Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for study 203162: An escalating dose, randomized, placebo-controlled, incomplete-block, 2-period cross-over study to assess the dose response for topical efficacy via airway responsiveness to adenosine-5'-monophosphate (AMP) challenge and the dose response for systemic activity via 24h plasma cortisol suppression and thereby the relative therapeutic index for fluticasone furoate (FF), fluticasone propionate (FP) and budesonide (BUD) in asthmatic subjects.
Compound Number	:	CCI18781 ((FP), Fluticasone Propionate), GW685698 ((FF), Fluticasone Furoate) and GR160288 **(**(BUD) Budesonide)
Effective Date	:	05-FEB-2019

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 203162 (2016N281231_03).
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverables

Author(s)

Author	Date
Lead PPD Associate Statistician, RD Respiratory, Biostatistics – India	05-FEB-2019

RAP Team Review Confirmations:

(Method: E-mail)

Approver	Date
PPD Principal Clinical Research Scientist [RD PCPS CPSSO]	28- JAN -2019
PPD Clinical Development Director, RD Respiratory HUP	31- JAN -2019
PPD Statistics Leader, RD Respiratory, Biostatistics	24- JAN -2019
PPD Associate Manager - Programming, RD Respiratory, Biostatistics – India	29- JAN -2019
PPD Physician Director, RD Respiratory HUP CPDM	29- JAN -2019
PPD Senior Clinical Data Scientist, Data Management	25- JAN -2019
PPD SERM Scientist, CMO GCSP SERM	30- JAN -2019
PPD Medical Director, CMO GCSP SERM	28-JAN-2019

Clinical Statistics & Clinical Programming Line Approvals:

(Method: Pharma TMF eSignature)

Approver	Date
PPD Director, Clinical statistics, Biostatistics RD Respiratory (e-signed on behalf of PPD Senior Manager - Statistics, Biostatistics, RD Respiratory)	05-FEB-2019
PPD Senior Manager - Programming, Biostatistics, RD Respiratory	05-FEB-2019

TABLE OF CONTENTS

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 203162 (2016N281231_03):

Revision Chronology:		
2016N281231_00	29-SEP-2016	Original
2016N281231_01	16-JAN-2017	Amendment No. 1 was to clarify the dose rationale, emergency unblinding procedure, and approval of substantial amendments procedure, as requested by the Medicines and Healthcare Products Regulatory Agency (MHRA), as well as to clarify the blood sample time points and volumes and update the medical monitor contact details.
2016N281231_02	03-OCT-2017	Amendment No. 2 was to change the following: The protocol design, to allow subjects to complete either 1 or 2 treatment periods. To allow recruitment of subjects taking low- dose inhaled corticosteroids (ICS) with appropriate washout period. To allow inclusion of light smokers. Removal of the Run-in and treatment period 2 baseline visits for adenosine-5'- monophosphate (AMP) challenge. To allow the subjects to leave the unit after Day 7 evening procedures. To allow in-stream data review. Changes laid down in MEMOs to protocol amendment 1 were also incorporated into this protocol amendment.
2016N281231_03	26-APR-2018	Amendment No. 3 is being issued to update the serious adverse event (SAE) contact and processing information, the pregnancy reporting timelines, as well as to include administrative changes clarifying the screening peak expiratory flow rate (PEFR) procedure.
2016N281231_04	27-APR-2018	Applies to Germany only Amendment 3 is being issued to: • exclude enrolment of vulnerable subjects, employees and relatives of employees • clarify the informed consent process as it relates to the 2013 version of the Declaration of Helsinki • clarify the criteria for partial or complete discontinuation of the study

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were deviations to the "Analysis population" as outlined in Table 1. However, no changes were made to the originally planned statistical analysis specified in the protocol amendment 3 [(Dated: 26/APR/2018)].

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Not Defined	• Screened: All Subjects screened and for whom a record exists on the study database • Enrolled: All Subjects who are enrolled into the study (i.e. passed screening, regardless of whether they are randomized or receive treatment)	• These populations are required for Study Population displays
• PD Population	• Subjects in All Subjects population who also have at least one post dose PD measurement.	• This change is to avoid assigning a Subject to the PD population if the Subject has received one dose and withdrawn before collecting at least one post dose PD (Escalation Phase 1 FEV1/Cortisol) measurement

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To characterize the dose response and relative potency for FF, FP and BUD in the adenosine monophosphate (AMP) challenge model at 12 hours after the last dose on Day 7	• Provocative concentration (PC) of AMP causing a 20% fall in forced expiratory volume in 1 second (FEV1) (AMP PC20)
To characterize the dose response and relative potency for FF, FP and BUD on 24hour plasma cortisol suppression on treatment from pre-	• Suppression of 24 hour weighted mean plasma cortisol compared to placebo

Objectives	Endpoints
dose PM dose on Day 6 to pre-dose PM dose Day 7	
• To assess the therapeutic index for FF, FP and BUD	• ED_{20} cortisol suppression (dose at which 20% cortisol suppression is reached) /ED80 for AMP PC_{20} (dose at which 80% of the maximum AMP PC_{20} is reached)
Secondary Objectives	**Secondary Endpoints**
• Safety and tolerability	• Safety and tolerability of all treatments as assessed by adverse events (AEs), peak expiratory flow rate (PEFR), vital signs, physical examinations, laboratory assessments, and spirometry
Exploratory Objectives	**Exploratory Endpoints**
• To estimate the dose of FF and BUD that gives the same AMP response as the FP doses administered in this study.	• AMP PC_{20}
• To estimate the dose of FF and BUD that gives the same cortisol suppression as the FP doses administered in this study.	• Suppression of 24 hour weighted mean plasma cortisol compared to placebo.
• To compare the systemic metabolic bioactivity profile of FF, FP and BUD with the aim of identifying qualitative, quantitative and dose related differences in on-target and off-target steroid receptor interactions using plasma metabolomics.	• Metabolic profiling of plasma samples collected pre-dose and 12 hours after the last dose on Day 7 compared to placebo.

2.3. Study Design

Overview of Study Design and Key Features	
Design Features	• This is a randomized, placebo-controlled, incomplete-block, 2-period cross-over, 7-day escalating repeat dose study in subjects with mild asthma

Dosing	• Subjects will consent to participate in either:
	  ○ one treatment period; or
	  ○ two treatment periods, separated by a washout period of 25-42 days.
	• Subjects who are taking low-dose ICS will have a 4-week ICS washout during which their asthma symptoms must remain stable.
	• Each treatment period will comprise five consecutive 7-day dosing phases with escalating doses of one of three ICS products or placebo.
	• Each 7-day period is referred to as an escalation phase. In each 7-day escalation phase, subjects will receive study treatment from the evening of Day 1 to the evening of Day 7.
	• Blood samples for plasma cortisol will be taken on pre-dose evening of Day 6 to 24 hours later Day 7.
	• After each 7-day dose escalation phase of each treatment period an AMP challenge 12-hour post-evening dose on Day 7 will be performed.
	• Subjects who consent to completing 2 treatment periods will be assigned to one of the treatment sequences. Subjects who consent to completing 1 treatment period will be randomized to treatment.
	• A follow-up visit will take place within 7-14 days after the last dose of study treatment.

Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	For subjects who consent to completing two treatment periods each Subject will receive 2 different treatments, one in treatment period 1, and one in treatment period 2; the possible treatment sequences are pre-defined in Table 3. Two Subjects will be randomized to each of the 12 treatment sequences (Table 3). For subjects who consent to completing one treatment period: Each subject will receive one treatment, as defined in Table 4. Six Subjects will be randomized to each treatment, including placebo overall (Table 4).

Overview of Study Design and Key Features

Table 2 Doses proposed per dose escalation phase

Treatment	1st escalation phase – 7 days		2nd escalation phase – 7 days		3rd escalation phase – 7 days		4th escalation phase – 7 days		5th escalation phase – 7 days
A	FF 25 µg	→	FF 100 µg	→	FF 200 µg	→	FF 400 µg	→	FF 800 µg
B	FP 50 µg	→	FP 200 µg	→	FP 500 µg	→	FP 1000 µg	→	FP 2000 µg
C	BUD 100 µg	→	BUD 400 µg	→	BUD 800 µg	→	BUD 1600 µg	→	BUD 3200 µg
D	ELLIPTA™ Placebo	→	ELLIPTA™ Placebo	→	ELLIPTA™ Placebo	→	ELLIPTA™ Placebo	→	ELLIPTA™ Placebo
E	DISKUS™ Placebo	→	DISKUS™ Placebo	→	DISKUS™ Placebo	→	DISKUS™ Placebo	→	DISKUS™ Placebo

Twenty-Four Subjects completing 2 treatment periods will be randomized to one of the treatment sequences

Overview of Study Design and Key Features

Table 3 Sequence and number of Subjects for two period treatment allocation

Sequence	Period 1	Period 2	n
1	A	B	2
2	A	C	2
3	A	D	2
4	B	A	2
5	B	C	2
6	B	E	2
7	C	A	2
8	C	B	2
9	C	E	2
10	D	A	2
11	E	B	2
12	D	C	2
Total subjects			24
Subjects per treatment			12

Twenty-Four Subjects completing 1 treatment period will be randomized to one of the treatments

Overview of Study Design and Key Features

Table 4 Sequence and number of Subjects for single period treatment allocation

Sequence	Treatment	N
13	A	6
14	B	6
15	C	6
16	D	3
17	E	3
	Total Subjects	24
	Subjects per treatment	6

Therefore, a total of 48 Subjects will be randomized, 18 Subjects in total per study treatment (for each active treatment and for placebo combined).

Interim Analysis

- No interim analysis is planned for this study

2.4. Statistical Hypotheses / Statistical Analyses

No formal hypothesis will be tested.

The main purpose of this study is to characterize the dose response and relative potency following repeat inhaled doses of FF, FP and BUD on AMP PC_{20} at 12 hours after the last dose on Day 7 as well as to characterize the dose response and relative potency for FF, FP and BUD on 24-hour plasma cortisol suppression (pre-dose PM dose on Day 6 to pre-dose PM dose Day 7). To achieve these objectives a dose response maximum effect (Emax) model will be fitted to the AMP PC_{20} data and the cortisol suppression 0-24 hour weighted mean data. There will be no formal hypothesis tested but point estimates and corresponding 95% confidence intervals will be constructed for each of the three parameters for the Emax model (Placebo response [E_0], E_{max}, and ED_{50}).

3. PLANNED ANALYSES

3.1. Interim Analyses

In-Stream Data Review will be carried out to assess the need for a sample size re-estimation or interim analysis based on the below graphs

1. Percentage change in FEV1 vs Doubling dose for each subject and for each treatment
2. AMP PC20 vs Each Escalation phases for each subject including screening AMP PC20 data

3.2. 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 release and database freeze has been declared by Data Management.

3. All criteria for unblinding the randomization codes have been met.

4. Randomization codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened Population	• All subjects screened and for whom a record exists on the study database.	• Study Population
Enrolled Population	• All subjects who are enrolled into the study (i.e. passed screening, regardless of whether they are randomized or receive treatment)	• Study Population
All Subjects Population	• All subjects population will consist of all subjects who are randomized and who receive at least one dose of trial medication.	• Study Population • Safety
Pharmacodynamic (PD) population	• Subjects in All Subjects population who also have at least one post dose PD measurement.	• PD

1. **NOTES:**
2. Please refer to Appendix 9: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarized and listed.
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with PAREXEL's Protocol Deviation Specification, as outlined in the study Data Management Plan.
- Data will be reviewed by study team members prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorized on the protocol deviations dataset.
- The SDTM dataset will include all protocol deviations, the analysis dataset (ADAM) will include only important protocol deviations. The analysis dataset will be used for the listing and summary of important protocol deviations.
- A separate summary and 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 except those mentioned in Appendix 1.
- If there are subjects with protocol deviations that may potentially impact the PD endpoints other than those mentioned in Appendix 1, exploratory sensitivity analyses may be considered. If 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

5.1. Study Treatment & Sub-group Display pooled treatment dose Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1,2]
A	FF 25 mcg/FF 100 mcg/FF 200 mcg/FF 400 mcg/FF 800 mcg	FF	2
B	FP 50 mcg/FP 200 mcg/FP 500 mcg/FP 1000 mcg/FP 2000 mcg	FP	3
C	BUD 100 mcg/BUD 400 mcg/BUD 800 mcg/BUD 1600 mcg/BUD 3200 mcg	BUD	4
D	ELLIPTA Placebo/ELLIPTA Placebo/ELLIPTA Placebo/ELLIPTA Placebo/ELLIPTA Placebo	Placebo	1
E	DISKUS Placebo/DISKUS Placebo/DISKUS Placebo/DISKUS Placebo/DISKUS Placebo	Placebo	1

5.1.1. Study Treatment & Sub-group Display Descriptors for displays other than pooled treatment dose Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	FF 25 mcg/FF 100 mcg/FF 200 mcg/FF 400 mcg/FF 800 mcg	FF 25 mcg	6
		FF 100 mcg	7
		FF 200 mcg	8
		FF 400 mcg	9
		FF 800 mcg	10
B	FP 50 mcg/FP 200 mcg/FP 500 mcg/FP 1000 mcg/FP 2000 mcg	FP 50 mcg	11
		FP 200 mcg	12
		FP 500 mcg	13
		FP 1000 mcg	14
		FP 2000 mcg	15

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
C	BUD 100 mcg/BUD 400 mcg/BUD 800 mcg/BUD 1600 mcg/BUD 3200 mcg	BUD 100 mcg	16
		BUD 400 mcg	17
		BUD 800 mcg	18
		BUD 1600 mcg	19
		BUD 3200 mcg	20
D	ELLIPTA Placebo/ELLIPTA Placebo/ELLIPTA Placebo/ELLIPTA Placebo/ELLIPTA Placebo DISKUS Placebo/DISKUS Placebo/DISKUS Placebo/DISKUS Placebo/DISKUS Placebo	Placebo 1	1
		Placebo 2	2
E		Placebo 3	3
		Placebo 4	4
		Placebo 5	5

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.
2. For Safety and Study Population displays, the Placebo data should be pooled and reported except in exposure displays. For study pop summaries, only total column is required unless otherwise specified.

1.

In displays “Subjects” will be used to refer to “Participants”.

5.2. Baseline Definitions

For all endpoints except Cortisol Suppression the baseline value will be the latest pre-dose assessment including unscheduled visits with a non-missing value. Baseline definitions are applicable to each period except for Dose response model.

For the calculation of AMP PC_{20} the latest pre-diluent FEV1 values will be considered as the baseline for each AMP challenge.

5.3. Multicenter Studies

In this multicenter study, enrolment will be presented by country and center. All other data will be pooled in the data displays and no adjustments will be made for country or center in the analyses.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

Category	Details
Covariates	Fixed effects: AMP escalation phase, dose and Period Random effects: subject

5.5. Multiple Comparisons and Multiplicity

No formal hypothesis is being tested in this study and so no adjustments will be made for multiplicity.

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
10.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Reporting Standards for Missing Data

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population will be based on the All Subjects population, unless otherwise specified. All the study population displays will be based on planned treatment.

Study population analyses including analyses of subject disposition, protocol deviations, demographic and baseline characteristics, concomitant medications, smoking history, inclusion/exclusion criteria deviations and treatment exposure will be summarized and listed based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 9: List of Data Displays.

6.1.1. Subject Disposition

The study population summary will show the number of subjects overall who were enrolled, the number of screen failures and the number with each reason for screen failure.

The end of study record summary will show the number of subjects who complete the study in each escalation phase as well as the number who withdrew early from the study along with reasons for early withdrawal.

6.1.2. Medical Conditions

The number and percentage of subjects reporting each current medical condition will be presented. All medical conditions must be summarized in this table regardless of frequency.

This will be repeated for past medical conditions.

7. PHARMACODYNAMIC AND BIOMARKER ANALYSES

7.1. Primary Pharmacodynamic Analyses

7.1.1. Endpoint / Variables

Primary endpoints:

- Provocative concentration (PC) of AMP causing a 20% fall in forced expiratory volume in 1 second (FEV1) (AMP PC_{20}).
- Suppression of 24 hour weighted mean plasma cortisol compared to placebo.
- ED_{20} cortisol suppression (dose at which 20% cortisol suppression is reached) /ED_{80} for AMP PC_{20} (dose at which 80% of the maximum AMP PC_{20} is reached).

7.1.2. Summary Measure

- Predicted dose response for AMP $PC_{20.}$ (Emax Parameters)
- Predicted dose response for 24 hour weighted mean plasma cortisol.
- ED_{20} for cortisol suppression/ ED_{80} for AMP PC_{20} as a Therapeutic Index.

7.1.3. Population of Interest

The primary efficacy analyses will be based on the PD population and actual treatment, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

The intercurrent event is treatment discontinuation. The dose response to be predicted will be the hypothetical effect with the assumption that any subjects who withdraw would have behaved the same as those who completed. Missing data due to any intercurrent events will not be imputed; all data will be analyzed as collected.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays.

7.1.5.1. Statistical Methodology Specification

Primary Statistical Analyses

Endpoints

- Provocative Concentration of AMP causing a 20% fall in FEV_1 (AMP PC_{20}).
- Suppression of 24 hour weighted mean plasma cortisol compared to placebo.
- ED_{20} cortisol suppression (dose at which 20% cortisol suppression is reached) /ED_{80} for AMP PC_{20} (dose at which 80% of the maximum AMP PC_{20} is reached).

Model Specification

$$log_2(PC_{20})_{ij} = E_0 + I_{FF,ij} * \frac{FF\_E_{max} * Dose_{ijk}^{\gamma}}{Dose_{ijk}^{\gamma} + FF\_ED\ 50^{\gamma}} + I_{FP,ij} * \frac{FP\_E_{max} * Dose_{ijk}^{\gamma}}{Dose_{ijk}^{\gamma} + FP\_ED\ 50^{\gamma}}$$

$$+I_{BUD,ij} * \frac{BUD\ \_E_{max} * Dose_{ijk}^{\gamma}}{Dose_{ijk}^{\gamma} + BUD\_ED\ 50^{\gamma}} + s_i + \varepsilon_{ijk}$$

where:

$I_{FF,ij}$,$I_{FP,ij}$ and $I_{BUD,ij}$ are indicator functions that take the value 1 if the i^{th} subject in the j^{th} period was associated study drug and its corresponding screening and zero otherwise.

E_0 = Response at dose 0 (Placebo response)
FF_E_{max} = Maximum effect for FF treatment
FF_ED_{50} = Dose at which 50% of the maximum effect is reached for FF treatment
FP_E_{max} = Maximum effect for FP treatment
FP_ED_{50} = Dose at which 50% of the maximum effect is reached for FP treatment
BUD_Emax = Maximum effect for BUD treatment
BUD_ED_{50} = Dose at which 50% of the maximum effect is reached for BUD treatment
i= Subject (i=1 to N), j= Period (j=1 to 2), k= Escalation phase within j^{th} period (k=1 to 5),

Primary Statistical Analyses

$Dose_{ijk}$ = Dose received by i^{th} subject in the j^{th} period and k^{th} escalation phase (if this corresponds to Placebo or screening (Pre-dose) then set Dose to zero).
γ= Slope constant (fixed as 1, converting four parameter model to three parameter Emax model)
s_i = Subject effect
ε_{ijk} = Residual error

Starting values for the iterations will be chosen based on the observed data as appropriate. For example:

E_0: Mean in placebo response (AMP PC20/Cortisol Suppression) or Screening/Pre-dose response based on the model we are fitting.
E_{max}: Mean of difference between the response from Maximum dose and E_0
ED_{50}= Median dose of each ICS.

σ_b^2: Between Subject variability: Estimate of between-subject variance from MMRM fitted with the random intercept model for the interested parameter (log_2 AMP PC20) with Treatment (FF, FP and BUD), Escalation phase and period as a fixed effect and subject as a random effect. The assumption for covariance structure to be used in the model will be CS where subjects are nested within period.

σ_w^2 Within Subject variability: Estimate of within-subject variance from MMRM fitted with the random intercept model for the interested parameter (log_2 AMP PC20) with Treatment (FF, FP and BUD), Escalation phase and period as a fixed effect and subject as a random effect. The assumption for covariance structure to be used in the model will be CS where subjects are nested within period.

In case of convergence issues in the dose response model, alternative starting values for the model parameters (E_0, ED_{50}, E_{max}, σ_b^2 and σ_w^2) will be considered. If appropriate, a grid of values will be used as initial values for the model and variance parameters.

The slope (hill) parameter gamma will be assumed to be 1 (i.e. if necessary to fit three parameter E_{max} model to each treatment, but four parameter E_{max} formulae are presented as gamma may be fitted as an additional model parameter as part of sensitivity analyses and will be detailed in the clinical study report). The subject term will be fitted as a random effect. This is equivalent to adding a random coefficient to the E_0 parameter. All other terms (except the residual error) in the model will be fitted as fixed effects.

The model initially will be fitted with three different E_{max} parameters (ie one for each ICS). If the estimated E_{max} values are appear similar, then the model will be re-fitted with a single E_{max} parameter.

Primary Statistical Analyses

RM-ANOVA Model:

Prior to dose response analysis, the AMP challenge/Cortisol suppression results for placebo across the five dose escalation phases will be investigated using RM-ANOVA model. If there appears to be an effect of repeated AMP challenge on placebo (e.g. a linear trend through time, or evidence contradicting the assumption that each of the placebo responses in the five escalation phases are the same) then the dose response modelling may be performed on an adjusted version of the dataset.

If an adjustment is deemed necessary, then the difference in adjusted means (relative to escalation phase one) would be derived for escalation phases two to five (and back transformed if necessary). Then, each point estimate for a mean difference would be subtracted from the individual subject response values of the corresponding escalation phase. The resulting dataset would be used to arrive the initial value of E_0 for the dose response modelling process.

The log transformed (base 2) AMP PC_{20} Placebo data (the data from both types of placebo device will be combined) across the five dose escalation phases will also be analyzed by fitting RM-ANOVA model with AMP escalation phase as fixed categorical effect and subject fitted as a random effect and escalation phase as repeated with the CS covariance structure. Visual examination of the data in conjunction with the Type III p-value for the main effect of AMP escalation phase (testing the underlying global hypothesis that the set of mean responses from all escalation phases are the same) will be used to determine whether the data provide evidence that an adjustment to the dataset is necessary before performing the dose response modelling. As a non-binding rule of thumb p-value < 0.1 would be considered potentially relevant but a clinically relevant change/trends could also be sufficient justification for an adjustment.

A separate model will be constructed considering summary of screening values as E_0 with all the parameters are same to dose response model above. Doubling dose difference will be calculated based on the model and will be reported as separate summary.

Plasma Cortisol

A similar dose response Emax model as mentioned for the AMP PC_{20} data will be constructed to characterize the dose response of FF, FP and BUD on cortisol suppression 0-24 hours weighted mean (ng/mL) after Day 6 dose with the pre-dose measurement on day 1 values as an extra covariate in the analysis to adjust for baseline variability. The cortisol 0-24 hours weighted mean will be log-transformed using natural logs (i.e. base e).

Therapeutic Index(TI)

Emax model as described above will also be used to obtain the ED_{20} (0-24 hr.) weighted mean cortisol suppression and the ED_{80} for AMP PC20. The TI is then calculated as ratio of ED20 cortisol suppression / ED80 for AMP PC20.

ED_{20} will be estimated for FF, FP and BUD $\log_e$ (cortisol suppression) by using estimated ED_{50} of respective ICS.

Primary Statistical Analyses
$ED_{20} = ED_{50} * (0.2/0.8)$ ED_{80} will be estimated for FF, FP and BUD $\log_2$(AMP PC_{20}) by using estimated ED_{50} of respective ICS. $ED_{80} = ED_{50} * (0.8/0.2)$ As an additional exploratory analysis, the therapeutic index will be computed as the ratio of ED50 cortisol suppression / ED50 AMP PC20.
Model Checking & Diagnostics
The model fit will be explored graphically, including a scatter plot of the log2 AMP PC20/cortisol Suppression values (y-axis) against dose (x-axis), with the predicted value for each dose from the model superimposed on the plot.
Model Results Presentation
The predicted value for each of the doses will be calculated and back transformed to the original scale. The 95% confidence interval for each of the predicted values of each of the doses will also be calculated and back transformed. Both the predicted values and the 95% confidence intervals will be produced using the ESTIMATE statement in the SAS procedure NLMIXED. The predicted value for the 3 parameters of interest (E_0, E_{max} and ED_{50}) for each of the treatments will be calculated and back transformed to the original scale. The 95% confidence interval for predicted values of each of the parameters will also be calculated and back transformed. Estimates and 95% confidence intervals for the doubling dose differences from placebo (i.e. treatment difference on the log (base 2) scale) from the model will also be presented for each active dose in original scale. Predicted AMP PC_{20} values and 95% confidence intervals will be plotted against dose for each of the active treatments. The potency of FF and BUD relative to FP will be assessed by comparing the estimates for ED_{50}. For the placebo data RM-ANOVA model, the point estimates and the 95% CI will be produced at each escalation phases in original scale. The cortisol 0-24 hours weighted mean will be log-transformed using natural logs (i.e. base e). Similar model as that for AMP PC_{20} will be used for this cortisol suppression as well. The back transformed Predicted Estimates and 95% confidence intervals will be plotted against dose for each of the active treatments. The estimates of ED_{20} (0-24 hr.) weighted mean cortisol suppression and the ED_{80} for AMP PC20 and corresponding Therapeutic Index(TI) will be presented for each of the ICS. For each of the AMP challenges, the concentrations of AMP (including saline) and corresponding FEV1 measurements after each of the AMP inhalations will be listed. The inhalation time and value of the FEV1 measurements and the percentage fall of the maximum of the two FEV1 measurements from the latest highest saline FEV1 will also be included in the listing.

Primary Statistical Analyses
A separate listing will be produced containing the latest highest pre-saline of first diluent and the latest highest post saline FEV1 measurements at each challenge. The percentage change between post-saline and pre-saline will be presented (with the pre-saline measurement as the denominator) and a column will be included in the listing detailing if there is a fall of greater than 10%. Lung function data collected for assessment of inclusion/exclusion criteria (i.e. Screening), pre-dose on Day 1 and at follow up, including any unscheduled assessments, will be listed. Individual subject plots of the AMP dose response curve will be generated. In these plots, the percentage change in FEV1 (y-axis) will be plotted against the dose of AMP (x-axis). One set of plots will contain one graph per subject, per treatment. On each of these graphs, data points from the same treatment group will be joined. For each of the AMP challenges, the AMP PC_{20} will be calculated as described in Section 10.6.3. This calculated PC20 will be listed alongside the date and start time of the challenge. The time deviation between the start time of AMP challenge in screening and actual start time of each AMP challenge during the treatment phase of the study will be calculated (post screening AMP challenge start time – Screening AMP challenge start time) and presented in this listing. Imputed PC_{20} values (e.g. when the FEV1 did not fall by 20% when the highest AMP concentration (320 mg/mL) was administered) will be flagged. The following summary statistics will be presented for the calculated PC_{20} for each treatment group and challenge: median, minimum, maximum, arithmetic mean, standard deviation, coefficient of variation, geometric mean, 95% confidence interval for the geometric mean and standard deviation of the logarithmically transformed data.

7.2. Exploratory Pharmacodynamic and Biomarker Analyses

7.2.1. Endpoint / Variables

Exploratory Endpoints:

- AMP PC_{20}
- Suppression of 24 hour weighted mean plasma cortisol compared to placebo.
- Metabolic profiling of plasma samples collected pre-dose and 12 hours after the last dose on Day 7 compared to placebo

7.2.2. Summary Measure

- Predicted dose of FF and BUD for AMP PC_{20}.
- Predicted dose of FF and BUD for 24 hour weighted mean plasma cortisol.
- Metabolic profiling sample analysis, data and statistical analysis and reporting will be conducted according to a separate analysis plan written and executed by Metabolon Inc, 617 Davis Drive, Suite 100, Morrisville, NC 27560.

7.2.3. Population of Interest

The exploratory efficacy analyses will be based on the PD population and actual treatment, unless otherwise specified.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

The intercurrent event is treatment discontinuation. The dose response to be predicted will be the hypothetical effect with the assumption that if all subjects who withdraw would have behaved the same as those who completed. Missing data due to any intercurrent events will not be imputed; all data will be analyzed as collected.

7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays

As described in the Section 7.1.5.1 the E_{max} model will also be used to address the exploratory endpoint to assess the dose of FF and BUD that gives the same AMP/Cortisol suppression response as the FP doses administered in the study.

The FF and BUD doses which can give the same predicted responses as the FP doses will be estimated from the model by using estimated E_0, ED_{50}, E_{max}, and predicted response of FP doses based on the below formula

$$\text{Dose to be estimated FF/ BUD} = \frac{((Y_X - E_0)}{Emax - (Y_X - E_0)} * ED50$$

where Y_X = Predicted response of FP

The estimates for the predicted values will be presented as a separate summary in log scale.

8. SAFETY ANALYSES

The safety analyses will be based on the All subjects' population and actual treatment, unless otherwise specified.

8.1. Adverse Events Analyses

On-treatment Adverse event analyses including the analysis of adverse events (AEs), Serious adverse events (SAEs) will be based on templates provided for the study. Pre- treatment and post-treatment AEs will be listed as per the GSK IDSL core standards. The details of the planned displays are provided in Appendix 9: List of Data Displays.

8.2. Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of adverse event of special interest (AESI) event for FF, FP and BUD as per the details are provided in Section 10.6.4. The details of the planned displays are provided in Appendix 9: List of Data Displays.

8.3. Clinical Laboratory

Laboratory evaluations of Chemistry laboratory tests and Hematology laboratory tests will be listed based on IDSL core standards. The details of the planned displays are provided in Appendix 9: List of Data Displays.

8.4. Other Safety Analyses

The non-laboratory safety test results such as Peak Expiratory Flow rate (PEFR) will be summarized and listed. Vital signs and ECG values will only be listed based on templates provided for the study. The details of the planned displays are presented in Appendix 9: List of Data Displays.

9. REFERENCES

GlaxoSmithKline Document Number 2016N281231_03 Study ID 203162. An escalating dose, randomized, placebo-controlled, incomplete block, 2 period cross-over study to assess the dose response for topical efficacy via airway responsiveness to adenosine-5' monophosphate (AMP) challenge and the dose response for systemic activity via 24 h plasma cortisol suppression and thereby the relative therapeutic index for fluticasone furoate (FF), fluticasone propionate (FP) and budesonide (BUD) in asthmatic subjects. Report date (26-APR-2018).

10. APPENDICES

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

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with PAREXEL's Protocol Deviation Specification, as outlined in the study Data 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.

A Per Protocol Population is not being defined for this study but exclusions to PD population as follows

1. If any escalated dose given prior to AMP collection of previous escalation phase then, previous escalation phase information will be excluded from the analysis.
2. If dose was not escalated as planned for the complete duration of each of escalation phase then, that corresponding escalation phase information should be excluded from the analysis.

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Events

Table 5 Screening and Follow-up Visit

Procedure	Screening Visit 1	Screening Visit 2	Treatment Period 1	Washout[d]	Treatment Period 2[d]	FU
Day	Day -42 to Day -4[b]	Day -14 to Day -4[c]	Assessments during treatment period are detailed in Table 6	Washout will be a minimum of 25 days to maximum of 42 days	Assessments during treatment period are detailed in Table 6	7 to 14 days[g]
Outpatient visit	X	X				X
Informed consent[a]	X					
Inclusion and exclusion criteria	X	X				
Demography	X					
Full physical examination including height and weight	X					
Urine drugs of abuse and alcohol breath test	X					
Brief physical						X
Medical history (includes substance usage)	X					
Urine pregnancy test (all female subjects)	X					X
HIV, Hep B and Hep C screen	X					
Safety labs: chemistry, hematology and urinalysis	X					X
12-lead ECG	X					
Vital signs	X					
Peak expiratory flow rate	X[b]	X[b]				
AMP challenge		X[f]				
Spirometry (FEV1 and FVC)	X	X				X
AE/SAE[e]	X	X				X
Concomitant medication	X	X				X

AE – Adverse event; AMP- Adenosine 5 monophosphate; ECG – Electrocardiogram; FEV1 – Forced expiratory volume in 1 second; FVC – Forced vital capacity; FU – Follow-up; HIV- Human immunodeficiency virus; Hep B –Hepatitis B; Hep C – Hepatitis C; SAE – Serious adverse event;

[a] Informed consent may be obtained on a separate visit prior to screening visit 1.

[b] Subjects who are receiving low-dose ICS may take part after a 4-week washout. For these subjects, screening visit 2 will be at least 28 days after screening visit 1. During the 4-week ICS washout subjects will keep a diary (from screening visit 1 to randomization) to record twice daily peak expiratory flow (subject to contact site if there is a 20% decrease) and SABA use (subject to contact site if SABA intake is increased). Salbutamol will be dispensed for rescue use.

[c] Subjects who do not require an ICS washout may have only one screening visit, these procedures may then be done at screening visit 1. Screening visit 1 procedures may be repeated

at screening visit 2 as deemed necessary by the Investigator or delegate.

[d] Subjects who consent to only 1 treatment period will not undergo the washout period or treatment period 2.

[e] AEs and concomitant medication will be documented on all days throughout the study, but review will only occur when the subject is in the unit.

[f] The screening visit 2 AMP challenge can be repeated only once; at least 72h after the first attempt.

[g] 7 to 14 days after the last dose of study treatment.

Table 6 Time and Events Treatment Period 1 and 2

	Treatment period 1 and 2								
	Day 1, pre-Dose[a]	**Day 1 dosing and post-dose, Days 8, 15, 22, 29**	**Days 2, 9, 16, 23, 30**	**Days 3, 10, 17, 24, 31**	**Days 4, 11, 18, 25, 32**	**Days 5, 12, 19, 26, 33**	**Days 6, 13, 20, 27, 34**	**Days 7, 14, 21, 28, 35**	**Day 36[b]**
Study treatment dispensing	X	X						X	
Outpatient visitd	X	X							
Confinemente							X	X	
Randomizationf	X								
Urine pregnancy test (all female subjects)	X	X							X
Vital signsg	X								X
Use of inhaler trainingh	X								
Peak expiratory flow ratei		X	X	X	X	X	X	X	
Study Treatmentj		X	X	X	X	X	X	X	
Patient diaryk		X	X	X	X	X	X	X	
AMP challengel		X							X
Spirometry (FEV1 and FVC)	X								
Blood sampling for plasma cortisolm	X						X	X	
Metabolomics samplen	X	X							X
AE/SAEo	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X

AE – Adverse event; AMP- Adenosine monophosphate; FEV_1 – Forced expiratory volume in 1 second; FVC – Forced vital capacity; SAE – Serious adverse event.

[a] Day 1 pre-dose completed at start of treatment period 1 and 2, respectively. Urine pregnancy test (where applicable), Vital signs, Spirometry (FEV_1 and FVC), blood sampling for plasma cortisol, metabolomics sample, AE/SAE review, restriction checks and concomitant medication review will be performed on the morning of Day 1 (Pre-dose) of each treatment period. Use of inhaler training, randomization (treatment period 1 only), AE/SAE review, restriction checks, concomitant medication review and study treatment dispensing will be performed in the evening of Day 1, prior to study treatment administration.

[b] Day 36 completed following completion of treatment period 1 and 2, respectively.

[c] Subjects are dispensed study treatments for the first dose level on Day 1 prior to evening dose. Study treatments for the subsequent 4 dose levels are dispensed prior to release after completion of the AMP challenge on Days 8, 15, 22, and 29.

[d] Subjects receive first dose for treatment Period 1 and 2 during the outpatient visit.

[e] Subject will be admitted to unit prior to evening dose on Days 6, 13, 20, 27 and 34 of each treatment period. Subjects will be confined in the unit until they have recovered from the AMP challenge on Days 8, 15, 22, 29, and 36, but may leave the unit on the evenings of Days 7, 14, 21, 28, and 35 after their last plasma cortisol sample and return the following morning, if they prefer.

[f] Prior to first dose of treatment period 1 only.

[g] Performed on Days 1 and 36.

[h] Reinforcement by the investigator on the proper use of the inhaler.

[i] Peak expiratory flow reading must be taken before each dose of study treatment at home. Three PEFR manoeuvres should be performed in each session. The highest PEFR of the 3 efforts from any session will be the one that will be recorded in a paper diary.

[j] Subjects will take doses of study treatment in the evening only (for all ELLIPTA FF/placebo doses, and the first escalation phase for FP [50 mcg dose] and BUD [100 mcg dose]) or in the morning and evening, 12 hours apart (for all other dose regimens). There will be no dosing in the mornings of Days 1, 8, 15, 22 and 29. When subjects are not at the unit, they will take their study treatments at home.

[k] On Days 1, 8, 15, 22, and 29, subjects will receive a patient diary to document day and time of each dose, the peak expiratory flow rate (PEFR) recording and any AEs or concomitant medication including the number of SABA doses. The subject will enter their data in a paper diary.

[l] The AMP challenges will be done in the morning of Days 8, 15, 22, 29, 36 and 12 hours after the preceding evening dose. If subjects cannot perform the AMP challenge, this may be rescheduled 1-3 days later, in this case; the subjects will continue dosing at the same level until the rescheduled AMP challenge and the study schedule will be shifted.

[m] Blood samples for plasma cortisol will be taken on Day 1 pre-dose (baseline) and at the following time points related to evening study drug administration on Days 6, 13, 20, 27, 34: pre-dose and at 1, 2, 3, 5, 10, 12 (before morning dose), 14, 16, 18 and 24 hours post-dose.

[n] The plasma metabolomics will be taken on Day 1 pre-dose (baseline) and on Days 8, 15, 22, 29 and 36, at the end of each dose escalation phase, at 12 hour after the last evening dose (before AMP challenge procedure).

[o] AEs and concomitant medication will be documented on all days throughout the study, but review will only occur when the subject is in the unit.

10.3. Appendix 3: Assessment Windows

10.3.1. Definitions of Assessment Windows for Analyses

In general, data collected at unscheduled time points will not be used to calculate any of the derived parameters. The exception to this is

1. In the assessment of the highest post-saline FEV1 to be used in the calculation of AMP PC_{20}. Where the saline control has been inhaled more than once yielding unscheduled baseline assessments, the FEV1 measurements at 60 and 180 seconds after the last administration of the saline control will be used to ascertain the highest post-saline FEV1.
2. If AMP PC20 collection gets postponed and it is captured as an unscheduled visit, then the unscheduled visit will be considered instead of the planned visit only for that Escalation phase.

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

10.4.1. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of the study treatment.

10.4.2. Treatment States for AE Data

Treatment State	Definition
Pre-Treatment	AE Start Date < Study Treatment Start Date
On-Treatment	AE onset date is on or after treatment start date & on or before treatment stop date plus 7 days. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date +7 days
Post-Treatment	AE onset date is after the treatment stop date plus 7 days. AE Start Date > Study Treatment Stop Date +7 days
Onset Time Since 1st Dose (Days)	Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date 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 On-Treatment.

10.4.2.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 28 days prior to screening visit
Concomitant	Any medication that is not a prior

NOTES:
• Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

10.4.3. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date plus 7 days • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date +7 days. • If AE onset is during first period and worsens during a second period, it would be counted in both periods. For the first period the logic would be as above. For the second period the logic would use the treatment dates associated with the second period: • Treatment Period Start Date ≤ AE Worsening Date ≤ Study Treatment Stop Date +7 days.

NOTES:

- If the study treatment stop date is missing and the AE onset date is on or after study treatment start date, then the AE will be considered as On-Treatment.

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Compound	: /arenv/arprod/gw685698/mid203162/final_05
Analysis Datasets	
• Analysis datasets will be created according CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.0).	
Generation of RTF Files	
• RTF files will be generated.	

10.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • 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 listings.

Unscheduled Visits	
• Unscheduled visits will not be included in summary tables and/or figures unless there is no AMP PC20 and cortisol suppression postponement visit as scheduled unless it is captured as unscheduled visit. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principles 7.01 to 7.13.	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Multiple Measurements at One Analysis Time Point
• For post-saline FEV1 and FEV1 measurement after the dose of AMP, the higher of the two measurements will be used for the summary.
Study Day

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

10.6.2. Study Population

Demographics
Age

• GSK standard 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'.
• Age will be calculated based on screening visit date.

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 = Escalation Phase Stop Date – (Escalation phase Start Date) + 1** • Subjects who were randomized but did not report a treatment start date will be categorized as having zero days of exposure. • Total daily dose will be based on the formula: **Total daily dose = the cumulative actual dose divided by the duration of exposure** F For dose escalation phases with twice-daily dosing (AM and PM) but only a single dose (PM) on the first day (AMP collection day) of the phase, that day will count as only 0.5 days in the calculation of duration of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of all Total Daily Dose during each Escalation Phase** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

10.6.3. Pharmacodynamic derivation

AMP PC_{20}

For each concentration of AMP, the percentage change in FEV_1 will be calculated using the following formula:

$$\%change = \frac{highest\ FEV_1(post\ AMP) - highest\ FEV_1\ (post\ saline)}{highest\ FEV_1(post\ saline)} \times 100$$

For each concentration of AMP, the percentage fall in FEV_1 will be calculated using the following formula:

$$\%fall = \frac{highest\ FEV_1(post\ saline) - highest\ FEV_1\ (post\ AMP)}{highest\ FEV_1(post\ saline)} \times 100$$

where:

i. highest FEV_1 (post saline) = the highest value of two FEV_1 measurements at 60 and 180 secs after the saline control

ii. highest FEV_1 (post AMP) = the highest value of the two FEV_1 measurements at 60 and 180 secs after the dose of AMP

The PC_{20} is then obtained by linear interpolation (on the log 2 concentration scale) between the lowest concentration of AMP that caused ≥20% fall from baseline (C_2) and the preceding concentration (C_1).

The formula is:

$$PC_{20} = anti\log\left\{\log C_1 + \frac{(\log C_2 - \log C_1)(20 - R_1)}{(R_2 - R_1)}\right\}$$

where:

i. C_1 = preceding concentration to C_2

ii. C_2 = lowest concentration of AMP that caused a fall of ≥20% from baseline

iii. R_1 = % fall in FEV_1 after C_1

iv. R_2 = % fall in FEV_1 after C_2

If a fall in FEV_1 of at least 20% is observed after inhalation of the first AMP concentration, the PC_{20} cannot be calculated using interpolation on the log 2 scale. In this case, PC_{20} will be calculated by linear interpolation on the original scale between 0 and the first AMP concentration inhaled. The formula is:

AMP PC_{20}

$$PC_{20} = \frac{20C_2}{R_2}$$

where:

i. C_2 = first AMP concentration inhaled

ii. R_2 = % fall in FEV_1 after C_2

In some instances, the FEV_1 may not fall by at least 20% from baseline for any of the AMP concentrations administered. This could occur when the maximum concentration of AMP (320 mg/mL) does not lead to a fall of a least 20% (e.g. if treatment provides protection to AMP at the highest concentration), or if the challenge was halted prematurely (e.g. if the site incorrectly calculated the percentage fall during the challenge). If the FEV_1 has not fallen by at least 20% the PC_{20} will be imputed by linear extrapolation (on the log 2 concentration scale) using the previous two AMP concentrations unless:

1. The highest FEV_1 at the last AMP concentration inhaled represents an increase or no change in FEV_1 from the previous AMP concentration inhaled.
2. The PC_{20} calculated by linear extrapolation is more than two times the last AMP concentration inhaled.

The formula for linear extrapolation is:

$$PC_{20} = anti\log\left\{\log C_3 + \frac{(\log C_4 - \log C_3)(20 - R_3)}{(R_4 - R_3)}\right\}$$

where:

i. C_3 = penultimate concentration of AMP inhaled

ii. C_4 = last concentration of AMP inhaled

iii. R_3 = % fall in FEV_1 after C_3

iv. R_4 = % fall in FEV_1 after C_4

In the case of condition 1 or 2, the following imputation of AMP PC_{20} will be made:

- If the last AMP concentration inhaled is the highest AMP concentration (i.e. 320 mg/mL) then the PC_{20} will be set to 320 mg/mL.
- If the last AMP concentration inhaled is not the highest AMP concentration (i.e. is less than 320 mg/mL) and the corresponding percentage fall from baseline in FEV_1 is <15% then the PC_{20} will be set to missing.
- If the last AMP concentration inhaled is not the highest AMP concentration (i.e. is less than 320 mg/mL) and the corresponding percentage fall from baseline in FEV_1 is ≥15% then the PC_{20} will be set to the last AMP concentration inhaled.

Calculation of Weighted Means
Weighted means (0-24h) will be derived for plasma cortisol All available (planned) data at the actual relative times will be included in the derivation of the weighted mean. If a measurement value is available and the actual time has not been captured, the time will be replaced with planned time for that value only. Pre-dose will be taken as the 0h timepoint, and all subsequent timepoints will be calculated relative to dosing in that escalation phase for each period. The weighted means will be derived by calculating the area under the curve (AUC) over the 0-24-hour period using the trapezoidal rule, and then dividing it by the actual time interval. $$\text{Weighted Mean (0-24hr)} = \left[\frac{1}{2}\sum_{i=1}^{I-1}(t_{i+1}-t_i)(y_i+y_{i+1})\right] / \left[t_l - t_f\right]$$ where y_i represents the value of the endpoint at the ith timepoint, t_i represents the actual relative time at the ith timepoint, t_f represents the actual relative time at the first timepoint (t_f = 0 as the pre-dose measurement is used), t_l represents the actual relative time at the last timepoint (for example, the 24h timepoint), l represent the number of timepoints used in the AUC calculation. For plasma cortisol there are 11 planned timepoints at pre-dose (0 hr.) and at 1, 2, 3, 5, 10, 12 (before morning dose), 14, 16, 18 and 24 hours post dose, weighted mean will be calculated for plasma cortisol values between PM dose on Day 6 to pre-dose PM dose Day 7.

10.6.4. Safety

Adverse Events

AEs of Special Interest

AE groups of special interest have been defined as AEs which have specified areas of interest for FF, FP and BUD.

AESI Group	MedDRA Terms
Hypersensitivity	Hypersensitivity SMQ, Angioedema (SMQ), Anaphylactic reaction (SMQ)
Infective Pneumonia	Infective Pneumonia SMQ
Corticosteroids associated eye disorders	Glaucoma SMQ
Adrenal Suppression	GSK defined PTs

If this reference data is updated between the RAP approval 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.

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, and 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.
  - Example 1: 2 Significant Digits = '< x' becomes x – 0.01
  - Example 2: 1 Significant Digit = '> x' becomes x + 0.1
  - Example 3: 0 Significant Digits = '< x' becomes x – 1

10.7. Appendix 7: Reporting Standards for Missing Data

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	Subject study completion (i.e. as specified in the protocol) was defined as "A completed subject is one who has completed the number of treatment periods they consented to, including the follow-up visit". Withdrawn subjects will be handled in the study as mentioned below: Withdrawn Subjects may be replaced. Replacement Subjects will be assigned to the same treatment sequence as the subject they are replacing. For Subjects completing two treatment periods: • Each subject will receive 2 different treatments, one in treatment period 1, and one in treatment period 2; the possible treatment sequences are pre-defined in Table 3. Two Subjects will be randomized to each of the 12 treatment sequences (Table 3). • If a subject withdraws during treatment period 1, the replacement subject will start from the beginning of period 1 of the same treatment sequence. • If a subject withdraws after period 1 or during period 2, the replacement subject may start from period 2; a maximum of 2 Subjects can be replaced from the start of period 2. If more than 2 Subjects withdraw after period 1 or during period 2, they will be replaced from the beginning of period 1. For Subjects completing one treatment period: • Each Subject will receive one treatment, as defined in Table 4. Six Subjects will be randomized to each treatment, including placebo overall (Table 4). Replacements for withdrawn Subjects will start from the beginning of period 1 of the same treatment. All available data from Subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. .

10.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated using 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", "Not Done" 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.
Weighted Mean	If missing values are present in data required for the calculation of the weighted

Element	Reporting Detail
Calculations	means, the following approach will be employed: • If more than a third of the observations are missing, then the weighted mean will be set to missing for that escalation phase of the subject. • If missing values occur at the first or last time-point and the number of missing observations is less than a third, then the missing values will be imputed using the first non-missing observation carried backwards or the last non-missing observation carried forwards respectively. • If missing values occur at a time-point between non-missing values, the value will be interpolated using the two non-missing values based on the below formula: $$x_i = f x_{i+j} + (1-f) x_{i-j}$$ Where x_i= missing value at timepoint x_{i+j}= first available non-missing value after the missing timepoint x_{i-j}= first available non-missing value before the missing timepoint $f = \frac{a}{a+b}$, where a is the distance from x_i to x_{i-j} and b is the distance from x_i to x_{i+j} • If it is considered that a non-negligible amount of missing data is present, a sensitivity analysis to assess the effect of the imputation described above may also be carried out and reported in CSR.

10.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year or only 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: Partially Missing Dates: ○ Missing Start Day: First of the month will be used as the Day (i.e. 01) unless the first of the month 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: Study Phases and Treatment Emergent Adverse Events ○ Missing Start Month: January will be used as the Month unless this is before the Month of start of the study treatment; in that case the Month of study treatment start, will be used. ○ Missing Stop Day: Last day of the month will be used as the Day (i.e. 28/29/30/31 dependent on the month and year) unless the last day of the month is after the stop date of study treatment; in this case the study treatment stop date will be used as the Day ○ Missing Stop Month: December will be used as the Month unless this is after the Month of stop of the study treatment; in that case the Month of study treatment stop will be used. Fully Missing Dates: • Completely missing start or end dates (i.e. no year specified) will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be reported as missing. The same approach will be adopted for all AEs regardless of whether the AE is assumed to have occurred during treatment or not
Concomitant Medications/Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

10.8. Appendix 8: Abbreviations & Trade Marks

10.8.1. Abbreviations

AE	Adverse Event
AMP	Adenosine-5-monophosphate
AMP PC20	Provocative concentration of AMP causing a 20% fall in forced expiratory volume in 1 second
ANOVA	Analysis of variance
BMI	Body mass index
BUD	Budesonide
CI	Confidence interval
CS	Compound Symmetry
CRF	Case report form
ECG	Electrocardiogram
eCRF	Electronic case report form
E0	Response at dose 0
ED20	Dose at which 20% of the maximum effect is reached
ED50	Dose at which 50% of the maximum effect is reached
ED80	Dose at which 80% of the maximum effect is reached
Emax	Maximum effect
FF	Fluticasone furoate
FP	Fluticasone propionate
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FU	Follow-up
FVC	Forced vital capacity
GSK	GlaxoSmithKline
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroids
ITT	Intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
Mcg	Microgram
PC	Provocative concentration
PD	Pharmacodynamic
PEFR	Peak expiratory flow rate
RAP	Reporting analysis plan
SAE	Serious adverse event
SD	Standard deviation

10.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
DISKUS
ELLIPTA

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
Turbuhaler

10.9. Appendix 9: List of Data Displays

10.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.16	N/A
Pharmacodynamic	2.1 to 2.15	2.1 to 2.5
Safety	3.1 to 3.13	N/A
Section	**Listings**	
ICH Listings	1 to 24	
Other Listings	25 to 36	

10.9.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated, and if required, example mock-up displays provided in Appendix 10: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Pharmacodynamic	PD_Fn	PD_Tn	PD_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln

NOTES:

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

10.9.3. Deliverables

Delivery [Priority]	Description
In-Stream Data Review	In-Stream Data Review will be conducted to assess the need for a sample size re-estimation or interim analysis
SAC	Final Statistical Analysis Complete

10.9.4. 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	Only total column is required	SAC
1.2.	All Subjects	ES4	Summary of Subject Disposition at Each Study Epoch	Summarize by escalation phase	SAC
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failures		SAC
1.4.	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID	Only total column is required	SAC
1.5.	Enrolled	IE2	Summary of Inclusion and Exclusion Criteria Deviations	Only total column is required	SAC
Protocol Deviation					
1.6.	All Subjects	DV1	Summary of Important Protocol Deviations	Only total column is required	SAC
Population Analyzed					
1.7.	Screened	SP1	Summary of Study Populations	Only total column is required Add footnote to explain the population based on Section 4	SAC
1.8.	All Subjects	POP_T1	Summary of Subject Completion at Each Escalation Phase	Only total column is required	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Demographic and Baseline Characteristics					
1.9.	All Subjects	DM3	Summary of Demographic Characteristics	Only total column is required Footnote: age is imputed as full date of birth is not collected Footnote: Race collected as AFRICAN AMERICAN/AFRICAN HERITAGE is shown as BLACK OR AFRICAN AMERICAN	SAC
1.10.	Enrolled	DM11	Summary of Age Ranges	Only total column is required Age categories Adult (18-64 years), >=65-84 years, >=85 years Footnote: age is imputed as full date of birth is not collected	SAC
1.11.	All Subjects	DM5	Summary of Race and Racial Combinations	Only total column is required Footnote: Note: Race collected as AFRICAN AMERICAN/AFRICAN HERITAGE is shown as BLACK OR AFRICAN AMERICAN.	SAC
Prior and Concomitant Medications					
1.12.	All Subjects	MH4	Summary of Current Medical Conditions	Only total column is required	SAC
1.13.	All Subjects	MH4	Summary of Past Medical Conditions	Only total column is required	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
1.14.	All Subjects	SU1	Summary of Smoking History at Screening	Only total column is required Present only Smoking HistorySee IDSL for options related to ATC groupings and multi-ingredient medications.	SAC
1.15.	All Subjects	CM1	Summary of Concomitant Medications by Generic Term	Only total column is required See IDSL for options related to ATC groupings and multi-ingredient medications.	SAC
Exposure and Treatment Compliance					
1.16.	All Subjects	POP_T2	Summary of Exposure to Study Treatment	Page by each treatment	SAC

10.9.5. Pharmacodynamic Tables

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Primary Endpoint – Dose Response Analysis					
2.1	PD	PD_T1	Summary of AMP PC_{20} (mg/mL) Data		SAC
2.2	PD	PD_T2	Summary of Log Transformed AMP PC_{20} (mg/mL) Data		SAC
2.3	PD	PD_T3	Summary of Statistical Analysis of AMP PC_{20} (mg/mL) Placebo Data (ANOVA Model)	Footnote: The Repeated Measures ANOVA model was fitted for log transformed AMP PC20 with Dose escalation phase as fixed categorical effects, subject fitted as a random effect and Dose escalation phase as repeated with the CS covariance structure. Note: SE = Standard Error. CI = Confidence Interval.	SAC
2.4	PD	PD_T4	Summary of Dose Response Analysis for Log Transformed AMP PC_{20} (mg/mL) Data	Footnote: Note: [1] E0 – Placebo response (log 2 scale). Emax - Maximum effect. ED50 - Dose at which 50% of the maximum effect is reached (mcg).	SAC
2.5	PD	PD_T8	Summary of the Mean Doubling Dose Differences (95% CI) from Placebo for AMP PC20 (mg/mL)		SAC
2.6	PD	PD_T1	Summary of Cortisol Suppression 0-24 Hours Weighted Mean (ng/mL)		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
2.7	PD	PD_T2	Summary of Log Transformed Cortisol Suppression 0-24 Hours Weighted Mean (ng/mL)		SAC
2.8	PD	PD_T3	Summary of Statistical Analysis of Cortisol Suppression Placebo Data (ANOVA Model)	Footnote: The Repeated Measures ANOVA model was fitted for log transformed Cortisol Suppression values with Dose escalation phase as fixed categorical effects, subject fitted as a random effect and Dose escalation phase as repeated with the CS covariance structure. Note: SE = Standard Error. CI = Confidence Interval.	SAC
2.9	PD	PD_T5	Summary of the Dose Response Analysis for Log Transformed Cortisol Suppression 0-24 Hours Weighted Mean (ng/mL)	Footnote: Note: [1] E0 – Placebo response (log 2 scale). Emax - Maximum effect. ED50 - Dose at which 50% of the maximum effect is reached (mcg).	SAC
Primary Endpoint - Therapeutic Index					
2.10	PD	PD_T6	Summary of the Dose Response Analysis for ED_{20} Cortisol Suppression (ng/mL) /ED_{80} for AMP PC_{20} (mg/mL)		SAC
2.11	PD	PD_T10	Summary of the Dose Response Analysis for ED_{50} Cortisol Suppression (ng/mL) /ED_{50} for AMP PC_{20} (mg/mL)		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Exploratory Endpoint					
2.12	PD	PD_T7	Summary of Dose of FF and BUD that gives the same AMP PC20 (mg/mL) response as the FP doses administered		SAC
2.13	PD	PD_T9	Summary of Dose of FF and BUD that gives the same cortisol suppression (ng/mL) as the FP doses administered		SAC
Others					
2.14	PD	PD_T4	Summary of Dose Response Analysis for Log Transformed AMP PC_{20} (mg/mL) Data - considering Screening values as E0		SAC
2.15	PD	PD_T8	Summary of the Mean Doubling Dose Differences from Screening/Pre-dose for AMP PC20 (mg/mL)		SAC

10.9.6. Pharmacodynamic and Biomarker Figures

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Primary Endpoint					
2.1	PD	PD_F1	Plot of Individual AMP Dose Response Curves by Subject and Treatment		SAC
2.2	PD	PD_F2	Plot of The Predicted AMP PC20 (95% CI) vs Dose by Treatment		SAC
2.3	PD	PD_F3	Plot of the Mean Doubling Dose Differences (95% CI) from Placebo for AMP PC20 (mg/mL)		SAC
2.4	PD	PD_F4	Plot of Individual Plasma Cortisol Suppression values by Subject and Treatment		SAC
2.5	PD	PD_F2	Plot of Predicted Cortisol Suppression 0-24 Hours Weighted Mean (ng/mL) (95% CI) vs Dose by Treatment		SAC

10.9.7. Safety Tables

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Adverse Events (AEs)					
3.1	All Subjects	AE13	Overview of Adverse Events	Summarize by PART	SAC
3.2	All Subjects	SAFE_T1	Summary of On-Treatment Adverse Events by System Organ Class and Preferred Term	Summarize by PART	SAC
3.3	All Subjects	SAFE_T2	Summary of Common (>=3%) Adverse Events by Overall Frequency	Summarize by PART Summarize by PART	SAC
3.4	All Subjects	SAFE_T1	Summary of Drug-Related Adverse Events by System Organ Class and Preferred Term		SAC
3.5	All Subjects	SAFE_T3	Summary of Common (>=3%) Non-Serious Adverse Events by System Organ Class and Preferred Term (Subjects & No. of Occurrences)	Summarize by PART Summarize by PART Summarize by PART Summarize by PART Summarize by PART	SAC
3.6	All Subjects	SAFE_T4	Summary of Adverse Events of Special Interest by System Organ Class and Preferred Term	Summarize by PART Summarize by PART	SAC
Serious and Other Significant Adverse Events					
3.7	All Subjects	SAFE_T2	Summary of Fatal Serious Adverse Events by System Organ Class and Preferred Term		SAC
3.8	All Subjects	SAFE_T2	Summary of Drug-Related Fatal Serious Adverse Events by System Organ Class and Preferred Term		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Adverse Events (AEs)					
3.9	All Subjects	SAFE_T2	Summary of Serious Adverse Events by System Organ Class and Preferred Term		SAC
3.10	All Subjects	SAFE_T2	Summary of Drug-Related Serious Adverse Events by System Organ Class and Preferred Term		SAC
3.11	All Subjects	SAFE_T5	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
3.12	All Subjects	SAFE_T1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term		SAC
Peak expiratory flow rate					
3.13	All Subjects	SAFE_T6	Summary of Peak Expiratory Flow Rate Measurements		SAC

10.9.8. ICH Listings

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Study Population					
1.	Screened population	ES7	Listing of Reasons for Screen Failure		SAC
2.	All Subjects	ES3	Listing of Reasons for Study Withdrawal	Include escalation phase in treatment column	SAC
3.	All Subjects	BL2	Listing of Subjects for Whom the Treatment Blind was Broken	Include escalation phase in treatment column	SAC
4.	All Subjects	TA2	Listing of Planned and Actual Treatments	Include escalation phase in treatment column	SAC
5.	All Subjects	DV2A	Listing of Important Protocol Deviations	Include escalation phase in treatment column Population flag columns are not required	SAC
6.	Enrolled population	IE4	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
7.	All Subjects	DM2	Listing of Demographic Characteristics		SAC
8.	All Subjects	DM9	Listing of Race		SAC
9.	All Subjects	SU2	Listing of Smoking History at Screening	Present only Smoking History	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
10.	All Subjects	CM4	Listing of Concomitant Medications by Generic Term	Include escalation phase in treatment column	SAC
11.	All Subjects	EX4	Listing of Exposure to Study Treatment	1.Include escalation phase in treatment column 2.Page by treatment 3.Add a total daily dose column	SAC
Adverse Events					
12.	All Subjects	AE9	Listing of All Adverse Events	Include escalation phase in treatment column	SAC
13.	All Subjects	AE9	Listing of Pre-Treatment Adverse Events		SAC
14.	All Subjects	AE9	Listing of Post-Treatment Adverse Events		SAC
15.	All Subjects	AE9	Listing of All Adverse Events of Special Interest	Include escalation phase in treatment column	SAC
16.	All Subjects	AE7	Listing of Subject Numbers for Individual Adverse Events	Include escalation phase in treatment column	SAC
17.	All Subjects	AE9	Listing of Fatal Serious Adverse Events	Include escalation phase in treatment column	SAC
18.	All Subjects	AE9	Listing of Non-Fatal Serious Adverse Events	Include escalation phase in treatment column	SAC
19.	All Subjects	AE9	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	Include escalation phase in treatment column	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Laboratory Parameters					
20.	All Subjects	LB6	Listing of Hematology Data	PCI ranges will not be reported	SAC
21.	All Subjects	LB6	Listing of Clinical Chemistry Data	PCI ranges will not be reported	SAC
22.	All Subjects	EG4	Listing of ECG Values	PCI ranges will not be reported	SAC
23.	All Subjects	EG6	Listing of ECG Findings	PCI ranges will not be reported	SAC
24.	All Subjects	VS5	Listing of Vital Signs		SAC

10.9.9. Non-ICH Listings

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Adverse Event					
25.	All Subjects	AE2	Listings of Relationship between System Organ Class and Verbatim Text		SAC
26.	All Subjects	SAFE_L3	AE Terms of Special Interest		SAC
Peak expiratory flow rate					
27.	All Subjects	SAFE_L1	Listing of Peak Expiratory Flow Rate Measurements		SAC
28.	All Subjects	SAFE_L2	Listing of Lung Function Test Data		SAC
Efficacy					
29.	PD	PD_L1	Listing of AMP PC_{20} Data		SAC
30.	PD	PD_L2	Listing of Lung Function Test Data by Part (During AMP Challenge)		SAC
31.	PD	PD_L3	Listing of Percentage Change Between Highest Pre-Saline & Post Saline FEV1 Measurements		SAC
32.	PD	PD_L4	Listing of Log Transformed Cortisol Suppression 0-24 Hours Weighted Mean (ng/mL)		SAC
33.	PD		Raw SAS Output from the Dose Response Analysis for Log Transformed AMP PC_{20} Data		SAC
34.	PD		Raw SAS Output from the Statistical Analysis of AMP PC_{20} Placebo Data (ANOVA Model)		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
35.	PD		Raw SAS Output from the Dose Response Analysis for Log Transformed Cortisol suppression 0-24 hours weighted mean		SAC
Patient Profile					
36.	Enrolled	CVD_DEATH	Listing of All Cause Deaths		SAC

10.10. Appendix 10: Example Mock Shells for Data Displays

POP_T1
Protocol: 203162
Population: All subjects

Table 1.x
Summary of Subject Completion at Each Escalation Phase

Visit	All Subjects Population (N=XXX)		PD Population (N=XXX)	
	Period 1	Period 2	Period 1	Period 2
Number of Subjects entering each period	XX	XX	XX	XX
Escalation Phase 1	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Escalation Phase 2	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Escalation Phase 3	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Escalation Phase 4	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Escalation Phase 5	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)

Footnote: Percentages were calculated for each escalation phases based on the number of subjects entering the period.

POP_T2
Protocol: 203162
Population: All subjects

Table X
Summary of Exposure to Study Treatment

		FF 50 mcg (N=100)	FF 100 mcg (N=100)	FF 200 mcg (N=100)	FF 400 mcg (N=100)	FF 800 mcg (N=100)
Time on Study Treatment (days) [1]	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	Xx	xx	xx
	Max.	xx	xx	Xx	xx	xx
Subject Daily Dose (mg) [2]	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	Xx	xx	xx
	Max.	xx	xx	Xx	xx	xx
Cumulative Actual Dose (mg)	n	xx	xx	Xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx	xx	Xx	xx	xx
	Max.	xx	xx	Xx	xx	xx

[1] The time on study drug does not include dose interruptions.
[2] the subject daily dose (the cumulative actual dose divided by the duration of exposure) is calculated for each subject first and summary statistics are calculated based on the subject average daily dose.
For dose escalation phases with twice-daily dosing (AM and PM) but only a single dose (PM) on the first day of the phase, that day is counted as only 0.5 days in the calculation of time on study treatment.

PPD

Example PD_T1
Protocol: 203162
Population: PD

Table 2.x
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Treatment	N	n	Mean	95% CI	SE	Median	Min.	Max.
Placebo	xx	xx	xx.xx	(x.xx, x.xx)	xx.xxx	x.xx	x.x	xxx.x
FF 25 mcg	xx	xx	xx.xx	(x.xx, x.xx)	xx.xxx	x.xx	x.x	xxx.x
FF 100 mcg	xx	xx	xx.xx	(x.xx, x.xx)	xx.xxx	x.xx	x.x	xxx.x
FF 200 mcg	xx	xx	xx.xx	(x.xx, x.xx)	xx.xxx	x.xx	x.x	xxx.x
FF 400 mcg	xx	xx	xx.xx	(x.xx, x.xx)	xx.xxx	x.xx	x.x	xxx.x
FF 800 mcg	xx	xx	xx.xx	(x.xx, x.xx)	xx.xxx	x.xx	x.x	xxx.x
FP 50 mcg	xx	xx	xx.xx	(x.xx, x.xx)	xx.xxx	x.xx	x.x	xxx.x
FP 200 mcg	xx	xx	xx.xx	(x.xx, x.xx)	xx.xxx	x.xx	x.x	xxx.x
FP 500 mcg	xx	xx	xx.xx	(x.xx, x.xx)	xx.xxx	x.xx	x.x	xxx.x
FP 1000 mcg	xx	xx	xx.xx	(x.xx, x.xx)	xx.xxx	x.xx	x.x	xxx.x
FP 2000 mcg	xx	xx	xx.xx	(x.xx, x.xx)	xx.xxx	x.xx	x.x	xxx.x
BUD 100 mcg	xx	xx	xx.xx	(x.xx, x.xx)	xx.xxx	x.xx	x.x	xxx.x
BUD 400 mcg	xx	xx	xx.xx	(x.xx, x.xx)	xx.xxx	x.xx	x.x	xxx.x
BUD 800 mcg	xx	xx	xx.xx	(x.xx, x.xx)	xx.xxx	x.xx	x.x	xxx.x
BUD 1600 mcg	xx	xx	xx.xx	(x.xx, x.xx)	xx.xxx	x.xx	x.x	xxx.x
BUD 3200 mcg	xx	xx	xx.xx	(x.xx, x.xx)	xx.xxx	x.xx	x.x	xxx.x

Note: CI = Confidence Interval, SE = Standard Error, Min. = Minimum, Max. = Maximum.
Note: N = Number of subjects randomized to receive the treatment.
Note: n = number of patients entering each dose escalation phase.
Note: FF-Fluticasone Furoate, FP- Fluticasone Propionate, BUD-Budesonide.
PPD

Example PD_T2
Protocol: 203162
Population: PD

Table 2.x
XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

Treatment	N	n	Geo. Mean	95% CI for Geo. Mean	CV%	SD Logs
Placebo	xx	xx	x.xx	(x.xx, x.xx)	xxx.x	x.xxx
FF 25 mcg	xx	xx	x.xx	(x.xx, x.xx)	xxx.x	x.xxx
FF 100 mcg	xx	xx	x.xx	(x.xx, x.xx)	xxx.x	x.xxx
FF 200 mcg	xx	xx	x.xx	(x.xx, x.xx)	xxx.x	x.xxx
FF 400 mcg	xx	xx	x.xx	(x.xx, x.xx)	xxx.x	x.xxx
FF 800 mcg	xx	xx	x.xx	(x.xx, x.xx)	xxx.x	x.xxx
FP 50 mcg	xx	xx	x.xx	(x.xx, x.xx)	xxx.x	x.xxx
FP 200 mcg	xx	xx	x.xx	(x.xx, x.xx)	xxx.x	x.xxx
FP 500 mcg	xx	xx	x.xx	(x.xx, x.xx)	xxx.x	x.xxx
FP 1000 mcg	xx	xx	x.xx	(x.xx, x.xx)	xxx.x	x.xxx
FP 2000 mcg	xx	xx	x.xx	(x.xx, x.xx)	xxx.x	x.xxx
BUD 100 mcg	xx	xx	x.xx	(x.xx, x.xx)	xxx.x	x.xxx
BUD 400 mcg	xx	xx	x.xx	(x.xx, x.xx)	xxx.x	x.xxx
BUD 800 mcg	xx	xx	x.xx	(x.xx, x.xx)	xxx.x	x.xxx
BUD 1600 mcg	xx	xx	x.xx	(x.xx, x.xx)	xxx.x	x.xxx
BUD 3200 mcg	xx	xx	x.xx	(x.xx, x.xx)	xxx.x	x.xxx

Note: Covariance percentage (CV%) of geometric mean was calculated based the formula: CV%= Square root (exp(variance for log transformed data)-1)*100.
Note: Geo = Geometric, CI = Confidence Interval, CV = Coefficient of Variation, SD = Standard Deviation.
Note: N = Number of subjects randomized to receive the Particular treatment.
Note: n = number of patients entering each dose escalation phase.
Note: FF-Fluticasone Furoate, FP- Fluticasone Propionate, BUD-Budesonide.

PPD

Example PD_T3
Protocol: 203162
Population: PD

Table 2.x

xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Treatment	Adjusted Mean	SE	95% CI
Placebo 1	xx.xx	xx.xxx	(xx.xx, xx.xx)
Placebo 2	xx.xx	xx.xxx	(xx.xx, xx.xx)
Placebo 3	xx.xx	xx.xxx	(xx.xx, xx.xx)
Placebo 4	xx.xx	xx.xxx	(xx.xx, xx.xx)
Placebo 5	xx.xx	xx.xxx	(xx.xx, xx.xx)

PPD

Example PD_T4
Protocol: 203162
Population: PD

Table 2.x
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Predicted AMP PC20 Values (mg/mL)			Model Parameters		
Dose	Estimate	95% CI	Parameter [1]	Estimate	95% CI
FF 25 mcg	x.xx	(x.xx, x.xx)	E0	x.xx	(x.xx, x.xx)
FF 100 mcg	x.xx	(x.xx, x.xx)	Emax	x.xx	(x.xx, x.xx)
FF 200 mcg	x.xx	(x.xx, x.xx)	ED50	x.xx	(x.xx, x.xx)
FF 400 mcg	x.xx	(x.xx, x.xx)			
FF 800 mcg	x.xx	(x.xx, x.xx)			
FP 50 mcg	x.xx	(x.xx, x.xx)	E0	x.xx	(x.xx, x.xx)
FP 200 mcg	x.xx	(x.xx, x.xx)	Emax	x.xx	(x.xx, x.xx)
FP 500 mcg	x.xx	(x.xx, x.xx)	ED50	x.xx	(x.xx, x.xx)
FP 1000 mcg	x.xx	(x.xx, x.xx)			
FP 2000 mcg	x.xx	(x.xx, x.xx)			
BUD 100 mcg	x.xx	(x.xx, x.xx)	E0	x.xx	(x.xx, x.xx)
BUD 400 mcg	x.xx	(x.xx, x.xx)	Emax	x.xx	(x.xx, x.xx)
BUD 800 mcg	x.xx	(x.xx, x.xx)	ED50	x.xx	(x.xx, x.xx)
BUD 1600 mcg	x.xx	(x.xx, x.xx)			
BUD 3200 mcg	x.xx	(x.xx, x.xx)			

Note: CI - Confidence Interval.
Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.

PPD

Example PD_T5
Protocol: 203162
Population: PD

Table 2.x
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Predicted Mean for Cortisol Suppression Values (ng/mL)			Model Parameters		
Dose	Estimate	95% CI	Parameter [1]	Estimate	95% CI
FF 25 mcg	x.xx	(x.xx, x.xx)	E0	x.xx	(x.xx, x.xx)
FF 100 mcg	x.xx	(x.xx, x.xx)	Emax	x.xx	(x.xx, x.xx)
FF 200 mcg	x.xx	(x.xx, x.xx)	ED50	x.xx	(x.xx, x.xx)
FF 400 mcg	x.xx	(x.xx, x.xx)			
FF 800 mcg	x.xx	(x.xx, x.xx)			
FP 50 mcg	x.xx	(x.xx, x.xx)	E0	x.xx	(x.xx, x.xx)
FP 200 mcg	x.xx	(x.xx, x.xx)	Emax	x.xx	(x.xx, x.xx)
FP 500 mcg	x.xx	(x.xx, x.xx)	ED50	x.xx	(x.xx, x.xx)
FP 1000 mcg	x.xx	(x.xx, x.xx)			
FP 2000 mcg	x.xx	(x.xx, x.xx)			
BUD 100 mcg	x.xx	(x.xx, x.xx)	E0	x.xx	(x.xx, x.xx)
BUD 400 mcg	x.xx	(x.xx, x.xx)	Emax	x.xx	(x.xx, x.xx)
BUD 800 mcg	x.xx	(x.xx, x.xx)	ED50	x.xx	(x.xx, x.xx)
BUD 1600 mcg	x.xx	(x.xx, x.xx)			
BUD 3200 mcg	x.xx	(x.xx, x.xx)			

Note: CI - Confidence Interval.
Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.

PPD

Example PD_T6
Protocol: 203162
Population: PD

Table 2.x
Summary of the Dose Response Analysis for ED20 Cortisol Suppression (ng/mL) /ED80 for AMP PC20 (mg/mL)

Treatment	Parameter	Estimate
FF	ED20 Cortisol Suppression	xx.x
	ED80 for AMP	xx.x
	ED20 / ED80	xx.x
FP	ED20 Cortisol Suppression	xx.x
	ED80 for AMP	xx.x
	ED20 / ED80	xx.x
BUD	ED20 Cortisol Suppression	xx.x
	ED80 for AMP	xx.x
	ED20 / ED80	xx.x

Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.
PPD

Example PD_T7
Protocol: 203162

Population: PD

Table 2.x
Summary of Dose of FF and BUD that gives the same AMP PC20 (mg/mL) response as the FP doses administered

FP Dose (mcg)	Estimated mean AMP PC20 (mg/mL) values	Predicted corresponding FF Doses (mcg)	Predicted corresponding BUD Doses (mcg)
50	xxx.xx	xx.xx	xx.xx
200	xxx.xx	xx.xx	xx.xx
500	xxx.xx	xx.xx	xx.xx
1000	xxx.xx	xx.xx	xx.xx
2000	xxx.xx	xx.xx	xx.xx

Note: The estimated AMP PC20 reported in Log 2 scale.
Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.
PPD

Example PD_T8
Protocol: 203162
Population: PD

Table x.xx

xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Treatment Comparison	Estimate	95% Confidence Interval
FF 25 mcg vs. Placebo	x.xx	(x.xx,x.xx)
FF 100 mcg vs. Placebo	x.xx	(x.xx,x.xx)
FF 200 mcg vs. Placebo	x.xx	(x.xx,x.xx)
FF 400 mcg vs. Placebo	x.xx	(x.xx,x.xx)
FF 800 mcg vs. Placebo	x.xx	(x.xx,x.xx)
FP 50 mcg vs. Placebo	x.xx	(x.xx,x.xx)
FP 200 mcg vs. Placebo	x.xx	(x.xx,x.xx)
FP 500 mcg vs. Placebo	x.xx	(x.xx,x.xx)
FP 1000 mcg vs. Placebo	x.xx	(x.xx,x.xx)
FP 2000 mcg vs. Placebo	x.xx	(x.xx,x.xx)
BUD 100 mcg vs. Placebo	x.xx	(x.xx,x.xx)
BUD 400 mcg vs. Placebo	x.xx	(x.xx,x.xx)
BUD 800 mcg vs. Placebo	x.xx	(x.xx,x.xx)
BUD 1600 mcg vs. Placebo	x.xx	(x.xx,x.xx)
BUD 3200 mcg vs. Placebo	x.xx	(x.xx,x.xx)

Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.

Example PD_T9
Protocol: 203162
Population: PD

Table 2.x
Summary of Dose of FF and BUD that gives the Same Cortisol Suppression (ng/mL)
as the FP Doses administered

FP Dose (mcg)	Estimated weighted mean of Cortisol Suppression (ng/mL) values	Predicted corresponding FF Doses (mcg)	Predicted corresponding BUD Doses (mcg)
50	xxx.xx	xx.xx	xx.xx
200	xxx.xx	xx.xx	xx.xx
500	xxx.xx	xx.xx	xx.xx
1000	xxx.xx	xx.xx	xx.xx
2000	xxx.xx	xx.xx	xx.xx

Note: The estimated Cortisol suppression (ng/mL) reported in $\log_e$ scale.
Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.

Example PD_T10
Protocol: 203162
Population: PD

Table 2.x
Summary of the Dose Response Analysis for ED50 Cortisol Suppression (ng/mL) /ED50 for AMP PC20 (mg/mL)

Treatment	Parameter	Estimate
FF	ED50 Cortisol Suppression	xx.x
	ED50 for AMP	xx.x
	ED50 / ED50	xx.x
FP	ED50 Cortisol Suppression	xx.x
	ED50 for AMP	xx.x
	ED50 / ED50	xx.x
BUD	ED50 Cortisol Suppression	xx.x
	ED50 for AMP	xx.x
	ED50 / ED50	xx.x

Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.
PPD

Example: SAFE_T1
Protocol: 203162
Population: All Subjects

Table 3.x
Summary of On-Treatment Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Placebo (N=6)	FF 25 mcg (N=6)	FF 100 mcg (N=6)	FF 200mcg (N=6)	FF 400 mcg (N=24)
ANY EVENT	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Infections and infestations					
Any event	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Abscess	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Gastroenteritis viral	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Herpes simplex	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Lower respiratory tract Infection	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Rhinitis	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Sinusitis	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Subcutaneous abscess	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Tooth infection	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.
PPD

Example: SAFE_T2
Protocol: 203162
Population: All Subjects

Table 3.x
Summary of Common (>=3%) Adverse Events by Overall Frequency

System Organ Class Preferred Term	Placebo (N=6)	FF 25 mcg (N=6)	FF 100 mcg (N=6)	FF 200mcg (N=6)	FF 400 mcg (N=24)
ANY EVENT	xx (xx%)	x (xx%)	xx (xx%)	x (xx%)	x (xx%)
Abscess	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Gastroenteritis viral	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Herpes simplex	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Lower respiratory tract Infection	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Rhinitis	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Sinusitis	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Subcutaneous abscess	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)
Tooth infection	x (x%)	x (x%)	x (x%)	x (x%)	x (x%)

Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.
PPD

Example: SAFE_T3
Protocol: 203162
Population: All Subjects

Table 3.x
Summary of Common Non-Serious Adverse Events by System Organ Class and Preferred Term
(Subjects & No. of Occurrences)

System Organ Class Preferred Term		Placebo (N=6)	FF 25 mcg (N=6)	FF 100 mcg (N=6)	FF 200 mcg (N=6)
ANY EVENT	Number of Subject with AEs	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Number of AEs	xx	xx	xx	xx
Nervous system disorders					
Dizziness	Number of Subject with AEs	xx (xx%)	xx (xx%)	x (<x%)	xx (xx%)
	Number of AEs	xx	xx	x	xx
Dyskinesia	Number of Subject with AEs	x (x%)	x (x%)	xx (xx%)	x (x%)
	Number of AEs	x	x	xx	x
Somnolence	Number of Subject with AEs	x (x%)	x (x%)	x	x (x%)
	Number of AEs	x	x	x	x
Gastrointestinal disorders					
Nausea	Number of Subject with AEs	xx (xx%)	xx (xx%)	x (<x%)	xx (xx%)
	Number of AEs	xx	xx	x	xx
Constipation	Number of Subject with AEs	x (<x%)	x (<x%)	xx (x%)	x (<x%)
	Number of AEs	x	x	xx	x

Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.

PPD

Example: SAFE_T4
Protocol: 203162
Population: All Subjects

Table 2.x
Summary of Adverse Events of Special Interest by System Organ Class and Preferred Term

Special Interest Group/Subgroup Sub-SMQ Preferred Term	Placebo (N=xx)	FF 25 mcg (N=xx)	FF 100 mcg (N=xx)	FF 200 mcg (N=xx)
Adrenal suppression				
Any event	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Adrenal insufficiency	x (xx%)	x (xx%)	x (xx%)	x (xx%)
Anticholinergic syndrome (SMQ)				
Any event	xx (x%)	xx (x%)	x (xx%)	x (xx%)
Dizziness	x (x%)	x (x%)	x (xx%)	x (xx%)
Dry mouth	x (x%)	x (x%)	x (xx%)	x (xx%)
Pyrexia	x (<x%)	x (x%)	x (xx%)	x (xx%)
Tachycardia	x (<x%)	x (x%)	x (xx%)	x (xx%)
Dry eye	x			
Dysphagia	x (<x%)	x (x%)	x (xx%)	x (xx%)
Vision blurred	x (<x%)	x (x%)	x (xx%)	x (xx%)

Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.
PPD

Example:SAFE_T5
Protocol: 203162
Population: All Subjects

Table 3.x
Summary of Serious Adverse Events by System Organ Class and Preferred Term
(Subjects & No. of Occurrences)

System Organ Class Preferred Term		Placebo (N=6)	FF 25 mcg (N=6)	FF 100 mcg (N=6)	FF 200 mcg (N=6)
ANY EVENT	Number of Subject with SAEs	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Number of SAEs	xx	xx	xx	xx
	Number of Drug-related SAEs	xx	xx	xx	xx
	Number of Fatal SAEs	xx	xx	xx	xx
	Number of Drug-related Fatal SAEs	x	x	x	x
Infections and infestations					
Diabetic Gangrene	Number of Subject with SAEs	xx (xx%)	xx (xx%)	x (<x%)	x (<x%)
	Number of SAEs	xx	xx	x	x
	Number of Drug-related SAEs	x	x	x	x
	Number of Fatal SAEs	x	x	x	x
	Number of Drug-related Fatal SAEs	x	x	x	x
Erysipelas	Number of Subject with SAEs	x (<x%)	x (<x%)	xx (x%)	xx (x%)
	Number of SAEs	x	x	xx	xx
	Number of Drug-related SAEs	x	x	x	x
	Number of Fatal SAEs	x	x	x	x
	Number of Drug-related Fatal SAEs	x	x	x	x

Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.
PPD

Table 3.x
Summary of Peak Expiratory Flow Rate Measurements

Period/ Escalation Phase/ Dose	Time point		Placebo (N=XX)	FF (N=XX)	FP (N=XX)	BUD (N=XX)
Period 1/ Escalation Phase 1	Day 1 AM	n	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x
		(95% CI)	(xx.x,xx.x)	(xx.x,xx.x)	(xx.x,xx.x)	(xx.x,xx.x)
		SD	x.xx	x.xx	x.xx	x.xx
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Day 2 AM	n	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x
		(95% CI)	(xx.x,xx.x)	(xx.x,xx.x)	(xx.x,xx.x)	(xx.x,xx.x)
		SD	x.xx	x.xx	x.xx	x.xx
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
…		…				

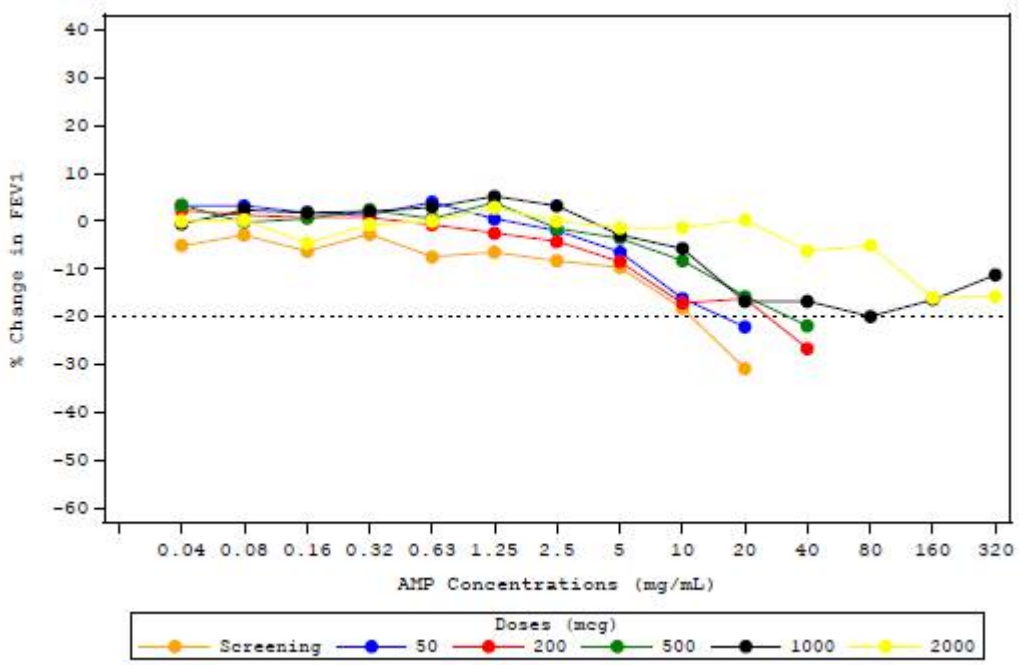
Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.
PPD

Programming note: repeat for all time points

Example PD_F1
Protocol: 203162
Population: PD

Figure 2.x
Plot of Individual AMP Dose Response Curves by Subject and Treatment

Subject=PP Treatment=FF

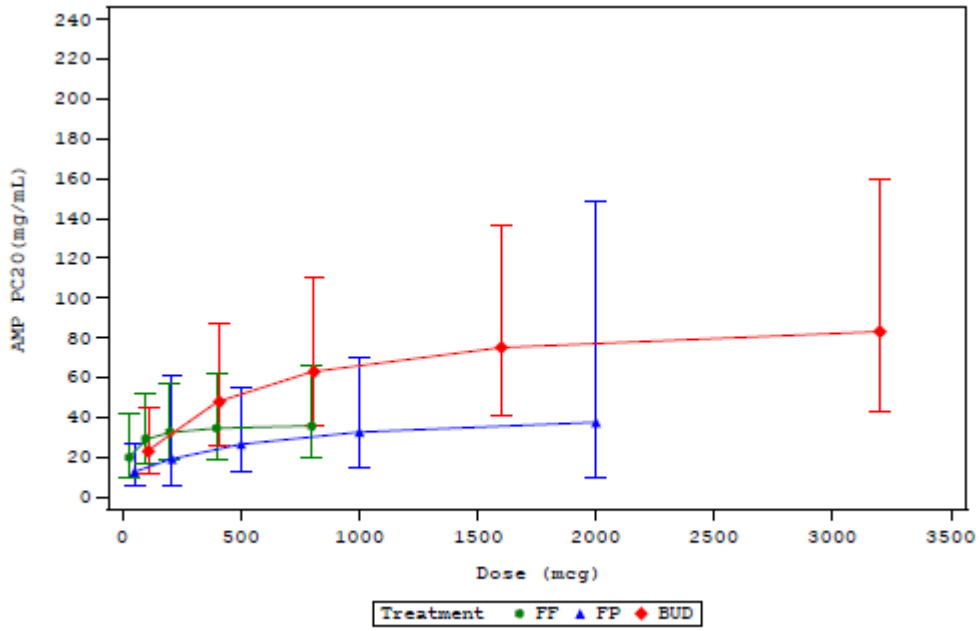


Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.

PPD

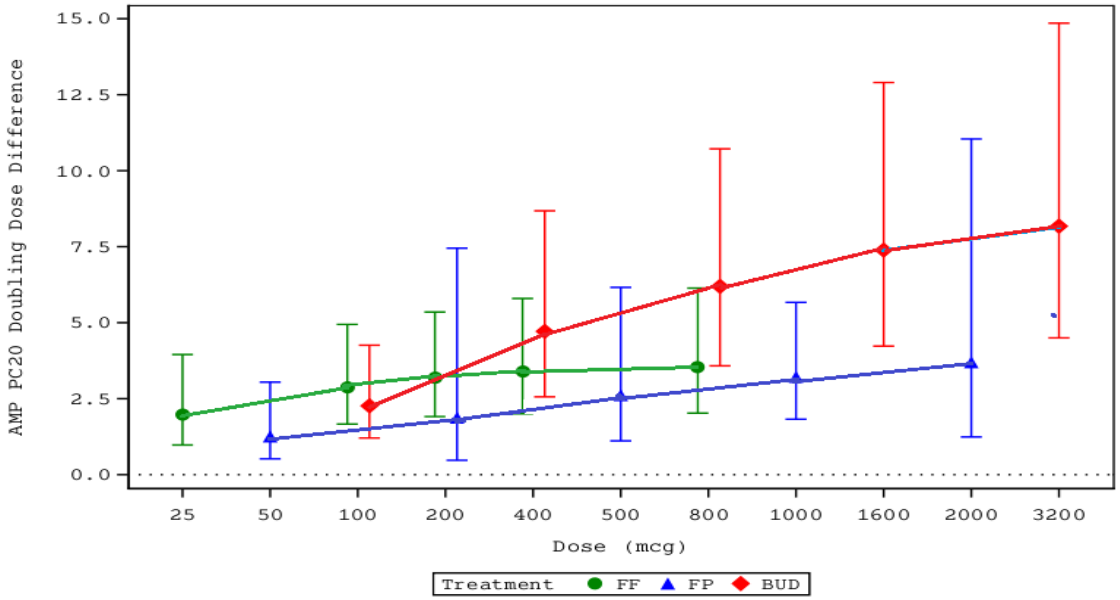
Example PD_F2
Protocol: 203162
Population: PD

Figure 3.x
XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX



Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.
Note: CI = Confidence Interval.
PPD
Programming note: Y-axis label = "Cortisol suppression"

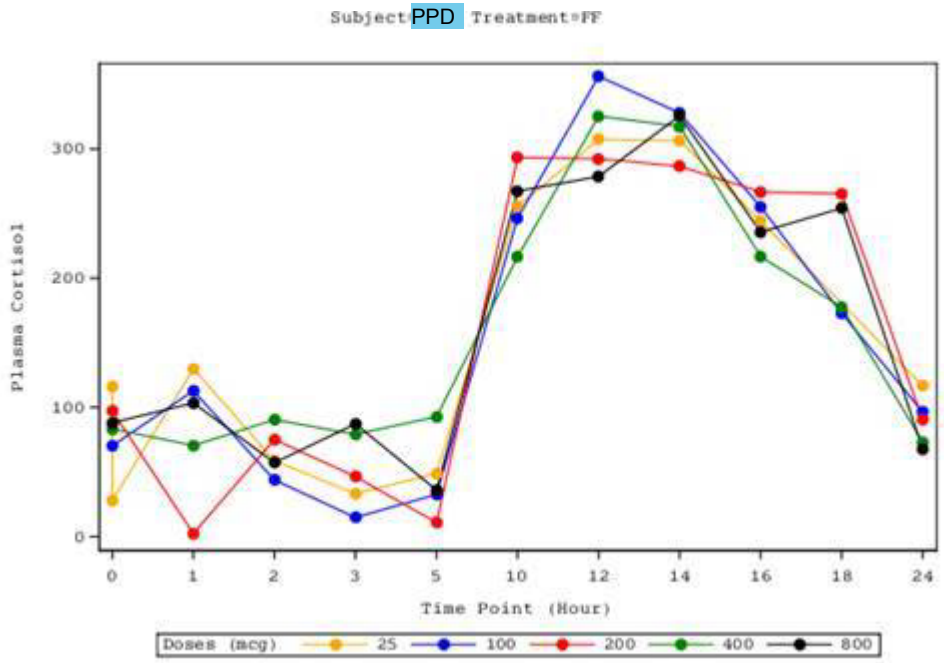
Figure 3.x
XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX



Note: CI = Confidence Interval.
Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.
PPD

Example PD_F4
Protocol: 203162
Population: PD

Figure 2.x
Plot of Individual Plasma Cortisol Suppression values by Subject and Treatment



Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.
PPD

Example PD_L1
Protocol: 203162
Population: PD

Listing xx
Listing of AMP PC20(mg/mL)Data

Site Id./ Unique Subject Id./ Seq.	Period/Escalation phase/ Visit	Treatment	Start Date Time	Time Deviation (mins)[1]	PC20 (mg/mL)
PPD	SCREENING		xxxxxxxxx xx:xx		x.xx
A/B	Period 1/ Escalation phase1/Day 8	FF 25 mcg	xxxxxxxxx xx:xx	x	x.xx
	Period 1/ Escalation phase 2/Day 14	FF 100 mcg	xxxxxxxxx xx:xx	x	x.xx
	Period 1/ Escalation phase 3/Day 22	FF 200 mcg	xxxxxxxxx xx:xx	x	x.xx
	Period 1/ Escalation phase 4/Day 29	FF 400 mcg	xxxxxxxxx xx:xx	x	x.xx
	Period 1/ Escalation phase 5/Day 36	FF 800 mcg	xxxxxxxxx xx:xx		x.xx

Note: * Indicates imputed PC20 value as the FEV1 did not fall by 20% for any AMP concentration administered.
[1] Time Deviation is calculated as start time for AMP challenge at that visit minus start time for Screening AMP challenge.
Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.

Example PD_L2
Protocol: 203162
Population: PD

Listing xx
Listing of Lung Function Test Data (During AMP Challenge)

Site Id./ Unique Subject ID/ Seq.	Period/ Escalation Phase/ Treatment/ Visit	DateTIme	AMP Conc. (mg/mL)	Planned Relative Time	Actual Time	FEV1 (L)	Highest FEV1 [1]	%Change [2]
PPD	Period 1/ Escalation Phase 1/ FF 100 mcg/ Day 1	xxxxxxxxx	DILUENT	60S	xx:xx	x.xx	x.xx	
PPD				180S	xx:xx	x.xx		
			0.04	60S	xx:xx	x.xx	x.xx	x.xx
				180S	xx:xx	x.xx		
			0.08	60S	xx:xx	x.xx	x.xx	x.xx
				180S	xx:xx	x.xx		
			0.16	60S	xx:xx	x.xx	x.xx	x.xx
				180S	xx:xx	x.xx		
			x.xx	60S	xx:xx	x.xx	x.xx	x.xx
				180S	xx:xx	x.xx		
			320.00	60S	xx:xx	x.xx	x.xx	x.xx
				180S	xx:xx	x.xx		

[1] Highest FEV1 is maximum of FEV1 collected at 60s and 180 seconds.
[2] Percentage change is calculated by ((Highest FEV1 post saline – Highest DIUENT FEV1)/ Highest DIUENT FEV1) * 100.

Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.
Example PD_L3
Protocol: 203162
Population: PD

Listing 30
Listing of Percentage Change Between Highest Pre-Saline and Post Saline FEV1 Measurements

Site Id./ Unique Subject Id./ Seq.	Treatment	Period/ Escalation Phase/ Visit	Date	Pre-saline FEV1 (L)	Highest Post-saline FEV1 (L)	% Change	>10% Fall?
PPD	SCREENING2	Screening	xxxxxxxxx	x.xx	x.xx	x.xx	
	FF 25 mcg	Period 1/ Escalation phase 1/Day 8	xxxxxxxxx	x.xx	x.xx	x.xx	Yes
A	FF 100 mcg	Period 1/ Escalation phase 2/Day 14	xxxxxxxxx	x.xx	x.xx	x.xx	
	FF 200 mcg	Period 1/ Escalation phase 3/Day 22	xxxxxxxxx	x.xx	x.xx	x.xx	
	FF 400 mcg	Period 1/ Escalation phase 4/Day 29	xxxxxxxxx	x.xx	x.xx	x.xx	
	FF 800 mcg	Period 1/ Escalation phase 5/Day 36	xxxxxxxxx	x.xx	x.xx	x.xx	

Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.

Example PD_L4
Protocol: 203162
Population: PD

Listing 31
Listing of Log-transformed Cortisol Suppression 0-24 Hours Weighted Mean (ng/mL)

Site Id./ Unique Subject Id./ Seq.	Period/ Escalation Phase/ Visit	Date	Cortisol 0-24 Hours Weighted Mean (mL)
PPD	Screening	xxxxxxxxx	x.xx
	Period 1/ Escalation phase 1/Day 8	xxxxxxxxx	x.xx
B	Period 1/ Escalation phase 2/Day 14	xxxxxxxxx	x.xx
	Period 1/ Escalation phase 3/Day 22	xxxxxxxxx	x.xx
	Period 1/ Escalation phase 4/Day 29	xxxxxxxxx	x.xx

Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.

Example SAFE_L1
Protocol: 203162
Population: All Subjects

Listing xx
Listing of Peak Expiratory Flow Rate Measurements

Site Id./ Unique Subject Id./ Seq.	Age (Years)/ Sex/ Race Detail	Visit/ Period/Escalation Phase	Planned Time	DateTime	Study Day	Peak Expiratory Flow Rate L/min.
PPD B	57/ M/ ASIAN - JAPANESE HERITAGE	Screening1		XXXXXXXXXTXX:XX	X	xx
		Day 1/ Period 1/ Escalation Phase 1	PM dose	XXXXXXXXXTXX:XX	X	xx
		Day 2/ Period 1/ Escalation Phase 1	AM dose	XXXXXXXXXTXX:XX	X	xx
			PM dose	XXXXXXXXXTXX:XX	x	xx

Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.
PPD

Example :SAFE_L2
Protocol: 203162
Population: PD

Listing xx
Listing of Lung Function Test Data

Site Id./ Unique Subject Id./ Seq.	Period/ Visit	Planned Time	DateTime	Study Day	FEV1 (L)	% Predicted FEV1	FVC (L)
PPD B	Screening1	SCREENING	XXXXXXXXXTXX:XX	XX	X.XX	XX.XX	X.XX
	Day 1/ Period 1	PRE-DOSE	XXXXXXXXXTXX:XX	XX	X.XX	XX.XX	X.XX

Note: FF-Fluticasone Furoate, FP-Fluticasone Propionate, BUD-Budesonide.
PPD

Example: SAFE_L3
Protocol: 203162
Population: All subjects

Listing xx

AE Terms of Special Interest

Special Interest Term	Subgroup	Preferred Term
xxxxx xxxxx xxxxxx	Xxxxxxx	Xxxxxxx
		xxxxxxx xxxxxxx
		Xxxx
		xxxxxxx xxx
xxxxxxx xxxxxxxxxx	Xxxxxxxxxxxxxx	xxxxxxx xxxxxx
		xxxxxxx xxxx xxxxx
		Xxxx
Xxxxxxxxxx	Xxxxxxx	Xxxxxxx
		xxxx xxxxxx xxxxxxx
xxxxxx xxxxxxx		Xxxxxxxxx
		xxxxx xxxxxx xxxxxxx xxxxxx

Note: All the pre-specified preferred terms that were assigned to special interest terms are shown, regardless of whether they occurred in the study.