Analysis of Number of Instructions from the HCP

Sub-study 1: ELLIPTA vs DISKUS + HandiHaler

	ELLIPTA (N=XXX)	DISKUS + HandiHaler (N=XXX)	Difference (ELLIPTA – DISKUS+HandiHaler)
n	X	X	X
Median (95% CI)	XXX (XXX – XXX)	XXX (XXX – XXX)	XXX (XXX – XXX)
Min	XXX	XXX	XXX
Max	XXX	XXX	XXX
Number of Insturctions			
0	XXX (XX%)	XXX (XX%)	
1	XXX (XX%)	XXX (XX%)	
2	XXX (XX%)	XXX (XX%)	
Failed to demonstrate correct use	XXX (XX%)	XXX (XX%)	

ELLIPTA vs DISKUS + HandiHaler

p-value	X.XXX

For the Diskus+Handihaler and Turbuhaler+HandiHaler groups, if a subject failed to demonstrate correct use on one device and not the other, the subject would be counted as failed to demonstrate correct use.
Note: P-value has come from the Wilcoxon signed rank test. This analysis did not take into account sequence of treatment options.
Programming notes: Page by sub-study.

Example : EFF_T06
Protocol : 206215
Population : Intent to Treat

Table X.X
Summary of Critical Errors

Timepoint: After reading PIL

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

Programming note: Repeat by sub-study and remaining timepoints, e.g. after first HCP instruction, second etc and by

Example : EFF_T07
Protocol : 206215
Population : Intent to Treat

Table X.X
Sensitivity Analysis of Percentage of Subjects making at least one Error after Reading the PIL(s)

Timepoint: After reading PIL

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

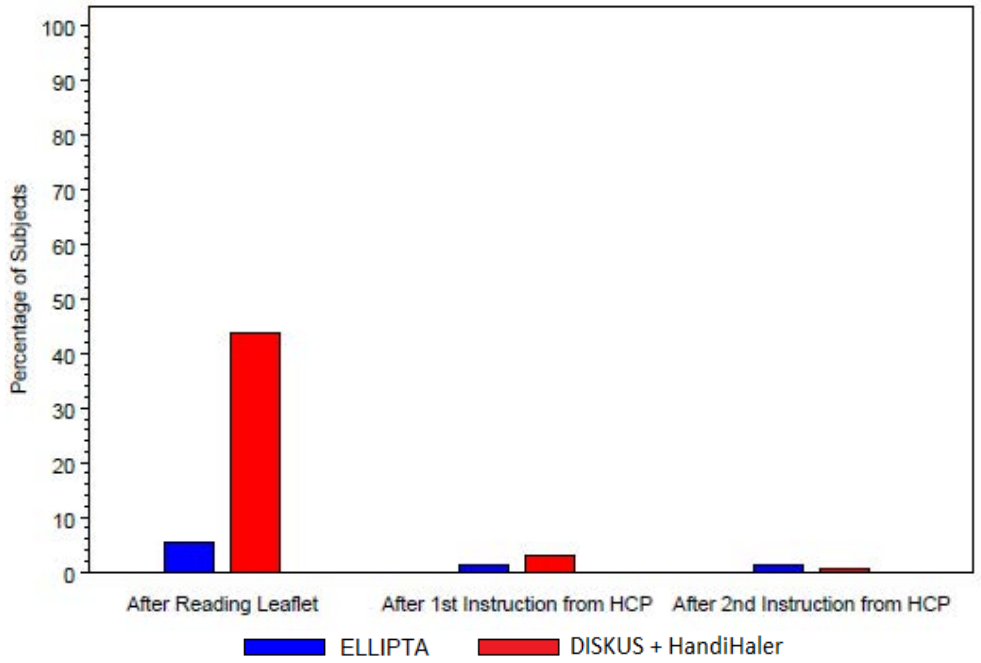
[1] Defined as an error in one device and not the other.
[2] Analysis performed using the Cochran-Mantel-Haenszel test *adjusted for country*.
Note: Subjects are only included in the analysis if they have discordant data.

Programming note: Page by sub-study

Example : EFF_F01
Protocol : 206215
Population : Intent to Treat

Figure X.X
Proportion of Subjects with at Least One Critical Error by Assessment

Sub-study 1: ELLIPTA vs DISKUS + HandiHaler
Assessment: After Reading the PIL(s)

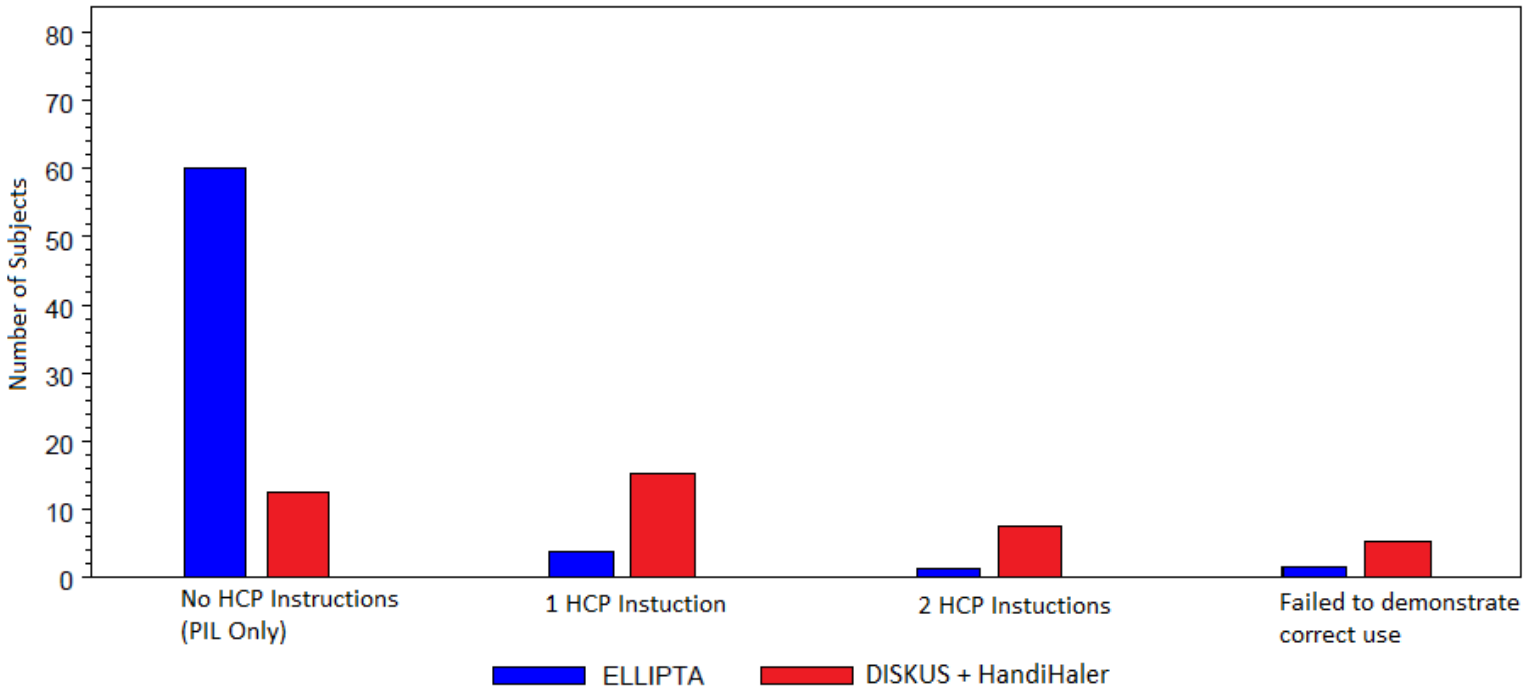


Programming notes: Page by sub-study.

Example : EFF_F02
Protocol : 206215
Population : Intent to Treat

Figure X.X
Number of Instructions required from a HCP

Sub-study 1: ELLIPTA vs DISKUS + HandiHaler

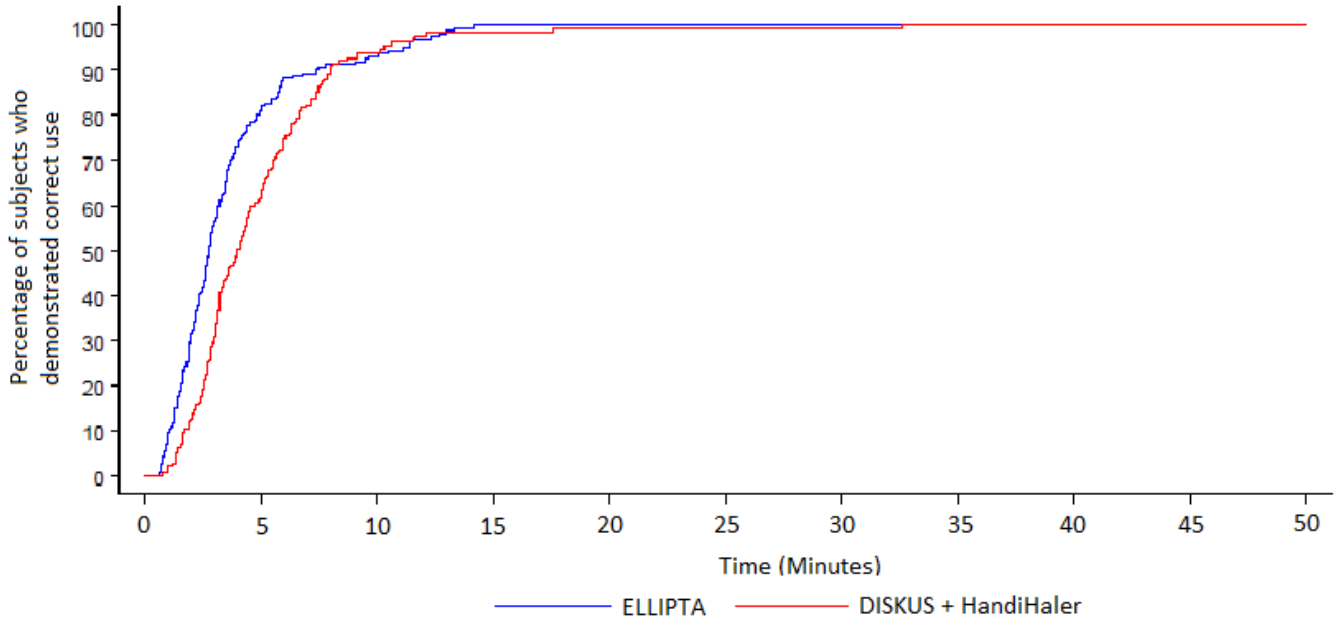


Programming notes: Page by sub-study.

Example : EFF_F03
Protocol : 206215
Population : Intent to Treat

Figure X.X
Kaplan-Meier Plot of Total Time Taken to Demonstrate Correct Inhaler Use

Sub-study 1: ELLIPTA vs DISKUS + HandiHaler
Assessment: Time to read the PIL and Demonstrate Correct Use



Note: For the Diskus+Handihaler and Turbuhaler +HandiHaler groups, if a subject made an error on one device and not the other the time to demonstrate correct use is censored at the total of time taken for both devices
Programming notes: Page by sub-study and assessment (Time taken to read the PIL and Demonstrate Correct Use/ Time for HCP Instruction and to Demonstrate Correct Use /Total Time to demonstrate correct use).

Example : EFF_L01
Protocol : 206215
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	Reading the PIL	2	ELLIPTA	Exhaled directly into mouthpiece Failed to open cover
			After 1st instruction from HCP	1	ELLIPTA	Did not hold breath
			After 2nd instruction from HCP	0		
	2	DISKUS + HandiHaler	Reading the PIL	3	DISKUS	Failed to open cover Lever is not pushed back
					HandiHaler	Did not hold breath
			After 1st instruction from HCP	2	DISKUS	Failed to open cover
					HandiHaler	Did not hold breath [1]
			After 2nd instruction from HCP	1	HandiHaler	Did not hold breath [1]

...

[1] Indicates a Critical Error.

Programming notes: Page by sub-study.

Example : EFF_L02
Protocol : 206215
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
XXXX	ELLITA/DISKUS + HandiHaler/Q1	ELLIPTA	ELLIPTA
XXXX	DISKUS + HandiHaler/ELLIPTA/Q2	DISKUS + HandiHaler	DISKUS + HandiHaler
XXXX	ELLITA/DISKUS + HandiHaler/Q2	No Preference	No Preference

...

Note: Q1 = Questionnaire 1, Q2 = Questionnaire 2
Question 1 = Which treatment do you prefer based on the number of the number of steps needed to take your medication?
Question 2 = Which treatment do you prefer for taking your medication?

Programming notes: Page by sub-study.

Example : EFF_L03
Protocol : 206215
Population : Intent to Treat

Listing X.X
Listing of Time Taken to Demonstrate Correct Inhaler Use (Minutes)

Sub-Study 1: ELLIPTA vs DISKUS + HandiHaler

Subject ID	Treatment Sequence	Time to Read PIL (T1)	Instruction Time by the HCP (T2)	Total Time (T1 + T2)
XXXX	ELLITA/DISKUS + HandiHaler	XXX	XXX	XXX
XXXX	DISKUS + HandiHaler/ELLIPTA	XXX	XXX	XXX
XXXX	ELLITA/DISKUS + HandiHaler	XXX	XXX	XXX

Programming notes: Page by sub-study.