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

| | | |
|---|---|---|
| **Title** | : | Reporting and Analysis Plan for 201832. A Randomised, Double-Blind, Double-Dummy, Crossover Comparison of Fluticasone Furoate/Vilanterol 100/25 mcg Once Daily Versus Fluticasone Propionate 250 mcg Twice Daily in Adolescent and Adult Subjects with Asthma and Exercise-Induced Bronchoconstriction. |
| **Compound Number** | : | GW685698+GW642444 |
| **Effective Date** | : | 15-DEC-2016 |

**Description :**

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report (CSR) for Protocol 201832.
- This RAP is intended to describe the planned efficacy and safety analyses required for the study.
- This RAP 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:**

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| PPD<br>Manager, Statistics (Clinical Statistics) | 15-DEC-2016 |

**Approved by:**

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# 1. REPORTING & ANALYSIS PLAN SYNPOSIS

| Overview | Key Elements of the RAP |
|---|---|
| Purpose | • This RAP details all of the planned analyses and output required for the final Clinical Study Report for study 201832. |
| Protocol | • This RAP is based on the third amendment of the protocol (Dated: 25-May-2016) of study 201832 [GlaxoSmithKline Document Number 2015N231308_03]. |
| Primary Objective | • To evaluate the protective effect of fluticasone furoate/vilanterol (FF/VI) 100/25 mcg once-daily compared with fluticasone propionate (FP) 250 mcg twice-daily against exercise-induced bronchoconstriction in adolescent and adult subjects aged 12 to 50 with persistent asthma. |
| Primary Endpoint | • Maximal percent decrease from pre-exercise $FEV_1$ following exercise challenge at12 hours post evening dose at the end of the 2-week treatment period |
| Study Design | • This is a multicenter, randomized, double-blind, double-dummy, crossover study with two 2-week treatment periods separated by a 2-week wash-out period. Subjects will participate in up to eight study visits (Visit 0 to Visit 7) over the course of the study and a follow up phone call approximately a week after Visit 7. Visits 1, 2, 3, 5 and 6 are evening visits that will be conducted between 5PM and 11PM. Visit 4 and Visit 7 are also evening visits that will begin between 5PM and 11PM and continue over a period of approximately 24 hours. Subjects will be required to attend three clinic visits during this 24-hour period. |
| Planned Analyses | • No interim analysis is planned for this study.<br>• All planned analyses will be carried out once the clinical study database freeze (DBF) has taken place. Once this has been achieved, unblinding will occur and the analyses will be performed. |
| Primary Analysis Populations | • The ITT Population will comprise all subjects randomized to treatment and who received at least one dose of trial medication. Randomized subjects will be assumed to have received trial medication unless definitive evidence to the contrary exists. This will constitute the primary population for all analyses of efficacy measures and safety measures. Outcomes will be reported according to the randomized treatment allocation.<br>• The PP Population will consist of all subjects in the ITT Population who do not have any full protocol deviations and have at least one treatment period without a partial deviation. Protocol deviations can either be full or partial. Subjects with only partial deviations in 1 treatment period will be considered part of the PP population but their data from the treatment period affected by the deviations will be excluded. The decision to exclude a subject, or part of their data, from the PP Population will be made prior to breaking the blind. This population will be used for confirmatory analyses of the primary efficacy endpoint only. |

| Overview | Key Elements of the RAP |
|---|---|
| Hypothesis | • Demonstration of efficacy will be based on a hypothesis testing approach, whereby the null hypothesis is that there is no difference between treatment groups for the endpoint of interest and the alternative hypothesis is that there is a difference between treatment groups |
| Primary Analyses | • The primary efficacy endpoint will be analysed using a mixed model repeated measures (MMRM) model allowing for fixed covariate effects of treatment, period baseline $FEV_1$, the mean of the two period baseline $FEV_1$ values, sex, age, treatment period and smoking history (number of pack years) as fixed effects, and a random intercept for each subject. The covariate-adjusted means for the primary endpoint for each treatment group will be presented together with the estimated difference between the treatment groups, a 95% confidence interval and a 2-sided p-value allowing the null hypothesis to be tested. |

# 2. SUMMARY OF KEY PROTOCOL INFORMATION

## 2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the planned statistical analysis specified in the third amendment of the protocol (Dated: 25-MAY-2016) of study 201832 [GlaxoSmithKline Document Number 2015N231308_03].

## 2.2. Study Objective and Endpoints

### 2.2.1. Primary Objective

To evaluate the protective effect of fluticasone furoate/vilanterol (FF/VI) 100/25 mcg once-daily compared with fluticasone propionate (FP) 250 mcg twice-daily against exercise-induced bronchoconstriction in adolescent and adult subjects aged 12 to 50 with persistent asthma.

### 2.2.2. Primary Efficacy Endpoint

- Maximal percent decrease from pre-exercise $FEV_1$ following exercise challenge at 12 hours post evening dose at the end of the 2-week treatment period

### 2.2.3. Secondary Efficacy Endpoint

- Maximal percent decrease from pre-exercise $FEV_1$ following exercise challenge at 23 hours post evening dose at the end of the 2-week treatment period
- Proportion of subjects with a 30 minute post-challenge $FEV_1$ that was no more than 5% lower than their pre-exercise $FEV_1$ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period
- Weighted mean for percentage decrease from pre-exercise $FEV_1$ following exercise challenge at 12 hours and 23 hours post evening dose (weighted mean 0-60 min) at the end of the 2-week treatment period

### 2.2.4. Other Efficacy Endpoints

- Categorical treatment response evaluation of the percentage of subjects who demonstrate a decrease from pre-exercise challenge $FEV_1$ (at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period) of:
  - $<10\%$,
  - $\geq 10\%$ to $<20\%$,
  - $\geq 20\%$
- Maximal percent decrease from treatment period baseline $FEV_1$ following exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period
- Change from baseline in Asthma Control Questionnaire -5 (ACQ-5) score at the end of the 2-week treatment period

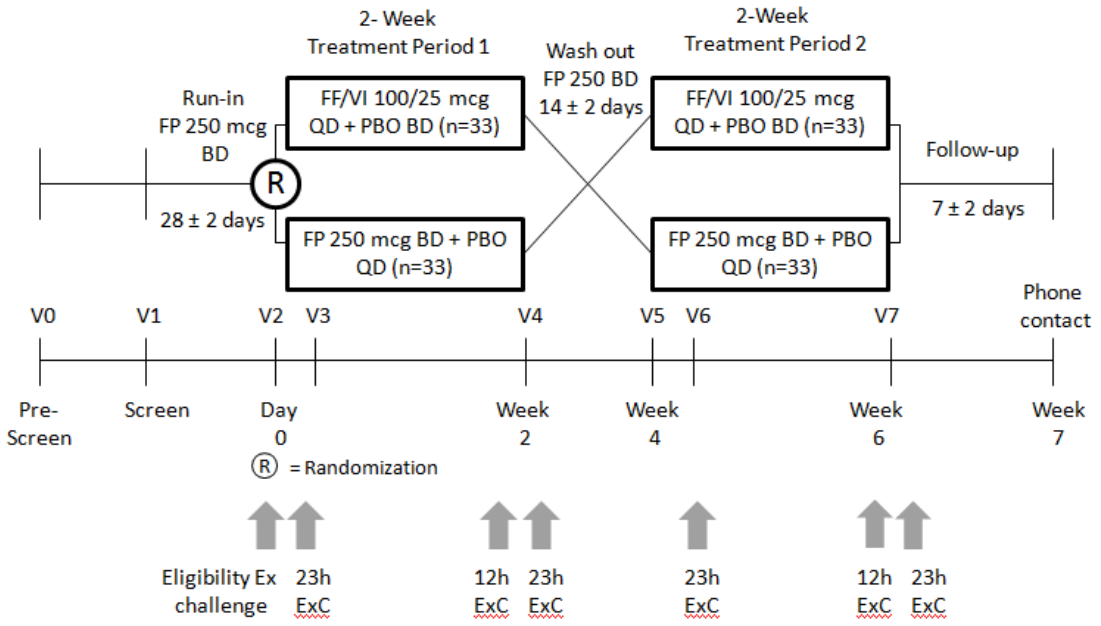
- Percentage of subjects controlled, defined as an ACQ-5 score ≤0.75, at the end of the 2-week treatment period
- Percentage of subjects achieving an improvement of ≥0.5 in ACQ-5 score at the end of the 2-week treatment
- Change in physical activity measures as assessed by a biosensor (SenseWear Armband) in terms of physical activity endpoints (e.g. daily step count, Metabolic Equivalent of Tasks (METs), sleep duration)
- Proportion of subjects with a 5 minute post-challenge $FEV_1$ that was no more than 5% lower than their pre-exercise $FEV_1$ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period. Repeat for the 10, 15, 45 and 60 minute time points.

### 2.2.5. Safety Endpoints

- Adverse events

## 2.3. Study Design

**Overview of Study Design and Key Features**




| | |
|---|---|
| **Design Features** | • This is a multicenter, randomized, double-blind, double-dummy, crossover study with two 2-week treatment periods separated by a 2-week wash-out period. Visits 1, 2, 3, 5 and 6 are evening visits that will be conducted between 5PM and 11PM. Visit 4 and Visit 7 are also evening visits that will begin between 5PM and 11PM and continue over a period of approximately 24 hours. Subjects will be required to attend three clinic visits during this 24-hour period.<br>• Subjects will complete a 4-week single blind run-in on FP 250 mcg twice daily, followed by 2-week double-blind Treatment Period 1 on randomized treatment, a 2-week single blind washout period on FP 250 mcg twice daily, 2-week double-blind Treatment Period 2 receiving the alternative treatment, and follow-up contact approximately 7-days after completing Treatment Period 2.<br>• The total duration of study participation is approximately 11 weeks; and up to 15 weeks for subjects with symptomatic allergic rhinitis at screening who may need to have a repeat screening visit performed.<br>• Subjects with symptomatic allergic rhinitis at Visit 1 (screening) may be treated for up to four weeks with intranasal corticosteroids followed by a repeat screening visit to determine eligibility prior to entry into the study. Eligible subjects will enter the run-in period<br>• At Visit 2 subjects will complete an exercise challenge. To be eligible for randomisation subjects must demonstrate a decrease in $FEV_1$ of ≥20% when compared to the $FEV_1$ obtained immediately pre-exercise for at least one of the post-exercise spirometry efforts obtained within 30 minutes post-challenge. Subjects who achieve a decrease in $FEV_1$ of 15% to <20% may continue taking their daily run-in medication and repeat the eligibility exercise challenge once within a week. |

| Overview of Study Design and Key Features | |
|---|---|
| | • Exercise challenges will be performed at Visits 2, 3, 4, 6 and 7. Serial spirometry will be conducted at 5, 10, 15, 30, 45 and 60 mins after each exercise challenge. For Visits 3 and 6, the exercise challenge will be performed at 23 hours after evening dosing (first dose of each treatment period). For Visits 4 and 7, the exercise challenges will be performed at 12 and 23 hours after evening dosing.<br>• In addition all subjects will be supplied with albuterol/salbutamol to use as needed throughout the study.<br>• Only subjects completing both treatment periods and follow-up period will be considered to have completed the study.<br>• Further details of the study design can be found in Section 5 (Study Design) of the 201832 protocol [GlaxoSmithKline Document Number 2015N231308_03]. |
| **Treatment Assignment** | • Subjects will be randomized in a 1:1 ratio to one of the 2 following treatment sequences:<br>o FF/VI 100/25 OD followed by FP 250 BD<br>o FP 250 BD followed by FF/VI 100/25 OD<br>• GSK RandAll NG will be used to generate the randomization schedule.<br>• Centralized randomization will be used.<br>• GSK RAMOS NG will be used for treatment allocation. |
| **Interim Analysis** | • No interim analysis is planned for this study. |

## 2.4. Statistical Hypotheses

The primary endpoint is the maximal percent decrease in $FEV_1$ following exercise challenge at 12-hours post-dose at the end of the 2-week treatment period. The primary treatment comparison is FF/VI 100/25 versus FP 250. Demonstration of efficacy will be based on a hypothesis testing approach, whereby the null hypothesis is that there is no difference between treatment groups for the endpoint of interest and the alternative hypothesis is that there is a difference between treatment groups. Specifically the null and alternative hypotheses for this comparison are:

- $H_0$: $\mu_{FF/VI} = \mu_{FP}$
- $H_1$: $\mu_{FF/VI} \neq \mu_{FP}$

where $\mu_{FF/VI}$ and $\mu_{FP}$ represent the population mean maximal percent decrease in $FEV_1$ following exercise challenge at 12-hours post-dose at the end of the 2-week treatment period for FF/VI and FP respectively.

## 2.5. Sample Size Assumptions

A total of approximately 275 subjects will be screened in order to achieve 66 randomized subjects. Allowing for a 15% withdrawal rate, this will give 56 evaluable subjects who complete the exercise challenges and the $FEV_1$ evaluations at the end of both treatment periods.

The sample size calculations are based on the primary efficacy endpoint of maximal percent decrease in $FEV_1$ following exercise challenge at 12 hours post-dose at the end of the 2-week treatment period.

With 56 evaluable subjects this study has approximately 90% power assuming a true population difference of 5% in maximal percent decrease in $FEV_1$ between the two treatment group means. This assumes a within-subject standard deviation (SD) of 8% where significance is declared at the two-sided 5% significance level.

A blinded sample size re-estimation will be conducted when approximately 50% of the subjects have completed their second exercise challenge. In order to assess the accuracy of the sample size assumption for the within-subject SD, the primary analysis will be run on this blinded interim data, but with a dummy variable to denote treatment group membership. If this suggests the original assumptions behind the sample size were incorrect, an adjustment may be made to the planned number of subjects to be recruited.

## 2.6. Treatment Comparisons

### 2.6.1. Primary Comparisons of Interest

The primary treatment comparison will be FF/VI 100/25 OD versus FP 250 BD for the primary efficacy endpoint of maximal percent decrease in $FEV_1$ following exercise challenge at 12 hours post-dose at the end of the 2-week treatment period..

### 2.6.2. Other Comparisons of Interest

FF/VI 100/25 OD will also be compared to FP 250 BD for the secondary and other efficacy endpoints.

# 3. PLANNED ANALYSES

## 3.1. Interim Analyses

No interim analysis is planned for this study.

## 3.2. Final Analyses

All planned analyses will be carried out once the clinical study database freeze (DBF) has taken place. Once this has been achieved, unblinding will occur and the analyses will be performed.

# 4. ANALYSIS POPULATIONS

| Population | Definition / Criteria | Analyses Evaluated |
|---|---|---|
| Total | • This population will comprise all subjects screened and for whom a record exists on the study database | • The tabulations of reasons for withdrawal before randomization. |
| Intent-To-Treat (ITT) | • This population will comprise all subjects randomized to treatment and who received at least one dose of study medication.<br>• Randomized subjects will be assumed to have received study medication unless definitive evidence to the contrary exists.<br>• Outcomes will be reported according to the randomized treatment allocation. | • Study population, efficacy and safety displays<br>• This will constitute the primary population for all analyses of efficacy measures and safety measures. |
| Per-Protocol (PP) | • The PP Population will consist of all subjects in the ITT Population who do not have any full protocol deviations and have at least one treatment period without a partial deviation.<br>• Protocol deviations can be either full or partial. Subjects with only partial deviations in 1 treatment period will be considered part of the PP population but their data from the treatment period affected by the deviations will be excluded.<br>• Protocol deviations that would exclude subjects or part of their data from the PP population are defined in Appendix 1 (Definitions for Per-Protocol Population). | • This population will be used for confirmatory analysis of the primary efficacy endpoint only. |
| ITT (12-17 Years Old) | • This will be a subset of the ITT population for subjects aged 12-17 years old. | • This population will be used for adolescent displays. |
| ITT (15 Years or Older) | • This will be a subset of the ITT population for subjects aged 15 years or older. | • This population will be used for displays on the subset of subjects aged 15 years or older. |

**NOTES :**

- Please refer to Appendix 13: List of Data Displays, which details the population to be used for each display being generated.

## 4.1. Protocol Deviations

- Important protocol deviations recorded in the eCRF (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- Protocol deviations impacting the Per Protocol population will also be summarised and listed. (Please refer to Appendix 1: Definitions for Per Protocol Population).
- Apart from any incorrect treatment deviations, all protocol deviations impacting the Per Protocol population (full and partial) will be agreed upon prior to unblinding the study.
- A separate summary and listing of inclusion/exclusion criteria deviations based on the data recorded on the inclusion/exclusion page of the eCRF will also be provided.

# 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 |
|---|---|
| 10.1 | Appendix 1: Definitions for Per Protocol Population |
| 10.2 | Appendix 2: Time & Events |
| 10.3 | Appendix 3: Assessment Windows |
| 10.4 | Appendix 4: Treatment States |
| 10.5 | Appendix 5: Data Display Standards & Handling Conventions |
| 10.6 | Appendix 6: Derived and Transformed Data |
| 10.7 | Appendix 7: Premature Withdrawals & Handling of Missing Data |
| 10.8 | Appendix 8: Multicenter Studies |
| 10.9 | Appendix 9: Examination of Covariates, Subgroups & Other Strata |
| 10.10 | Appendix 10: Multiple Comparisons & Multiplicity |
| 10.11 | Appendix 11: Model Checking and Diagnostics for Statistical Analyses. |

# 6. STUDY POPULATION ANALYSES

## 6.1. Overview of Planned Analyses

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

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 13: List of Data Displays.

**Table 2 Overview of Planned Study Population Analyses**

| Display Type | Data Displays Generated | | |
|---|---|---|---|
| | Table | Figure | Listing |
| **Subject Disposition** | | | |
| Subject Populations | Y[1] | | |
| Screen Failures | Y[1] | | |
| Run-in Failures | Y[1] | | |
| Study Completion/Withdrawal | Y | | Y |
| Treatment Completion/Withdrawal | Y | | |
| Clinic Visit Attendance | Y | | |
| Number of Subjects by Centre | Y[4] | | |
| Randomized and Actual Treatments | | | Y |
| Incorrect Medication | | | Y |
| **Protocol Deviations** | | | |
| Inclusion/Exclusion Criteria Deviations Recorded in the eCRF | Y | | Y |
| Subjects for Whom Treatment Blind was Broken | | | Y |
| Important Protocol Deviations Recorded in the eCRF | Y | | Y |
| Protocol Deviations Impacting the Per Protocol Population | Y | | Y |
| **Demographic and Baseline Characteristics** | | | |
| Demographic Characteristics | Y[2] | | Y |
| Race and Racial Combinations | Y | | |
| Race and Racial Combination Details | Y | | Y |
| History of Tobacco Use at Screening | Y | | Y |
| Duration of Asthma and Exacerbation History | Y[3] | | Y |
| Current Medical Conditions | Y | | Y |
| Past Medical Conditions | Y | | Y |
| Family History of CV Risk Factors | Y | | Y |
| Screening and Study Baseline Lung Function | Y[3] | | Y |
| Study Baseline Serial $FEV_1$ | Y | | Y |
| Maximal Percent Decrease from Pre-Exercise $FEV_1$ at Study Baseline | Y[5] | | |
| Study Baseline Lung Function by Completion Status | Y | | |
| **Exposure and Treatment Compliance** | | | |
| Exposure | Y | | Y |
| Treatment Compliance | Y | | Y |

| Display Type | Data Displays Generated | | |
|---|---|---|---|
| | Table | Figure | Listing |
| **Concomitant Medications** | | | |
| Pre-Treatment Asthma Concomitant Medications | Y | | Y |
| During Treatment Asthma Concomitant Medications | Y | | Y |
| Post Treatment Asthma Concomitant Medications | Y | | Y |
| Pre-Treatment Non-Asthma Concomitant Medications | Y | | Y |
| During Treatment Non-Asthma Concomitant Medications | Y | | Y |
| Post Treatment Non-Asthma Concomitant Medications | Y | | Y |
| Relationship Between ATC Level 1, Ingredient and Verbatim Text | | | Y |

**NOTES :**

- Y = Yes display generated.
- [1]: Display will be based on Total population
- [2]: Display will be based on the ITT population and repeated for the Per Protocol, Total, ITT (12-17 Years Old) and ITT (15 Years or Older) populations
- [3]: Display will be based on the ITT population and repeated for both the ITT (12-17 Years Old) population and the ITT (15 Years or Older) population
- [4]: Display will be based on the ITT population and repeated for Total population
- [5]: Display will be based on the ITT population and repeated for the ITT (15 Years or Older) population

## 6.2. Supplementary Information for Study Population Tables and Listings

### 6.2.1. Concomitant Medications

Concomitant medications will be coded using the GSK Drug coding dictionary. A summary of the number and percentage of subjects with concomitant medications will be displayed by ingredient without regard to ATC classifications. This summary will present multi-ingredient medications according to the combination of the component ingredients, and will also include single-ingredient medications. Summaries will be split into asthma and non-asthma concomitant medications, as well as into those taken pre-, during, and post-treatment.

# 7. EFFICACY ANALYSES

## 7.1. Primary Efficacy Analyses

### 7.1.1. Overview of Planned Primary Efficacy Analyses

The primary efficacy endpoint is the maximal percent decrease from pre-exercise $FEV_1$ following exercise challenge at12 hours post evening dose at the end of the 2-week treatment period.

Table 3 provides an overview of the planned efficacy analyses, with full details of data displays being presented in Appendix 13: List of Data Displays.

**Table 3 Overview of Planned Primary Efficacy Analyses**

| | Stats Analysis | | Summary | | Individual |
|---|---|---|---|---|---|
| | T | F | T | F | L |
| **Primary Analysis** | | | | | |
| Max % Decrease - ITT | Y | Y | Y | | |
| **Sensitivity Analysis** | | | | | |
| Max % Decrease - PP | Y | Y | Y | | |
| Max % Decrease - ITT (15 Years or Older) | Y | Y | | | |
| **Supporting Analyses and Other Summaries** | | | | | |
| Max % Decrease - ITT (12-17 Years Old) | | | Y | | |
| Max (L) Decrease - ITT | Y | Y | Y | | |
| Max (L) Decrease - ITT (15 Years or Older) | 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 FL related to any displays of individual subject observed raw data.

### 7.1.2. Planned Primary Efficacy Statistical Analyses

**Primary Statistical Analyses**

**Endpoint(s)**

- Maximal percent decrease from pre-exercise $FEV_1$ following exercise challenge at 12 hours post evening dose at the end of the 2-week treatment period

**Populations**

- This analysis will be performed on both the Intent-to-Treat (ITT) and the Per Protocol (PP) populations.

**Model Specification**

The mixed model repeated measures (MMRM) model will include the following covariates (with example variable names): treatment (ptrtcd), sex (sex), age (age), treatment period (pernum), smoking history (supkyr: number of pack years), period baseline $FEV_1$ (pbli) and the mean of the two period baseline $FEV_1$ values (mpbli) as fixed effects, and a random intercept for each subject (subjid). A SAS procedure of the following structure will be used:

```
proc mixed data=start cl nobound ;
    class subjid ptrtcd sex pernum ;
    model maxd = ptrtcd pernum pbli mpbli age sex supkyr
                 / solution ddfm=kr ;
    random int / subject=subjid type=simple ;
    repeated pernum / subject=subjid type=simple ;
    lsmeans ptrtcd / diff cl e om=OMdset
                     at (age mpbli)=(&agem. &mpblim.) ;
    ods output lsmeans=lsmeans ;
    ods output diffs=diffs ;
run ;
```

Where OMdset is a dataset with a row for every period-subject combination that contains all of the covariates and mpblim and agem are macro variables containing the means for mpbli and age for the subjects used in the analysis. These are used to derive the adjusted means using coefficients which are based on the subjects used in the analysis.

**Model Checking & Diagnostics**

- Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.

**Model Results Presentation**

- The adjusted means for each treatment and the estimated treatment difference for the treatment comparison will be presented together with a 95% confidence interval for the difference and a p-value. The adjusted treatment difference and 95% confidence interval will be plotted.

**Sensitivity and Supportive Statistical Analyses**

**Maximal Decrease (L) from Pre-Exercise $FEV_1$ Analysis**

This supporting analysis will be analysed using a model of the same structure as described for the primary analysis.

## 7.2. Secondary and Other Efficacy Analyses

### 7.2.1. Overview of Planned Secondary and Other Efficacy Analyses

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

Table 4 provides an overview of the planned efficacy analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

**Table 4 Overview of Planned Secondary and Other Efficacy Analyses**

| | Stats Analysis | | Summary | | Individual |
|---|---|---|---|---|---|
| | T | F | T | F | L |
| **Max % Decrease from Pre-Exercise $FEV_1$ Following 23 Hr Challenge** | | | | | |
| Max % Decrease | Y[3] | Y[3] | Y[1] | | |
| Max (L) Decrease | Y[3] | Y[3] | Y | | |
| **Proportion of Subjects with a 5/10/15/30/45/60 min Post-Challenge $FEV_1$ no More Than 5% Lower Than Pre-Exercise $FEV_1$ Following Exercise Challenge** | | | | | |
| Proportion of Subjects | Y[3] | Y[3] | Y[2] | | |
| **Weighted Mean 0-60 min for % Decrease from Pre-Exercise $FEV_1$ Following Exercise Challenge** | | | | | |
| Weighted Mean 0-60 min | Y[3] | Y[3] | Y[1] | | |
| **Percentage of Subjects With a Decrease from Pre-Exercise Challenge $FEV_1$ in 3 Categories** | | | | | |
| Percentage of Subjects | Y | Y | | | |
| **Maximal % Decrease from Treatment Period Baseline $FEV_1$ Following Exercise Challenge** | | | | | |
| Max % Decrease | Y | Y | Y | | |
| Max (L) Decrease | Y | Y | Y | | |
| Change in Individual Serial Measurements (L) | Y[3] | Y[3] | Y | | |
| **ACQ-5 Score** | | | | | |
| Change from period baseline in ACQ-5 score | Y | Y | Y | | |
| % of subjects controlled (ACQ-5 score ≤0.75) | Y | Y | | | |
| % of subjects with an improvement of ≥0.5 | Y | Y | | | |
| **Change in Physical Activity Measures as Assessed by a Biosensor** | | | | | |
| Step Count | | | Y | | |
| METs | | | Y | | |
| Sleep Duration | | | 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 FL related to any displays of individual subject observed raw data.
- [1]: Display will be based on the ITT population and repeated for the ITT (12-17 Years Old) population
- [2]: Display will be based the ITT (12-17 Years Old) population
- [3]: Display will be based on the ITT population and repeated for the ITT (15 Years or Older) population

## 7.2.2. Planned Secondary and Other Efficacy Statistical Analyses

### 7.2.2.1. Maximal Percent Decrease from Pre-Exercise $FEV_1$ Following Exercise Challenge at 23 Hours Post Evening Dose at the End of the 2-Week Treatment Period

| Statistical Analyses |
|---|
| **Endpoint(s)** |
| • Maximal percent decrease from pre-exercise $FEV_1$ following exercise challenge at 23 hours post evening dose at the end of the 2-week treatment period |
| **Populations** |
| • This analysis will be performed on the Intent-to-Treat (ITT) populations |
| **Model Specification** |
| This endpoint will be analysed using a model of the same structure as described for the primary endpoint in Section 7.1.2. |
| **Model Checking & Diagnostics** |
| • Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses. |
| **Model Results Presentation** |
| • The adjusted means for each treatment and the estimated treatment difference for the treatment comparison will be presented together with a 95% confidence interval for the difference and a p-value. The adjusted treatment difference and 95% confidence interval will be plotted.<br>• The analysis will also be performed for the maximal percent decrease from pre-exercise $FEV_1$ following exercise challenge at 23 hours post evening dose on day 1 of the treatment period. |

### 7.2.2.2. Proportion of Subjects with a 5/10/15/30/45/60 Minute Post-Challenge $FEV_1$ that was no More Than 5% Lower Than Their Pre-exercise $FEV_1$ Following the Exercise Challenge at 12 Hours and 23 Hours Post Evening Dose at the End of the 2-Week Treatment Period

| Statistical Analyses |
|---|
| **Endpoint(s)** |
| • Proportion of subjects with a 30 minute post-challenge $FEV_1$ that was no more than 5% lower than their pre-exercise $FEV_1$ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period<br>• Proportion of subjects with a 5 minute post-challenge $FEV_1$ that was no more than 5% lower than their pre-exercise $FEV_1$ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period. Repeat for the 10, 15, 45 and 60 minute time points. |
| **Populations** |
| • These analyses will be performed on the Intent-to-Treat (ITT) populations |
| **Model Specification** |
| The repeated measures logistic regression model will include the following covariates (with example variable names): treatment (ptrtcd), period baseline $FEV_1$ (pbli), sex (sex), age (age), treatment period (pernum) and smoking history (supkyr: number of pack years) as fixed effects. A SAS procedure of the following structure will be used: |

**Statistical Analyses**

```
proc genmod data=start descending ;
    class ptrtcd sex pernum subjid / param=ref ;
    model binv = ptrtcd pernum pbli age sex supkyr / dist=bin ;
    repeated subject=subjid / type=unstr corrw;
    estimate "logit FF/VI Vs FP" ptrtcd 1 / exp ;
    ods output Estimates=GEE_or_est ;
run ;
```

Where binv is the binary variable that takes the value 1 if at the given post-challenge time point a subject has an $FEV_1$ measurement that is >= 95% of their pre-exercise $FEV_1$ measurement and 0 otherwise.

The above code specifies a repeated measures logistic regression model where parameters are estimated using the Generalized Estimating Equation (GEE) method. GEE uses a "working" covariance matrix to model the within-subject dependences during estimation but calculates parameter estimator standard errors using an empirical estimate of the within-subject covariance matrix.

The "estimate" statement estimates the odds ratio of FF/VI compared to FP with 95% confidence limits which are displayed in the SAS output in the "L'Beta Estimate" and "L'Beta Confidence Limits" columns using the "Exp(logit FF/VI Vs FP)" row - these can be found in the "GEE_or_est" dataset produced by the "ods output" statement in the "LBetaEstimate" and "LBetaLowerCL/ LBetaupperCL" columns using the entry in row 2. Note that the quantity displayed in the SAS output in the "Mean Estimate" column is the inverse logit of the FF/VI estimate which is not equal to the odds ratio of FF/VI relative to FP.

**Model Checking & Diagnostics**

- Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.

**Model Results Presentation**

- The estimated treatment difference will be displayed as an odds ratio together with the 95% CI and p-value for the treatment comparison along with the number and percentage of subjects in each category. The adjusted treatment ratio and 95% confidence interval will be plotted.
- The analysis will also be performed for the proportion of subjects with a post-challenge $FEV_1$ that was no more than 5% lower than their pre-exercise $FEV_1$ following the exercise challenge at 23 hours post evening dose on day 1 of the treatment period.

#### 7.2.2.3. Weighted Mean 0-60 min for Percentage Decrease from Pre-Exercise $FEV_1$ Following Exercise Challenge at 12 Hours and 23 Hours Post Evening Dose at the End of the 2-Week Treatment Period

| Statistical Analyses |
|---|
| **Endpoint(s)** |
| • Weighted mean 0-60 min for percentage decrease from pre-exercise $FEV_1$ following exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period |
| **Populations** |
| • These analyses will be performed on the Intent-to-Treat (ITT) populations |
| **Model Specification** |
| This endpoint will be analysed using a model of the same structure as described for the primary endpoint in Section 7.1.2. |
| **Model Checking & Diagnostics** |
| • Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses. |
| **Model Results Presentation** |
| • The adjusted means for each treatment and the estimated treatment difference for the treatment comparison will be presented together with a 95% confidence interval for the difference and a p-value. The adjusted treatment difference and 95% confidence interval will be plotted.<br>• The analysis will also be performed for the weighted mean 0-60 min for percentage decrease from pre-exercise $FEV_1$ following exercise challenge at 23 hours post evening dose on day 1 of the treatment period. |

#### 7.2.2.4. Categorical Treatment Response Evaluation of the Percentage of Subjects who Demonstrate a Decrease from Pre-Exercise Challenge $FEV_1$ in 3 Categories

| Statistical Analyses |
|---|
| **Endpoint(s)** |
| • Categorical treatment response evaluation of the percentage of subjects who demonstrate a decrease from pre-exercise challenge $FEV_1$ (at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period) of:<br>○ <10%,<br>○ ≥10% to <20%,<br>○ ≥20% |
| **Populations** |
| • These analyses will be performed on the Intent-to-Treat (ITT) populations |
| **Model Specification** |
| The repeated measures ordinal multinomial regression model will include the following covariates (with example variable names): treatment (ptrtcd), period baseline $FEV_1$ (pbli), sex (sex), age (age), treatment period (pernum) and smoking history (supkyr: number of pack years) as fixed effects. A SAS procedure of the following structure will be used: |

**Statistical Analyses**

```
proc genmod data=start descending ;
    class ptrtcd sex pernum subjid  / param=ref ;
    model catv = ptrtcd pernum pbli age sex supkyr
            / dist=multinomial ;
    repeated subject=subjid / type=ind corrw ;
    estimate "logit FF/VI Vs FP" ptrtcd 1 / exp ;
    ods output Estimates=GEE_or_estm ;
run ;
```

Where catv is the multinomial variable that takes the value 1, 2 or 3 if a subject has a post-exercise minus pre-exercise $FEV_1$ value, denoted by X, of $-10<X$, $-20<X\leq-10$, or $X\leq-20$ respectively.

The above code specifies a repeated measures ordinal multinomial regression model where parameters are estimated using the Generalized Estimating Equation (GEE) method. GEE uses a "working" covariance matrix to model the within-subject dependences during estimation but calculates parameter estimator standard errors using an empirical estimate of the within-subject covariance matrix. The multinomial regression model assumes proportional odds, that is, the odds ratio of catv ≤ 1 for FF/VI compared to FP is the same as the odds ratio of catv ≤ 2 for FF/VI compared to FP. Thus it is assumed there is a single true odds ratio of catv being in an equal or lower category than j, for j=1, 2 (henceforth referred to simply as the odds ratio).

The "estimate" statement estimates the odds ratio of FF/VI compared to FP with 95% confidence limits which are displayed in the SAS output in the "L'Beta Estimate" and "L'Beta Confidence Limits" columns using the "Exp(logit FF/VI Vs FP)" row - these can be found in the "GEE_or_est" dataset produced by the "ods output" statement in the "LBetaEstimate" and "LBetaLowerCL/ LBetaupperCL" columns using the entry in row 2. Note that the quantity displayed in the SAS output in the "Mean Estimate" column is the inverse logit of the FF/VI estimate which is not equal to the odds ratio of FF/VI relative to FP.

**Model Checking & Diagnostics**

- Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.

**Model Results Presentation**

- The estimated treatment difference will be displayed as an odds ratio together with the 95% CI and p-value for the treatment comparison along with the number and percentage of subjects in each category. The adjusted treatment ratio and 95% confidence interval will be plotted.
- The analysis will also be performed for the percentage of subjects who demonstrate a decrease from pre-exercise challenge $FEV_1$ following the exercise challenge at 23 hours post evening dose on day 1 of the treatment period.

### 7.2.2.5. Maximal Percent Decrease from Treatment Period Baseline $FEV_1$ Following Exercise Challenge at 12 Hours and 23 Hours Post Evening Dose at the End of the 2-Week Treatment Period

| Statistical Analyses |
|---|
| **Endpoint(s)** |
| • Maximal percent decrease from treatment period baseline $FEV_1$ following exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period |
| **Populations** |
| • These analyses will be performed on the Intent-to-Treat (ITT) populations |
| **Model Specification** |
| This endpoint will be analysed using a model of the same structure as described for the primary endpoint in Section 7.1.2.<br><br>An analysis of the change from period baseline in each of the individual serial $FEV_1$ measurements will be performed separately (by their planned time). In each case the analysis will use a model of the same structure as described for the primary endpoint in Section 7.1.2. |
| **Model Checking & Diagnostics** |
| • Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses. |
| **Model Results Presentation** |
| • For the maximal percent decrease, the adjusted means for each treatment and the estimated treatment difference for the treatment comparison will be presented together with a 95% confidence interval for the difference and a p-value. The adjusted treatment difference and 95% confidence interval will be plotted.<br>• For the individual serial $FEV_1$ measurements, the adjusted means for the measurements as well as the adjusted means for the changes from period baseline for each treatment will be presented. In addition the estimated treatment difference for the treatment comparison will be presented together with a 95% confidence interval for the difference and a p-value. The adjusted mean changes from period baseline will be plotted along with their 95% confidence intervals.<br>• The analyses will also be performed using the data from day 1 of the treatment period. |

### 7.2.2.6. ACQ-5 Score at the End of the 2-Week Treatment Period

| Statistical Analyses |
|---|
| **Endpoint(s)** |
| • Change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at the end of the 2-week treatment period<br>• Percentage of subjects controlled, defined as an ACQ-5 score ≤0.75, at the end of the 2-week treatment period<br>• Percentage of subjects achieving an improvement of ≥0.5 in ACQ-5 score at the end of the 2-week treatment period |
| **Populations** |
| • These analyses will be performed on the Intent-to-Treat (ITT) populations |

| Statistical Analyses |
|---|
| **Model Specification** |
| For the change from period baseline analysis, a mixed model repeated measures (MMRM) model will include the following covariates (with example variable names): treatment (ptrtcd), sex (sex), age (age), treatment period (pernum), smoking history (supkyr: number of pack years), period baseline ACQ-5 score (pbli) and the mean of the two period baseline ACQ-5 scores (mpbli) as fixed effects, and a random intercept for each subject (subjid). A SAS procedure of a similar structure to that shown for the primary endpoint in Section 7.1.2 will be used.<br><br>For both of the binary endpoints, a repeated measures logistic regression model will include the following covariates (with example variable names): treatment (ptrtcd), sex (sex), age (age), treatment period (pernum), smoking history (supkyr: number of pack years), period baseline ACQ-5 score (pbli) as fixed effects. A SAS procedure will be used that is of a similar structure to that shown in Section 7.2.2.2 for the secondary endpoint of the proportion of subjects with a 30 minute post-challenge $FEV_1$ that was no more than 5% lower than their pre-exercise $FEV_1$ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period. |
| **Model Checking & Diagnostics** |
| • Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses. |
| **Model Results Presentation** |
| • For the change from period baseline analysis, the adjusted means for each treatment and the estimated treatment difference for the treatment comparison will be presented together with a 95% confidence interval for the difference and a p-value. The adjusted treatment difference and 95% confidence interval will be plotted.<br>• For both of the binary endpoints, the estimated treatment difference will be displayed as an odds ratio together with the 95% CI and p-value for the treatment comparison along with the number and percentage of subjects in each category. The adjusted treatment ratio and 95% confidence interval will be plotted. |

#### 7.2.2.7. Change in Physical Activity Measures as Assessed by a Biosensor

No statistical analysis is planned for this endpoint, but summary statistics will be produced for the following variables:

- Daily Step Count
- Daily Average Metabolic Equivalent of Tasks (METs)
- Daily Sleep Duration

## 7.3. Supplementary Information for Efficacy Tables, Listings and Figures

An overall forest plot will be produced showing the adjusted treatment differences/ratios and 95% confidence intervals for the primary and secondary efficacy endpoints. This will be produced for the ITT population and repeated for the ITT (15 Years or Older) population.

# 8. SAFETY ANALYSES

## 8.1. Safety Analyses

### 8.1.1. Overview of Planned Safety Analyses

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

Table 5 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

**Table 5 Overview of Planned Safety Analyses**

| Display Type | Data Displays Generated | | |
|---|---|---|---|
| | Table | Figure | Listing |
| **Adverse Events** | | | |
| Overview | Y | | |
| AEs for Subjects not in ITT | | | Y[2] |
| Pre-Treatment AEs | | | Y |
| On-Treatment AEs | Y[3] | | Y |
| Post-Treatment AEs | Y | | Y |
| Most Frequent On-Treatment AEs (≥3% after rounding) | Y | | |
| Top Ten Most Common On-Treatment AEs | Y | | |
| Drug-Related AEs | Y | | |
| Drug-Related SAEs | Y | | |
| AEs Leading to Withdrawal | Y | | Y |
| On-Treatment SAEs | Y | | Y |
| Post-Treatment SAEs | Y | | Y |
| Common On-Treatment Non-Serious AEs (≥3% without rounding including event numbers and drug-related event numbers) | Y | | |
| On-Treatment SAEs (including event numbers and drug-related event numbers) | Y | | |
| On-Treatment Fatal AEs (including event numbers and drug-related event numbers) | Y | | |
| Post-Treatment Fatal SAEs (including event numbers and drug-related event numbers) | Y | | |
| AEs of Special Interest | Y[1] | | |
| SAEs of Special Interest | Y | | |
| Relationship of AE System Organ Class, Preferred Term and Verbatim Text | Y | | |
| Record of all Preferred Term's That Could Have Mapped to Special Interest Terms | Y | | |
| **Pneumonia** | | | |
| On-Treatment Pneumonia | Y | | Y |
| Post-Treatment Pneumonia | Y | | Y |
| Chest X-ray | | | Y |
| **Severe Asthma Exacerbations** | | | |
| Severe Asthma Exacerbations | Y[3] | | Y |

| Display Type | Data Displays Generated | | |
|---|---|---|---|
| | Table | Figure | Listing |
| **Other** | | | |
| Vital Signs | Y | | Y |
| Change from Baseline in Vital Signs | Y | | |
| Family History of CV Risk Factors | Y | | Y |
| IP Inhaler Malfunctions | | | Y |

**NOTES :**

- Y = Yes display generated.
- [1]: Display will be based on the ITT population and repeated for the ITT (12-17 Years Old) population
- [2]: Display will be based on the inverse of the ITT population i.e. all subjects not in the ITT population
- [3]: Display will be based on the ITT population and repeated for the ITT (12-17 Years Old) population and also for the ITT (15 Years or Older) population

## 8.2. Supplementary Information for Safety Tables and Listings

### 8.2.1. Adverse Events

The version of MedDRA used to report the study will be noted in a footnote of the AE overview table.

For the main on-treatment and post-treatment AE tables, the number and percentage of subjects with all adverse events (regardless of causality) will be summarized for each treatment by system organ class (SOC) and preferred term (PT). The ordering of the SOCs and the PTs within the SOCs will both be in descending order of total incidence. A SOC will not be presented when the overall incidence for any adverse event within the particular system is 0. If the total incidence for any two or more adverse events is equal, the events will be presented in alphabetical order.

#### 8.2.1.1. Adverse Events of Special Interest

The number and percentage of subjects with adverse events of special interest to FF and/or VI will be summarized for each treatment by special interest term, subgroup and preferred term (PT). The ordering of the special interest terms, the subgroups and the PTs within them will all be in descending order of total incidence. If the total incidence for any two or more adverse events is equal, the events will be presented in alphabetical order. This summary will include both on-treatment and post-treatment AEs.

# 9. REFERENCES

GlaxoSmithKline Document Number 2015N231308_03. Study 201832: A Randomised, Double-Blind, Double-Dummy, Crossover Comparison of Fluticasone Furoate/Vilanterol 100/25mcg Once Daily Versus Fluticasone Propionate 250 mcg Twice Daily in Adolescent and Adult Subjects with Asthma and Exercise-Induced Bronchoconstriction. Effective date: 25-MAY-2016.

Kenward MG, Roger, JH. Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood. Biometrics. 1997;53:983-997.

# 10. APPENDICES

| Section | Appendix |
|---|---|
| **RAP Section 4 : Analysis Populations** | |
| Section 10.1 | Appendix 1: Definitions for Per Protocol Population |
| **RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions** | |
| Section 10.2 | Appendix 2: Time and Events |
| Section 10.3 | Appendix 3: Assessment Windows |
| Section 10.4 | Appendix 4: Treatment States |
| Section 10.5 | Appendix 5: Data Display Standards & Handling Conventions<br>• Study Treatment & Sub-group Display Descriptors<br>• Baseline Definitions & Derivations<br>• Reporting Process & Standards |
| Section 10.6 | Appendix 6: Derived and Transformed Data<br>• General, Study Population & Safety<br>• Efficacy |
| Section 10.7 | Appendix 7: Premature Withdrawals & Handling of Missing Data<br>• Premature Withdrawals<br>• Handling of Missing Data |
| Section 10.8 | Appendix 8: Multicentre Studies |
| Section 10.9 | Appendix 9: Examination of Covariates and Subgroups |
| Section 10.10 | Appendix 10: Multiple Comparisons and Multiplicity |
| Section 10.11 | Appendix 11: Model Checking and Diagnostics for Statistical Analyses |
| **Other RAP Appendices** | |
| Section 10.12 | Appendix 12: Abbreviations & Trade Marks |
| Section 10.13 | Appendix 13: List of Data Displays |
| Section 10.14 | Appendix 14: Example Mock Shells for Data Displays |

# 10.1. Appendix 1: Definitions for Per Protocol Population

## 10.1.1. Protocol Deviations Impacting the Per Protocol Population

A protocol deviation which could affect all treatment periods will be considered a full deviation and will result in exclusion from the Per Protocol population. A protocol deviation which would only affect a specific treatment period will be considered a partial deviation and the data from the treatment period affected by the deviation will be excluded. If a subject has partial deviations in both treatment periods then the subject will be excluded from the Per Protocol population, however if a subject only has partial deviations in 1 treatment period, they will be considered part of the PP population but their data from the treatment period affected by the deviations will be excluded.

Reasons for protocol deviations that will impact the Per Protocol population include the following:

| Number | Exclusion Description | Full or Partial? |
|---|---|---|
| 1 | Failure of inclusion criteria 3, 4, 5, 6 or 9; exclusion criteria 1, 3, 4, 7, 8, 9, 12, 13 or 15; randomization inclusion criteria 1 or 2 or randomization exclusion criteria 2, 4 or 5 as described in Section 6 of the protocol [GlaxoSmithKline Document Number 2015N231308_03]. | Full |
| 2 | Remaining in the study after meeting the following withdrawal criteria described in Section 6 of the protocol [GlaxoSmithKline Document Number 2015N231308_03]:<br>• Severe asthma exacerbation | Full if during 1st treatment period. Otherwise partial. |
| 3 | Taking of prohibited medication as described in Section 7.10.2 of the protocol [GlaxoSmithKline Document Number 2015N231308_03], where that medication could conceivably have an effect on a subject's efficacy. | Full if it affects both periods. Otherwise partial. |
| 4 | Overall treatment compliance for either DISKUS or ELLIPTA of < 80% or > 120%. (The protocol required subjects to take their study medication each day. For reporting and analysis purposes, treatment compliance of 80% and 120% are defined here as lower and upper limits for subjects to remain in the Per Protocol population.) Only treatment periods affected will be excluded. | Partial |
| 5 | Taking the wrong treatment at any time during the study. Only treatment periods affected will be excluded. | Partial |
| 6 | The 12 hour exercise challenge on day 14 of a treatment period (Visit 4/7) occurring on day 11 or earlier of the treatment period i.e. 11 days or less after day 0 of the treatment period (Visit 2/5). | Partial |
| 7 | The pre-exercise $FEV_1$ prior to the 12 hour challenge on day 14 of a treatment period (Visit 4/7) occurring <11 hours or >13 hours after the previous dose of study medication. | Partial |

Apart from any incorrect treatment deviations, all full and partial protocol deviations will be agreed upon prior to unblinding the study.

In addition to the subject level protocol deviations mentioned above, a given $FEV_1$ measurement must not be within 6 hours after the last use of rescue medication to be included in the Per Protocol analysis of the primary endpoint. Any $FEV_1$ measurement that was taken within 6 hours after the last use of rescue medication will be considered missing in the Per Protocol analysis of the primary endpoint.

Any $FEV_1$ measurements that are labelled as 'Unacceptable' will be considered missing for both the Intent-to-Treat and the Per Protocol populations.

# 10.2. Appendix 2: Time & Events

## 10.2.1. Protocol Defined Time & Events

| Procedures | Pre-Screen | Screen/ Run-in | Treatment Period 1 | | | Treatment Period 2 | | | Early Withdrawal Visit | Follow-up Phone Call |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit/Contact** | **0** | **1** | **2[12] Randomization** | **3** | **4[12, 14]** | **5[12]** | **6** | **7[12, 14]** | | |
| **Week** | | **-4** | **0** | **0** | **2** | **4** | **4** | **6** | | **7** |
| **Treatment Day** | | **-26 to -30 days** | **0** | **1[18]** | **14 (-2/+2) days** | **28 (-2/+2) days** | **29[18]** | **42 (-2/+2) days** | | **47 to 51 days** |
| Written Informed Consent | **X** | | | | | | | | | |
| Genetics Consent | **X[1]** | | | | | | | | | |
| Subject Demography | **X** | | | | | | | | | |
| Medical History (including CV) | | **X** | | | | | | | | |
| Disease (Asthma) History | | **X** | | | | | | | | |
| Medication History | **X** | **X** | | | | | | | | |
| Smoking history/status | | **X** | | | | | | | | |
| Inclusion/Exclusion Criteria | | **X** | | | | | | | | |
| Evidence of EIB | | **X** | | | | | | | | |
| **Efficacy Assessments** | | | | | | | | | | |
| Spirometry (full $FEV_1$ and FVC) | | **X** | **X[2]** | **X[2]** | **X[2]** | **X** | **X[2]** | **X[2]** | **X** | |
| Exercise Challenge Testing (Treadmill) | | | **X[3, 17]** | **X[4]** | **X[5]** | | **X[4]** | **X[5]** | | |
| Post-Challenge Serial $FEV_1$ Measurements | | | **X[3]** | **X[6]** | **X[6]** | | **X[6]** | **X[6]** | | |
| Asthma Control Questionnaire-5 | | | **X** | | **X** | **X** | | **X** | **X** | |
| Dispense SenseWear[15] accelerometer | | **X** | | | | | | | | |
| Collect SenseWear accelerometer | | | | | | | | **X** | **X** | |
| **Safety Assessments** | | | | | | | | | | |

| Procedures | Pre-Screen | Screen/ Run-in | Treatment Period 1 | | | Treatment Period 2 | | | Early Withdrawal Visit | Follow-up Phone Call |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit/Contact** | **0** | **1** | **2[12] Randomization** | **3** | **4[12, 14]** | **5[12]** | **6** | **7[12, 14]** | | |
| **Week** | | **-4** | **0** | **0** | **2** | **4** | **4** | **6** | | **7** |
| **Treatment Day** | | **-26 to -30 days** | **0** | **1[18]** | **14 (-2/+2) days** | **28 (-2/+2) days** | **29[18]** | **42 (-2/+2) days** | | **47 to 51 days** |
| Concomitant Medication | X | X | X | X | X | X | X | X | X | X[7] |
| Physical Examination | | X | | | | | | | | |
| Vital Signs | | X | X[8] | X[8] | X[8] | X | X[8] | X[8] | X | |
| 12-lead ECG | | X | | | | | | | | |
| Adverse Event Assessment | X[9] | X[9] | X | X | X | X | X | X | X | X |
| Issue Medical Conditions Diary Card | | X | X | | X | X | | | | |
| Review Medical Conditions Diary Card | | | X[10] | X | X[10] | X[10] | X | X[10] | X | |
| **Laboratory Assessments** | | | | | | | | | | |
| Genetics Saliva Sample | | | X[1] | | | | | | | |
| Urine Pregnancy Test | | X | X | | | X | | | X | X[13] |
| **Investigational Product** | | | | | | | | | | |
| Dispense Fluticasone Propionate | | X | | | X | | | | | |
| Collect Fluticasone Propionate | | | X | | | X | | | | |
| Dispense Rescue[16] Albuterol/salbutamol | | X | X | X | X | X | X | | | |
| Collect Rescue Albuterol/salbutamol | | | X | | X | X | | X | | |
| Dispense IP | | | X[11] | | | X | | | | |
| Assess study drug compliance | | | X | X | X | X | X | X | X | |
| Collect IP | | | | | X | | | X | X | |

1. Genetics saliva sample collected at Visit 2 (following Randomization) or at any scheduled visit thereafter. Genetics consent MUST be obtained PRIOR to collection of the Genetics sample.
2. Pre-exercise spirometry (full $FEV_1$ and forced vital capacity (FVC) testing), conducted immediately pre-exercise (and after vital signs), if applicable. Subject should have withheld albuterol/salbutamol within previous 6 hours.
3. Performed for determination of eligibility. Serial spirometry performed 5, 10, 15, 30, 45 and 60 minutes post- exercise challenges. Subjects must demonstrate a decrease in $FEV_1$ of $\geq$20% at one time point within 30 minutes of the end of a standardized exercise challenge.
4. Exercise challenge testing will be performed at 23 hours following the evening study treatment doses given at Visit 2 and Visit 5
5. Exercise challenge testing will be performed at 12 hours and 23 hours following the evening study treatment doses given at the beginning of Visits 4 and 7.
6. Serial spirometry performed at time points 5, 10, 15, 30, 45 and 60 minutes post- exercise challenges. Longer monitoring may be required for those subjects who do not return to 95% of baseline $FEV_1$ values within 60 minutes.
7. Concomitant medications collected for adverse events only between end of treatment and follow-up phone contact.
8. Vital signs will be collected before (prior to the pre-exercise spirometry) and after each exercise challenge test.
9. Adverse Event and Serious Adverse Events to be collected from the start of study Drug (Visit 1) until the follow up contact. However, any SAE related to study participation will be recorded from the time of Informed Consent
10. Review medical conditions diary card, including an assessment of any potential change in exercise capacity
11. An unblinding card will be dispensed along with double blind IP.
12. Subjects will be contacted by telephone 8-9 days prior to Visits 2, 4, 5 and 7 and reminded to wear the SenseWear accelerometer for the 7 days preceeding these visits.
13. Pregnancy test will be conducted via home test kit and results will be reported at the Follow-up phone contact.
14. Visit 4 and Visit 7 will begin between 5PM and 11PM and continue over a period of approximately 24 hours. Subjects will return to the clinic at 12 hours (±1 hour) and 23 hours (±1 hour) (after the evening dose of study medication from the evening visit) for an exercise challenge procedure.
15. Subjects will be contacted by telephone 8-9 days prior to Visits 2, 4, 5 and 7 and reminded to wear the SenseWear Armband accelerometer for the 7 days preceding these visits.
16. Collect and re-dispense rescue as needed from Visit 1
17. Subjects who achieve a decrease in $FEV_1$ of 15% to <20% may continue taking their daily run-in medication and repeat the eligibility exercise challenge and associated procedures **once** within a week of the original procedure.
18. Visit 3 must be performed on the day immediately following Visit 2. Visit 6 must be performed on the day immediately following Visit 5.

## 10.3. Appendix 3: Assessment Windows

Clinic visits are scheduled to take place as specified in Section 10.2.1. Individual measurements will be reported based on the visits and planned relative times they are assigned to in the study database without adjustment.

If a circumstance should arise where multiple measurements have been collected and recorded against the same time point, then the first valid value will be used for that time point.

# 10.4. Appendix 4: Treatment States

## 10.4.1. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of the study treatment. The earliest and latest exposure treatment start and stop dates will be used to determine whether an assessment or event was pre-treatment, on-treatment or post-treatment. If it is not possible to tell whether an assessment or event was on-treatment or not it will be considered as on-treatment.

### 10.4.1.1. Treatment States for Concomitant Medications

A medication will be summarized in every classification (pre/during/post) in which it was taken, so a medication that was started in the run-in and stopped during treatment will appear in both the pre-treatment and the during treatment tables.

Medications will be classified by comparing the start date and end dates of the medication to the dates of the first and last doses of study medication within the treatment periods using the following definitions:.

| Treatment State | Definition |
|---|---|
| Pre-Treatment | Date medication taken ≤ first dose date of the study |
| During Treatment | First dose date of treatment period + 1 ≤ date medication taken ≤ last dose date of treatment period |
| During Treatment (washout) | Last dose date of treatment period + 1 ≤ date medication taken ≤ first dose date of next treatment period |
| Post-Treatment | Date medication taken ≥ last dose date of study + 1 |

### 10.4.1.2. Treatment States for Adverse Events and Severe Asthma Exacerbations

Treatment states for adverse events are described below. Severe asthma exacerbations will be treated in the same way, with the exacerbation start date used in place of the AE start date.

| Treatment State | Definition |
|---|---|
| Pre-Treatment | AE start date ≤ first dose date of the study -1 |
| On-Treatment | First dose date of treatment period ≤ AE start date ≤ last dose date of treatment period + 1 |
| Post-Treatment | AE start date ≥ last dose date of study + 2<br>OR<br>Last dose date of treatment period + 2 ≤ AE start date ≤ first dose date of next treatment period - 1 |

AEs occurring during the washout period or during the follow-up period are therefore classified as post-treatment and will be summarized under the treatment from the previous period.

Note: Time Since 1st Dose will be derived as follows:

- If the First Dose Date or the AE Onset Date are missing then => missing
- If First Dose Date > AE Onset Date then => AE Onset Date – First Dose Date
- If First Dose Date ≤ AE Onset Date then => AE Onset Date - First Dose Date +1

# 10.5. Appendix 5: Data Display Standards & Handling Conventions

## 10.5.1. Study Treatment & Sub-group Display Descriptors

| Treatment Group Descriptions | | | |
|---|---|---|---|
| RandAll NG | | Data Displays for Reporting | |
| Code | Description | Description | Order [1] |
| A | FF/VI 100/25mcg OD | FF/VI 100/25 OD | 1 |
| B | FP 250mcg BD | FP 250 BD | 2 |

**NOTES:**

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

If a subject attends at least one scheduled clinic visit for a treatment period, then they will be counted as having taken part in that treatment period and will contribute to the population numbers (i.e. "Big N" numbers) for the treatment that they were randomized to receive in that period.

## 10.5.2. Baseline Definition & Derivations

### 10.5.2.1. Baseline Definitions

In general, the subject level baseline (or study baseline) is defined as the value taken at visit 2 (randomization), and the period level baseline is defined as the pre-treatment value taken at the start of each treatment period (visit 2 and visit 5). Using these definitions the period baseline for treatment period 1 is the same as the subject level baseline.

For $FEV_1$ and Vital Signs, the baseline value at visit 2 will be taken from the "Pre Challenge" planned time.

The primary analysis will include as a covariate, the period baseline value as well as including as a covariate, the mean of the two period baseline values.

For the physical activity measures assessed by the biosensor, the period baseline will be derived using all the available data from the last 7 calendar days prior to, but not including the first clinic visit of the treatment period (Visit 2/5). For example, if the randomisation visit (Visit 2) was on the 18th May then the period baseline for treatment period 1 would be derived as the average of the non-missing data that is available from the 11th May to the 17th May inclusive.

### 10.5.2.2. Derivations and Handling of Missing Baseline Data

Change from baseline will be defined as the difference between the value of the endpoint at the time point of interest and the baseline value as defined in Section 10.5.2.1.

If the baseline for an endpoint is missing it will not be imputed using a different time point or derivation but will remain missing.

### 10.5.3. Reporting Process & Standards

| **Reporting Process** | |
|---|---|
| **Software** | |
| • The currently supported versions of SAS software will be used. | |
| **Reporting Area** | |
| HARP Server | : uk1salx00175 |
| HARP Area | : /arenv/arprod/gw685698_gw642444/mid201832/final/ |
| QC Spreadsheet | : \\hlwdsntv006a\med_ds_rgm\Projects\Respiratory & Inflammation\Horizon\201832 (Exercise study)\Statistics\QC Tracking\ |
| **Analysis Datasets** | |
| • Analysis and reporting (A&R) datasets will be created according to Integrated Data Standards Library (IDSL) standards. | |
| **Generation of RTF Files** | |
| • RTF files will be generated. | |

| **Reporting Standards** |
|---|
| **General** |
| • The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated:<br>o 4.03 to 4.23: General Principles<br>o 5.01 to 5.08: Principles Related to Data Listings<br>o 6.01 to 6.11: Principles Related to Summary Tables<br>o 7.01 to 7.13: Principles Related to Graphics |
| **Formats** |
| • All data will be reported according to the treatment the subject was randomized to unless otherwise stated.<br>• Numeric data will be reported at the precision collected on the eCRF or recorded in the raw dataset if from non eCRF sources.<br>• For summaries and analyses the decimal places shown below will be applied in the data displays: |

| Reporting Standards | | |
|---|---|---|
| **Specification of Number of Decimal Places for Descriptive Statistics** | | |
| **Label** | **Description** | **No. of decimal places (dp) more than raw data** |
| N | Number of subjects in the treatment group | Always present to 0 dp |
| n | Number of subjects with non-missing values | Always present to 0 dp |
| Mean | Arithmetic Mean | 1 dp |
| SD | Standard Deviation | 2 dp |
| Median | Median | 1 dp |
| Min. | Minimum | 0 dp |
| Max. | Maximum | 0 dp |
| **Specification of Number of Decimal Places for Statistical Analysis** | | |
| **Label** | **Description** | **No. of decimal places (dp) more than raw data** |
| LS Mean | Adjusted mean for the treatment group | 1 dp |
| LS Mean Change | Adjusted mean change from baseline for the treatment group | 1 dp |
| Std Err | Standard error | 2 dp |
| Difference | Treatment difference | 1 dp |
| Odds Ratio | Treatment odds ratio | Always present to 2 dp |
| 95% CI | 95% Confidence interval around treatment difference/ratio | Same number of dp as the difference/ratio |
| p-value | p-value | Always present to 3 dp (or <0.001 or >0.999) |
| **Planned and Actual Time** | | |
| • Reporting for tables, figures and formal statistical analyses :<br>  • Planned time will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.<br>• Reporting for Data Listings:<br>  • Planned and actual time will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).<br>  • Unscheduled or unplanned measurements will be presented within the subject's listings. | | |
| **Unscheduled Visits** | | |
| • Unscheduled visits will not be included in summary tables or figures.<br>• 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, % | |

| Reporting Standards |
| --- |
| **Graphical Displays** |
| • Refer to IDSL Statistical Principals 7.01 to 7.13.<br>• The programs for statistical analysis tables will create SAS datasets with the unrounded numbers from the statistical models to be used in any graphs. This will included all LS means, standard errors, treatment differences or ratios and confidence intervals. This will be done for all analysis tables regardless of whether or not a figure is planned as part of SAC.<br>• The programs for all graphical displays will additionally create a CSV file with the final data that is used in the graph in order to allow the graph to be redrawn for any potential publication requirement in the future. |

# 10.6. Appendix 6: Derived and Transformed Data

## 10.6.1. General

**Multiple Measurements at One Time Point**

- Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.

**Time Since Study First Dose / Time Since Period First Dose**

- Calculated as the number of days from the date of first dose:
  - Ref Date = Missing → Time Since First Dose = Missing
  - Ref Date < First Dose Date → Time Since First Dose = Ref Date – First Dose Date
  - Ref Data ≥ First Dose Date → Time Since First Dose = Ref Date – (First Dose Date) + 1

**Study Day / Period Day**

- Study day will be calculated as the number of days from the Visit 1 (Screening) visit:
  - Ref Date = Missing → Study Day = Missing
  - Ref Date < Visit 1 Date → Study Day = Ref Date – Visit 1 Date
  - Ref Data ≥ Visit 1 Date → Study Day = Ref Date – (Visit 1 Date) + 1
- For a treatment period, the dates of the first and last clinic visits for that treatment period will be used as the period start date and the period end date.
- For the washout period, imputed dates will be used. The washout period start date will be the day after the period end date for the previous treatment period and the washout period end date will be the day before the period start date for the next treatment period.
- Period day will be calculated as the number of days from the period start date:
  - Ref Date = Missing → Period Day = Missing
  - Ref Date < Period Start Date → Period Day = Ref Date – Period Start Date
  - Ref Data ≥ Period Start Date → Period Day = Ref Date – (Period Start Date) + 1

## 10.6.2. Study Population

**Demographics**

**Age**

- GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  - Any subject with a missing day will have this imputed as day '15'.
  - Any subject with a missing date and month will have this imputed as '30th June'.
- Birth date will be presented in listings as 'YYYY'.
- Completely missing dates of birth will remain as missing, with no imputation applied. Consequently, the age of the subject will not be calculated and will remain missing.
- Age, in whole years, will be calculated with respect to the date of screening (Visit 1).

**Demographics**

**Body Mass Index (BMI)**

- Calculated as **Weight (kg) / [Height (m)$^2$]**

**Race**

The high level FDA race categories and designated Asian subcategories are:

1. African American/African Heritage
2. American Indian or Alaska Native
3. Asian
    a. Central/South Asian Heritage
    b. Japanese/East Asian Heritage/South East Asian Heritage
    c. Mixed Asian Heritage (only required if data exists)
4. Native Hawaiian or other Pacific Islander
5. White

These will be summarized along with all combinations of high level categories which exist in the data. All five of the high level race categories and the two Asian subcategories must appear on the display even if there are no subjects in a particular category, but combinations that do not exist in the data do not need to be represented. Combinations will be represented as the concatenation of the high level category terms, e.g., "White & Asian." The designated Asian subcategories will not be summarized as combinations with other categories.

In addition the twelve standard race categories collected on the IDSL eCRF page will be summarized along with categories for mixed race. The categories are:

1. African American/African Heritage
2. American Indian or Alaska Native
3. Asian - Central/South Asian Heritage
4. Asian – East Asian Heritage
5. Asian – Japanese Heritage
6. Asian – South East Asian Heritage
7. Asian – Mixed Race
8. Native Hawaiian or other Pacific Islander
9. White – Arabic/North African Heritage
10. White – White/Caucasian/European Heritage
11. White – Mixed Race
12. Mixed Race

"Asian – Mixed Race" is only used if more than one Asian category is selected, but no non-Asian races. Similarly, "White – Mixed Race" is only used if both of the White categories are selected, and

**Demographics**

no non-White races. If multiple races of different types are selected, then the overall "Mixed Race" category is used.

A subject will only be represented in a single category. A subject who selects a combination of races will be counted as "Asian – Mixed Race," "White – Mixed Race," or "Mixed Race," but not in each of the constituent terms. Therefore the counts will add up to the total number of subjects with a response, and the percentages will add to 100%.

**Extent of Exposure**

Exposure will be calculated for each type of inhaler (DISKUS and ELLIPTA) separately. The number of days on study drug for each subject and treatment period will be calculated as (date treatment stopped – date treatment started) + 1. The treatment start and stop dates used will be the earliest and latest of all dates recorded for the subject and treatment period in question.

**Treatment Compliance**

Overall percentage treatment compliance for every subject will be calculated for each type of inhaler (DISKUS and ELLIPTA) and for each treatment period separately.

Compliance for the DISKUS and ELLIPTA will be based on the total number of inhalations taken from each type of inhaler and the expected number of inhalations to be taken. The expected number of inhalations will be derived as the expected number of inhalations per day (from each inhaler) multiplied by the number of days on study drug for the treatment period in question based on the subjects treatment start and stop date for that type of inhaler.

The total number of inhalations taken will be based on the dose counter for each type of inhaler. If there is no dose counter information at all for a given treatment period then the compliance will be missing, however, as long as the information from one dose counter is present, the compliance for that treatment period will be calculated. If a dose counter start count is missing then it will be assumed to be 30 for the ELLIPTA and 60 for the DISKUS.

In each calculation, all inhalers dispensed will be used, provided the dose counter stop counts are non-missing. The following formula will be used:

$$Overall\_Compliance = \left( \frac{Total\_Number\_of\_Inhalations\_Taken}{Expected\_Inhalations \times (Stop\_Date - Start\_Date + 1)} \right) \times 100$$

Where $Total\_Number\_of\_Inhalations\_Taken$ is the total number of doses taken from all DISKUS or ELLIPTA inhalers in the treatment period in question, $Expected\_Inhalations$ is equal to 2 for the DISKUS and 1 for the ELLIPTA and $Start\_Date$ and $Stop\_Date$ are the earliest treatment start date and the latest treatment stop date recorded for all of the inhalers used in the calculation.

### 10.6.3. Efficacy

| Primary Endpoint |
|---|
| **Maximal % Decrease from Pre-Exercise $FEV_1$ Following 12 Hour Challenge at Day 14** |
| The primary endpoint will be derived as follows:<br>$$\frac{\text{Pre-Exercise } FEV_1 - \text{Minimum Post Exercise } FEV_1}{\text{Pre-Exercise } FEV_1} \times 100$$<br>Where pre-exercise $FEV_1$ will be defined as the $FEV_1$ value collected immediately prior to the exercise challenge.<br><br>And the minimum post exercise $FEV_1$ will be the smallest $FEV_1$ value recorded from the planned post-challenge time points (5, 10, 15, 30, 45 and 60 minutes) using only those with an actual time that is no more than 65 minutes after the challenge stop time.<br><br>The minimum post exercise $FEV_1$ will only be calculated if there are at least the following non-missing $FEV_1$ values:<br>• A post-exercise measurement with an actual time of ≤17 minutes<br>• A post-exercise measurement with an actual time of ≥25 and ≤50 minutes<br>If there are not values meeting both of these criteria available then the endpoint will not be calculated and will be treated as missing. |

| Secondary and Other Endpoints |
|---|
| **Maximal % Decrease from Pre-Exercise $FEV_1$ Following Exercise Challenge** |
| Maximal percent decrease from pre-exercise $FEV_1$ will be derived for other time points in the same way as for the primary endpoint. |
| **Maximal Decrease from Pre-Exercise $FEV_1$ (L) Following Exercise Challenge** |
| Maximal decrease from pre-exercise $FEV_1$ (L) will be derived as:<br>$$\text{Pre-Exercise } FEV_1 - \text{Minimum Post Exercise } FEV_1$$<br>Where pre-exercise $FEV_1$ and minimum post-exercise $FEV_1$ are defined in the same way as for the primary endpoint and the same minimum number of non-missing $FEV_1$ values are required for the endpoint to be calculated. |
| **Maximal % Decrease from Period Baseline $FEV_1$ Following Exercise Challenge** |
| Maximal percent decrease from period baseline $FEV_1$ will be derived as:<br>$$\frac{\text{Period Baseline } FEV_1 - \text{Minimum Post Exercise } FEV_1}{\text{Period Baseline } FEV_1} \times 100$$<br>Where minimum post-exercise $FEV_1$ is defined in the same way as for the primary endpoint and the same minimum number of non-missing $FEV_1$ values are required for the endpoint to be calculated. |

**Secondary and Other Endpoints**

**Maximal Decrease from Period Baseline $FEV_1$ (L) Following Exercise Challenge**

Maximal decrease from period baseline $FEV_1$ (L) will be derived as:

$$\text{Period Baseline } FEV_1 - \text{Minimum Post Exercise } FEV_1$$

Where minimum post-exercise $FEV_1$ is defined in the same way as for the primary endpoint and the same minimum number of non-missing $FEV_1$ values are required for the endpoint to be calculated.

**Proportion of Subjects With a Post-Challenge $FEV_1$ No More Than 5% Lower Than Their Pre-Exercise $FEV_1$**

Subjects meeting the criteria will be those who had a post-challenge $FEV_1 \geq 95\%$ of their pre-exercise $FEV_1$. For the time point in question, each subject's post-challenge $FEV_1$ as a percentage of their pre-exercise $FEV_1$ will be derived as follows:

$$\frac{\text{Post Exercise } FEV_1}{\text{Pre-Exercise } FEV_1} \times 100$$

If this number is ≥ 95% then the subject will have met the criteria.

**% of Subjects with a Decrease from Pre-Exercise $FEV_1$ in 3 Categories**

For the time point in question, each subject's percentage decrease from pre-exercise $FEV_1$ will be derived as follows:

$$\frac{\text{Pre-Exercise } FEV_1 - \text{Post Exercise } FEV_1}{\text{Pre-Exercise } FEV_1} \times 100$$

Subjects will then be allocated to one of the 3 categories.

**Weighted Mean 0-60 Minutes for % Decrease from Pre-Exercise $FEV_1$ Following Exercise Challenge**

For each time point, the percentage decrease from pre-exercise $FEV_1$ will be derived as follows:

$$\frac{\text{Pre-Exercise } FEV_1 - \text{Post Exercise } FEV_1}{\text{Pre-Exercise } FEV_1} \times 100$$

The weighted mean will then be calculated as the average area under the curve (AAUC) using the trapezoidal rule, and dividing by the relevant time interval. The 0 minute value, coming from the pre-exercise measurement, will be 0 by definition and actual times will be used for all other measurements in the calculation of the AAUC.

The AAUC will be calculated from the first non-missing time point to the last non-missing time point. If one or more observations are missing between two non-missing observations, the value(s) will be linearly interpolated between the two non-missing values.

The $AAUC_{(t_0 - t_L \text{ mins})}$ will be calculated as follows:

**Secondary and Other Endpoints**

$$AAUC_{(t_0-t_L \text{ mins})} = \frac{\frac{1}{2}\sum_{i=0}^{L-1}(C_i + C_{i+1})(t_{i+1} - t_i)}{t_L - t_0}$$

Where,

i = collected measurement

L = last collected measurement

$C_i$ = result of collected measurement i

$t_i$ = actual time of assessment for collected measurement i

For the weighted mean over 0-60 minutes, only scheduled planned times (5, 10, 15, 30, 45 and 60 minutes) will be used for the post-exercise time points and only those with an actual time that is less than or equal to 65 minutes after the challenge stop time. The AAUC will only be calculated if there are at least the following non-missing values:

- The 0 hour (pre-exercise) measurement
- A post-exercise measurement with an actual time of ≤17 minutes
- A post-exercise measurement with an actual time of ≥25 and ≤50 minutes
- A post-exercise measurement with an actual time of ≥55 and ≤65 minutes

If any of these values are missing then the AAUC will not be calculated, and the endpoint will be treated as missing.

**ACQ-5**

The Asthma Control Questionnaire-5 (ACQ-5) is a five-item questionnaire and there are 7 answers to each question that are associated with the numbers 0-6, where 0 represents no impairment and 6 represents maximum impairment. The ACQ-5 score is the mean of the 5 items and therefore gives a value between 0 (well controlled) and 6 (extremely poorly controlled). The ACQ-5 score will only be calculated if all 5 items of the questionnaire are non-missing.

**Physical Activity Measures Assessed by Biosensor**

For the physical activity measures assessed by the biosensor, the week 2 time point will be derived using all the available data from the last 7 calendar days prior to, but not including the last scheduled clinic visit of the treatment period (Visit 4/7). For example, if Visit 4 was on the 18th May then the week 2 time point for treatment period 1 would be derived as the average of the non-missing data that is available between the 11th May and the 17th May inclusive.

### 10.6.4. Safety

| Adverse Events |
| --- |
| • Adverse events will be coded using the MedDRA coding dictionary, to give a preferred term and a system organ class. |
| **Adverse Events of Special Interest** |
| • The adverse events of special interest terms, their subgroups and the preferred terms which will be counted towards each of them will be agreed upon prior to unblinding the study. |
| **Pneumonia and Chest X-rays** |
| • A chest x-ray will be considered to be associated with a pneumonia assessment if it was performed within -7 to +14 days of the date of onset. If more than one chest x-ray is within that window then the data displays will use the worst case from the answers to “Was an infiltrate present?” i.e. “Yes” will be taken over “Unknown” and “Unknown” will be taken over “No”. |

# 10.7. Appendix 7: Premature Withdrawals & Handling of Missing Data

## 10.7.1. Premature Withdrawals

| Element | Reporting Detail |
|---|---|
| General | • Subject study completion is defined in the protocol as completing all phases of the study including the follow-up phone contact.<br>• Withdrawn subjects will not be replaced in the study.<br>• All available data from subjects who were withdrawn from the study is included in listings and where possible any available data from withdrawn subjects is included in any summaries or analyses |

## 10.7.2. Handling of Missing Data

| Element | Reporting Detail |
|---|---|
| Maximal % Decrease / Maximal Decrease | • As detailed in Section 10.6.3, the only post-exercise $FEV_1$ values that will be used will be those recorded against the planned post-challenge time points (5, 10, 15, 30, 45 and 60 minutes) and only those with an actual time that is no more than 65 minutes after the challenge stop time.<br>• These endpoints will only calculated if there are at least the following non-missing $FEV_1$ values:<br>o A post-exercise measurement with an actual time of ≤17 minutes<br>o A post-exercise measurement with an actual time of ≥25 and ≤50 minutes<br>If there are not values meeting both of these criteria available then the endpoint will not be calculated and will be treated as missing. |
| Weighted Mean 0-60 Minutes | • As detailed in Section 10.6.3, only scheduled planned times (5, 10, 15, 30, 45 and 60 minutes) will be used for the post-exercise time points and only those with an actual time that is less than or equal to 65 minutes after the challenge stop time.<br>• The weighted mean will only be calculated if there are at least the following non-missing values:<br>o The 0 hour (pre-exercise) measurement<br>o A post-exercise measurement with an actual time of ≤17 minutes<br>o A post-exercise measurement with an actual time of ≥25 and ≤50 minutes<br>o A post-exercise measurement with an actual time of ≥55 and ≤65 minutes<br>If any of these values are missing then the weighted mean will not be calculated, and the endpoint will be treated as missing. |
| Physical Activity Measures | • For the physical activity measures assessed by the biosensor, all time periods including baseline, will be calculated from all available data over the time period of interest. No imputations will be performed on missing data. |

| Element | Reporting Detail |
|---|---|
| Assessed by Biosensor | • A day will only be considered valid if the biosensor was worn for at least 21.5 hours in that day. Any day where the biosensor was worn for less than 21.5 hours will not be used and the data from that day will be considered missing.<br>• All time periods including baseline, will be considered missing if less than 3 valid days are recorded in the time-period of interest. |
| ACQ-5 | • For ACQ-5, all questions must be answered to generate an overall score; if any individual questions are missing then the overall score will be missing. |

#### 10.7.2.1. Handling of Missing/Partial Dates

| Element | Reporting Detail |
|---|---|
| General | • Partial dates will be displayed as captured in subject listing displays. |
| Concomitant Medications | • The eCRF allows partial dates to be captured for concomitant medications.<br>• The methods for dealing with partial drug start and stop dates will be the same for all medications and will be to include each drug in every period in which it could conceivably have been taken. For example, if we only know that the month and year for the drug start date is the same as the month and year of the treatment start date, then the drug will be considered to have started pre-treatment. Similarly if we only know that the year the drug was stopped is the same as the year that the treatment was stopped then the drug will be considered to have stopped post-treatment.<br>• The answers to the questions “Taken Prior to Study?” and “Ongoing?” which are recorded on the eCRF will also be taken into consideration to determine if the medication was started pre-treatment or continued post-treatment. In each case, should the answers suggest a different classification than the dates, the medication will be summarized in all possible classifications (pre/during/post) and in all possible periods (treatment period 1, washout, treatment period 2) in which it could conceivably have been taken. |
| Adverse Events | • The eCRF does not allow partial dates to be captured for AEs. All dates will either be complete or missing.<br>• Where AE onset dates are missing then the AE will be considered on-treatment unless there is evidence to the contrary. |
| Severe Asthma Exacerbations | • Exacerbations are treated in the same way as adverse events. |

## 10.8. Appendix 8: Multicenter Studies

### 10.8.1. Definition of Country

- Country is determined by the location of the centre, as entered into GSK systems by the site monitor.

# 10.9. Appendix 9: Examination of Covariates, Subgroups & Other Strata

## 10.9.1. Covariates

- The primary efficacy analysis will be adjusted for period baseline, the mean of the two period baselines, period, smoking history (number of pack years), sex, age, and treatment group. Subject will be fitted as a random effect.

## 10.9.2. Subgroups

- The statistical analysis for selected endpoints will be repeated for the ITT (15 Years or Older) population.
- Selected summary tables will be repeated for the ITT (15 Years or Older) population.
- Selected summary tables will be repeated for the ITT (12-17 Years Old) population.

# 10.10. Appendix 10: Multiple Comparisons & Multiplicity

## 10.10.1. Handling of Multiple Comparisons & Multiplicity

A 2-sided 5% risk associated with incorrectly rejecting any of the null hypotheses (significance level) is considered acceptable for this study. In order to account for multiplicity, the hypothesis test for the FF/VI versus FP treatment comparison using the primary ITT analysis on the primary endpoint will act as a gatekeeper for all other hypothesis tests using the secondary endpoints, where these tests will proceed in the pre-defined order shown below. If a given statistical test fails to reject the null hypothesis of no treatment difference at the significance level of 0.05, then all tests lower down in the hierarchy will be interpreted as descriptive only.

**Primary Efficacy Endpoint (Gatekeeper)**

1. Test at the 5% level the null hypothesis that the true population difference between the treatment group means in maximal percent decrease from pre-exercise $FEV_1$ following exercise challenge at 12 hrs post-dose at the end of the 2-week treatment period is zero.

**Secondary Efficacy Endpoints**

2. If 1 is significant then test at the 5% level the null hypothesis that the true odds ratio between the two treatment groups of recovering to within 5% of pre-exercise $FEV_1$ at the 30 minute post-exercise time point following the exercise challenge at 12 hours post evening dose is equal to one.

3. If 2 is significant then test at the 5% level the null hypothesis that the true population difference between the treatment group means in maximal percent decrease from pre-exercise $FEV_1$ following exercise challenge at 23 hrs post-dose at the end of the 2-week treatment period is zero.

4. If 3 is significant then test at the 5% level the null hypothesis that the true odds ratio between the two treatment groups of recovering to within 5% of pre-exercise $FEV_1$ at the 30 minute post-exercise time point following the exercise challenge at 23 hours post evening dose is equal to one.

5. If 4 is significant then test at the 5% level the null hypothesis that the true population difference between the treatment group means in weighted mean 0-60 minutes for percentage decrease from pre-exercise $FEV_1$ following the exercise challenge at 12 hrs post-dose at the end of the 2-week treatment period is zero.

6. If 5 is significant then test at the 5% level the null hypothesis that the true population difference between the treatment group means in weighted mean 0-60 minutes for percentage decrease from pre-exercise $FEV_1$ following the exercise challenge at 23 hrs post-dose at the end of the 2-week treatment period is zero.

If either the gatekeeper hypothesis or any of the other above null hypotheses are not rejected, then although all of the subsequent analyses will still be performed, the results and the associated p-value, will be used for descriptive purposes only.

The treatment comparisons defined as part of the multiple testing strategy will be limited to the specified key comparisons above. Other pairwise comparisons will be performed, but will not form part of the multiple testing strategy. Analyses of other efficacy measures for the FF/VI versus FP treatment comparison are nested under the secondary efficacy measures and no multiplicity adjustment is planned for these other efficacy endpoints.

If significance is achieved for the FF/VI versus FP treatment comparison on the primary efficacy endpoint, then the secondary endpoints will be tested in a closed-testing manner using the hierarchy of comparisons. If significance is also achieved for each of the secondary efficacy endpoints, then all other efficacy endpoints will be tested for the FF/VI versus FP treatment comparison without further multiplicity adjustment.

# 10.11. Appendix 11: Model Checking and Diagnostics for Statistical Analyses

## 10.11.1. Model Checking

| Analysis | • MMRM |
|---|---|

- The Kenward-Roger method [Kenward MG, Roger, JH, 1997] for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used in the analyses. This will be achieved by specifying the DDFM=KR option in the MODEL statement within PROC MIXED.
- Appropriate graphs will be reviewed as part of the model checking process to ensure that distributional assumptions hold. These will include a normal probability plot of the residuals and a plot of the residuals versus the fitted values.
- Interactions with treatment will be explored for all covariates and tests for interactions will be at the 2-sided 10% significance level. Any significant interactions that are found will be thoroughly investigated and where necessary, extra outputs will be produced.

# 10.12. Appendix 12: Abbreviations & Trade Marks

## 10.12.1. Abbreviations

| Abbreviation | Description |
|---|---|
| A&R | Analysis and reporting |
| AAUC | Average area under the curve |
| ACQ | Asthma control questionnaire |
| AE | Adverse event |
| ATC | Anatomical therapeutic chemical |
| BD | Bis in die (twice daily) |
| BMI | Body mass index |
| CI | Confidence interval |
| CS | Clinical statistics |
| CSR | Clinical study report |
| CSV | Comma-separated values |
| CV | Cardiovascular |
| DBF | Database freeze |
| dp | Decimal places |
| eCRF | Electronic case record form |
| FDA | US food and drug administration |
| $FEV_1$ | Forced expiratory volume in 1 second |
| FF/VI | Fluticasone furoate/vilanterol |
| FP | Fluticasone propionate |
| FVC | Forced vital capacity |
| GEE | Generalized estimating equation |
| HARP | Harmonisation for analysis and reporting program |
| hr | Hour |
| ICH | International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use |
| IDSL | Integrated data standards library |
| IP | Investigational product |
| ITT | Intent-To-Treat |
| GSK | GlaxoSmithKline |
| GUI | Guidance |
| L | Litre |
| LS | Least squares |
| Max. | Maximum |
| mcg | Microgram |
| MedDRA | Medical dictionary for regulatory activities |
| METs | Metabolic equivalent of tasks |
| Min. | Minimum |
| MMRM | Mixed model repeated measures |
| N | Number of subjects in the treatment group |
| n | Number of subjects with non-missing values |

| Abbreviation | Description |
|---|---|
| OD | Once daily |
| PBO | Placebo |
| PM | Post-meridian (evening) |
| PP | Per Protocol |
| PT | Preferred term |
| QC | Quality control |
| RAP | Reporting & analysis plan |
| RAMOS NG | Randomization & medication ordering system next generation |
| RTF | Rich text format |
| SAC | Statistical analysis complete |
| SAE | Serious adverse events |
| SD | Standard deviation |
| SOC | System organ class |
| SOP | Standard operation procedure |
| Std Err | Standard error |
| TFL | Tables, figures & listings |

### 10.12.2. Trademarks

| Trademarks of the GlaxoSmithKline Group of Companies |
|---|
| DISKUS |
| ELLIPTA |

| Trademarks not owned by the GlaxoSmithKline Group of Companies |
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| SAS |

# 10.13. Appendix 13: List of Data Displays

## 10.13.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

| Section | Tables | Figures |
|---|---|---|
| Study Population | 1.1 to 1.40 | - |
| Efficacy | 2.1 to 2.36 | 2.1 to 2.16 |
| Safety | 3.1 to 3.28 | - |
| **Section** | **Listings** | |
| ICH Listings | 1 to 18 | |
| Other Listings | 19 to 30 | |

## 10.13.2. Study Population Tables

| Study Population Tables | | | |
|---|---|---|---|
| **No.** | **Population** | **IDSL Basis** | **Title** |
| **Subject Disposition** | | | |
| 1.1. | Total | - | Summary of Subject Populations |
| 1.2. | Total | ES6 | Summary of Reasons For Screen Failure |
| 1.3. | Total | ES6 | Summary of Reasons For Run-in Failure |
| 1.4. | ITT | ES1 | Summary of End of Study Record |
| 1.5. | ITT | - | Summary of Treatment Completion |
| 1.6. | ITT | - | Summary of Attendance at Each Clinic Visit |
| 1.7. | ITT | - | Summary of Number of Subjects by Centre - Intent-to-Treat |
| 1.8. | Total | - | Summary of Number of Subjects by Centre - Total |
| **Protocol Deviations** | | | |
| 1.9. | ITT | IE2 | Summary of Inclusion/Exclusion Criteria Deviations Recorded in the eCRF |
| 1.10. | ITT | DV1 | Summary of Important Protocol Deviations Recorded in the eCRF |
| 1.11. | ITT | - | Summary of Protocol Deviations Impacting the Per Protocol Population |
| **Demographic and Baseline Characteristics** | | | |
| 1.12. | ITT | DM3 | Summary of Demographic Characteristics - Intent-to-Treat |
| 1.13. | PP | DM3 | Summary of Demographic Characteristics - Per Protocol |
| 1.14. | Total | DM3 | Summary of Demographic Characteristics - Total |
| 1.15. | ITT (12-17 Years Old) | DM3 | Summary of Demographic Characteristics - ITT (12-17 Years Old) |
| 1.16. | ITT (15 Years or Older) | DM3 | Summary of Demographic Characteristics - ITT (15 Years or Older) |
| 1.17. | ITT | DM5 | Summary of Race and Racial Combinations |
| 1.18. | ITT | DM6 | Summary of Race and Racial Combination Details |
| 1.19. | ITT | - | Summary of History of Tobacco Use at Screening |
| 1.20. | ITT | - | Summary of Duration of Asthma and Exacerbation History - Intent-to-Treat |
| 1.21. | ITT (12-17 Years Old) | - | Summary of Duration of Asthma and Exacerbation History - ITT (12-17 Years Old) |
| 1.22. | ITT (15 Years or Older) | - | Summary of Duration of Asthma and Exacerbation History - ITT (15 Years or Older) |
| 1.23. | ITT | MH4 | Summary of Current Medical Conditions |
| 1.24. | ITT | MH4 | Summary of Past Medical Conditions |
| 1.25. | ITT | FH1 | Summary of Family History of Cardiovascular Risk Factors |

| Study Population Tables | | | |
|---|---|---|---|
| **No.** | **Population** | **IDSL Basis** | **Title** |
| 1.26. | ITT | - | Summary of Screening and Study Baseline Lung Function Test Results - Intent-to-Treat |
| 1.27. | ITT (12-17 Years Old) | - | Summary of Screening and Study Baseline Lung Function Test Results - ITT (12-17 Years Old) |
| 1.28. | ITT (15 Years or Older) | - | Summary of Screening and Study Baseline Lung Function Test Results - ITT (15 Years or Older) |
| 1.29. | ITT | - | Summary of Study Baseline Serial FEV1 |
| 1.30. | ITT | - | Summary of Maximal Percent Decrease from Pre-Exercise FEV1 at Study Baseline - Intent-to-Treat |
| 1.31. | ITT (15 Years or Older) | | Summary of Maximal Percent Decrease from Pre-Exercise FEV1 at Study Baseline - ITT (15 Years or Older) |
| 1.32. | ITT | - | Summary of Study Baseline Lung Function Test Results by Completion Status |
| **Exposure and Treatment Compliance** | | | |
| 1.33. | ITT | - | Summary of Exposure |
| 1.34. | ITT | - | Summary of Treatment Compliance |
| **Concomitant Medications** | | | |
| 1.35. | ITT | CM8b | Summary of Asthma Concomitant Medications Taken Pre-Treatment |
| 1.36. | ITT | CM8b | Summary of Asthma Concomitant Medications Taken During Treatment |
| 1.37. | ITT | CM8b | Summary of Asthma Concomitant Medications Taken Post Treatment |
| 1.38. | ITT | CM8b | Summary of Non-Asthma Concomitant Medications Taken Pre-Treatment |
| 1.39. | ITT | CM8b | Summary of Non-Asthma Concomitant Medications Taken During Treatment |
| 1.40. | ITT | CM8b | Summary of Non-Asthma Concomitant Medications Taken Post Treatment |

## 10.13.3. Efficacy Tables

| Efficacy: Tables | | |
|---|---|---|
| **No.** | **Population** | **Title** |
| **Primary Endpoint** | | |
| 2.1. | ITT | Summary of Maximal Percent Decrease from Pre-Exercise FEV1 Following 12 Hour Exercise Challenge - Intent-to-Treat |
| 2.2. | ITT | Statistical Analysis of Maximal Percent Decrease from Pre-Exercise FEV1 Following 12 Hour Exercise Challenge - Intent-to-Treat |
| 2.3. | ITT (15 Years or Older) | Statistical Analysis of Maximal Percent Decrease from Pre-Exercise FEV1 Following 12 Hour Exercise Challenge - ITT (15 Years or Older) |
| 2.4. | PP | Summary of Maximal Percent Decrease from Pre-Exercise FEV1 Following 12 Hour Exercise Challenge - Per Protocol |
| 2.5. | PP | Statistical Analysis of Maximal Percent Decrease from Pre-Exercise FEV1 Following 12 Hour Exercise Challenge - Per Protocol |
| 2.6. | ITT (12-17 Years Old) | Summary of Maximal Percent Decrease from Pre-Exercise FEV1 Following 12 Hour Exercise Challenge - ITT (12-17 Years Old) |
| 2.7. | ITT | Summary of Maximal Decrease from Pre-Exercise FEV1 (L) Following 12 Hour Exercise Challenge |
| 2.8. | ITT | Statistical Analysis of Maximal Decrease from Pre-Exercise FEV1 (L) Following 12 Hour Exercise Challenge - Intent-to-Treat |
| 2.9. | ITT (15 Years or Older) | Statistical Analysis of Maximal Decrease from Pre-Exercise FEV1 (L) Following 12 Hour Exercise Challenge - ITT (15 Years or Older) |
| **Secondary and Other Endpoints** | | |
| 2.10. | ITT | Summary of Maximal Percent Decrease from Pre-Exercise FEV1 Following 23 Hour Exercise Challenge - Intent-to-Treat |
| 2.11. | ITT (12-17 Years Old) | Summary of Maximal Percent Decrease from Pre-Exercise FEV1 Following 23 Hour Exercise Challenge - ITT (12-17 Years Old) |
| 2.12. | ITT | Statistical Analysis of Maximal Percent Decrease from Pre-Exercise FEV1 Following 23 Hour Exercise Challenge - Intent-to-Treat |
| 2.13. | ITT (15 Years or Older) | Statistical Analysis of Maximal Percent Decrease from Pre-Exercise FEV1 Following 23 Hour Exercise Challenge - ITT (15 Years or Older) |
| 2.14. | ITT | Summary of Maximal Decrease from Pre-Exercise FEV1 (L) Following 23 Hour Exercise Challenge |
| 2.15. | ITT | Statistical Analysis of Maximal Decrease from Pre-Exercise FEV1 (L) Following 23 Hour Exercise Challenge - Intent-to-Treat |
| 2.16. | ITT (15 Years or Older) | Statistical Analysis of Maximal Decrease from Pre-Exercise FEV1 (L) Following 23 Hour Exercise Challenge - ITT (15 Years or Older) |
| 2.17. | ITT | Summary of Maximal Percent Decrease from Period Baseline FEV1 Following Exercise Challenge |

| Efficacy: Tables | | |
|---|---|---|
| **No.** | **Population** | **Title** |
| 2.18. | ITT | Statistical Analysis of Maximal Percent Decrease from Period Baseline FEV1 Following Exercise Challenge |
| 2.19. | ITT | Summary of Maximal Decrease from Period Baseline FEV1 (L) Following Exercise Challenge |
| 2.20. | ITT | Statistical Analysis of Maximal Decrease from Period Baseline FEV1 (L) Following Exercise Challenge |
| 2.21. | ITT | Summary of Change from Period Baseline in Individual Serial FEV1 Measurements (L) |
| 2.22. | ITT | Statistical Analysis of Change from Period Baseline in Individual Serial FEV1 Measurements (L) - Intent-to-Treat |
| 2.23. | ITT (15 Years or Older) | Statistical Analysis of Change from Period Baseline in Individual Serial FEV1 Measurements (L) - ITT (15 Years or Older) |
| 2.24. | ITT | Statistical Analysis of Proportion of Subjects with a Post-Challenge FEV1 No More Than 5% Lower Than Pre-Exercise FEV1 - Intent-to-Treat |
| 2.25. | ITT (15 Years or Older) | Statistical Analysis of Proportion of Subjects with a Post-Challenge FEV1 No More Than 5% Lower Than Pre-Exercise FEV1 - ITT (15 Years or Older) |
| 2.26. | ITT (12-17 Years Old) | Summary of Proportion of Subjects with a Post-Challenge FEV1 No More Than 5% Lower Than Pre-Exercise FEV1 |
| 2.27. | ITT | Summary of Weighted Mean 0-60 min for Percentage Decrease from Pre-Exercise FEV1 Following Exercise Challenge - Intent-to-Treat |
| 2.28. | ITT | Statistical Analysis of Weighted Mean 0-60 min for Percentage Decrease from Pre-Exercise FEV1 Following Exercise Challenge - Intent-to-Treat |
| 2.29. | ITT (15 Years or Older) | Statistical Analysis of Weighted Mean 0-60 min for Percentage Decrease from Pre-Exercise FEV1 Following Exercise Challenge - ITT (15 Years or Older) |
| 2.30. | ITT (12-17 Years Old) | Summary of Weighted Mean 0-60 min for Percentage Decrease from Pre-Exercise FEV1 Following Exercise Challenge - ITT (12-17 Years Old) |
| 2.31. | ITT | Statistical Analysis of Percentage of Subjects with a Decrease from Pre-Exercise FEV1 in 3 Categories |
| 2.32. | ITT | Summary of Change from Period Baseline in ACQ-5 Score |
| 2.33. | ITT | Statistical Analysis of Change from Period Baseline in ACQ-5 Score |
| 2.34. | ITT | Statistical Analysis of Percentage of Subjects Controlled (ACQ-5 Score <=0.75) |
| 2.35. | ITT | Statistical Analysis of Percentage of Subjects Achieving an Improvement of >=0.5 in ACQ-5 Score |
| 2.36. | ITT | Summary of Change from Period Baseline in Physical Activity Measures Over Week 2 of Treatment Period |

## 10.13.4. Efficacy Figures

| Efficacy: Figures | | |
|---|---|---|
| **No.** | **Population** | **Title** |
| **Primary Endpoint** | | |
| 2.1. | ITT/PP | Adjusted Treatment Differences for Maximal Percent Decrease from Pre-Exercise FEV1 Following Exercise Challenge |
| 2.2. | ITT (15 Years or Older) | Adjusted Treatment Differences for Maximal Percent Decrease from Pre-Exercise FEV1 Following Exercise Challenge - ITT (15 Years or Older) |
| **Secondary and Other Endpoints** | | |
| 2.3. | ITT | Adjusted Treatment Differences for Maximal Decrease from Pre-Exercise FEV1 (L) Following Exercise Challenge - Intent-to-Treat |
| 2.4. | ITT (15 Years or Older) | Adjusted Treatment Differences for Maximal Decrease from Pre-Exercise FEV1 (L) Following Exercise Challenge - ITT (15 Years or Older) |
| 2.5. | ITT | Adjusted Treatment Differences for Maximal Percent Decrease from Period Baseline FEV1 Following Exercise Challenge |
| 2.6. | ITT | Adjusted Treatment Differences for Maximal Decrease from Period Baseline FEV1 (L) Following Exercise Challenge |
| 2.7. | ITT | Adjusted Mean Change from Period Baseline in Individual Serial FEV1 Measurements (L) - Intent-to-Treat |
| 2.8. | ITT (15 Years or Older) | Adjusted Mean Change from Period Baseline in Individual Serial FEV1 Measurements (L) - ITT (15 Years or Older) |
| 2.9. | ITT | Adjusted Treatment Ratios for Proportion of Subjects with a Post-Challenge FEV1 No More Than 5% Lower Than Pre-Exercise FEV1 - Intent-to-Treat |
| 2.10. | ITT (15 Years or Older) | Adjusted Treatment Ratios for Proportion of Subjects with a Post-Challenge FEV1 No More Than 5% Lower Than Pre-Exercise FEV1 - ITT (15 Years or Older) |
| 2.11. | ITT | Adjusted Treatment Differences for Weighted Mean 0-60 min for Percentage Decrease from Pre-Exercise FEV1 Following Exercise Challenge - Intent-to-Treat |
| 2.12. | ITT (15 Years or Older) | Adjusted Treatment Differences for Weighted Mean 0-60 min for Percentage Decrease from Pre-Exercise FEV1 Following Exercise Challenge - ITT (15 Years or Older) |
| 2.13. | ITT | Adjusted Treatment Ratios for Percentage of Subjects with a Decrease from Pre-Exercise FEV1 in 3 Categories |
| 2.14. | ITT | Adjusted Treatment Differences and Ratios for ACQ-5 Endpoints at Day 14 |
| **Forest Plot Across Endpoints** | | |
| 2.15. | ITT | Adjusted Treatment Differences and Ratios for Primary and Secondary Efficacy Endpoints at Day 14 - Intent-to-Treat |
| 2.16. | ITT (15 Years or Older) | Adjusted Treatment Differences and Ratios for Primary and Secondary Efficacy Endpoints at Day 14 - ITT (15 Years or Older) |

## 10.13.5. Safety Tables

| Safety : Tables | | | |
|---|---|---|---|
| **No.** | **Population** | **IDSL Basis** | **Title** |
| **Adverse Events Including Pneumonia** | | | |
| 3.1. | ITT | - | Adverse Event Overview |
| 3.2. | ITT | AE1 | Summary of On-Treatment Adverse Events - Intent-to-Treat |
| 3.3. | ITT (15 Years or Older) | AE1 | Summary of On-Treatment Adverse Events - ITT (15 Years or Older) |
| 3.4. | ITT (12-17 Years Old) | AE1 | Summary of On-Treatment Adverse Events - ITT (12-17 Years Old) |
| 3.5. | ITT | AE1 | Summary of Post-Treatment Adverse Events |
| 3.6. | ITT | AE3 | Summary of Most Frequent On-Treatment Adverse Events |
| 3.7. | ITT | - | Summary of the Most Frequent On-treatment Adverse Events - Top Ten Most Commonly Reported On-treatment Adverse Events Per Treatment Group |
| 3.8. | ITT | AE1 | Summary of Drug-Related Adverse Events |
| 3.9. | ITT | AE1 | Summary of Drug-Related Serious Adverse Events |
| 3.10. | ITT | AE1 | Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal From the Study |
| 3.11. | ITT | AE1 | Summary of On-Treatment Serious Adverse Events |
| 3.12. | ITT | AE1 | Summary of Post-Treatment Serious Adverse Events |
| 3.13. | ITT | - | Summary of Common On-Treatment Non-Serious Adverse Events (>=3% without rounding) |
| 3.14. | ITT | - | Summary of On-Treatment Serious Adverse Events |
| 3.15. | ITT | - | Summary of On-Treatment Fatal Adverse Events |
| 3.16. | ITT | - | Summary of Post-Treatment Fatal Adverse Events |
| 3.17. | ITT | - | Summary of On-Treatment and Post-Treatment Adverse Events of Special Interest - Intent-to-Treat |
| 3.18. | ITT (12-17 Years Old) | - | Summary of On-Treatment and Post-Treatment Adverse Events of Special Interest - ITT (12-17 Years Old) |
| 3.19. | ITT | - | Summary of On-Treatment and Post-Treatment Serious Adverse Events of Special Interest - Intent-to-Treat |
| 3.20. | ITT | - | Summary of On-Treatment Pneumonia |
| 3.21. | ITT | - | Summary of Post-Treatment Pneumonia |
| 3.22. | ITT | AE2 | Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text |
| 3.23. | ITT | - | Record of all Preferred Terms That Could Have Mapped to Special Interest Terms |

| Safety : Tables | | | |
|---|---|---|---|
| **No.** | **Population** | **IDSL Basis** | **Title** |
| **Severe Asthma Exacerbations** | | | |
| 3.24. | ITT | - | Summary of Subjects with Severe Asthma Exacerbations - Intent-to-Treat |
| 3.25. | ITT (15 Years or Older) | - | Summary of Subjects with Severe Asthma Exacerbations - ITT (15 Years or Older) |
| 3.26. | ITT (12-17 Years Old) | - | Summary of Subjects with Severe Asthma Exacerbations - ITT (12-17 Years Old) |
| **Other** | | | |
| 3.27. | ITT | VS1 | Summary of Vital Signs |
| 3.28. | ITT | VS1 | Summary of Change from Baseline in Vital Signs |

## 10.13.6. ICH Listings

| ICH : Listings | | | |
|---|---|---|---|
| **No.** | **Population** | **IDSL Basis** | **Title** |
| **Study Population** | | | |
| 1. | ITT | ES3 | Listing of Reasons for Premature Withdrawal |
| 2. | ITT | IE4 | Listing of Subjects with Inclusion/Exclusion Criteria Deviations Recorded in the eCRF |
| 3. | ITT | BL2 | Listing of Subjects for Whom the Treatment Blind was Broken During the Study |
| 4. | ITT | DM4 | Listing of Demographic Characteristics |
| 5. | ITT | DM10 | Listing of Race |
| 6. | ITT | - | Listing of Randomized and Actual Treatments |
| 7. | ITT | - | Listing of Exposure and Compliance Data |
| **Efficacy** | | | |
| 8. | ITT | - | Listing of Clinic Lung Function Data |
| **Safety** | | | |
| 9. | ITT | AE7 | Listing of Subject Numbers for Individual Adverse Events |
| 10. | ITT | AE9 | Listing of Pre-Treatment Adverse Events |
| 11. | ITT | AE9 | Listing of On-Treatment Adverse Events |
| 12. | ITT | AE9 | Listing of Post-Treatment Adverse Events |
| 13. | ITT | AE9 | Listing of Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal From the Study |
| 14. | ITT | AE9 | Listing of Non-Fatal Serious Adverse Events |
| 15. | ITT | AE9 | Listing of Fatal Adverse Events |
| 16. | Not in ITT | AE9 | Listing of Adverse Events for Subjects not in Intent-to-Treat Population |
| 17. | ITT | - | Listing of Pneumonia Data |
| 18. | ITT | - | Listing of Chest X-ray Data |

## 10.13.7. Non-ICH Listings

| Non-ICH : Listings | | | |
|---|---|---|---|
| **No.** | **Population** | **IDSL Basis** | **Title** |
| **Study Population** | | | |
| 19. | ITT | - | Listing of Important Protocol Deviation Recorded in the eCRF |
| 20. | ITT | - | Listing of Protocol Deviations Impacting the Per Protocol Population |
| 21. | ITT | - | Listing of Subjects who Received Incorrect Medication |
| 22. | ITT | - | Listing of History of Tobacco Use |
| 23. | ITT | - | Listing of Duration of Asthma and Exacerbation History |
| 24. | ITT | MH2 | Listing of Medical Conditions |
| 25. | ITT | - | Listing of Family History of Cardiovascular Risk Factors |
| 26. | ITT | CM3 | Listing of Concomitant Medications |
| 27. | ITT | CM6 | Listing of Relationship Between ATC Level 1, Ingredient and Verbatim Text |
| **Safety** | | | |
| 28. | ITT | - | Listing of Severe Asthma Exacerbations |
| 29. | ITT | VS5 | Listing of Vital Signs |
| 30. | ITT | - | Listing of IP Inhaler Malfunctions |

## 10.14. Appendix 14: Example Mock Shells for Data Displays

The data display shells are contained in separate documents which are available on request.