Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for HZC102972, a multi-centre, randomised, double-blind, parallel-group study evaluating the effect of Fluticasone Furoate/ Vilanterol (FF/VI) Inhalation Powder once daily compared with Vilanterol (VI) Inhalation Powder Once Daily on Bone Mineral Density (BMD) in subjects with Chronic Obstructive Pulmonary Disease (COPD)
Compound Number	:	GW685698+GW642444
Effective Date	:	17-MAY-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol HZC102972 (2012N150072_01).
- This RAP is intended to describe the final analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol HZC102972:

Revision Chronology:		
2012N150072_00	07-JAN-2013	Original
2012N150072_01	14-AUG-2013	Amendment No.: 01 This protocol amendment is being implemented to revise and clarify exclusion criteria concerning participation in pulmonary rehabilitation programs; clarify the description of DEXA procedures and clinical labs; correction of typographical errors.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

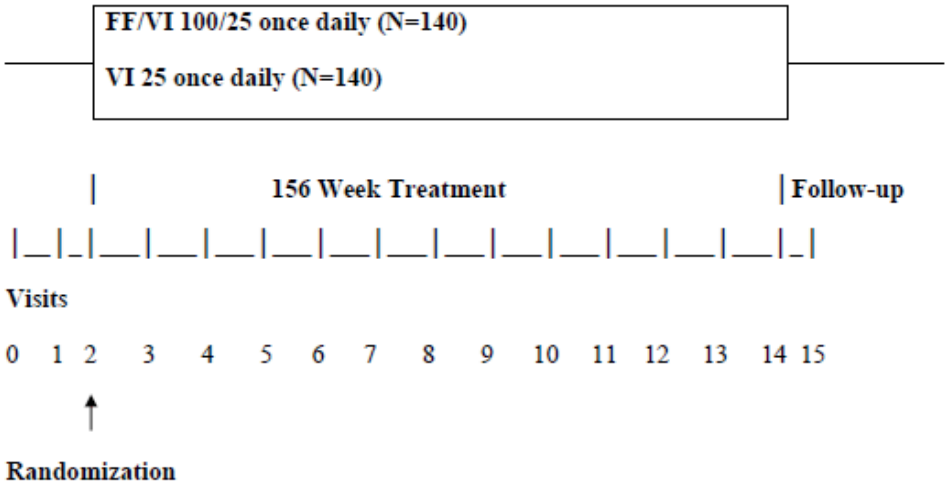
Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• The percent change from baseline in BMD for the total hip will be the primary endpoint, and analysed using a repeated measures model with terms for treatment, time, time by treatment, baseline BMD, baseline BMI and gender.	• The primary endpoint will be analysed using a repeated measures model with terms for treatment, visit, visit by treatment, baseline BMD, baseline BMI, age and gender. Weighted contrasts will be formed between all visits to calculate the average change per year over the 3 year study treatment period.	• The wording in protocol used time and not visit, which may imply time as a continuous variable, rather than categorical. The analysis was clarified in the RAP text. Additional text added around contrast statement as use of SAS code in RAPs is now discouraged. In addition, age was missed from the model
• Only included analysis of the ITT population	• Safety and ITT population will be defined.	• As this is a safety and not an efficacy study it is more appropriate to use the Safety population.
• Section 8.2.2 of the Protocol Sample Size Sensitivity – the power calculations are inconsistent	• Section 2.5 of this RAP provides the amended power calculations	• Previous power calculations for sample size sensitivity were inconsistent, and have been corrected.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• Evaluate the effect of FF/VI on BMD at the total hip	• BMD measured at the total hip
Secondary Objectives	**Secondary Endpoints**
• Evaluate the effect of FF/VI on BMD by gender	• BMD measurements by gender
• Evaluate the effect of FF/VI on BMD as assessed at the lumbar spine L1-L4	• BMD measured at the lumbar spine (L1-L4)
Other Objectives	**Other Endpoints**
• Evaluate safety of FF/VI	• Adverse Event reporting
	• Serious Adverse Event reporting
	• Incidence of Fractures
	• Incidence of Pneumonias
	• COPD exacerbations

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• Multi-center, randomised, double-blind, parallel-group study
Dosing	• FF/VI 100/25 mcg once daily via ELLIPTA inhaler • VI 25 mcg once daily via ELLIPTA inhaler • Note: ELLIPTA was previously referred to as NDPI
Treatment Assignment	• Following a 14-21 day run-in period, eligible subjects will be randomised (1:1) to either Fluticasone Furoate /Vilanterol 100/25 mcg once daily or Vilanterol 25 mcg once daily, administered as one inhalation each morning. • Approximately 400 male and female subjects will be screened to randomise approximately 280 subjects, to obtain at least 224 who complete 156 weeks of treatment. • The randomisation will be stratified by gender.
Interim Analysis	• No interim analysis is planned for this study

2.4. Statistical Hypotheses / Statistical Analyses

The null hypothesis for the primary measure is that the decrease in BMD assessed at the total hip is larger for the FF/VI combination product arm compared with the VI arm. The alternative hypothesis that the change in BMD assessed at the total hip is not worse for the FF/VI arm compared with the VI arm. The 95% confidence interval will be compared to a lower bound of -1%/year in order to assess clinical non-inferiority such that:

$$H_0: \mu_{FF/VI} \leq \mu_{VI} - 1\%$$
$$H_1: \mu_{FF/VI} > \mu_{VI} - 1\%$$

This is also the null and alternative hypothesis for the secondary measure of BMD assessed at the L1-L4 lumbar spine.

2.5. Sample Size Sensitivity

For the primary endpoint of BMD at the total hip, males and females will be combined in order to have >90% power to demonstrate non-inferiority. This will be done by comparing the lower boundary of a two-sided 95% confidence interval of the treatment difference to -1 % year, assuming a true treatment difference of -0.3 %/year with a standard deviation of 1.3 %/year.

As detailed in Section 2.1, the power calculations for sample size sensitivity given in the protocol were inconsistent, and hence have been corrected as shown in Table 2. These demonstrate that across a true treatment difference of -0.2 to -0.4 %/year and a true standard deviation of 1.3 to 1.5 %/year, the primary endpoint of BMD at the total hip for males and females combined will have at least 85% power.

Table 2 Sample Size Sensitivity

	True Treatment Difference between FF/VI and VI		
SD	**-0.2%/yr**	**-0.3%/yr**	**-0.4%/yr**
1.3%/yr	>99%	98%	93%
1.4%/yr	99%	96%	89%
1.5%/yr	98%	94%	85%

3. PLANNED ANALYSES

3.1. Final Analyses

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

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

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All subjects enrolled (ASE)	• All subjects for whom a record exists on the study database, including screen failures and any subjects who were not screened but signed the informed consent form.	• Study Population
Pre-screen, Screen and Run-in Failures (SRIF)	• All subjects who were enrolled but were either pre-screen failures, screen failures, run-in failures or subjects randomised in error.	• Study Population
Randomised	• All subjects who were given a randomisation number, including subjects who were randomised in error.	• Study Population
(Modified) Intent to treat (ITT)	• All randomised subjects who received at least one dose of study treatment. • This population will be based on the treatment the subject was randomised to.	• Study Population
Safety (SAF)	• All randomised subjects who received at least one dose of study treatment. • This population will be based on the treatment the subject took for the majority of the treatment period (>50%).	• Study Population • Safety
Safety excluding closed sites	• This population would be the same as the safety population but excluding any sites that were closed due to audit findings, failures to adhere to GCP or any other findings. • This population will not be used unless there is a need to exclude sites.	• Study Population • Safety

Refer to Appendix 12: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

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

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan Version 2 (26-Sep-2016) or higher.

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

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

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. FF/VI vs VI

Treatment Group Descriptions			
RandAll NG		**Data Displays for Reporting**	
Code	**Description**	**Description**	**Order [1]**
3	FF/VI 100/25mcg QD	FF/VI 100/25	2
4	VI 25mcg QD	VI 25	1

NOTES:

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

QD = Once Daily

5.2. Baseline Definitions

For all endpoints, the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display [1]
	Screening	Day -1	Day 1 (Pre-Dose)	
Primary/Secondary Endpoint				
BMD	X			Screening
Other Endpoints				
FEV_1			X	Day 1 (Pre-Dose)
Vital Signs			X	Day 1 (Pre-Dose)

NOTES :

- Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.
- [1] = If any additional assessments closer to Day 1 (Dose) are taken then these will be used instead.

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

5.3. Multicentre Studies

In this multicentre global study, enrolment will be presented by investigative site and country.

Central randomisation was used for this study. It is likely that many centres will enrol a very small number of subjects and hence data from all participating centres will be pooled prior to analysis.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

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

Category	Details
Covariates: All models	Age, Gender, Baseline BMD, Visit, Baseline BMI
Covariates: To be investigated	Treatment*covariate interactions will be included in the model, and if these are significant (10% level) then a split model will be investigated.

5.4.2. Examination of Subgroups

The analysis of bone mineral density will be presented overall and by gender (males and females). For the gender analysis, each individual gender will have its own separate model fitted excluding any data from the opposite gender (split model).

There are no other planned subgroup analyses unless the treatment*covariate interaction is shown to be significant at the 10% level, in which case subgroups will be calculated and presented in the same way as gender. For example, if smoking status was shown to be significant it would be categorised as demonstrated below and then presented by these categories.

Table 3 shows all potential subgroups that will be investigated.

Table 3 Potential Subgroups

Covariate	Categorical or Continuous
Age	Continuous
Baseline BMI	BMI will be modelled as continuous but if it needs to be categorised for the purposes of producing summaries by subgroups the following categories will be used; < 25, 25 <= to < 30 and >= 30. This is based on the WHO definition for categorising BMI but combining the < 18.5 and 18.5 <= to <25 categories due to low number of subjects in the HZC102972 study having a BMI < 18.5.
Smoking Status	Categorical: Current or Former.

5.5. Multiple Comparisons and Multiplicity

No multiple comparison adjustments will be made.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
9.3	Appendix 3: Assessment Windows
9.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
9.5	Appendix 5: Data Display Standards & Handling Conventions
9.6	Appendix 6: Derived and Transformed Data
9.7	Appendix 7: Reporting Standards for Missing Data

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

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

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 12: List of Data Displays.

6.1.1. Study Populations

The number of subjects randomised and the number of subjects who were in the mITT and Safety population will be presented by treatment group and overall.

The number of subjects in the ASE population, the number and percentage of subjects who were screening and run-in failures, and who had exacerbations during the run-in period will be presented. In addition, the reasons for screening failures will also be provided.

The number and percentage of subjects who completed the study, who withdrew prematurely from the study and who reported each primary and sub-reason for withdrawal will be presented for each treatment group and overall. Similarly, tables of demography and baseline characteristics will be produced by treatment group and overall.

If any sites were closed due to audit findings, failures to adhere to GCP or any other findings, an additional 'Safety excluding closed sites' population will be added to all study population tables, or in the case of demography and baseline characteristic tables a repeat table for this population will be produced. If no sites were closed, this information will be included in the footnote and no additional tables will be provided.

6.2. Medical Conditions

The number and percentage of subjects reporting each current medical condition specified in the eCRF will be presented by randomised treatment group and overall. All medical conditions must be summarised on this table regardless of frequency, and will be repeated for current and past medical conditions.

A separate table of 'Cardiovascular Risk Factors' will also be produced. This will summarise the number and percentages of subjects with the following current or past medical conditions: Arrhythmia, Cerebrovascular Accident, Congestive Heart Failure, Coronary Artery Disease, Diabetes Mellitus, Hypertension, Hypercholesterolemia, Myocardial Infarction.

6.3. Concomitant Medications

Medications categorised as 'Other medications' will include medications not used to treat COPD or low bone mineral density [BMD] and will be summarised by Anatomical-Therapeutic-Chemical (ATC) level 1 and ingredient. COPD medications not given for an exacerbation will be summarised by Respiratory Medication Class (RMC). COPD medications given for exacerbations whilst on treatment will also be summarised by RMC. Multi-ingredient medications will be presented according to their combination ATC classification rather than the classifications of the individual ingredients.

BMD medications, taken to improve bone mineral density, will be summarised by treatment group and overall. Bone mineral density medications will be identified using ATC codes along with reviewing all concomitant medications prior to database freeze to ensure all relevant medications are included.

COPD, BMD and Other medications will be listed separately. The COPD medications listing will indicate whether each medication was taken for an exacerbation. Listings will indicate in which study phases each medication was taken (pre-treatment and/or on-treatment and/or post-treatment).

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

6.4. Screening Results

Screening (which will be baseline) bone mineral density results at both total hip and lumbar spine (L1-L4) will be summarised overall and by gender according to treatment.

Pre- and post-bronchodilator FEV_1, FVC, FEV_1/FVC ratio, post-bronchodilator FEV_1 percentage of predicted normal and FEV_1 reversibility to bronchodilator (expressed in mL and as a percentage of post-bronchodilator and grouped into the following categories: "<12% or <200mL" "≥12% and ≥200mL"; reversibility will also be expressed also as a percentage of predicted) at screening (see Section 5.2) will be summarised by treatment group and overall. At randomisation FEV1, FVC and FEV1/FVC will be summarised by treatment group and overall.

7. SAFETY ANALYSES

7.1. Primary Safety Analyses

Due to the known variability between sites and scanners, prior to the end of the study each machine has a phantom scanned. This phantom is a standardised bone image with a set density. As the true density of the phantom is known, it means that the difference between the true value and the machine value can be calculated, this is known as the correction factor.

Throughout the reporting of this study, all summaries and analysis of bone mineral density will use the corrected bone mineral density values only as these can be considered as standardised values where machine variability had been accounted for.

It is also important to highlight that if a subject was affected by a hip fracture during the study then the other native hip was used for all subsequent BMD assessments.

7.1.1. Endpoint / Variables

Bone mineral density measured at the Total Hip

7.1.2. Summary Measure

Percentage change from baseline per annum

7.1.3. Population of Interest

The primary safety analyses will be based on the Safety populations, unless otherwise specified. In the instance that all subjects are assigned their randomised treatment for at least 50% of the treatment period, the Safety population will be identical to the mITT.

7.1.4. Strategy for Intercurrent (Post-Randomisation) Events

The four key intercurrent events in this study are;

- Use of concomitant medication taken to increase a subject's bone mineral density (which we will term "BMD medication")
- Use of systemic corticosteroids (SCS) which may decrease a subject's BMD
- Temporary discontinuation of investigational product
- Permanent discontinuation of IP.

The primary aim of this study is to generate the 'while on treatment' estimand of the difference in percentage change from baseline per annum between FF/VI ± BMD medication/SCS and VI ± BMD medication/SCS.

Therefore, after a subject takes BMD medication or SCS, or temporarily discontinues IP, BMD will continue to be collected, and this data will be used in the analysis.

However, once a subject has permanently discontinued IP their inhaled therapy may be switched, and so data after this event will no longer reflect the treatment comparison of

interest. As this is a non-inferiority study, focusing on safety not efficacy, BMD data collected after this event will not be used in the analysis.

Intermittent missing data not due to an intercurrent event, e.g. sporadic missing of a visit, will not be explicitly imputed and will be treated as missing at random. Subsequent data collected will be included in the analysis.

7.1.5. Statistical Analyses / Methods

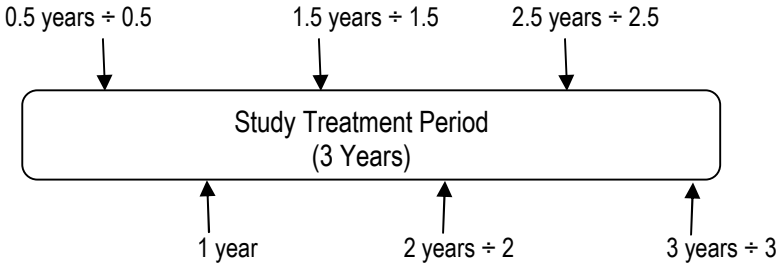
Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

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

7.1.5.1. Statistical Methodology Specification

Endpoint(s)
• Bone mineral density measured at the total hip
Model Specification
Model: • The ratio of post-baseline BMD values to baseline BMD values will be log transformed prior to analysis. Note: Log(post baseline BMD/baseline BMD) is equivalent to log(post baseline BMD) – log(baseline BMD). • A repeated measures model with terms for treatment, visit, visit by treatment, the logarithm of baseline BMD, the logarithm of baseline BMD by visit, baseline BMI (continuous), age (continuous) and gender will be fitted. • This will make the analysis model: log(post baseline BMD/baseline BMD)= treatment + visit + visit*treatment + log(baseline BMD) + log(baseline BMD)*visit + BMI + age + gender • The difference between FF/VI and VI will be calculated using the log estimate for FF/VI – the log estimate for VI. **Estimates:** • The estimates of the mean and difference for each treatment group from the model will be exponentiated to produce ratios. This will then be presented as a percentage change in BMD per year with 95% confidence intervals. I.e. percentage change = (exp(estimate)-1)*100. • In addition, these percent changes will be converted to annual percent changes by dividing by the year. E.g. the 1.5 year visit annual percent change will be calculated as (exp(estimate/1.5)-1)*100 • For the treatment difference, this will be presented as a percent difference in change in BMD per year with 95% confidence interval. I.e. difference = [exp(log_estimate for FF/VI – log_estimate for VI)-1]*100. In addition, the difference will be converted to annual percent difference as explained above.

- The estimates of the percent change in BMD and the percent change per year by treatment arm and the treatment difference will be presented at each 6 monthly analysis visit to check for consistency.
- These 6 monthly estimates will be averaged (see diagram below) to calculate the overall treatment estimates and the treatment difference, which will be used for the primary test of non-inferiority.
- The calculation would be: Overall estimate of percentage change in BMD per year = (a/0.5 + b/1 + c/1.5 + d/2 +e/2.5 + f/3) / 6, where a to f are the estimates at each 6 monthly post-baseline analysis visit.



Model Structure:

- The variance-covariance matrix will be assumed unstructured.
- Kenward Roger (KR) method will be used for calculating degrees of freedom. If the analysis does not run using the KR method then the residual method will be used instead.
- An observed margins (OM) dataset will be used to derive the LS means using coefficients which are based on the subjects used in the analysis. This is a dataset with a row for every subject-visit combination that contains all of the covariates. The OM will be at the average logarithm of baseline BMD, the average baseline age and the average baseline BMI.

Covariates to be investigated:

- Treatment*Covariate interactions will be included in the model individually. If these are significant at the 10% level then a model split by the covariate of interest will be investigated.

Model Checking & Diagnostics

- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

Model Results Presentation

Overall Estimate of % Change in BMD:

- The overall raw percentage change in BMD per year along with the LS means ratio and % change from baseline will be presented by treatment.
- In addition, the LS means ratio and % change from baseline for the treatment comparison will also be produced.

Estimates of % Change in BMD by visit:

- For each visit the raw baseline, raw mean and raw % change from baseline will be presented by treatment.
- The adjusted mean and adjusted ratio to baseline will be produced along with the % change from baseline by treatment.
- In addition, the LS means treatment difference for the ratio and % change at visit along with the % change per annum will be produced.

All LS means will be presented with their associated 95% confidence intervals.

Plots of BMD:

- Plots of raw mean, raw % change from baseline and LS mean percentage change from baseline by visit will be generated for each treatment.

7.2. Secondary Safety Analyses

7.2.1. Endpoint / Variables

- Bone mineral density measured at the Total Hip by Gender
- Bone mineral density measured at the Lumbar Spine L1-L4
- Bone mineral density measured at the Lumbar Spine L1-L4 by Gender

7.2.2. Summary Measure

- Percentage change from baseline

7.2.3. Population of Interest

The secondary analyses will be based on the Safety populations, unless otherwise specified.

7.2.4. Strategy for Intercurrent (Post-Randomisation) Events

See Section 7.1.4.

7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

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

7.2.5.1. Statistical Methodology Specification

Endpoint(s)
• Bone mineral density measurements by Gender • Bone mineral density measured at the Lumbar Spine (L1-L4) • Bone mineral density measured at the Lumbar Spine (L1-L4) by Gender
Model Specification
• See Section 7.1.5.1. • For the models of bone mineral density measurements by Gender, each gender will have their own model fitted excluding any data from the opposite gender (split model).
Model Checking & Diagnostics
• See Section 7.1.5.1.
Model Results Presentation
• See Section 7.1.5.1.

7.3. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 12: List of Data Displays.

7.4. Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting. These will be produced for both LABA and ICS AESIs. The details of the planned displays are provided in Appendix 12: List of Data Displays.

7.5. On-treatment Fractures

Fracture events including the number and percentage of subjects recorded as having at least one bone fracture, location of fractures and whether they were traumatic or not traumatic (severity) will be summarised. If a subject suffers fractures in multiple locations with the same date of fracture, this is considered to be one fracture incident. The frequency and percentage of subjects with 0, 1, 2 and more than 2 fracture incidents will also be summarised.

In addition, the rates of fractures will be summarised as described in Section 9.6.3. The details of the planned displays are in Appendix 12: List of Data Displays.

7.6. On-treatment Pneumonia

Pneumonia events including severity, outcomes, those supported by x-rays, those within 14 days of moderate/severe exacerbations and number of events per subject will be summarised.

A chest x-ray/CT scan is associated with pneumonia if it is performed within the duration of the pneumonia or between -7 to +10 days (inclusive) of the date of onset.

In addition, the rates of events will be summarised as described in Section 9.6.3. The details of the planned displays are in Appendix 12: List of Data Displays.

7.7. On-treatment Moderate/Severe COPD Exacerbations

The number and percentage of subjects reporting an on-treatment moderate/severe exacerbation along with the outcome category (fatal, resolved or not resolved), result (withdrawal, treatment by corticosteroids, antibiotics, emergency room visits or hospitalisations) will be presented along with the primary cause.

A moderate COPD exacerbation is defined as requires treatment with antibiotics and/or systemic corticosteroids. A severe COPD exacerbation is defined as requires hospitalization.

The details of the planned displays are in Appendix 12: List of Data Displays.

7.8. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 12: List of Data Displays.

7.9. Vital Signs and Non-Laboratory Analyses

The analyses of non-laboratory safety test results including vital signs will be based on GSK Core Data Standards, unless otherwise specified.

8. REFERENCES

GSK Document 2012N150072_01, Multi-centre, randomized, double-blind, parallel-group study evaluating the effect of Fluticasone Furoate/ Vilanterol (FF/VI) Inhalation Powder once daily compared with Vilanterol (VI) Inhalation Powder Once Daily on Bone Mineral Density (BMD) in subjects with Chronic Obstructive Pulmonary Disease (COPD), 14-AUG-2013

9. APPENDICES

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

9.1.1. Exclusions from Per Protocol Population

There will be no per protocol population analysed in this study.

9.2. Appendix 2: Schedule of Activities

Protocol Defined Schedule of Events

			Double-Blind Treatment period														
Visit Number	**0 Pre-screen[1]**	**1 Screen-ing[2]**	**2 Random-ization**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Early With-draw**	**15 Follow-up**
			Day 1	13 wks ±14 Days	26 wks ±14 Days	39 wks ±14 Days	52 wks ±14 Days	65 wks ±14 Days	78 wks ±14 Days	91 wks ±14 Days	104 wks ±14 Days	117 wks ±14 Days	130 wks ±14 Days	143 wks ±14 Days	156 wks ±14 Days		Visit 14/EW + 7±2 Days
Assessments																	
Informed consent[3]	X																
PGx Consent & Sampling[4]			X														
Demography	X																
Medical History		X															
Physical Exam		X					X				X				X	X	
Spirometry Testing		X	X		X		X		X		X		X		X	X	
Reversibility Testing		X															
Smoking history/ smoking status		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Smoking cessation counseling		X					X				X				X	X	
Register visit on IVRS[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments																	
BMD DEXA scans[6]		X			X		X		X		X		X		X	X	
Oropharyngeal examination[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chest X-ray[8]		X															
Lab Tests[9] / Serum Pregnancy Test[10]		X															

			Double-Blind Treatment period														
Visit Number	**0 Pre-screen[1]**	**1 Screen-ing[2]**	**2 Random-ization**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Early With-draw**	**15 Follow -up**
			Day 1	13 wks ±14 Days	26 wks ±14 Days	39 wks ±14 Days	52 wks ±14 Days	65 wks ±14 Days	78 wks ±14 Days	91 wks ±14 Days	104 wks ±14 Days	117 wks ±14 Days	130 wks ±14 Days	143 wks ±14 Days	156 wks ±14 Days		Visit 14/EW + 7±2 Days
12-lead ECG & Rhythm Strip		X															
Exacerbation Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment[11]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event Assessment[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Diary		X	X	X	X	X	X	X	X	X	X	X	X	X			
Collect/Review Diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medication Assessments																	
Concurrent Medication Assessment[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense albuterol (salbutamol)[14]		X	X	X	X	X	X	X	X	X	X	X	X	X			
Collect albuterol (salbutamol)[14]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Single-Blind Medication		X															
Dispense Double-Blind Medication			X	X	X	X	X	X	X	X	X	X	X	X			
Collect Blinded Medication			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Other Assessment																	

			Double-Blind Treatment period														
Visit Number	**0 Pre-screen[1]**	**1 Screen-ing[2]**	**2 Random-ization**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Early With-draw**	**15 Follow -up**
			Day 1	13 wks ±14 Days	26 wks ±14 Days	39 wks ±14 Days	52 wks ±14 Days	65 wks ±14 Days	78 wks ±14 Days	91 wks ±14 Days	104 wks ±14 Days	117 wks ±14 Days	130 wks ±14 Days	143 wks ±14 Days	156 wks ±14 Days		Visit 14/EW + 7±2 Days
Discharge from Study[15]															X	X	

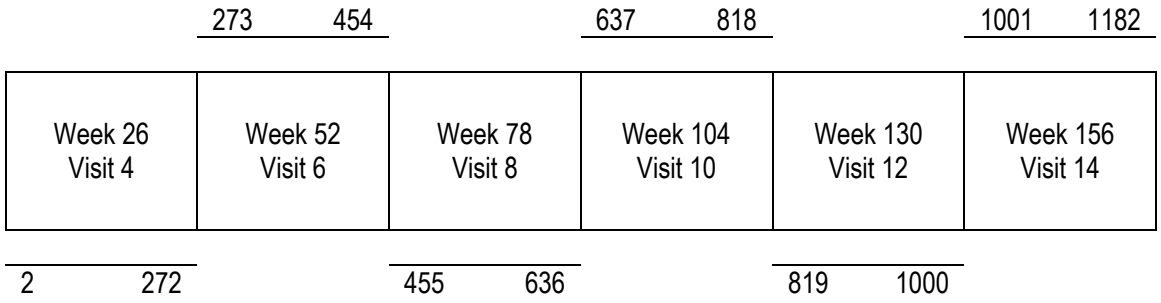
1. **Visit 0** and **Visit 1** may occur on the same day if the subject does not take or has not taken any protocol excluded medications.
2. Following Screening **Visit 1**, subjects enter a 14 to 21 day single-blind run-in period.
3. Subjects will be assigned a subject number at the time ICF is signed. The ICF must be signed before any study procedures including medication exclusion period(s).
4. Saliva (2ml) sample is collected in the DNA self-collection kit. This should ideally be taken as soon after randomization (Visit 2) as possible, but may be taken at any other visit after randomization if necessary. PGx consent must be signed prior to PGx sampling.
5. A telephone based IVRS system (RAMOS) which will be used by the investigator or designate to register the subject, randomize the subject and provide medication assignment information.
6. Baseline BMD measurements will be collected between **Visit 1** and **Visit 2**.
7. If evidence of infection, culture swab may be taken and appropriate therapy should be instituted at Investigator discretion. Subjects with culture-positive infection may continue in the study on appropriate anti-infective treatment at Investigator discretion.
8. Chest X-ray must be taken if a Chest X-ray or CT scan is not available within the 12 months preceding **Visit 1**. Chest x-rays will be requested for suspected cases of pneumonia.
9. Non-fasting and pre-dose. A blood sample for repeat analysis is collected only if any part of Screening lab needs to be repeated. Results of repeat labs should be received prior to Randomization at Visit 2.
10. Females of child-bearing potential only
11. Adverse events are to be collected from the start of blinded study medication (Visit 2) until the follow-up phone contact.
12. Serious adverse events are to be collected from the start of study drug (Visit 2) until the follow-up phone contact. However, any SAEs assessed as related to study participation will be recorded from the time subjects sign informed consent.
13. All COPD medications taken within 30 days prior to **Visit 0** will be collected.
14. Collect and re-dispense as needed after **Visit 1**.
15. Discharge from study on appropriate therapy.

9.3. Appendix 3: Assessment Windows

9.3.1. Definitions of Assessment Windows for Analyses: BMD Data

Analysis Set / Domain	Target	Analysis Window		Analysis Timepoint
		Beginning Timepoint	Ending Timepoint	
ITT", "Safety"	Week 26	Day 2	Day 272	VISIT 4
ITT", "Safety"	Week 52	Day 273	Day 454	VISIT 6
ITT", "Safety"	Week 78	Day 455	Day 636	VISIT 8
ITT", "Safety"	Week 104	Day 637	Day 818	VISIT 10
ITT", "Safety"	Week 130	Day 819	Day 1000	VISIT 12
ITT", "Safety"	Week 156	Day 1001	Day 1182	VISIT 14

In order to include all bone mineral density assessments, the analysis window has been increased to ± 3 months. A schematic of the above windowing is given below.



If there are multiple assessments within a window these will be averaged on the raw scale (i.e. before log transformation).

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

Subjects who do not take study treatment who have will have events, log recordings and measurements assigned to pre-treatment.

Events, log recordings and measurements with missing dates will be assigned to on-treatment for subjects who have taken study treatment, unless there is evidence it was not on-treatment.

9.4.1. Study Phases for Measurements Taken at Visits (FEV_1 and Vital Signs Only)

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

These definitions would only apply to vital signs and FEV_1 data, in which baseline measurements are taken on Day 1 pre-dose (as define in the Schedule of Activities). If the standard definition (Section 9.4.3) were used then the baseline data would be considered on-treatment as it occurs on Day 1 even though it occurs prior to first dose. As a result, a separate definition of study phase has been used to ensure this data to captured appropriately.

9.4.2. Study Phases for Bone Mineral Density Measurements Taken at Visits (Bone Mineral Density Data Only)

Study Phase	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date ≤ Study Treatment Stop Date + 30 days (1 month)
Post-Treatment	Date > Study Treatment Stop Date + 30 days

9.4.3. Study Phases for Adverse Events and All Other Data Recorded in Logs (excluding Concomitant Medications)

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

9.4.4. Study Phases for Concomitant Medications

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

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

NOTES:

- A concomitant medication will be classed in every period of the study in which it was taken (e.g., run-in, on-treatment or post-treatment).
- See Section 9.7.2.1 for handling of partial dates.
- If the study treatment stop date is missing, it will be imputed as described in Section 9.6.2.
- Medications that stopped prior to Screening will not be assigned a treatment phase and will not be summarized.

9.4.5. Treatment Emergent Flag for Adverse Events, Pneumonia and Exacerbations

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date plus one day. • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 1.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

9.5. Appendix 5: Data Display Standards & Handling Conventions

9.5.1. Reporting Process

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	UK1SALX00175
HARP Area	gw685698_gw642444\hzc102972\final_02
QC Spreadsheet	gw685698_gw642444\hzc102972\final_02\documents
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards	
Generation of RTF Files	
• RTF files will be generated for all reporting efforts	

9.5.2. Reporting Standards

Reporting Standards
General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated:
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.

Reporting Standards	
Planned and Actual Time	

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.
  • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	

Unscheduled Visits	
• Unscheduled visits will not be included in summary tables. • Unscheduled visits will not be included in figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

9.6. Appendix 6: Derived and Transformed Data

9.6.1. General

Multiple Measurements at One Analysis Time Point
Bone Mineral Density Data: • If there are two values within a time window (as per Section 9.3.1) the mean of the measurements will be calculated and used in any derivation of summary statistics and for any analysis. • If the data is listed however all data will be presented.
Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Date ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

9.6.2. Study Population

Age
• Date of birth will be set as 30-JUN-YYYY where YYYY is the year of birth taken from the CRF. For subjects who attended a screening visit, age will be calculated at the screening visit date. For pre-screen failures, age will be calculated at the pre-screening visit date.
Body Mass Index (BMI)
• BMI = Weight (kg) / Height(m)^2
Study Treatment Stop Date
If the treatment stop date is missing, it will be imputed as the minimum of: • Date of death • Study conclusion date • Last dispensed date + number of doses dispensed and not returned
Treatment Compliance
• Treatment compliance will be calculated based on the formula: **Treatment Compliance = Number of Actual Doses / (Treatment Duration in Days * Frequency)** • Frequency is once daily. Treatment compliance could be greater than 100% if there are events of overdose. Cumulative compliance (since Day 1) at each visit will be calculated. • Compliance is based on number of doses taken across all containers dispensed and returned during the study – ie, it is calculated regardless of incorrect containers being dispensed. Any containers that are dispensed and not returned during the study are not included in the calculation. If any dose counter stop is missing, then the number of doses taken will be set to missing for that inhaler. • Compliance will be summarized by the following categories: <80%, ≥ 80% to < 95%, ≥95% to <105%, ≥ 105% to <120% and ≥120%

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Years = (Treatment Stop Date – (Treatment Start Date) + 1) / 365.25** • This will also be the exposure used to calculate rate of events • Duration of exposure will be summarised by the following categories: ≤ 3months, > 3 months < to ≤ 6 months, > 6 months to ≤ 12 months, >12 months to ≤ 24 months, >24 months to ≤ 36 months and >36 months where 1 month is equal to (365.25 days/12).

9.6.3. Safety

Adverse Events
AE'S OF Special Interest
The following AESI have been selected using the reference dataset (arenv/arprod/respiratory/res_safety/aesi/refdata) and sub setting on the relevant study medications (VI or FF) with an indication of COPD along with review by Global Clinical Safety Pharmacovigilance (GCSP): Adrenal Suppression (Selected PTs) Asthma/Bronchospasm (SMQ) Cardiovascular effects including the following subgroups: • Cardiac Arrhythmia (Selected SMQs) • Cardiac failure (SMQ) • Stroke (CNS system haemorrhages and cerebrovascular conditions SMQ) • Hypertension (SMQ) • Cardiac Ischaemia (Ischaemic heart disease SMQ) Decreased Bone Mineral Density and associated Fractures (Selected PTs + Osteoporosis/Osteopenia SMQ) Effects on potassium (Selected PTs) Effects on glucose (Hyperglycaemia/New onset Diabetes Mellitus SMQ) Hypersensitivity (Selected PTs) LRTI Excluding Pneumonia (Selected PTs) Local Steroid Effects (Selected PTs) Ocular effects including the following subgroups: • Glaucoma (SMQ) • Lens Disorders (SMQ) Pneumonia (Selected PTs) Tremor (Selected PTs) If this reference data is updated between the RAP being approved and the reporting of the study, then this list will be updated and re-reviewed. A listing of all preferred terms used to identify AESIs will be produced.

Rate of Adverse Events per 100 Treatment Years
Rate of on-treatment adverse events per 100 treatment years will be calculated using: Rate = number of events * 100 / total treatment exposure in years

Rate of Adverse Events per 100 Treatment Years
where subjects can contribute more than one event. This is equivalent to: Rate = number of events * 100 / (number of subjects in treatment group * mean treatment exposure in years). Note: The rate must be produced to sufficient decimal places to allow the conversion to rate of adverse events per 1000 treatment years if required. Exposure will be calculated as defined in Section 9.6.2.

Kaplan-Meier Plot of Time to Premature Discontinuation from Investigational Product
Within the Kaplan Meier plot subjects will either be counted as an event or they will be censored. Events: • Subjects who discontinue investigational product before the end of the study will be counted as an event, with the date of IP discontinuation being used as the treatment end date. • Subjects who die will be considered as having withdrawn from the IP at the date of death, unless they discontinued IP prior to death in which case the IP discontinuation date will be used as treatment end date. Censoring: • Subjects who continue study treatment until the end of the study will be censored at their treatment end date. A subject takes IP for more than 156 weeks will be censored at 156 weeks (1092 days). Time on investigational product = Treatment end date – Treatment start date + 1

Maximum/Minimum On-Treatment Definitions for Vital Signs Data
Maximum and Minimum on-treatment**:** Maximum and Minimum on-treatment value over all time-points (including scheduled and unscheduled assessments) will be presented.

FEV_1
Absolute Reversibility
Absolute reversibility (mL) = (post-bronchodilator FEV_1 – pre-bronchodilator FEV_1)
Percent Reversibility
Definition of Percentage Reversibility as a percentage of predicted FEV_1 = ((post-bronchodilator FEV_1– pre-bronchodilator FEV_1) / predicted FEV_1) x 100% Definition of Percentage Reversibility as a percentage of pre-bronchodilator FEV_1 = ((post-bronchodilator FEV_1– pre-bronchodilator FEV_1) / pre-bronchodilator FEV_1) x 100%

9.7. Appendix 7: Reporting Standards for Missing Data

9.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as attendance at 13 post-randomisation visits over the schedule. • Withdrawn subjects were not replaced in the study • Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.

9.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

9.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. • Any partial dates for adverse events will be raised to data management. • In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: o Missing Start Day: First of the month will be used o Missing Stop Day: Last day of the month will be used, unless the subject died and this date is after the subject's death date in which case the stop date will be set to the death date • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. If this imputed stop date is after the subject death date then the stop date will be set to the death date. • The recorded partial date will be displayed in listings. • Completely missing start or end dates will remain missing, with no imputation applied.
Protocol Devaiations	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for protocol deviation dates; that is, the day of the month may be missing. • In this case the first day of the month will be used. This is to allow the protocol deviation to have occurred at the earliest possible date.

9.8. Appendix 11: Abbreviations & Trade Marks

9.8.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CS	Clinical Statistics
CSR	Clinical Study Report
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
FF/VI	Fluticasone Furoate/ Vilanterol Inhalation Powder Combination
GCSP	Global Clinical Safety Pharmacovigilance
GSK	GlaxoSmithKline
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
GUI	Guidance
LRTI	Lower Respiratory Tract Infection
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PDMP	Protocol Deviation Management Plan
PP	Per Protocol
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomisation & Medication Ordering System
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
VI	Vilanterol Inhalation Powder

9.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
ELLIPTA

Trademarks not owned by the GlaxoSmithKline Group of Companies
HARP
SAS

9.9. Appendix 12: List of Data Displays

9.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.001 to 1.XXX	1.001 to 1.XXX
Safety	2.001 to 2.XXX	2.001 to 2.XXX
Section	**Listings**	
ICH Listings	1 to XX	
Other Listings	XX to YY	

9.9.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 13 15: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_F	POP_T	POP_L
Safety	SAFE_F	SAFE_T	SAFE_L

NOTES:

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

9.9.3. Deliverable [Priority]

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

NOTES:

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

9.9.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Enrolled	SP1	Summary of Study Populations	IDSL	SAC [1]
1.2.	SAF	ES1	Summary of Subjects Disposition for the Subjects Conclusion Record	ICH E3, FDAAA, EudraCT	SAC [1]
1.3.	SRIF	ES6	Summary of Pre-screening, Screening and Run-in Status and Reasons for Screen and Run-in Failure	Journal Requirements, Page by Screening and Run-in	SAC [1]
1.4.	Enrolled	NS1	Summary of Number of Subjects Enrolled by Country and Site ID	EudraCT/Clinical Operations	SAC [1]
1.5.	SAF	SP2	Summary of Attendance at Each Clinic Visit		SAC [1]
Protocol Deviation					
1.6.	SAF	DV1	Summary of Important Protocol Deviations	ICH E3	SAC [1]
1.7.	SAF	IE1	Summary of Inclusion/ Exclusion Deviations		SAC [1]
1.8.	Screened	IE2	Summary of Failed Inclusion/ Exclusion Criteria	Include 'Number of Screen or Run-in Failures' row at the top of the table. This is to be used as the denominator for the % calculations.	SAC [1]
Demographic and Baseline Characteristics					
1.9.	SAF	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC [1]
1.10.	SAF	DM1	Summary of Demographic Characteristics by Country		SAC [1]
1.11.	Enrolled	DM11	Summary of Age Ranges	EudraCT	SAC [1]
1.12.	SAF	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC [1]
1.13.	SAF	DM6	Summary of Race and Racial Combination Details		SAC [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Prior and Concomitant Medications					
1.14.	SAF	MH4	Summary of Current Medical Conditions	ICH E3	SAC [1]
1.15.	SAF	MH4	Summary of Past Medical Conditions	ICH E3	SAC [1]
1.16.	SAF	POP_T01	Summary of Cardiovascular History/Risk Factors		SAC [1]
1.17.	SAF	SP07	Summary of Family History of Cardiovascular Risk Factors at Screening		SAC [1]
1.18.	SAF	POP_T02	Summary of Disease Duration	ICH E3	SAC [1]
1.19.	SAF	CM1	Summary of Pre-treatment COPD Medications	ICH E3	SAC [1]
1.20.	SAF	CM1	Summary of On-treatment COPD Concomitant Medications	ICH E3	SAC [1]
1.21.	SAF	SP11	Summary of On-treatment Concomitant Medications Not Given for a COPD Exacerbation	ICH E3	SAC [1]
1.22.	SAF	SP11	Summary of On-treatment Concomitant Medications Given for a COPD Exacerbation	ICH E3	SAC [1]
1.23.	SAF	CM1	Summary of Post-treatment COPD Medications	ICH E3	SAC [1]
1.24.	SAF	CM1	Summary of On-treatment BMD Concomitant Medications	ICH E3	SAC [1]
1.25.	SAF	CM1	Summary of Post-treatment BMD Medications	ICH E3	SAC [1]
1.26.	SAF	CM1	Summary of On-treatment Other Concomitant Medications	ICH E3. Other concomitant mediations are all non-BMD and non-COPD medications.	SAC [1]
1.27.	SAF	CM1	Summary of Post-treatment Other Medications	ICH E3	SAC [1]
1.28.	SAF	SU1	Summary of Smoking History at Screening		SAC [1]
1.29.	SAF		Summary of Baseline Bone Mineral Density Test Results		SAC [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Baseline Spirometry					
1.30.	SAF	SP12	Summary of Lung Function Test Results at Screening and Randomisation	Include Pre- and Post- albuterol (salbutamol) $FEV_{1,}$ FVC, FEV_1/FVC and % Predicted Normal and post-BD at screening %predicted. Page by visit. Include overall and by treatment group.	SAC [1]
Treatment Compliance					
1.31.	SAF	SP6	Summary of Treatment Compliance	ICH E3	SAC [1]

9.9.5. Study Population Figures

Study Population Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Time to Withdrawal					
2.1.	SAF	POP_F01	Kaplan-Meier Plot of Time to Premature Discontinuation from Investigational Product		SAC [1]

9.9.6. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
2.1.	SAF	EX1	Summary of Exposure to Study Treatment	ICH E3	SAC [1]
BMD at Total Hip					
2.2.	SAF	SAFE_T01	Summary of On-treatment Bone Mineral Density (g/cm^2) at the Total Hip		SAC [1]
2.3.	SAF	SAFE_T01	Summary of On-treatment Bone Mineral Density (g/cm^2) at the Total Hip by Gender		SAC [1]
2.4.	SAF	SAFE_T02	Summary of On-treatment Percentage Change in Bone Mineral Density (g/cm^2) at the Total Hip	Page by Gender	SAC [1]
2.5.	SAF	SAFE_T02	Summary of On-treatment Percentage Change in Bone Mineral Density (g/cm^2) at the Total Hip by Gender		SAC [1]
2.6.	SAF	SAFE_T03	Summary of On-treatment T and Z Scores for Bone Mineral Density at the Total Hip	Page by Gender	SAC [1]
2.7.	SAF	SAFE_T03	Summary of On-treatment T and Z Scores for Bone Mineral Density at the Total Hip by Gender		SAC [1]
2.8.	SAF	SAFE_T04	Analysis of On-treatment Percentage Change from Baseline in Bone Mineral Density (g/cm^2) at the Total Hip		SAC [1]
2.9.	SAF	SAFE_T04	Analysis of On-treatment Percentage Change from Baseline in Bone Mineral Density (g/cm^2) at the Total Hip by Gender		SAC [1]
2.10.	SAF	SAFE_T05	On-treatment Bone Mineral Density (g/cm^2) at the Total Hip Mixed Model Repeated Measures Analysis Interaction Test		SAC [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
BMD at Lumbar Spine (L1-L4)					
2.11.	SAF	SAFE_T01	Summary of On-treatment Bone Mineral Density (g/cm^2) at the Lumbar Spine		SAC [1]
2.12.	SAF	SAFE_T01	Summary of On-treatment Bone Mineral Density (g/cm^2) at the Lumbar Spine by Gender		SAC [1]
2.13.	SAF	SAFE_T02	Summary of On-treatment Percentage Change in Bone Mineral Density (g/cm^2) at the Lumbar Spine		SAC [1]
2.14.	SAF	SAFE_T02	Summary of On-treatment Percentage Change in Bone Mineral Density (g/cm^2) at the Lumbar Spine by Gender		SAC [1]
2.15.	SAF	SAFE_T03	Summary of On-treatment T and Z Scores for Bone Mineral Density at the Lumbar Spine		SAC [1]
2.16.	SAF	SAFE_T03	Summary of On-treatment T and Z Scores for Bone Mineral Density at the Lumbar Spine by Gender		SAC [1]
2.17.	SAF	SAFE_T04	Analysis of On-treatment Percentage Change from Baseline in Bone Mineral Density (g/cm^2) at the Lumbar Spine		SAC [1]
2.18.	SAF	SAFE_T04	Analysis of On-treatment Percentage Change from Baseline in Bone Mineral Density (g/cm^2) at the Lumbar Spine by Gender		SAC [1]
2.19.	SAF	SAFE_T05	On-treatment Bone Mineral Density (g/cm^2) at the Lumbar Spine Mixed Model Repeated Measures Analysis Interaction Test	Only include the interaction for gender	SAC [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs, Incidence of Fracture, Pneumonia, X-rays and COPD Exacerbations					
2.20.	SAF	VS1	Summary of Vital Signs	All variables to have a row for minimum and maximum on-treatment values along with having a row for early withdrawal.	SAC [1]
2.21.	SAF	VS1	Summary of Change from Baseline in Vital Signs	All variables to have a row for minimum and maximum on-treatment values along with having a row for early withdrawal.	SAC [1]
2.22.	SAF	SAFE_T07	Summary of On-treatment Pneumonia		SAC [1]
2.23.	SAF	SAFE_T08	Summary of On-treatment Fractures		SAC [1]
2.24.	SAF	SAFE_T09	Summary of On-treatment Moderate/Severe COPD Exacerbations		SAC [1]
2.25.	SAF	SAFE_T09	Summary of On-treatment Severe COPD Exacerbations		SAC [1]
Spirometry					
2.26.	SAF	SAFE_T10	Summary of On-treatment FEV_1 (L) at Clinic Visits		SAC [1]
2.27.	SAF	SAFE_T10	Summary of On-treatment FVC (L) at Clinic Visits		SAC [1]
Adverse Events					
2.28.	SAF		Overview of On-treatment Adverse Events During the Study		SAC [1]
2.29.	SAF	AE1	Summary of On-treatment Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from the Study by System Organ Class and Preferred Term	IDSL - Include rates.	SAC [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.30.	SAF	AE1	Summary of On-treatment Adverse Events by System Organ Class and Preferred Term	ICH E3. Include rates.	SAC [1]
2.31.	SAF	AE1	Summary of On-treatment Adverse Events by Age	IDSL. Use age ranges: 40 to ≤ 65, >65 to ≤ 74, and ≥75	SAC [1]
2.32.	SAF	AE1	Summary of On-treatment Adverse Events by Region	IDSL, North America vs Europe	SAC [1]
2.33.	SAF	AE1	Summary of On-treatment Adverse Events by Gender	IDSL	SAC [1]
2.34.	SAF	AE1	Summary of On-treatment Adverse Events by Smoking Status	IDSL	SAC [1]
2.35.	SAF	AE1	Summary of Post-treatment Adverse Events by System Organ Class and Preferred Term	ICH E3. Include rates.	SAC [1]
2.36.	SAF	AE1	Summary of On-treatment Drug-related Adverse Events by System Organ Class and Preferred Term	Include rates.	SAC [1]
2.37.	SAF	AE1	Summary of On-treatment Drug Related Adverse Events	Number and % of subjects	SAC [1]
2.38.	SAF	AE1	Summary of On-treatment Drug Related Serious Adverse Events	Number and % of subjects	SAC [1]
2.39.	SAF	AE3	Summary of Common (>=3%) On-treatment Adverse Events by Overall Frequency	ICH E3	SAC [1]
2.40.	SAF	AE15	Summary of Common (>=3%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC [1]
Serious Adverse Events					
2.41.	SAF	AE1	Summary of On-treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC [1]
2.42.	SAF	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT. Include rates.	SAC [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.43.	SAF	AE1	Summary of On-treatment Serious Adverse Events Leading to Permanent Discontinuation of Study Treatment by System Organ Class and Preferred Term	IDSL	SAC [1]
2.44.	SAF	AE16	Summary of On-treatment Fatal Serious Adverse Events by System Organ Class and Preferred Term		SAC [1]
2.45.	SAF	AE16	Summary of On-treatment Non-fatal Serious Adverse Events by System Organ Class and Preferred Term		SAC [1]
2.46.	SAF	AE16	Summary of On-treatment Drug-related Serious Adverse Events by System Organ Class and Preferred Term		SAC [1]
Adverse Events of Special Interest					
2.47.	SAF	AE1	Summary of On-treatment Adverse Events of Special Interest	Include rates.	SAC [1]
2.48.	SAF	AE1	Summary of On-treatment Serious Adverse Events of Special Interest	Include rates.	SAC [1]

9.9.7. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
BMD					
2.1.	SAF	SAFE_F01	Raw Geometric Percentage Change from Baseline in On-treatment Bone Mineral Density (g/cm^2) at the Total Hip Over Time		SAC [1]
2.2.	SAF	SAFE_F01	Raw Geometric Percentage Change from Baseline in On-treatment Bone Mineral Density (g/cm^2) at the Total Hip Over Time By Gender		SAC [1]
2.3.	SAF	SAFE_F01	Adjusted Mean Percentage Change from Baseline in On-treatment Bone Mineral Density (g/cm^2) at the Total Hip	Add -1% per year clinical non-inferiority boundary with footnote.	SAC [1]
2.4.	SAF	SAFE_F01	Adjusted Percentage Change from Baseline in On-treatment Bone Mineral Density (g/cm^2) at the Total Hip Over Time		SAC [1]
2.5.	SAF	SAFE_F01	Adjusted Percentage Change from Baseline in On-treatment Bone Mineral Density (g/cm^2) at the Total Hip Over Time by Gender		SAC [1]
2.6.	SAF	SAFE_F01	Raw Geometric Percentage Change from Baseline in On-treatment Bone Mineral Density (g/cm^2) at the Lumbar Spine Over Time		SAC [1]
2.7.	SAF	SAFE_F01	Raw Geometric Percentage Change from Baseline in On-treatment Bone Mineral Density (g/cm^2) at the Lumbar Spine Over Time by Gender		SAC [1]
2.8.	SAF	SAFE_F01	Adjusted Percentage Change per Year from Baseline in On-treatment Bone Mineral Density (g/cm^2) at the Lumbar Spine	Add -1% per year clinical non-inferiority boundary with footnote.	SAC [1]

2.9.	SAF	SAFE_F01	Adjusted Mean Percentage Change from Baseline in On-treatment Bone Mineral Density (g/cm^2) at the Lumbar Spine Over Time		SAC [1]
2.10.	SAF	SAFE_F01	Adjusted Mean Percentage Change from Baseline in On-treatment Bone Mineral Density (g/cm^2) at the Lumbar Spine Over Time by Gender		SAC [1]
Adverse Events					
2.11.	SAF	AE10	Plot of Common (>=3%) On-treatment Adverse Events and Relative Risk	IDSL	SAC [1]

9.9.8. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen and Run-in Failure	Journal Guidelines	SAC [1]
2.	SAF	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC [1]
3.	SAF	BL1	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	SAC [1]
4.	SAF	TA1	Listing of Planned and Actual Treatments	IDSL	SAC [1]
Protocol Deviations					
5.	SAF	DV2	Listing of Important Protocol Deviations	ICH E3	SAC [1]
6.	SAF	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC [1]
Populations Analysed					
7.	SAF	SP3	Listing of Subjects Excluded from the Safety Population	ICH E3. Note: Only create if this population is used.	SAC [1]
Demographic and Baseline Characteristics					
8.	SAF	DM2 / DM4	Listing of Demographic Characteristics	ICH E3	SAC [1]
9.	SAF	DM9 / DM10	Listing of Race	ICH E3	SAC [1]
Exposure and Treatment Compliance					
10.	SAF	EX3	Listing of Exposure Data	ICH E3	SAC [1]
Adverse Events					
11.	SAF	AE8	Listing of All Adverse Events	ICH E3	SAC [1]
12.	SAF	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC [1]
13.	SAF	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC [1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Serious and Other Significant Adverse Events					
14.	SAF	AE8	Listing of All Serious Adverse Events	ICH E3	SAC [1]
15.	SAF	AE8	Listing of Fatal Serious Adverse Events	ICH E3	SAC [1]
16.	SAF	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	SAC [1]
17.	SAF	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC [1]
18.	SAF	AE8	Listing of Non-Serious Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	SAC [1]
19.	SAF	AE8	Listing of Serious Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	SAC [1]
Hepatobiliary (Liver)					
20.	SAF	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	IDSL	SAC [1]
21.	SAF	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	IDSL	SAC [1]
All Laboratory					
22.	SAF	LB14	Listing of Laboratory Data	ICH E3	SAC [1]
Bone Mineral Density					
23.	SAF	SAFE_L01	Listing of Bone Mineral Density, T and Z Scores at the Total Hip		SAC [1]
24.	SAF	SAFE_L01	Listing of Bone Mineral Density, T and Z Scores at the Lumbar Spine		SAC [1]

9.9.9. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
25.	SAF	SP2	Listing of the Follow-up Contact		SAC [1]
26.	SAF	TA1	Listing of Treatment Misallocations	Change Centre ID to Investigator ID: xxxxxx and also Investigator at Centre: xxxxxx	SAC [1]
27.	SAF	SP4	Listing of Overall Percentage Treatment Compliance		SAC [1]
Adverse Events					
28.	SAF	S3	Listing of COPD Exacerbation	Include a column for severity	SAC [1]
29.	SAF	S3	Listing of Pneumonia Data, Including Chest X-Ray Finding	Include a column for severity and total events per subject	SAC [1]
30.	SAF	S3	Listing of Bone Fractures	Include a column for pre- treatment /on- treatments / Follow-up	SAC [1]
31.	SAF	ESI8	Listing of AE Terms of Special Interest	IDSL	SAC [1]

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Medical History and Concomitant Medications					
32.	SAF	MH2	Listing of Medical Conditions at Screening		SAC [1]
33.	SAF	SP5	Listing of Family History of Cardiovascular Risk Factors		SAC [1]
34.	SAF	SP6	Listing of COPD History		SAC [1]
35.	SAF	SP7	Listing of Smoking History and Smoking Status		SAC [1]
36.	SAF	CM2	Listing of COPD Concomitant Medications	Include COPD history and Exacerbation history for pre-, on- and post- treatment	SAC [1]
37.	SAF	CM2	Listing of Bone Mineral Density Medications	Include pre-, on- and post-treatments	SAC [1]
38.	SAF	CM2	Listing of Other Concomitant Medications	Include pre-, on- and post-treatments. Other concomitant mediations are all non-BMD and non-COPD medications.	SAC[1]
39.	SAF	CM6	Relationship between ATC Level 1, Ingredient and Verbatim Text for Bone Mineral Density and Other Medications		SAC [1]
Other Safety Data					
40.	SAF	VS4	Listing of All Vital Signs Data	IDSL	SAC [1]
Lung Function					
41.	SAF	SP10	Listing of Lung Function Results		SAC [1]
Liver Events: Note only produced if there is a Liver Event					
42.	SAF	VS4	Listing of Liver Events		SAC [1]
43.	SAF	VS4	Listing of Liver Event Information for RUCAM Score		SAC [1]
44.	SAF	VS4	Listing of Liver Biopsy		SAC [1]

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
45.	SAF	VS4	Listing of Liver Imaging Details		SAC [1]
Cardiovascular Events: Note only produced if there is a Cardiovascular Event					
46.	SAF	VS4	Listing of Myocardial infarction/unstable angina		SAC [1]
47.	SAF	VS4	Listing of Congestive heart failure		SAC [1]
48.	SAF	VS4	Listing of Arrhythmias		SAC [1]
49.	SAF	VS4	Listing of Valvulopathy		SAC [1]
50.	SAF	VS4	Listing of Pulmonary hypertension		SAC [1]
51.	SAF	VS4	Listing of Cerebrovascular events/stroke and transient ischemic attack		SAC [1]
52.	SAF	VS4	Listing of Peripheral arterial thromboembolism		SAC [1]
53.	SAF	VS4	Listing of Deep venous thrombosis/pulmonary embolism		SAC [1]
54.	SAF	VS4	Listing of Revascularisation		SAC [1]
55.	SAF	VS4	Listing of Deaths		SAC [1]

9.10. Appendix 13: Example Mock Shells for Data Displays

Data Display Specification will be made available on Request.