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

Title	:	Reporting and Analysis Plan for Study 201499 : A randomised, placebo-controlled, double-blind, two period crossover study to characterise the exhaled nitric oxide time profile as a biomarker of airway inflammation in adult asthma patients following repeat administration of inhaled Fluticasone Furoate (FF)/ Vilanterol (VI) 100/25 mcg
Compound Number	:	GW685698+GW642444
Effective Date	:	11-Apr-2017

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 2015N241692_00
- The planned analyses and output to be included in Clinical Pharmacology Study Report for Protocol 201499. This RAP is intended to describe the pharmacodynamic, biomarker, safety and tolerability analyses required for the study which will be provided to the study team members to convey the content of the reporting efforts, specifically Statistical Analysis Complete (SAC).

Author's Name and Functional Area:

PPD Associate Statistician (QSI)	31-Mar-2017

Approved by:

PPD Manager, Statistics	11-Apr-2017

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1. REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the RAP
Purpose	• The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol GlaxoSmithKline Document Number 2015N241692_00 • The planned analyses and output to be included in Clinical Pharmacology Study Report for Protocol 201499. This RAP is intended to describe the pharmacodynamic, biomarker, safety and tolerability analyses required for the study which will be provided to the study team members to convey the content of the reporting efforts, specifically Statistical Analysis Complete (SAC).
Protocol	• Reporting and Analysis Plan is based on original protocol (Dated: [12-JAN-2016]) for study 201499 [GlaxoSmithKline Document Number: 2015N241692_00]
Primary Objective / Endpoint	To characterise the fraction of exhaled nitric oxide (FeNO) time profile following repeat administration of fluticasone furoate/vilanterol (FF/VI) 100/25mcg combination in comparison with placebo in subjects with asthma as measured by : • Change from baseline FeNO over time following the cessation of repeat dose treatment with FF/VI.
Secondary Objective/ Endpoint	Change in FeNO over the treatment period following repeat administration of FF/VI 100/25mcg combination in comparison with placebo in subjects with asthma measured by: • Change from baseline FeNO over the FF/VI treatment period. To determine the Peak Expiratory Flow (PEF) during and following repeat administration of FF/VI 100/25mcg combination in comparison with placebo in subjects with asthma measured by: • Measurement of PEF during treatment and following cessation of repeat dose treatment with FF/VI. To determine forced expiratory volume in 1 second (FEV1) following repeat administration of FF/VI 100/25mcg combination in comparison with placebo in subjects with asthma as measured by: • Measurement of FEV1 pre-treatment and for up to 7 days after cessation of repeat dose treatment with FF/VI.

Overview	Key Elements of the RAP
Exploratory Objective / Endpoint	To investigate the effect of repeat administration of FF/VI 100/25mcg combination on exploratory biomarkers, including but not limited to, blood eosinophil levels and serum periostin levels, in comparison with placebo in subjects with asthma as measured by: • Measurement of exploratory biomarkers, including but not limited to, blood eosinophil and serum periostin levels at baseline, and at various time points after cessation of repeat dose treatment with FF/VI
Study Design	Randomised, double blind, placebo-controlled, two-period, crossover repeat dose study in adult subjects with asthma. Approximately twenty eight adult asthmatic subjects will be enrolled to ensure 24 subjects complete dosing and critical assessments for both treatment periods. Each subject will participate in two treatment periods of 14 (+ 2 days). FF/VI 100/25mcg will be received once daily (AM dosing) in one period and placebo (AM dosing) will be administered in the other period. At the end of each treatment period , there will be a monitoring period of 21 days. Following the 21 day monitoring period following treatment period 1, there may be a period of up to a further 4 weeks before the subjects start treatment period 2.
Planned Analyses	• No interim analysis is planned. • The final planned analyses will be performed after database freeze has been declared.
Analysis Population	• All Subjects Population comprise of all subjects randomised to treatment who received at least one dose of study medication • Pharmacodynamic Population comprise of all Subjects in the 'All Subjects' population who had at least one PD assessment
Hypothesis	No formal hypothesis will be tested, an estimation approach will be adopted to address the primary objective. A point estimate and corresponding 95% CI will be constructed for the treatment ratio of test treatment, μ(test) and reference treatment, μ(reference), where FF/VI 100/25mcg is the test treatment and placebo the reference treatment
Primary Analyses	FeNO, change from baseline ratio will be formally analysed following $\log_e$-transformation. A mixed effects repeated measures model will be fitted with fixed effect terms for period, treatment, day, time, (period-level baseline)*day*time interaction term, treatment*day*time interaction term, period-level baseline and subject-level baseline. Day*time interaction term will be fitted as repeated measure. FeNO will be $\log_e$-transformed prior to deriving subject-level baseline and period-level baseline.

Overview	Key Elements of the RAP
Secondary Analyses	FeNO change from baseline ratio during treatment and FEV1 will be analysed similarly to the primary FeNO endpoint. FEV1 will not be log-transformed prior to analysis. PEF will be summarised.
Safety Analyses	Safety data will be summarized
Biomarker Analyses	Exploratory endpoints of biomarkers will be summarized

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol [Dated: 12-JAN-2016].

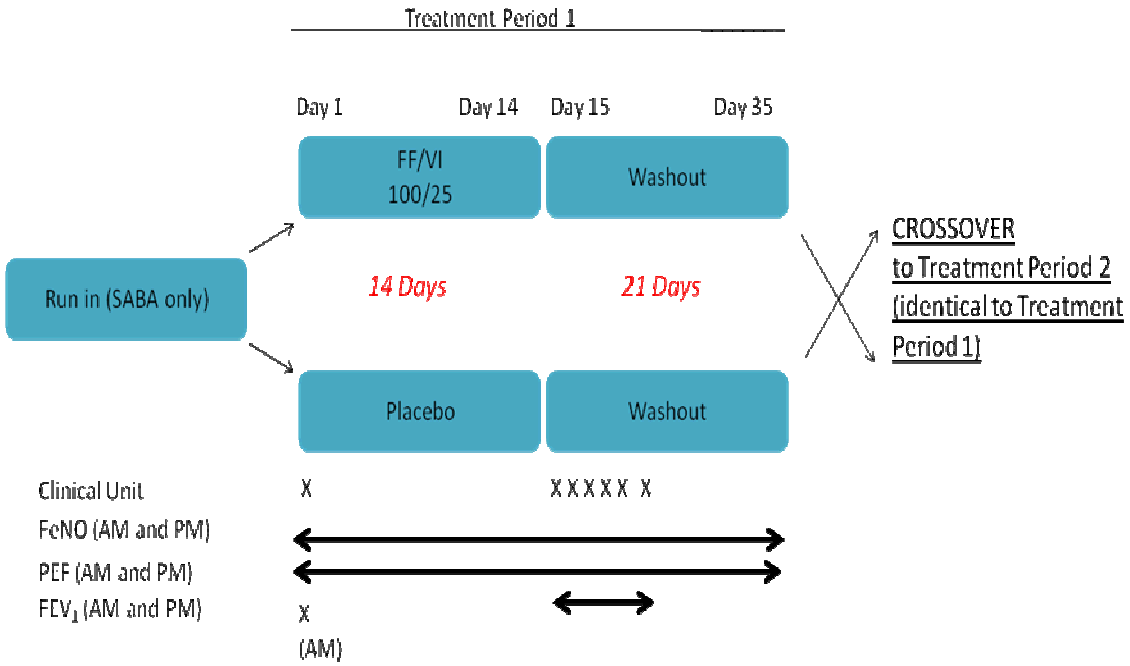
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary (Pharmacodynamic)	**Primary (Pharmacodynamic)**
To characterise the fraction of exhaled nitric oxide (FeNO) time profile following repeat administration of fluticasone furoate/vilanterol (FF/VI) 100/25mcg combination in comparison with placebo in subjects with asthma.	Change from baseline FeNO over time following the cessation of repeat dose treatment with FF/VI.
Secondary (Pharmacodynamic)	**Secondary (Pharmacodynamic)**
Change in FeNO over the treatment period following repeat administration of FF/VI 100/25mcg combination in comparison with placebo in subjects with asthma.	Change from baseline FeNO over the FF/VI treatment period
To determine the Peak Expiratory Flow (PEF) during and following repeat administration of FF/VI 100/25mcg combination in comparison with placebo in subjects with asthma.	Measurement of PEF during treatment and following cessation of repeat dose treatment with FF/VI.
To determine FEV1 following repeat administration of FF/VI 100/25mcg combination in comparison with placebo in subjects with asthma	Measurement of FEV1 pre-treatment and for up to 7 days after cessation of repeat dose treatment with FF/VI

Objectives	Endpoints
Exploratory (Biomarker)	**Exploratory (Biomarker)**
To investigate the effect of repeat administration of FF/VI 100/25mcg combination on exploratory biomarkers, including but not limited to, blood eosinophil levels and serum periostin levels, in comparison with placebo in subjects with asthma	Measurement of exploratory biomarkers, including but not limited to, blood eosinophil and serum periostin levels at baseline, and at various time points after cessation of repeat dose treatment with FF/VI

2.3. Study Design

Overview of Study Design and Key Features



Design Features	This study is a randomized, double-blind, placebo-controlled, two-period, crossover repeat dose study to characterise the exhaled nitric oxide time profile as a biomarker of airway inflammation in adult asthmatics.
Dosing	Each subject will participate in two treatment periods of 14 (+/- 2 days). FF/VI 100/25 mcg will be received once daily (AM dosing) in one period and placebo (AM dosing) will be administered in the other period. At the end of each treatment period, there will be a monitoring period of 21 days. Following the 21 day monitoring period following treatment period 1, there may be a period of up to a further 4 weeks before the subjects start treatment period 2. Total duration for each subject (from screening to follow-up) will be a minimum of 11 weeks, with a maximum of up to 21 weeks, depending on the screening period and the time period between Treatment Periods 1 and 2

Overview of Study Design and Key Features	
Treatment Assignment	Subjects will be randomized to one of two sequences AB or BA. Where, A=Placebo and B=FF/VI 100/25mcg. Subjects will be administered the first treatment in the sequence in the first period and the second treatment in the sequence in the second period.

2.4. Statistical Hypotheses

No formal hypothesis will be tested, an estimation approach will be adopted to address the primary objective. A point estimate and corresponding 95% CI will be constructed for the treatment ratio of test treatment, μ (test) and reference treatment, μ (reference), where, FF/VI 100/25mcg is the test treatment and placebo the reference treatment.

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analysis is planned.

3.2. Final Analyses

Analysis	Details
Final Analyses	The final planned analyses will be performed after all subjects have completed the study and after database freeze/unblinding. See Section 6 Section 9 for all final planned analyses for this study.

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

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

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses/Endpoint(s) Evaluated
Screened Subjects	• Comprise of all subjects who attended the screening visit	• Study Population
All Subjects Population	• Comprise of all subjects randomised to treatment who received at least one dose of study medication.	• Study Population • Biomarker • Safety
Pharmacodynamic Population	• Subjects in the 'All Subjects' population who had at least one PD assessment	• Pharmacodynamic ▪ FeNO ▪ FEV1 ▪ PEF

NOTES: Please refer to Appendix 10which details the population to be used for each display being generated.

4.1. Protocol Deviations

- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
  - Data will be reviewed by the study team prior to database release to ensure all important deviations are captured and categorised on the protocol deviations dataset.
  - The SI dataset will include all protocol deviations, the analysis dataset will include only important protocol deviations. The analysis dataset will be used for the listing and summary of important protocol deviations.
- A separate listing of all inclusion/exclusion criteria deviations will also be provided.
- The study endpoints will be reported using the populations detailed in Section 4 of this document regardless of whether the subjects deviate from the protocol.
- If there are subjects with protocol deviations that may potentially impact the PD endpoints which needs to be confirmed prior to unblinding, exploratory sensitivity analyses may be considered. It further sensitivity analyses of the data are produced, they will be detailed in the clinical study report.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

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

Table 1 Overview of Appendices

Section	Component
11.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
11.2	Appendix 2: Data Management
11.3	Appendix 3: Time and Event
11.4	Appendix 4: Treatment States and Phases
11.5	Appendix 5: Data Display Standards & Handling Conventions
11.6	Appendix 6: Derived and Transformed Data
11.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
11.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses
11.9	Appendix 9: Abbreviations & Trade Marks
11.10	Appendix 10: List of Data Displays
11.11	Appendix 11: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the "All Subjects" 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 10: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Endpoint	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Disposition for the Subject Conclusion Record	Y		
Reasons for Subject Withdrawal			Y
Screening Status and Reasons for Screen Failure	Y		Y
Subjects Enrolled by Country and Site ID	Y		
Subjects for Whom the Treatment Blind was Broken			Y
Planned and Actual Treatments			Y
Protocol Deviations			
Important Protocol Deviations	Y		Y
Subjects with Inclusion/Exclusion Criteria Deviations			Y
Populations Analysed			
Study Populations	Y		
Subjects Excluded from Any Population			Y
Demographic and Baseline Characteristics			
Demographic Characteristics	Y[1]		Y
Age Ranges	Y		
Race and Racial Combinations	Y		Y[2]
Prior and Concomitant Medications			
Current & Past Medical Conditions			Y
Concomitant Medications			Y
Exposure			
Exposure to Study Treatment	Y		Y

NOTES :

- Y = Yes display generated.

[1] Conditional Display for PD Population.
[2] Listing of race.

7. PRIMARY STATISTICAL ANALYSES

7.1. Pharmacodynamic Analyses

Statistical Analysis of Pharmacodynamic endpoints will be performed by or under the direct auspices of, Clinical Statistics, GlaxoSmithKline.

7.1.1. Overview of Planned Pharmacodynamic Analyses

The primary Pharmacodynamic analyses will be based on the "Pharmacodynamic (PD)" population, unless otherwise specified.

Table 3 provides an overview of the planned Pharmacodynamic analyses, with full details of data displays being presented in Appendix 10: List of Data Displays.

Table 3 Overview of Planned Pharmacodynamic Analyses

Endpoint	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
FeNo	Y			Y	Y			

Endpoint	Log_e transformed							
	Stats Analysis			Summary			Individual	
	T	F	L	T	F	L	F	L
FeNO	Y	Y	Y	Y			Y	Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated.
- Summary = Represents TF related to any summaries (descriptive statistics) of the observed raw data. Individual = Represents FL related to any displays of individual subject observed raw data.

7.1.1.1. Statistical Analysis of Pharmacodynamic Parameters

For the PD parameter of FeNO, the following summary statistics will be calculated and tabulated by treatment:

- **Untransformed Data :** N, n, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, SD, median, minimum, maximum
- **Log_e-transformed Data:** Geometric mean, 95% CI for the geometric mean, SD of log_e-transformed data and %CVb

7.1.2. Planned Primary Pharmacodynamic Statistical Analyses

Primary Statistical Analyses
Endpoint
• Change from baseline ratio of $\log_e$ transformed FeNO over time following the cessation of repeat dose treatment with FF/VI.
Model Specification
Endpoints will be statistically analysed using a mixed models repeated measures (MMRM) model. Terms fitted in the MMRM model will include: Fixed effect terms: Period, Treatment, Day, Time, Period-level baseline*Day*Time interaction term, Treatment*Day*Time interaction term, Period-level baseline and Subject-level baseline. Repeated: Day*Time interaction term. **Note**: FeNO will be $\log_e$-transformed prior to deriving subject-level baseline and period-level baseline.
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics will be performed for mentioned Statistical Analyses as required.
Model Results Presentation
• Point estimates and their associated 95% confidence intervals will be constructed for the difference [FF/VI 100/25mcg] – [Placebo] at each timepoint (AM and PM i.e. pre-dose & 12 hours) on each day. The point estimates and their associated 95% confidence intervals will then be back-transformed to provide point estimates and 95% confidence intervals for the ratios, [FF/VI 100/25mcg]/[Placebo] for each day and AM/PM timepoint. • Estimates of within-subject variability for FeNO will also be provided, where CVw(%) = SQRT(exp(MSE) – 1)×100 and MSE is the residual mean squared error from the model. CVw represents a pooled measure of within-subject variability across the regimens FF/VI 100/25mcg, Placebo and timepoints.

8. SECONDARY STATISTICAL ANALYSES

8.1. Pharmacodynamic Analyses

8.1.1. Overview of Planned Pharmacodynamic Analyses

The secondary Pharmacodynamic analyses will be based on the "Pharmacodynamic (PD)" population, unless otherwise specified.

Table 4 provides an overview of the planned Pharmacodynamic analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 4 Overview of Planned Pharmacodynamic Analyses

Endpoint	Absolute				Change from Baseline						
	Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	F	L	T	F	L	T	F	F	L
FeNO[1]					Y	Y	Y				
FEV1	Y			Y	Y	Y	Y	Y			
PEF	Y			Y							

NOTES:
[1] FeNO will be $\log_e$ transformed prior to analysis.

- T = Table, F = Figures, L = Listings, Y = Yes display generated.
- Summary = Represents TF related to any summaries (descriptive statistics) of the observed raw data.
  Individual = Represents FL related to any displays of individual subject observed raw data.

8.1.2. Planned Secondary Pharmacodynamic Statistical Analyses

Secondary Statistical Analyses
Endpoint
• Change from baseline ratio of $\log_e$ transformed FeNO during treatment with FF/VI.
Model Specification
Endpoints will be statistically analysed using a mixed models repeated measures (MMRM) model. Terms fitted in the MMRM model will include: Fixed effect terms: Period, Treatment, Day, Time, Period-level baseline*Day*Time interaction term, Treatment*Day*Time interaction term, Period-level baseline and Subject-level baseline. Repeated: Day*Time interaction term. **Note**: FeNO will be $\log_e$-transformed prior to deriving subject-level baseline and period-level baseline.
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics will be performed for mentioned Statistical Analyses as required.
Model Results Presentation
• Point estimates and their associated 95% confidence intervals will be constructed for the difference [FF/VI 100/25mcg] – [Placebo] at each timepoint (AM/PM i.e. pre-dose & 12 hours) on each day. • Estimates of within-subject variability for FeNO will also be provided, where CVw(%) = SQRT(exp(MSE) – 1)×100 and MSE is the residual mean squared error from the model. CVw represents a pooled measure of within-subject variability across the regimens FF/VI 100/25mcg, Placebo and timepoints.
Endpoint
• Change from baseline of FEV1 during treatment with FF/VI.

Secondary Statistical Analyses
Model Specification
Endpoints will be statistically analysed using a mixed models repeated measures (MMRM) model. Terms fitted in the MMRM model will include: Fixed effect terms: Period, Treatment, Day, Time, Period-level baseline*Day*Time interaction term, Treatment*Day*Time interaction term, Period-level baseline and Subject-level baseline. • Repeated: Day*Time interaction term.
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics will be performed for mentioned Statistical Analyses as required.
Model Results Presentation
• Point estimates and their associated 95% confidence intervals will be constructed for the difference [FF/VI 100/25mcg] – [Placebo] at each timepoint (AM/PM i.e. pre-dose & 12 hours) on each day. • Estimates of within-subject variability for FEV1 will also be provided, where CVw(%) = SQRT(exp(MSE) – 1)×100 and MSE is the residual mean squared error from the model. CVw represents a pooled measure of within-subject variability across the regimens FF/VI 100/25mcg, Placebo and timepoints.

9. OTHER STATISTICAL ANALYSES

9.1. Overview of Planned Biomarker Analyses

Blood Eosinophil and Serum Periostin levels will be listed and summarised if data is available. The biomarker displays will be based on the "All Subjects" population.

9.1.1. Overview of Planned Analyses

Table 5 provides an overview of the planned analyses, with full details of data displays being presented in Appendix 10: List of Data Displays.

Table 5 Overview of Planned Biomarker Analyses

Endpoint	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Biomarker								
Biomarker Parameters	Y		Y	Y	Y			

NOTES :
- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.

Endpoint	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L

- Individual = Represents FL related to any displays of individual subject observed raw data.

9.2. Overview of Safety Analyses

9.2.1. Overview of Planned Adverse Events Analyses

The safety analyses will be based on the "All Subjects" population, unless otherwise specified.

Table 6 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 6 Overview of Planned Adverse Event Analyses

Endpoint	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
All AEs by SOC and PT	Y		Y
Drug-Related AEs by SOC and PT	Y		
Subject Numbers for Individual AEs			Y
Relationship Between AE SOCs, PT and Verbatim Text			Y
Serious AEs by SOC and PT			Y
AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by SOC and PT	Y		Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, SOC = System Organ Class, PT = Preferred Term.
- Summary = Represents TF 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.

9.2.2. Overview of Planned Clinical Laboratory Analyses

The safety analyses will be based on the "All Subjects" population, unless otherwise specified.

Table 7 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 7 Overview of Planned Clinical Laboratory Analyses

	Summary		Individual
	T	F	L
Lab Parameters			Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated
- 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.

9.2.3. Overview of Planned Other Safety Analyses

The safety analyses will be based on the "All Subjects" population, unless otherwise specified.

Table 8 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 8 Overview of Planned Other Safety Analyses

	Summary		Individual
	T	F	L
Vital Signs by Visit			Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated.
- 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.

10. REFERENCES

GlaxoSmithKline Document Number 2015N241692_00 (Original – 12-JAN-2016):
A randomised, placebo-controlled, double-blind, two period crossover study to characterise the exhaled nitric oxide time profile as a biomarker of airway inflammation in adult asthma patients following repeat administration of inhaled Fluticasone Furoate (FF)/ Vilanterol (VI) 100/25 mcg.

11. APPENDICES

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 11.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 11.2	Appendix 2: Data Management
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Section 11.6	Appendix 6: Derived and Transformed Data • General, Study Population
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Section 11.11	Appendix 11: Example Mock Shells for Data Displays

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

As detailed in Section 4.1, Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan and a listing and summary of important Protocol Deviations will be provided. A separate listing and summary of inclusion/exclusion criteria deviations will also be produced based on the eligibility eCRF page.

A Per Protocol Population is not being defined for this study. However additional exploratory sensitivity summaries may be considered, if there are protocol deviations that may affect the primary PD endpoint analysis will be confirmed prior to unblinding. Any additional sensitivity summaries will be documented in the CSR

11.2. Appendix 2: Data Management

Data Type	Source	Format of Data	Planned Date of Final File[1]	Responsibility
Study Population	**Database**	**IDSL**	**DBF**	**CPSSO**
Safety	Database	IDSL	DBF	CPSSO
Pharmacodynamic	Database	IDSL	DBF	CPSSO
Biomarker	Database	IDSL	DBF	CPSSO

1. Provided source data is clean

11.3. Appendix 3: Time & Events

Procedure	Screening (up to 42 days prior to Day 1)	Study Day (each treatment period)						Follow-up (Days 35-42)[12]	Notes
		Day -7 (start of run-in)[1]	Day 1	Days 2-13	Days 14-19	Day 21	Day 35		
Out-patient visit to the unit	X	X	X			X	X	X	[1] Day -7 is the start of the one week run-in period and therefore this visit and the assessments on this day only apply to Treatment Period 1
Admission to the unit					X				
Informed consent	X								
Inhaler, PEF meter and FeNO device practice	X								
Inclusion and exclusion criteria/eligibility review	X	X	X						
Demography	X								
Full physical exam including height and weight	X								
Medical history (includes substance usage [and family history of premature CV disease])	X								Substances: [Drugs, Alcohol, tobacco and caffeine]
Past and current medical conditions [including cardiovascular medical history]	X								

Procedure	Screening (up to 42 days prior to Day 1)	Study Day (each treatment period)						Follow-up (Days 35-42)[12]	Notes
		Day -7 (start of run-in)[1]	Day 1	Days 2-13	Days 14-19	Day 21	Day 35		
Urine pregnancy test (WCBP)	X		X[2]			X		X	[2] Collected pre-dose
Vital signs	X								
Set up PEF and FeNO monitoring		X							
Study Treatment			X[3]		X[4]				[3] Dosing every morning; dosing in the unit on Days 1 and 14 and at home on Days 2-13 [4] Dosing on the morning of Day 14 only
Exploratory biomarker sampling[5]		X			X	X	X		[5] These measurements are taken at baseline (Day -7), at the end of treatment (Day 15), on Day 21 and on Day 35.
FEV_1 readings[6]	X		X[7]		X[8]	X[9]			[6] Measured in the unit only [7] Taken pre-dose [8] Collected AM (pre-dose on Day 14) and PM [9] Collected AM only
FeNO assessment[10]	X	←==========→							[10] Start of collection 7 days before Day 1 (Day -7), then collected every day AM and PM through to Day 35 of each treatment period.

Procedure	Screening (up to 42 days prior to Day 1)	Study Day (each treatment period)						Follow-up (Days 35-42)[12]	Notes
		Day -7 (start of run-in)[1]	Day 1	Days 2-13	Days 14-19	Day 21	Day 35		
PEF[11]		←==========→							[11] Collected AM and PM every day from Day -7 through to Day 35 for Treatment Period 1, and from Day 1 through to follow up for Treatment Period 2.
AE/SAE review		←==========→							
Concomitant medication review		←==========→							[12] Follow up visit only after Treatment period 2. The follow-up visit can be combined with the Day 35 visit for Treatment Period 2.
Issue of diary card	X					X[13]			[13] Second diary card given out on Day 21 of Treatment Period 1, to capture data for Treatment Period 2

11.4. Appendix 4: Treatment States and Phases

11.4.1. Treatment States for AE Data

Treatment State	Definition
Pre-Treatment	AE Start Date < Study Treatment Start Date
On-Treatment	If AE onset date is on or after treatment start date & on or before treatment stop date. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date [+ Lag Time]
Post-Treatment	If AE onset date is after the treatment stop date. AE Start Date > Study Treatment Stop Date
Onset Time Since 1st Dose (Days)	If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1 Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on [Inform/CRF OR value is missing].

NOTES:

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

11.5. Appendix 5: Data Display Standards & Handling Conventions

11.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	Placebo	Placebo	1
B	FF/VI 100/25 mcg	FF/VI 100/25 mcg	2

NOTES:

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

11.5.2. Baseline Definition & Derivations

11.5.2.1. Baseline Definitions

For all endpoints (expect as noted in baseline definitions) the baseline value will be the latest pre-dose assessment.

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Screening	Day -7	Day 1 (Pre-Dose)	
PD				
FeNO	X	X	X	Day 1 (Pre-dose)
FEV1	X		X	Day 1 (Pre-dose)
PEF		X	X	Day 1 (Pre-dose)
Biomarker			X	Day 1 (Pre-dose)

- Note: Baseline definitions are applicable to each period

For FeNO, FEV1 analyses:

- Subject level baseline is defined as the mean of baseline across periods for each subject.
- Period level baseline is defined as the difference between the baseline and subject level baseline for each period and each subject.

11.5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 11.5.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

11.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175-HARP PROD-UK
HARP Area	: \ARPROD\ GW685698+GW642444\mid201499\Final
QC Spreadsheet	: \ARWORK\ GW685698+GW642444\mid201499\Final\Documents
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards	
Generation of RTF Files	
• RTF files will be generated for summary displays.	

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the actual treatment 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.

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 Pharmacodynamic Parameters	
Descriptive Summary Statistics (Log Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and [between and or within] geometric coefficient of variation (CVb/w (%)) will be reported. [1] CVb (%) = √ (exp(SD2) - 1) * 100 (SD = SD of log transformed data) [2] CVw (%) = √ (exp(MSE) - 1) * 100 (MSE = mean square error from mixed effect model of loge-transformed data).
Parameters Not Being Log Transformed	FEV1
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

11.6. Appendix 6: Derived and Transformed Data

11.6.1. General

Multiple Measurements at One Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target then the mean will be taken.
Study Day

• Calculated as the number of days from randomisation date :
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Treatment start Date → Study Day = Ref Date – Treatment start Date
  • Ref Data ≥ Treatment start Date → Study Day = Ref Date – (Treatment start Date) + 1

11.6.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  o Any subject with a missing day will have this imputed as day '15'.
  o Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)^2]**

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = (Treatment Stop Date – Treatment Start Date) + 1** • Subjects who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)**

11.6.3. Pharmacodynamic

FeNO
Period level baseline
• The Period-Specific Baseline value is the pre-dose assessment collected on day 1 of each treatment period • Period level baseline is defined as the difference between the baseline and subject level baseline for each period and each subject.
Subject level baseline
• Subject level baseline is defined as the mean of baseline across periods for each subject.

Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. o Example 1: 2 Significant Digits = '< x ' becomes x – 0.01 o Example 2: 1 Significant Digit = '> x' becomes x + 0.1 o Example 3: 0 Significant Digits = '< x' becomes x – 1

11.7. Appendix 7: Premature Withdrawals & Handling of Missing Data

11.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as subject is one who has completed both treatment periods, all assessments up to Day 35 of both treatment periods, and all of the follow-up assessments. The end of the study is defined as the last subject's last visit. • Withdrawn subjects were not replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

11.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument : ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.7.2.1. Handling of Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Treatment States and Phases. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used.

Element	Reporting Detail
	• Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.

11.7.2.2. Handling of Partial Dates

Element	Reporting Detail

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

Adverse Events	• Any partial dates for adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made:
	  ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month.
	  ○ However, if these results in a date prior to Week 1 Day 1 and the event could possibly have occurred during treatment from the partial information, then the Week 1 Day 1 date will be assumed to be the start date.
	  ○ The AE will then be considered to start on-treatment (worst case).
	  ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
	• The recorded partial date will be displayed in listings.

11.7.2.3. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.8. Appendix 8: Model Checking and Diagnostics for Statistical Analyses

11.8.1. Statistical Analysis Assumptions

Endpoint(s)	• Log_e (FeNO) and FEV1
Analysis	• MMRM

- Model assumptions will be applied, but appropriate adjustments maybe made based on the data.
- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
- An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line.
  - In the event that this model fails to converge, alternative correlation structures may be considered such as CSH or CS.
  - Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
- 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.
- If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.

11.9. Appendix 9 – Abbreviations & Trade Marks

11.9.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CI	Confidence Interval
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
GUI	Guidance
MMRM	Mixed Model Repeated Measures
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
QC	Quality Control
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
GSK	GlaxoSmithKline

11.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

11.10. Appendix 10: List of Data Displays

11.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.10	-
Pharmacodynamic	2.1 to 2.8	2.1 to 2.6
Safety	3.1 to 3.3	
Biomarker	4.1 to 4.2	4.1
Section	**Listings**	
ICH Listings	1 to 18	
Other Listings	19 to 25	

11.10.2. Mock Example Shell Referencing

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

Section	Figure	Table	Listing
Study Population	N/A	POP_Tn	POP_Ln
Pharmacodynamic/Biomarker	PD_Fn	PD_Tn	PD_Ln
Safety	N/A	SAFE_Tn	SAFE_Ln

NOTES:

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

11.10.3. Deliverable [Priority]

Delivery Priority	Description
Headline [1]	Headline Results
SAC [2]	Final Statistical Analysis Complete

11.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Subjects	ES1A	Summary of Subject Disposition for the Subject Conclusion Record		Headline [1] SAC [2]
1.2.	Screened Subjects	ES6	Summary of Screening Status and Reasons for Screen Failure		SAC [2]
1.3.	Screened Subjects	NS1	Summary of Number of Subjects by Country and Site ID		SAC [2]
Protocol Deviation					
1.4.	All Subjects	DV1	Summary of Important Protocol Deviations		SAC [2]
Population Analysed					
1.5.	Screened Subjects	SP1	Summary of Study Populations		SAC [2]
Demographics					
1.6.	All Subjects	DM3	Summary of Demographic characteristics	Include BMI	Headline [1] SAC [2]
1.7.	PD	DM3	Summary of Demographic characteristics	Include BMI. Conditional Display	SAC [2]
1.8.	All Subjects	DM11	Summary of Age Ranges	Include only Adult (18-64) and (65-84) years category	SAC [2]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.9.	All Subjects	DM5	Summary of Race and Racial Combinations		SAC [2]
Exposure					
1.10.	All Subjects	EX1	Summary of Exposure Data		SAC [2]

11.10.5. Pharmacodynamic Tables

Efficacy: Tables					
No.	**Population**	**Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacodynamic Parameters					
2.1.	PD	LB1	Summary of Exhaled Nitric Oxide Data	Parameter with units, both untransformed and transformed	Headline [1] SAC [2]
2.2.	PD	LB1	Summary of Change from Baseline Exhaled Nitric Oxide Data	Parameter with units for untransformed data	SAC [2]
2.3.	PD	LB1	Summary of Ratio from Baseline Exhaled Nitric Oxide Data	Parameter with units for transformed data	Headline [1] SAC [2]
2.4.	PD	PD_T1	Summary of Repeated Measures Statistical Analysis of Ratio from Baseline Exhaled Nitric Oxide Data after cessation of repeat dose of treatment		Headline [1] SAC [2]
2.5.	PD	PD_T1	Summary of Repeated Measures Statistical Analysis of Ratio from Baseline Exhaled Nitric Oxide Data		SAC [2]
2.6.	PD	LB1	Summary of Spirometry data		SAC [2]
2.7.	PD	LB1	Summary of Change from Baseline in Spirometry data		SAC [2]
2.8.	PD	PD_T1	Summary of Repeated Measures Statistical Analysis of Change from Baseline FEV1 Data		SAC [2]

11.10.6. Pharmacodynamic Figures

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacodynamic Parameters					
2.1.	PD	PD_F1	Plot of Individual Subject of Exhaled Nitric Oxide Time-Profile after cessation of repeat dose treatment		SAC [2]
2.2.	PD	PD_F2	Plot of Adjusted Geometric Mean Exhaled Nitric Oxide Ratio from Baseline Time-Profile by Treatment	With confidence intervals taken from repeated measures analysis. Plot to present Day & AM/PM on x-axis and change from baseline ratio on y-axis. One line for each treatment.	Headline [1] SAC [2]
2.3.	PD	PD_F2	Plot of Exhaled Nitric Oxide Ratio from Baseline Treatment Ratios Against Time	With confidence interval taken from repeated measures analyses. Similar to Figure 2.02 but present treatment ratio instead of adjusted mean. Include horizontal line through 1.	SAC [2]
2.4.	PD	PD_F1	Plot of Individual Subject of FEV1 Time-Profile		SAC [2]
2.5.	PD	PD_F2	Plot of Adjusted Mean FEV1 Change from Baseline Time-Profile by Treatment	With confidence interval taken from repeated measures analysis. Present as for FeNO except present for change from baseline instead of change from baseline ratio.	SAC [2]
2.6.	PD	PD_F2	Plot of FEV1 Change from Baseline Treatment Differences Against Time	With confidence intervals taken from repeated measures analysis. Present as for FeNO except present for change from baseline instead of change from baseline ratio.	SAC [2]

11.10.7. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	All Subjects	AE1CP	Summary of Adverse Events by System Organ Class and Preferred Term		Headline [1] SAC [2]
3.2.	All Subjects	AE1CP	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term		SAC [2]
3.3.	All Subjects	AE1CP	Summary of AEs Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study		SAC [2]

11.10.8. Biomarker Tables

Biomarker Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Biomarker parameter					
4.1.	All Subjects	LB1	Summary of Biomarker Data		SAC [2]
4.2.	All Subjects	LB1	Summary of Change from Baseline Biomarker Data		SAC [2]

11.10.9. Biomarker Figures

Biomarker: Figure					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Biomarker Parameter					
4.1	PD	PD_F3	Plot of Histogram of Biomarker Data by Treatment		SAC [2]

11.10.10. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened Subjects	ES7	Listing of Reasons for Screening Failure		SAC [2]
2.	All Subjects	ES3	Listing of Reasons for Withdrawal		SAC [2]
3.	All Subjects	BL2	Listing of Subjects for Whom the Treatment Blind was Broken During the Study		SAC [2]
4.	All Subjects	TA2	Listing of Randomised and Actual Treatments		SAC [2]
Protocol Deviations					
5.	All Subjects	DV2A	Listing of all Protocol Deviations		SAC [2]
6.	All Subjects	IE4	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC [2]

ICH : Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
7.	Screened Subjects	SP3A	Listing of Subjects Excluded from Any Population		SAC [2]
Demographics					
8.	All Subjects	DM4	Listing of Demographic Characteristics		SAC [2]
9.	All Subjects	DM10	Listing of Race		SAC [2]
Prior and Concomitant Medication					
10.	All Subjects	MH2	Listing of Medical Conditions		SAC [2]
11.	All Subjects	CP_CM4	Listing of Concomitant Medications by Generic Terms		SAC [2]
Exposure					
12.	All Subjects	EX4	Listing of Exposure Data		SAC [2]
AE					
13.	All Subjects	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC [2]
14.	All Subjects	AE9CP	Listing of All Adverse Events		SAC [2]
15.	All Subjects	AE9CP	Listing of Serious Adverse Events		SAC [2]
16.	All Subjects	AE9CP	Listing of AEs Leading to Withdrawal from Study		SAC [2]
Vitals/LAB					
17.	All Subjects	VS5	Listing of Vital Signs		SAC [2]
18.	All Subjects	CP_LB6	Listing of Laboratory Data for Subjects		SAC [2]

11.10.11. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
AE					
19.	All Subjects	AE2	Listing of Relationship between System Organ Class and Verbatim Text		SAC [2]
Pharmacodynamic/Biomarker					
20.	PD	EG4	Listing of Exhaled Nitric Oxide Data		SAC [2]
21.	PD	EG4	Listing of Spirometry Data		SAC [2]
22.	PD	EG4	Listing of Biomarker Data		SAC [2]
23.	PD		Raw SAS Output from Repeated Measures Statistical Analysis of Change from Baseline RatioExhaled Nitric Oxide Data after cessation of repeat dose treatment		SAC [2]
24.	PD		Raw SAS Output from Repeated Measures Statistical Analysis of Change from Baseline RatioExhaled Nitric Oxide Data		SAC [2]
25.	PD		Raw SAS Output from Repeated Measures Statistical Analysis of Change from Baseline FEV1		SAC [2]

11.11. Appendix 11: Example Mock Shells for Data Displays

Example : PD_T1 Page 1 of 2
Protocol : 201499
Population : PD

Table 2.3

Summary of Repeated Measures Statistical Analysis of Ratio from Baseline Exhaled Nitric Oxide Data after cessation of repeat dose of treatment

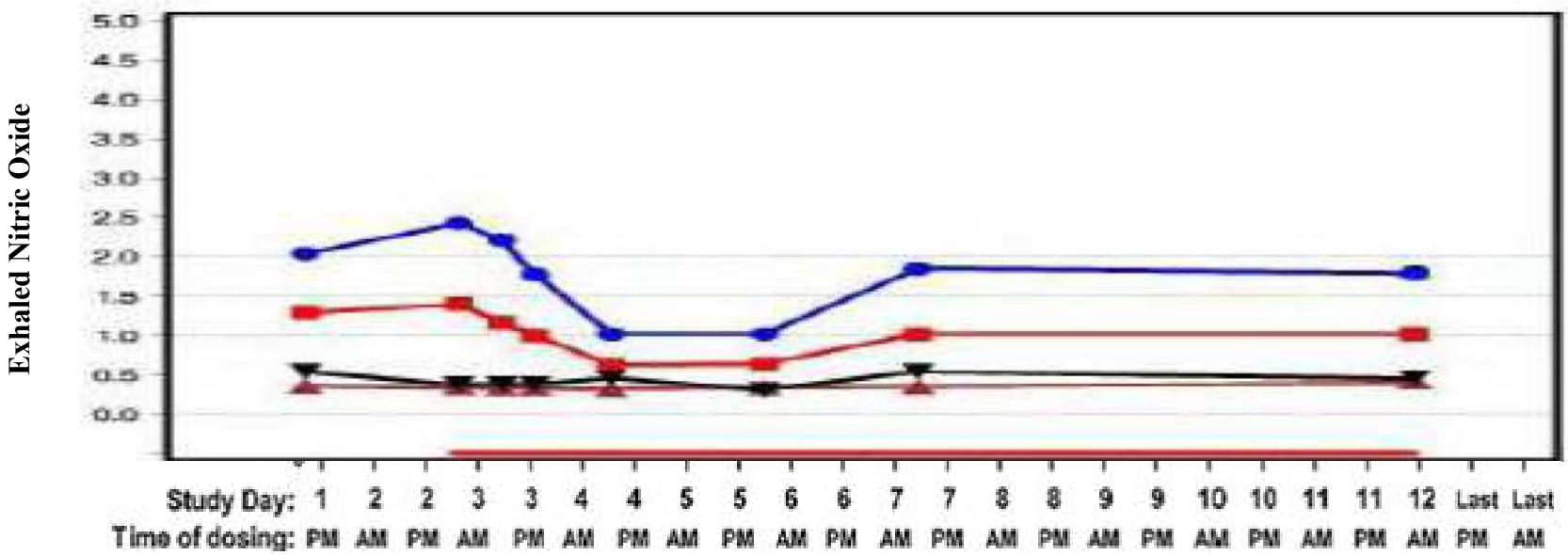
Parameter	Visit	Planned Timepoint	Comparison	Adjusted Geometric Mean				Ratio (Test/Ref)	95% Confidence Interval for Ratio	%CVw
				n	Test	n	Ref			
FeNO			Test vs Ref	x	xx.xx	x	xx.xx	x.xxxx	(x.xxxx, x.xxxx)	xx.x

Example : PD_F1 Page 1 of 1

Protocol : 201499
Population : PD

Figure 2.1.

Plot of Individual Subject of Exhaled Nitric Oxide Time-Profile after cessation of repeat dose treatment



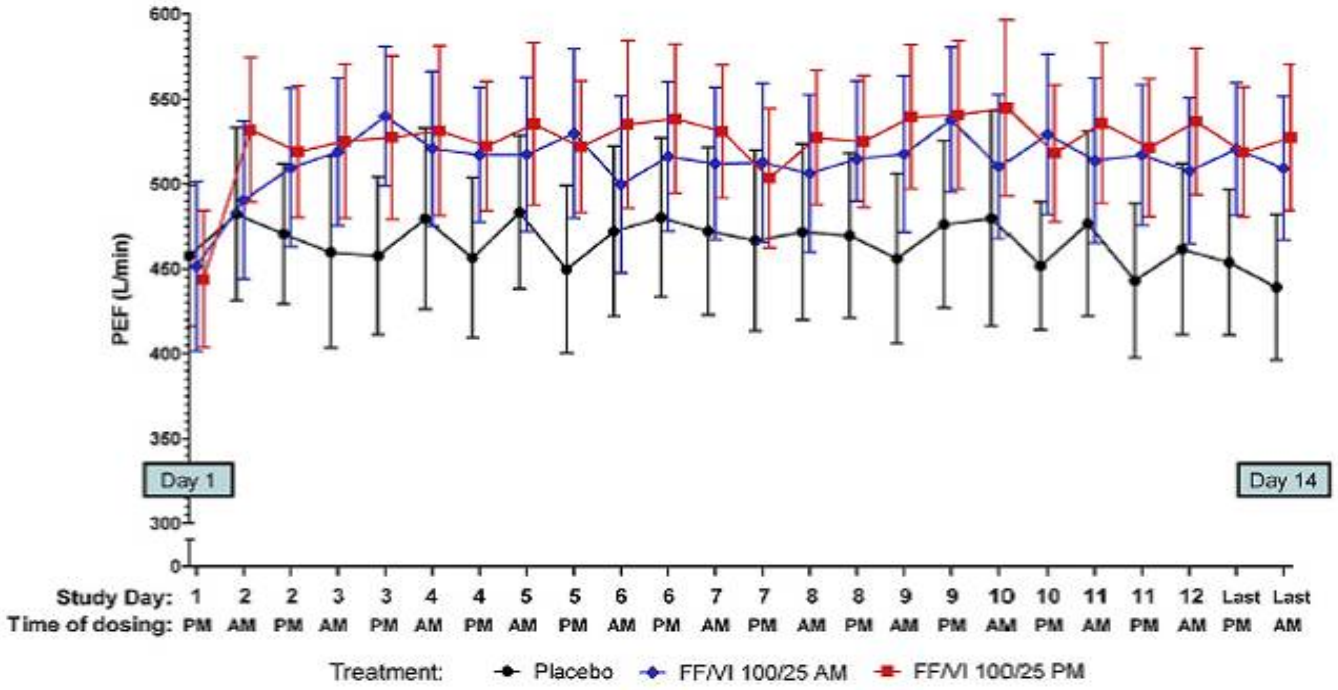
Plot to present Day & AM/PM on x-axis and PD endpoints on y-axis. One line for each treatment.

Example : PD_F2

Protocol : 201499
Population : PD

Figure 2.2

Plot of Adjusted Geometric Mean Exhaled Nitric Oxide Ratio from Baseline Time-Profile by Treatment



Plot to present Day & AM/PM on x-axis but change from baseline ratio on y-axis. One line for each treatment.

Example : PD_F3

Protocol : 201499
Population : PD

Figure 4.1

Plot of Histogram of Biomarker Data by Treatment