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

Title	:	Reporting and Analysis Plan for Study 205715, a Phase III, randomized, double-blind, active controlled, parallel group study, comparing the efficacy, safety and tolerability of the fixed dose combination FF/UMEC/VI with the fixed dose dual combination of FF/VI, administered once-daily via a dry powder inhaler in subjects with inadequately controlled asthma
Compound Number	:	GSK573719 + GW642444 + GW685698 (GSK2834425)
Effective Date	:	28-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 205715.
- This RAP is intended to describe the efficacy, safety, and health outcomes analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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TABLE OF CONTENTS

PAGE

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 for study 205715.

1.1. Reporting & analysis plan synopsis

Overview	Key Elements of the RAP
Purpose	• This Reporting and Analysis Plan (RAP) details planned analyses and outputs required for the final Clinical Study Report (CSR) of study 205715.
Protocol	This RAP is based on the following protocol and protocol amendments: • Original protocol (Dated: 09Jun2016, GSK Document No.: 2016N271022_01). • Protocol amendment #1 (Dated: 13Dec2016, GSK Document No.: 2016N271022_02). • Protocol amendment #2 (Dated: 23Jun2017, GSK Document No.: 2016N271022_03). • Protocol amendment #3 (Dated: 29Sep2017, GSK Document No.: 2016N271022_04). • Protocol amendment #4 (Dated: 05Dec2017, GSK Document No.: 2016N271022_05).
Primary Objective	• To evaluate the effects of FF/UMEC/VI on lung function compared with FF/VI after 24 weeks of treatment
Key Secondary Objective	• To evaluate the efficacy of FF/UMEC/VI compared with FF/VI
Other Secondary Objective	• To evaluate other efficacy assessments of FF/UMEC/VI compared with FF/VI
Primary Endpoint	• Mean change from baseline in trough Forced Expiratory Volume in 1 second (FEV_1) at Week 24
Key Secondary Endpoint	• Annualized rate of moderate/severe asthma exacerbations
Other Secondary Endpoints	• Mean change from baseline in clinic FEV_1 at 3 hours post-study treatment at Week 24 • Mean change from baseline in Asthma Control Questionnaire-7 (ACQ-7) total score at Week 24 • Mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 24

Overview	Key Elements of the RAP
	• Mean change from baseline in Evaluating Respiratory Symptoms (E-RS) total score over the Weeks 21-24 (inclusive) of the treatment period
Other Endpoints	• Mean change from baseline in clinic trough FEV_1 over the first 24 weeks of the treatment period • Mean change from baseline in home daily trough FEV_1 over the first 24 weeks of the treatment period • Annualized rate of severe asthma exacerbations • Time to first severe asthma exacerbation • Time to first moderate/severe asthma exacerbation • Percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-7 at Week 24 • Percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-6 at Week 24 • Percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-5 at Week 24 • Percentage of patients that have achieved asthma control based on ACQ-7 (i.e. a total score ≤0.75) at both Week 12 and Week 24 • Percentage of patients that have achieved asthma control based on ACQ-6 (i.e. a total score ≤0.75) at both Week 12 and Week 24 • Percentage of patients that have achieved asthma control based on ACQ-5 (i.e. a total score ≤0.75) at both Week 12 and Week 24 • Mean change from baseline in SGRQ domain scores at Week 24 • Percent of patients meeting a responder threshold of ≥ 4 points improvement (decrease) from baseline for the SGRQ total score at Week 24 • Mean change from baseline in E-RS domain scores over the Weeks 21-24 (inclusive) of the treatment period • Percent of patients meeting a responder threshold of ≥ 2 points improvement (decrease) from baseline for the E-RS total score over the Weeks 21-24 (inclusive) of the treatment period • Mean change from baseline in the Asthma Quality of Life Questionnaire (AQLQ) total score at Week 24 • Percent of patients meeting a responder threshold of ≥ 0.5 points improvement (increase) from baseline for the AQLQ total score at Week 24 • Mean change from baseline in morning (AM) pre-dose Peak Expiratory Flow (PEF) over the first 24 weeks of the treatment period • Mean change from baseline in evening (PM) PEF over the first 24 weeks of the treatment period

Overview	Key Elements of the RAP
	• Mean change from baseline in the percentage of symptom-free days over the first 24 weeks of the treatment period • Mean change from baseline in the percentage of rescue medication-free days over the first 24 weeks of the treatment period • Mean change from baseline in daily rescue medication use over the first 24 weeks of the treatment period • Unscheduled asthma-related healthcare resource utilization over the first 24 weeks of the treatment period
Study Design	• This is a phase IIIa, randomized, double-blind, active controlled, 6-arm parallel group, global multi-center study evaluating FF/UMEC/VI (100/31.25/25, 100/62.5/25, 200/31.25/25 and 200/62.5/25 micrograms [mcg]) versus FF/VI (100/25 and 200/25 mcg), given once daily (OD) in the morning (AM) via ELLIPTA. • The target total number of randomized participants is approximately 2250, with 375 participants randomized to each of the 6 double-blind treatment arms. • Participants who permanently discontinue study treatment are not required to withdraw from the study. Participants who have permanently discontinued study treatment and have not withdrawn consent are encouraged to continue in the study and complete all remaining protocol specified clinic visits.
Planned Analyses	• No interim analysis is planned for this study. • The final analysis will be conducted after Data Base Freeze (DBF) of the study data. All decisions regarding the final analysis, as defined in this RAP document, will be made by Source Data Lock (SDL) based on the treatment-blinded study data.
Analysis Populations	• Intent-to-treat (ITT) population, which comprises all randomized participants, excluding those who were randomized in error. A participant who is recorded as a screen failure, run-in failure, or stabilisation failure, but is randomized and does not receive a dose of study treatment, is considered to be randomized in error. Any other participant who receives a randomization number will be considered to have been randomized. All efficacy and safety analyses will be based on the ITT population. • All Subjects Enrolled population, which comprises all participants for whom a record exists on the study database, including pre-screened participants that sign the informed consent document but do not complete a Visit 1 (screening) procedure (i.e., pre-screening failures), or participants that complete at least one Visit 1 procedure but do not enter the run-in period (i.e., screening failures). This population will be used for the summary of participant disposition. • All Subjects Screened population, which comprises all participants that complete at least one Visit 1 (Screening) procedure.

Overview	Key Elements of the RAP
	• PK population: This population will comprise all participants in the ITT Population for whom a PK sample was obtained and analysed.
Hypothesis	The primary objective of this study is to evaluate the efficacy and safety of UMEC in combination with FF/VI in participants with asthma over a 24-week treatment period. This is a superiority study to demonstrate the add-on benefit of UMEC at two dosage strengths 62.5 mcg and 31.25 mcg in a single inhaler when compared to FF/VI. The primary efficacy endpoint is the mean change from baseline in trough FEV_1 at the end of the 24-week treatment period. For each test on each efficacy endpoint, the null hypothesis is that there is no difference between treatment groups. H_0: $T_1 - T_2 = 0$ The alternative hypothesis is that there is a difference between treatment groups. H_1: $T_1 - T_2 \neq 0$ For the primary endpoint and other lung function related efficacy endpoints, the primary treatment comparisons of interest are the comparisons for each triple therapy and the respective dual therapy FF/VI without the UMEC component as follows: UMEC 62.5 mcg: • FF/UMEC/VI 100/62.5/25 mcg vs. FF/VI 100/25 mcg • FF/UMEC/VI 200/62.5/25 mcg vs. FF/VI 200/25 mcg UMEC 31.25 mcg: • FF/UMEC/VI 100/31.25/25 mcg vs. FF/VI 100/25 mcg • FF/UMEC/VI 200/31.25/25 mcg vs. FF/VI 200/25 mcg Therefore, T_1 and T_2 for these endpoints are the mean changes from baseline for the individual triple therapy and dual therapy, respectively, as listed above. For the key secondary endpoint and all other non-lung function efficacy endpoints, the primary treatment comparisons of interest are the comparisons between triple therapy and dual therapy for a fixed dose of UMEC: • (FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25) • (FF/UMEC/VI 100/31.25/25, 200/31.25/25) vs. (FF/VI 100/25, 200/25) For example, T_1 and T_2 in the hypothesis associated with the key secondary efficacy endpoint are the averages of the mean annualized rate of moderate/severe exacerbations for the triple therapies over two FF doses at a given UMEC dose, and for the dual therapies over two FF doses, respectively.
Primary	• The primary efficacy analysis will evaluate the “de facto” type estimand in the

Overview	Key Elements of the RAP
Analyses	Intent-to-Treat population, using a mixed-model repeated measures (MMRM) analysis, including all trough FEV_1 recorded post-randomization prior to and at Week 24, both on- and post-treatment, and without imputation. Analyses will include age, sex, region, baseline value, stratification by pre-study ICS dosage at screening, treatment, visit, treatment by visit interaction, and baseline value by visit interaction.
Secondary Analyses	• The analysis for the key secondary endpoint on the annualized rate of moderate/severe asthma exacerbations will be analyzed using a generalized linear model, assuming the number of exacerbations has a negative binomial probability distribution and that its mean is related to covariate factors with a 'log link' function. The logarithm of time (year) on study will be used as an offset variable. The model will include covariates for age, sex, region, treatment group, stratification by pre-study ICS dosage at screening, and severe asthma exacerbations in the previous year (0, 1, >=2). For the pooled analysis, all 6-arm data will be included in the analysis model, and treatment comparisons will be performed using LSMESTIMATE statement in SAS PROC GENMOD, appropriately for the treatments and treatment comparisons of interest. Moderate/severe asthma exacerbations from the start to the end of treatment period will be used in the analysis, regardless of participant's IP completion status.
Multiplicity	• A step-down closed testing approach will be applied for the primary efficacy endpoint, the key secondary efficacy endpoint, and the secondary efficacy endpoints SGRQ, ACQ-7, and E-RS. • Specifically, if the defined treatment comparisons for the primary efficacy endpoint between triple therapy and dual therapy at the high dose of UMEC 62.5 mcg are statistically significant at the 0.05 level for both fixed FF doses (100 and 200mcg), then the replicate efficacy of UMEC 62.5mcg is demonstrated, and the defined treatment comparison between triple therapy and dual therapy will be tested for the key secondary efficacy endpoint of moderate/severe asthma exacerbations based on the combined data of both FF doses for UMEC 62.5mcg. If the test for the key secondary efficacy endpoint is significant at the 0.05 level, then the secondary efficacy endpoints for SGRQ and ACQ-7 will be tested sequentially based on the combined data of both FF doses for UMEC 62.5mcg at significance level 0.05. • If all tests mentioned above for UMEC 62.5 mcg are statistically significant at the 0.05 level, the above testing hierarchy will be repeated for the low dose of UMEC 31.25 mcg. • If all tests for the primary, the key secondary, and the secondary efficacy endpoints for SGRQ and ACQ-7 are statistically significant at the 0.05 level for both UMEC 62.5mcg and 31.25mcg, the secondary endpoint for E-RS will be tested at the significance level 0.05 for UMEC 62.5 and UMEC 31.25 in sequence. • The family-wise Type I Error is strongly controlled at 0.05 level for both UMEC 62.5mcg and UMEC 31.25mcg on the primary endpoint (trough FEV_1), the

Overview	Key Elements of the RAP
	key secondary endpoint (moderate/severe asthma exacerbations), and the secondary endpoints on SGRQ, ACQ-7, and E-RS.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the planned statistical analysis specified in the protocol are outlined in the table below. In addition, in order to comply with regulatory guidance where the protocol referred to "Subjects" the analysis plan refers to "Participants", with the exception of displays and study populations.

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
Key secondary endpoint: The pooled analysis was to include the pooled (FF doses) 3-arm data and the FF dosage as a (categorical) covariate in the analysis model.	Key secondary endpoint: The pooled analysis will include all 6-arm data in the model. The treatment effect (pooled over FF doses) will be estimated using LSMESTIMATE statement in SAS PROC GENMOD.	This change is to ensure a consistent analysis method for pooled analyses (FF doses) in the CSR and the pooled analyses (FF doses, UMEC doses, FF and UMEC doses) planned for the submission (SDAP). The method proposed in the protocol for pooled (FF doses) analysis cannot be applied for the pooled (UMEC doses, FF and UMEC doses) analyses in SDAP due to study design.
Region was not included as a covariate for the proposed primary and key secondary analysis.	Region is added as a covariate for all statistical analysis models.	The study is a global study with 15 participating countries across multiple regions. The change is to ensure that the statistical analysis adjusts for possible region effect due to differences in local medical practices in the treatment of asthma.
Exacerbation history was not included as a covariate in the proposed statistical analysis for the key secondary endpoint.	The severe asthma exacerbations in the previous year (0, 1, >=2) is added as a covariate for all asthma exacerbation related analyses.	This change is to ensure that the exacerbation analysis is adjusted for asthma severity based on exacerbation history.
No mention of a randomized	Defines a randomized	In order for the randomized

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
population	population	population to be included in the summary of analysis populations and so clearly show the flow of participants through the study, see Section 4.
Refers to randomization stratification variable	Analyses and subgroup analyses will use the actual pre-study ICS dosage at screening as collected in the eCRF.	Interest is in the impact of actual pre-study ICS dosage at screening rather than randomized strata, and so due to participants being mis-stratified at randomization, the RAP has been updated to clarify the actual strata a participant belongs to will be used (i.e. their actual pre-study ICS dosage at screening), rather than the strata under which they were randomized.
NA	Addition of endpoint for home daily PM FEV_1 and analysis.	To give complete picture of the home daily FEV_1 data.
For all efficacy endpoints primary, secondary, and other), treatment comparisons between triple therapy at low dose FF vs. dual therapy with high dose FF, or the benefit of increasing FF dose in a triple therapy, or the benefit of increasing UMEC dose in a triple therapy will be made without adjusting for multiplicity.	All comparisons will be carried out for the primary and secondary endpoints. For the other endpoints, only the primary comparisons will be presented, unless the endpoint is supportive of a secondary endpoint.	Simplify the analyses to focus on only the data needed to achieve the objectives of the study. See Section 7 for the comparisons to be presented.

2.2. Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
• To evaluate the effects of FF/UMEC/VI on lung function compared with FF/VI after 24 weeks of treatment	• Mean change from baseline in trough Forced Expiratory Volume in 1 second (FEV_1) at Week 24
Key Secondary Objective	**Key Secondary Endpoint**
• To evaluate the efficacy of FF/UMEC/VI compared with FF/VI	• Annualized rate of moderate/severe asthma exacerbations

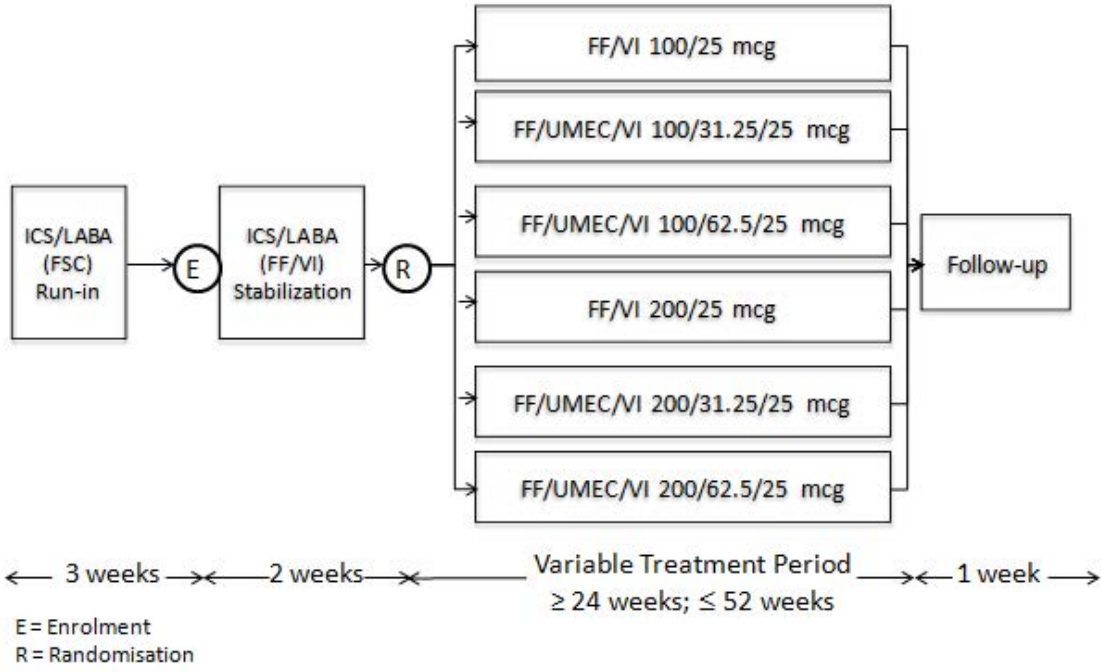
Objectives	Endpoints
Other Secondary Objectives	**Other Secondary Endpoints**
• To evaluate the efficacy of FF/UMEC/VI compared with FF/VI	• Mean change from baseline in clinic FEV_1 at 3 hours post study treatment at Week 24 • Mean change from baseline in Asthma Control Questionnaire-7 (ACQ-7) total score at Week 24 • Mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 24 • Mean change from baseline in Evaluating Respiratory Symptoms (E-RS) total score over Weeks 21-24 (inclusive) of the treatment period
• To evaluate the safety of FF/UMEC/VI compared with FF/VI	• Incidence and type of adverse events (AEs) • Electrocardiogram (ECG) measurements • Vital signs • Clinical hematological and chemistry parameters
Other Objectives	**Other Efficacy Endpoints**
• To evaluate other efficacy assessments of FF/UMEC/VI compared with FF/VI	• Mean change from baseline in clinic trough FEV_1 over the first 24 weeks of the treatment period • Mean change from baseline in home daily trough FEV_1 over the first 24 weeks of the treatment period • Annualized rate of severe asthma exacerbations • Time to first severe asthma exacerbation • Time to first moderate/severe asthma exacerbation • Percent of patients meeting a responder threshold of $\geq$0.5 points improvement (decrease) from baseline for the ACQ-7 at Week 24 • Percent of patients meeting a responder threshold of $\geq$0.5 points improvement (decrease) from baseline for the ACQ-6 at Week 24 • Percent of patients meeting a responder threshold of $\geq$0.5 points improvement (decrease) from baseline for the ACQ-5 at Week 24 • Percentage of patients that have achieved asthma control based on ACQ-7 (i.e. a total score $\leq$0.75) at both Week 12 and Week 24 • Percentage of patients that have achieved asthma control based on ACQ-6 (i.e. a total score

Objectives	Endpoints
	≤0.75) at both Week 12 and Week 24 • Percentage of patients that have achieved asthma control based on ACQ-5 (i.e. a total score ≤0.75) at both Week 12 and Week 24 • Mean change from baseline in SGRQ domain scores at Week 24 • Percent of patients meeting a responder threshold of ≥ 4 points improvement (decrease) from baseline for the SGRQ total score at Week 24 • Mean change from baseline in E-RS domain scores over Weeks 21-24 (inclusive) of the treatment period • Percent of patients meeting a responder threshold of ≥ 2 points improvement (decrease) from baseline for the E-RS total score over Weeks 21-24 (inclusive) of the treatment period • Mean change from baseline in the Asthma Quality of Life Questionnaire (AQLQ) total score at Week 24 • Percent of patients meeting a responder threshold of ≥ 0.5 points improvement (increase) from baseline for the AQLQ total score at Week 24 • Mean change from baseline in morning (AM) pre-dose Peak Expiratory Flow (PEF) over the first 24 weeks of the treatment period • Mean change from baseline in evening (PM) PEF over the first 24 weeks of the treatment period • Mean change from baseline in the percentage of symptom-free days over the first 24 weeks of the treatment period • Mean change from baseline in the percentage of rescue medication-free days over the first 24 weeks of the treatment period • Mean change from baseline in daily rescue medication use over the first 24 weeks of the treatment period • Unscheduled asthma-related healthcare resource utilization over the first 24 weeks of the treatment

Objectives	Endpoints
	period
• To evaluate the systemic exposure of FF, UMEC and VI following FF/UMEC/VI	Area Under the Curve (AUC(0-τ) [τ=24h]), Cmax
• To collect blood samples for a genetics research study	To be described in a separate document

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• This is a phase IIIa, randomized, double-blind, active controlled, 6-arm parallel group, global multi-centre study evaluating FF/UMEC/VI (100/31.25/25, 100/62.5/25, 200/31.25/25 and 200/62.5/25 mcg) versus FF/VI (100/25 and 200/25 mcg), given OD AM. • The target total number of randomized participants is approximately 2250, with 375 participants randomized to each of the 6 double-blind treatment arms. • Participants who permanently discontinue study treatment are not required to withdraw from the study. Participants who have permanently discontinued study treatment and have not withdrawn consent are encouraged to continue in the study and complete all remaining protocol specified clinic visits.
Dosing	• The double-blind treatment will be delivered via an ELLIPTA dry powder inhaler [DPI] OD AM during the treatment period. • The duration of the treatment period is variable but will be a minimum of 24 weeks and a maximum of 52 weeks. The study completion date will be determined based on the date of last participant randomized in the study, who will be on the double-blind study treatment for 24 weeks with a follow up visit 1-

Overview of Study Design and Key Features	
	week post-treatment. To determine when the final treatment/End of Study (EOS) visit will occur for each randomized participant in this variable duration study (i.e. at Week 24, Week 36 or Week 52 of the treatment period), a transition date will be determined and communicated to the study sites by GSK. A participant's final treatment/EOS visit will be defined as follows: - Participants who complete 52 weeks of study treatment prior to the actual transition date being communicated will have their final treatment/EOS visit at their Week 52 clinic assessment visit. - Participants whose Week 24 clinic assessment visit is scheduled to occur on or after the actual transition date (without consideration of available visit time windows) will have their final treatment/EOS visit at their Week 24 clinic assessment visit. - Participants who have their Week 24, Week 36 or Week 52 clinic assessment visit scheduled to occur before the actual transition date (without consideration of available visit time windows) will have their final treatment/EOS visit at the clinic assessment visit that is scheduled to occur before but closest to the actual transition date (without consideration of available visit time windows).
Time & Events	• Refer to Appendix 2: Protocol Defined Schedule of Events
Treatment Assignment	• Eligible participants will enter a 3-week run-in period on fluticasone/salmeterol [FSC], 250/50 mcg twice a day via the DISKUS DPI, followed by a 2-week stabilization period on FF/VI 100/25 mcg via the ELLIPTA DPI once a day in the morning. • At the conclusion of the stabilisation period, eligible participants are to be randomized 1:1:1:1:1:1 to receive one of the following six double-blind study treatments: o FF/UMEC/VI 100/62.5/25 mcg o FF/UMEC/VI 200/62.5/25 mcg o FF/UMEC/VI 100/31.25/25 mcg o FF/UMEC/VI 200/31.25/25 mcg o FF/VI 100/25 mcg o FF/VI 200/25 mcg • The randomization code will be generated using GlaxoSmithKline (GSK) software (RANDALL NG) and stratified by pre-study ICS dosage at screening. The study will use one central randomization schedule to allocate treatments for all randomized participants except those from Japan. A separate randomization schedule will be generated for Japan to ensure the treatment balance in a total number of approximately 300 randomized participants for the country specific requirement. • Participants will be randomized using an IRT system (RAMOS NG).
Interim Analysis	• No interim analysis is planned for this study.

2.4. Statistical Hypotheses / Statistical Analyses

The primary objective of this study is to evaluate the efficacy and safety of UMEC in combination with FF/VI in participants with asthma over a 24-week treatment period. This is a superiority study to demonstrate the add-on benefit of UMEC at two dosage strengths 62.5 mcg and 31.25 mcg in a single inhaler when compare to FF/VI. The primary efficacy endpoint is the mean change from baseline in trough FEV_1 at the end of the 24-week treatment period.

For each test on each efficacy endpoint, the null hypothesis is that there is no difference between treatment groups.

H_0: $T_1 - T_2 = 0$

The alternative hypothesis is that there is a difference between treatment groups.

H_1: $T_1 - T_2 \neq 0$

For the primary endpoint and other lung function related efficacy endpoints, the primary treatment comparisons of interest are the comparisons for each triple therapy and the respective dual therapy FF/VI without the UMEC component as follows:

UMEC 62.5 mcg:

- FF/UMEC/VI 100/62.5/25 mcg vs. FF/VI 100/25 mcg
- FF/UMEC/VI 200/62.5/25 mcg vs. FF/VI 200/25 mcg

UMEC 31.25 mcg:

- FF/UMEC/VI 100/31.25/25 mcg vs. FF/VI 100/25 mcg
- FF/UMEC/VI 200/31.25/25 mcg vs. FF/VI 200/25 mcg

Therefore, T_1 and T_2 for these endpoints are the mean changes from baseline for the individual triple therapy and dual therapy, respectively, as listed above.

For the key secondary endpoint and all other non-lung function efficacy endpoints, the primary treatment comparisons of interest are the comparisons between triple therapy and dual therapy for a fixed dose of UMEC:

- (FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25)
- (FF/UMEC/VI 100/31.25/25, 200/31.25/25) vs. (FF/VI 100/25, 200/25)

For example, T_1 and T_2 in the hypothesis associated with the key secondary efficacy endpoint are the averages of the mean annualized rate of moderate/severe exacerbations for the triple therapies over two FF doses at a given UMEC dose, and for the dual therapies over two FF doses, respectively.

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analysis is planned for this study.

3.2. Final Analyses

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

1. All participants have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) has been declared by Data Management (DM).
3. System Independent (SI) data to Study Data Tabulation Model (SDTM) data conversion has completed by Conversion Service Provider at Source Data Lock (SDL).
4. All criteria for unblinding the randomization codes have been met. Randomization codes have been distributed according to RandAll NG procedures. Release of randomization code and treatment container list, unblinding of study treatment and participant level treatment of SDTM data, and related quality control activities have been completed by Statistics and Programming (S&P).
5. Database freeze on SDTM datasets has been declared by DM upon receipt of the final, treatment unblinded SDTM data from S&P.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled	• This population will comprise all participants for whom a record exists on the study database, including pre-screened participants that sign the informed consent document but do not complete a Visit 1 (screening) procedure (i.e., pre-screening failures), or participants that complete at least one Visit 1 procedure but do not enter the run-in period (i.e., screening failures).	• Study Population
All Subjects Screened	• This population contains all participants that complete at least one Visit 1 (Screening) procedure	• Study Population • Adverse events for non-ITT participants
Randomized	• This population will comprise of all participants who were randomized (i.e. received a randomization number)	• Study population
Intent-to-Treat (ITT)	• This population will comprise all randomized participants, excluding those who were randomized in error. A participant who is	• Study population • Efficacy • Safety

Population	Definition / Criteria	Analyses Evaluated
	recorded as a screen failure, run-in failure, or stabilisation failure, but is randomized and does not receive a dose of study treatment, is considered to be randomized in error.	• Health outcomes
Pharmacokinetic	• This population will comprise all participants in the ITT Population for whom a PK sample was obtained and analysed.	• PK

Refer to Appendix 10: List of Data Displays which details the population used for each display.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions				
RandAll NG		Data Displays for Reporting		
Code	Description	Description	Displays	Order in TFL
1	FF/VI 100/25 QD	FF/VI 100/25	FF/VI 100/25	1
2	FF/VI 200/25 QD	FF/VI 200/25	FF/VI 200/25	4
3	FF/UMEC/VI 100/31.25/25 QD	FF/UMEC/VI 100/31.25/25	FF/UMEC/VI 100/31.25/25	2
4	FF/UMEC/VI 200/31.25/25 QD	FF/UMEC/VI 200/31.25/25	FF/UMEC/VI 200/31.25/25	5
5	FF/UMEC/VI 100/62.5/25 QD	FF/UMEC/VI 100/62.5/25	FF/UMEC/VI 100/62.5/25	3
6	FF/UMEC/VI 200/62.5/25 QD	FF/UMEC/VI 200/62.5/25	FF/UMEC/VI 200/62.5/25	6
7*	N/A	FF/VI 100/25 or 200/25	FF/VI	7
8*	N/A	FF/UMEC/VI 100/31.25/25 or 200/31.25/25	FF/UMEC/VI UMEC 31.25	8
9*	N/A	FF/UMEC/VI 100/62/5/25 or 200/62.5/25	FF/UMEC/VI UMEC 62.5	9

NOTES:

*: applicable only to the displays based on the pooled analysis.

The details on the treatment comparisons of interest are provided in Section 7.

5.2. Baseline Definition & Derivations

For clinic FEV_1, the Baseline value is the last acceptable/borderline acceptable pre-dose FEV_1 prior to randomized treatment start date (either from pre-dose at Day 1 or pre-bronchodilator at Enrolment Visit or at an unscheduled visit which occurs between the Enrolment Visit and Day 1).

For ACQ, SGRQ, and AQLQ, baseline value for each endpoint is the derived value based on the questionnaire administered at the randomization visit.

For the safety assessments of clinical laboratory, vital signs, and ECGs, the baseline value is the latest value recorded prior to first dose, including pre-dose unscheduled visits.

For diary data the baseline is the average value over the last 14 days prior to randomized treatment start (for more details see Section 5.3.2). If fewer than 7 days of data over the baseline period are available, the baseline value will be set as missing.

If time is not collected, Day 1 clinic assessments (or Day 1 AM diary assessments) are assumed to be taken prior to first dose and used in the derivation for baseline.

All baselines will be referred to as 'Baseline' in the summary outputs.

Parameter	Study Assessments Considered as Baseline	
Clinic Assessments		
	Screening	**Day 1 (Pre-Dose)**
Efficacy		
Trough FEV_1, FEV_1 3h post study treatment		X*
ACQ-5, ACQ-6, ACQ-7, SGRQ, AQLQ, Global Assessment of Severity		X
Safety		
Clinical Laboratory (incl. total serum IgE and FeNO) †	X	
ECGs†	X	
Vital signs†		X
Diary Assessments		
	Baseline Period	
Efficacy		
Home Daily Trough FEV_1, Home Daily AM PEF	Last 14 AM assessments during the stabilisation period, including AM assessment on the day of first treatment, prior	

Parameter	Study Assessments Considered as Baseline
	to first dose (i.e., treatment start date per protocol)
Home Daily PM FEV_1, Home Daily PM PEF	Last 14 PM assessments immediately preceding first treatment during the stabilisation period
%Symptom free days, % rescue medication free days, daily rescue medication use	Last 14 days during the stabilisation period, including AM assessments on the day of treatment i.e., treatment start date per protocol).
E-RS total score and domain scores	Last 14 PM assessments immediately preceding first treatment date during the stabilisation period

*: last acceptable/borderline acceptable (pre-dose) FEV_1 value obtained prior to treatment (either from pre-dose at Visit 3 (Randomization) or from pre-bronchodilator at Visit 2 or unscheduled assessments between Visit 2 and Visit 3).
† latest value taken prior to first dose including pre-randomized treatment unscheduled visits.

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

For participants that did not receive any randomized study treatment, baseline is defined as the value from the protocol schedule baseline visit. Unscheduled visits will not be considered.

5.3. Change from Baseline Definitions and Derivations

5.3.1. Clinic Assessments

For any efficacy and safety endpoint based on clinic assessment, the change from baseline value at a given clinic visit is the value at the clinic visit minus the baseline value.

Maximum increase from baseline is the maximum on-treatment value over all timepoints – baseline value.

Maximum decrease from baseline is the minimum on-treatment value over all timepoints – baseline value.

5.3.2. Diary Assessments

Day 1 of post-randomization diary data consist of PM assessment on Day 1 (the day of Randomization Visit) and AM assessment on the day after Randomization Visit. Similarly, for any given day, daily assessments consist of the PM assessment on that day and the AM assessment the day after.

The periods over the 52 weeks with 4-week time intervals are defined as follows:

Weeks	AM assessment Days	PM assessment / E-RS Days	Rescue medication use/ Symptoms free days
Weeks -2 and -1 (Baseline)	-13 to 1	-14 to -1	PM day -14 to AM day 1
1-4	2-29	1-28	PM day 1 to AM day 29
5-8	30-57	29-56	PM day 29 to AM day 57
9-12	58-85	57-84	PM day 57 to AM day 85
13-16	86-113	85-112	PM day 85 to AM day 113
17-20	114-141	113-140	PM day 113 to AM day 141
21-24	142-169	141-168	PM day 141 to AM day 169
25-28	170-197	169-196	PM day 169 to AM day 197
29-32	198-225	197-224	PM day 197 to AM day 225
33-36	226-253	225-252	PM day 225 to AM day 253
37-40	254-281	251-280	PM day 251 to AM day 281
41-44	282-309	281-308	PM day 281 to AM day 309
45-48	310-337	309-336	PM day 309 to AM day 337
49-52	328-365	327-364	PM day 327 to AM day 365
1-24	2-169	1-168	PM day 1 to AM day 169

For any given period (e.g., over a 4-week period), the value for a given diary endpoint is calculated using all available data as the average of the non-missing daily values over that period. If fewer than 14 days of data are available over a 4-week period, the period value will be set as missing. In general, if the data are available for fewer than 50% of the days

in the period, the period value will be set as missing. The change from baseline over that period will be calculated as the participant's period value minus the baseline value.

For the purpose of efficacy analyses and summaries based on diary data, data collected outside of the defined periods will be excluded.

5.4. Multi-Centre Studies

Due to the large number of centers participating in this study, a geographical region will be used rather than adjusting for center in the statistical analyses. The center grouping will be created based on geographical region and number of randomized participants in a country, in order to define groups of roughly similar size.

Geographic Region	Countries	Total # Randomized / Planned
Europe	Germany, Italy, Netherlands, Poland, Romania, Spain, United Kingdom,	766 / 575
Russia	Russian Federation	643 / 500
United States	United States	399 / 400
Rest of World	Argentina, Australia, Canada, Japan, Republic of Korea, South Africa	631 / 735

5.5. Examination of Covariates, Other Strata and Subgroups

5.5.1. Covariates and Other Strata

Covariates will be included in statistical analyses as detailed in the statistical model specifications in Section 7.

The covariates to be included in the primary analysis model are sex, age, region, pre-study ICS dosage at screening and baseline FEV_1. A summary of significance levels for the main effects from the primary analysis model and their interactions with treatment will be provided, see Section 7.1.5 for details.

The rationale for including each of these covariates are as follows:

- Sex and age are known to be strongly associated with lung function (Quanjer 2012).
- Region will account for any differences in background standard of care between regions. In particular, due to a high proportion of participants from Russia, the inclusion of region will help ensure the results are applicable across all regions.
- Inclusion of Baseline as a covariate is standard statistical practice, and recommended by the EMA guidance, Points to Consider on Adjustment for Baseline Covariates.
- Inclusion of the stratification variable pre-study ICS dosage at screening as a covariate is recommended by ICH-E9 (Statistical Principles for Clinical Trials). The actual strata a participant belongs to, as indicated in the eCRF will be used for this covariate, regardless of mis-stratification.

5.5.2. Examination of Subgroups

The following subgroups will be used in descriptive summaries for the primary and the key secondary efficacy endpoints, and the on-treatment adverse events.

Subgroup	Categories	Derivation
Gender	Male Female	N/A
Age (years)	5 categories: <18 18 to <65 65 to <75 75 to <85 ≥85	Calculated as age at Pre-screening Visit. Only year of birth is collected, therefore age will be imputed.
	2 categories: <65 ≥65	

Race	Black
	Asian
	White
	Other
		• Black includes African American/African Heritage.
		• 'Other' includes:
		  • American Indian or Alaskan Native
		  • Native Hawaiian or Other Pacific Islander
		  • Multiple race

Region	Europe Russia United States (USA) Rest of World (RoW)	See Section 5.4
Pre-study ICS dosage at screening	Mid High	Per stratification collected in the eCRF.
Body Mass Index (BMI)	<25 kg/m^2 ≥25 kg/m^2	Defined at baseline (last measurement prior to randomized treatment start date, including unscheduled visits)
CV History/Risk Factor at Screening	Yes No	'Yes' is defined as having had at least one of the following past or current medical conditions at screening: - Arrhythmia - Congestive Heart Failure - Coronary Artery Disease - Myocardial Infarction - Cerebrovascular Accident - Hypertension - Diabetes - Hypercholesterolemia

NOTES: details on the derivations are provided in Section 11.6.

Subgroups will be summarized in a descriptive manner only. The following will be presented for each subgroup:

- Summary of FEV_1 and change from baseline in FEV_1 over time
- Summary of moderate and severe exacerbations (Pooled FF doses)
- Summary of On-treatment AEs

5.6. Multiple Comparisons and Multiplicity

In order to account for multiple tests involving two UMEC doses and across multiple efficacy endpoints, a step-down testing procedure will be applied whereby inference for a test in the pre-defined hierarchy is dependent upon statistical significance having been achieved for the previous tests in the hierarchy.

A step-down closed testing approach will be applied for the primary efficacy endpoint, the key secondary efficacy endpoint, and the secondary efficacy endpoints SGRQ, ACQ-7, and E-RS. Specifically, if the defined treatment comparisons for the primary efficacy endpoint between triple therapy and dual therapy at the high dose of UMEC 62.5 mcg are statistically significant at the 0.05 level for both fixed FF doses (100 and 200mcg), then the replicate efficacy of UMEC 62.5mcg is demonstrated, and the defined treatment comparison between triple therapy and dual therapy will be tested for the key secondary efficacy endpoint of moderate/severe asthma exacerbations based on the combined data of both FF doses for UMEC 62.5mcg. If the test for the key secondary efficacy endpoint is statistically significant at the 0.05 level, then the secondary efficacy endpoints for SGRQ (Mean change from baseline in SGRQ at Week 24) and ACQ-7 (Mean change from baseline in ACQ-7 at Week 24) will be tested sequentially based on the combined data of both FF doses foe UMEC 62.5mcg at significance level 0.05.

If all tests mentioned above for UMEC 62.5 mcg are statistically significant at the 0.05 level, the above testing hierarchy for the primary efficacy endpoint, the key secondary efficacy endpoint, and the secondary efficacy endpoints SGRQ and ACQ-7 will be repeated for the low dose of UMEC 31.25 mcg.

If all tests for the primary, the key secondary, and the secondary efficacy endpoints for SGRQ and ACQ-7 are statistically significant at the 0.05 level for both UMEC 62.5mcg and 31.25mcg, the secondary endpoint for E-RS (Mean change from baseline in E-RS score over the Weeks 21-24 [inclusive] of the treatment period) will be tested at the significance level 0.05 for UMEC 62.5 and UMEC 31.25 in sequence.

The family-wise Type I Error is strongly controlled at 0.05 level for both UMEC 62.5mcg and UMEC 31.25mcg on the primary endpoint (trough FEV_1), the key secondary endpoint (moderate/severe asthma exacerbations), and the secondary endpoints on SGRQ, ACQ-7, and E-RS.

All secondary non-lung function efficacy endpoints will be tested for triple vs. dual using the combined data of both FF doses, at a given UMEC dose. The full testing hierarchy is provided below:

Multiplicity Adjustment Plan

Level 1: Primary endpoint, UMEC 62.5 mcg: Mean change from baseline in trough FEV_1 at Week 24,

Two comparisons:

FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25

FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25

Both tests need to be significant at 0.05 level in order to demonstrate replicate efficacy for UMEC 62.5 mcg in order to move to Level 2 test.

⇩

Level 2: Key secondary endpoint, UMEC 62.5 mcg: Annualized rate of moderate/severe asthma exacerbations,

One comparison based on pooled data:

(FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25)

Test needs to be significant at 0.05 level in order to move to Level 3 test.

⇩

Level 3: Secondary endpoint, UMEC 62.5 mcg: Mean change from baseline in SGRQ at Week 24,

One comparison based on pooled data:

(FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25)

Test needs to be significant at 0.05 level in order to move to Level 4 test.

⇩

Level 4: Secondary endpoint, UMEC 62.5 mcg: Mean change from baseline in ACQ-7 at Week 24,

One comparison based on pooled data:

(FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25)

Test needs to be significant at 0.05 level in order to move to Level 5 tests.

⇩

Level 5: Primary endpoint, UMEC 31.25mcg: Mean change from baseline in trough FEV_1 at Week 24,

Two comparisons:

FF/UMEC/VI 100/31.25/25 vs. FF/VI 100/25

FF/UMEC/VI 200/31.25/25 vs. FF/VI 200/25

Both tests need to be significant at 0.05 level in order to demonstrate replicate efficacy for UMEC 31.25mcg and move to Level 6 test.

⇩

Level 6: Key secondary endpoint, UMEC 31.25 mcg: Annualized rate of moderate/severe asthma exacerbations,

One comparison based on pooled data:

(FF/UMEC/VI 100/31.25/25, 200/31.25/25) vs. (FF/VI 100/25, 200/25)

Test needs to be significant at 0.05 level in order to move to Level 7 test.

⇩

Level 7: Secondary endpoints, UMEC 31.25 mcg: Mean change from baseline in SGRQ at Week 24.

One comparison based on pooled data:

(FF/UMEC/VI 100/31.25/25, 200/ 31.25/25) vs. (FF/VI 100/25, 200/25)

Test needs to be significant at 0.05 level in order to move to Level 8 test.

⇩

Level 8: Secondary endpoint, UMEC 31.25 mcg: Mean change from baseline in ACQ-7 at Week 24.

One comparison based on pooled data:

(FF/UMEC/VI 100/31.25/25, 200/ 31.25/25) vs. (FF/VI 100/25, 200/25)

Test needs to be significant at 0.05 level in order to move to Level 9 test.

⇩

Level 9: Secondary endpoint, UMEC 62.5 mcg: Mean change from baseline in E-RS score over Weeks 21-24 (inclusive) of the treatment period.

One comparison based on pooled data:

(FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25)

Test needs to be significant at 0.05 level in order to move to Level 10 test.

⇩

Level 10: Secondary endpoint, UMEC 31.25 mcg: Mean change from baseline in E-RS score over Weeks 21-24 (inclusive) of the treatment period.

One comparison based on pooled data:

(FF/UMEC/VI 100/31.25/25, 200/31.25/25) vs. (FF/VI 100/25, 200/25)

For any endpoints and/or treatment comparisons not mentioned in the multiplicity adjustment plan, treatment comparisons will be made without adjusting for multiplicity.

5.7. 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
11.3	Appendix 3: Assessment Windows
11.4	Appendix 4: Study Phases
11.5	Appendix 5: Data Display Standards & Handling Conventions
11.6	Appendix 6: Derived and Transformed Data
11.7	Appendix 7: Reporting Standards for Missing Data
11.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses

6. STUDY POPULATION ANALYSES

The study population analyses include the summaries of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. All summaries will be based on the ITT population, unless otherwise specified. Displays which use the All Subject Enrolled population are identified below.

An overview of the planned study population analyses is provided below, with the detailed list of data displays being presented in Appendix 10: List of Data Displays

Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Study Populations	Y[1]		
Reasons for Screen Failures, Run-in Failures, and Stabilization Failure	Y[1]		Y[2]
Rescreen Subjects	Y[1]		Y[1]
Number of Subjects by Country and Investigator	Y, Y[1]		
Study Treatment Status	Y	Y	Y
Study Disposition	Y	Y	Y
Inclusion and Exclusion Criteria Deviations	Y		Y
Important Protocol Deviations	Y		Y[1]
Clinic Visits (Attendance/Phone Contact)	Y		
Planned and Actual EOS Visit	Y		
Demography and Baseline Characteristics			
Demographic Characteristics	Y		Y
Age Ranges	Y		
Race	Y		Y
Medical Conditions (Current/ Past)	Y		Y
Pneumonia history	Y		Y
Cardiovascular Risk Factors	Y		Y
Smoking Status	Y		Y
Disease Duration	Y		Y
Asthma Medical History Questionnaire	Y		
Asthma Exacerbation History	Y		Y
Lung Function Based on Clinic Spirometry	Y		Y
Lung Function Based on Home Spirometry	Y		Y
Fractional Exhaled Nitric Oxide (FeNO)	Y		
Serum IgE	Y		
ACQ Score	Y		
Concomitant Medications			
Asthma Medications	Y		Y
Non-Asthma Medications	Y		Y
Asthma Maintenance Therapy	Y		
Relationship between ATC Level 1/Ingredient/Verbatim Text for Non-Asthma Medications			Y
Treatment Compliance			
Treatment Compliance	Y		Y

Display Type	Data Displays Generated		
	Table	Figure	Listing
Randomized and Actual Treatments			Y
Treatment Blind Broken During Study			Y
Treatment Misallocations			Y

NOTES:

Y = Yes display generated.

1. All Subjects Enrolled population
2. All Subjects Screened population

6.1. Disposition of Participants

The overall subject disposition will be summarized for the All Subjects Enrolled population, including the number and percentage of participants in each treatment group and overall, who were pre-screened (All Subject Enrolled population), screened (All Subjects Screened), randomized, ITT population, and have a PK sample obtained and analysed (PK population). Additionally, the reasons for Screen Failure, Run-in Failure, or Stabilisation Failure will be summarized for the All Subjects Enrolled Population. Listings of failures prior to randomization will be generated. A listing will also be generated for the rescreened participants (All Subjects Enrolled population) to include information on unique subject id, all subject ids, all visit dates, and final status (screen failure, run-in failure, enrolment failure, randomized) under each subject ID.

The number and percentage of participants at each centre and within each country will be summarized. This will be repeated using the ITT population.

The number and percentage of participants who completed the double-blind study treatment as well as the number who stopped the study treatment prior to the end of the study will be summarized, along with the reasons for discontinuation of the study treatment, and these will also be listed. A Kaplan-Meier curve will be generated for time to early discontinuation from study treatment. Time to early withdrawal from study treatment is measured from the date of treatment initiation to the date of treatment stop. For participants who are lost to follow up prior to their EOS visit, these participants will be considered as discontinuing from treatment early and the last study treatment date will be used, see Section 11.7.2 for details of handling missing dates. Participants who complete the study treatment per protocol are censored at the date of end of study visit.

The number and percentage of participants who completed the study as well as the number who withdrew early from the study will be summarized, along with reasons for early withdrawal from the study, and these will also be listed. A Kaplan-Meier curve will be generated for time to early withdrawal from study. Time to early withdrawal from study is measured from the date of treatment initiation the date of early withdrawal from the study for participants who have early withdrawal (EW) visit. Participants who complete the study per protocol are censored at the date of end of study visit. For participants who lost to follow-up without EW visit, the study conclusion date will be used or date of last contact if no study conclusion record is available.

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

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

The number and percentage of participant's study treatment status (on-treatment/post-treatment) at each clinic visit will be summarized. The number and percentage of participants attending the safety follow-up contact will also be summarized.

The number and percentage of participants for the planned End of Study (EOS) visit at Week 24, 36, 52, as well as the number and percentage of participants for the actual EOS visit and EW prior to the planned EOS visit will be summarized

6.2. Demographic and Baseline Characteristics

Each of the following types of data will be summarized:

- Demographic data (age, sex, ethnicity, weight, height, body mass index (BMI))
- Pre-study ICS Dosage at Screening)
- Age ranges (12-17, 18-64, >=65-84, >=85)
- Race and racial combinations, race and racial combination details
- Disease Duration (duration of asthma, onset age (year) of asthma)
- Asthma medical history questionnaire
- History of exacerbations over the previous year (Number of exacerbations in previous year (0,1, ≥2) treated without oral/systemic corticosteroids, treated with oral/systemic corticosteroids, requiring hospitalization, treated with oral/systemic corticosteroids or requiring hospitalization, and total number of exacerbations)
- Smoking history (smoking status of non-smoker or former smoker, and pack years for former smokers)
- Cardiovascular history/risk factors and family history of cardiovascular risk factors.
- Spirometry at Visit 1 and Visit 2: pre- and post-bronchodilator for FEV_1, FVC, and FEV_1/FVC, reversibility by albuterol/salbutamol at Visit 1 and by ipratropium at Visit 2, and associated percent predicted values. Note: Predicted values will be based upon the European Respiratory Society (ERS) Global Lung Function Initiative [Quanjer, 2012].
- Spirometry at Visit 3: pre-dose FEV_1, FVC, FEV_1/FVC, and associated percent predicted values.

- Change in pre-bronchodilator / pre-dose FEV_1 from Visit 1 to Visit 2 during run-in period, from Visit 2 to Visit 3 during the stabilisation period, and from Visit 1 to Visit 3 during the run-in/stabilisation periods.

- Home spirometry during the three weeks of the run-in period and the two weeks of the stabilisation period.

- FeNO at Visit 3.

- Total serum IgE at Visit 1.

- ACQ-5, ACQ-6, and ACQ-7 scores at Visit 1, Visit 2, and Visit 3.

- Change in ACQ-5, ACQ-6, and ACQ-7 scores from Visit 1 to Visit 2 during run-in period, from Visit 2 to Visit 3 during the stabilisation period, and from Visit 1 to Visit 3 during the run-in/stabilisation periods.

- Summary of past and current medical histories.

- Summary of pneumonia history.

In addition to the tables listed above; demography, race and racial combination details, disease history and history of exacerbations will also be summarized by pooled FF treatment groups.

6.3. Concomitant Medications

Summaries will be provided for the asthma medications at

- Study entry
- During the screening/run-in period
- During the stabilisation period
- On-treatment period
- Post-treatment period
- Post-study period
- Asthma medication tables will report by respiratory medication class (RMC) and ingredient

Non-asthma medications will be summarized for the:

- On-treatment period
- Post-treatment period
- Post-study period

Non-Asthma medication tables will report by Anatomical Therapeutic Chemical (ATC) level 1 and ingredient. Multi-ingredient medications will be presented according to their combination ATC classification rather than the classification of the ingredients.

Listings will be provided for the asthma and non-asthma concomitant medications.

At study entry, asthma maintenance therapy containing inhaled corticosteroid (ICS), long-acting beta-2-agonist (LABA) long-acting muscarinic antagonist (LAMA), oral corticosteroid (OCS), leukotriene receptor antagonist (LTRA), xanthines (oral prescription only) or biologic will also be summarized and combinations presented. An "other" category will also be presented including nedocromil or cromolyn sodium. Combination therapies may be in a single inhaler or separate inhalers. A similar table will be produced to display maintenance therapy following IP discontinuation.

In addition, the asthma maintenance therapy at study entry will be presented by pooled FF treatment groups

The concomitant medications used for the treatment of moderate and severe asthma exacerbations during the study will also be summarized. These include, but not limited to, the protocol permitted concomitant medications of inhaled corticosteroids (including but not limited to the use of study provided FP), the systemic corticosteroids (tablets, suspension or injection), an investigator-advised change in SABA use (i.e., routinely scheduled versus as needed use), leukotriene receptor antagonists (LTRAs) and leukotriene modifiers, and oral xanthines.

6.4. Treatment Compliance

Treatment compliance will be assessed for the entire treatment period as well as the first 24 weeks of the treatment period for each individual treatment arm. Additional details on the derivations, are provided in Section 11.6.2.

Compliance will also be presented by pooled FF doses.

7. EFFICACY ANALYSES

All efficacy analyses will evaluate the "de facto" type estimand (see Section 7.1.4 for details) based on the ITT population, including data collected during the study, both on- and post-treatment without imputation, unless otherwise specified.

To demonstrate the benefit of UMEC when added to FF/VI treatment arms with the same FF dose, the primary comparisons of interest for the primary efficacy endpoint are:

1) The replicate efficacy for UMEC 62.5 mcg dosage:

   - FF/UMEC/VI 100/62.5/25 mcg vs. FF/VI 100/25 mcg
   - FF/UMEC/VI 200/62.5/25 mcg vs. FF/ VI 200/25 mcg

2) The replicate efficacy for UMEC 31.25 mcg dosage:

   - FF/UMEC/VI 100/31.25/25 mcg vs. FF/VI 100/25 mcg
   - FF/UMEC/VI 200/31.25/25 mcg vs. FF/ VI 200/25 mcg

Other pairwise treatment comparisons of interest consist of the following assessments for the primary efficacy endpoint:

3) Triple therapy with low dose FF vs. dual therapy with high dose FF:

   - FF/UMEC/VI 100/62.5/25 vs. FF/VI 200/25
   - FF/UMEC/VI 100/31.25/25 vs. FF/VI 200/25

4) The impact of increasing FF dose in triple therapy:

   - FF/UMEC/VI 200/62.5/25 vs. FF/UMEC/VI 100/62.5/25
   - FF/UMEC/VI 200/31.25/25 vs. FF/UMEC/VI 100/31.25/25

5) The impact of increasing UMEC dose in triple therapy:

   - FF/UMEC/VI 100/62.5/25 vs. FF/UMEC/VI 100/31.25/25
   - FF/UMEC/VI 200/62.5/25 vs. FF/UMEC/VI 200/31.25/25

6) The benefit of FF 200 containing therapies over FF/VI 100/25, the asthma medication used prior to randomization, during the stabilization phase:

   - FF/VI 200/25 vs. FF/VI 100/25
   - FF/UMEC/VI 200/31.25/25 vs. FF/VI 100/25
   - FF/UMEC/VI 200/62.5/25 vs. FF/VI 100/25

To allow evaluation of the effect of FF/UMEC/VI on non-lung function efficacy endpoints, including the key secondary efficacy endpoint on moderate/severe exacerbations, for each fixed UMEC dose, the data from the two FF/UMEC/VI arms will be pooled and compared to the pooled data from the two FF/VI arms.

7) Benefit of UMEC added on to FF/VI: UMEC 62.5 mcg dosage:

   - FF/UMEC/VI (100/62.5/25 and 200/62.5/25) vs. FF/VI (100/25 and 200/25)

8) Benefit of UMEC added on to FF/VI: UMEC 31.25 mcg dosage:

   - FF/UMEC/VI (100/31.25/25 and 200/31.25/25) vs. FF/VI (100/25 and 200/25)

The pooled analyses will provide a more precise overall estimate for the treatment effect size of the addition of UMEC to FF/VI.

The benefit of increasing UMEC dose in triple therapy will also be assessed by comparing triple therapies containing UMEC 62.5mcg vs triple therapies containing UMEC 31.25mcg for all non-lung function endpoints:

9) UMEC 62.5 vs. UMEC 31.25

   - FF/UMEC/VI (100/62.5/25 & 200/62.5/25) vs. FF/UMEC/VI (100/31.25/25 & 200/31.25/25)

All comparisons will be carried out for the primary and secondary endpoints. For the other endpoints, only the primary comparisons will be presented, unless the endpoint is supportive of a secondary endpoint. Details on the comparisons presented for each endpoint are given in the table below.

Endpoint	**Treatment comparisons (as specified above)**								
	1)	**2)**	**3)**	**4)**	**5)**	**6)**	**7)**	**8)**	**9)**
Primary endpoint									
Trough FEV_1	P[1]	P[5]	O	O	O	O	O	O	O
Secondary endpoints									
Moderate/ Severe exacerbations	O	O	O	O	O	O	P[2]	P[6]	O
FEV_1 at 3 hours post study treatment	P	P	O	O	O	O	O	O	O
SGRQ total score	O	O	O	O	O	O	P[3]	P[7]	O
ACQ-7	O	O	O	O	O	O	P[4]	P[8]	O
E-RS total score	O	O	O	O	O	O	P[9]	P[10]	O
Other endpoints									
Clinic trough FEV_1 over the first 24 weeks of the treatment period	P	P							
Home daily trough FEV_1	P	P							
Home daily PM FEV_1	P	P							
Annualized rate of severe asthma exacerbations	O	O					P	P	
Time to first severe asthma exacerbation	O	O					P	P	
Time to first moderate/severe asthma exacerbation	O	O	O	O	O	O	P	P	O
ACQ-7 responder	O	O	O	O	O	O	P	P	O
ACQ-6 and ACQ-5 responder							P	P	
ACQ-7 Asthma Control	O	O	O	O	O	O	P	P	O
ACQ-6 and ACQ-5 Asthma Control							P	P	
SGRQ domain scores							P	P	
SGRQ responder	O	O	O	O	O	O	P	P	O

Endpoint	Treatment comparisons (as specified above)								
	1)	2)	3)	4)	5)	6)	7)	8)	9)
E-RS domain scores							P	P	
E-RS responder	O	O	O	O	O	O	P	P	O
Asthma Quality of Life Questionnaire (AQLQ) total							P	P	
AQLQ responder							P	P	
AM PEF	P	P							
PM PEF	P	P							
Symptom-free days							P	P	
Rescue medication-free days							P	P	
Daily rescue medication use							P	P	
P=primary comparison of interest for given endpoint, O=Other comparison of interest for given endpoint Superscripts denote where analysis comes into the multiplicity hierarchy.									

The pooled (FF doses) statistical analyses will be performed using all 6-arm data and LSMESTIMATE statement in SAS PROC MIXED for the secondary endpoints with repeated measurements during the study (e.g., SGRQ, ACQ-7, and E-RS), PROC GENMOD for the key secondary endpoint and other endpoints related to the rate of asthma exacerbations), or PROC PHREG for time to event endpoints, with the corresponding specification of treatment codes with order, see illustrative examples in the table below, for a given linear function of the least square means.

LSMESTIMATE Statement for Pooled Analyses

Analysis Type	Display Type	Description for treatments and treatment comparisons of Interest	LSMESTIMATE Statement: specification of linear function of 6-arm treatments by data display order*
Pooled FF doses	LS mean	FF/VI	0.5, 0, 0, 0.5, 0, 0
		FF/UMEC/VI at UMEC 31.25	0, 0.5, 0, 0, 0.5, 0
		FF/UMEC/VI at UMEC 62.5	0, 0, 0.5, 0, 0, 0.5
	LS mean difference	FF/UMEC/VI at UMEC 31.25 vs FF/VI	-0.5, 0.5, 0, -0.5, 0.5, 0
		FF/UMEC/VI at UMEC 62.5 vs FF/VI	-0.5, 0, 0.5, -0.5, 0, 0.5
		FF/UMEC/VI at UMEC 62.5 vs FF/UMEC/VI at UMEC 31.25	0, -0.5, 0.5, 0, -0.5, 0.5

*: as defined in Section 5.1.

This pooled analysis method for the key secondary endpoint is deviated from the proposed analysis method in the protocol. The rationale for this deviation is provided in Section 2.1.

The multiplicity adjustment for the multiple comparisons in the efficacy analyses across multiple endpoints and multiple doses are provided in Section 5.6.

7.1. Primary Efficacy Analyses

The overview of the planned efficacy analyses for the primary endpoint is provided below. The full details of primary efficacy analysis data displays are presented in Appendix 10: List of Data Displays

Primary Efficacy Endpoint	Absolute			Change from Baseline				
	Stats Analysis	Summary	Individual	Stats Analysis		Summary		Individual
	T	T	L	T	F	T	F	L
Clinic Trough FEV_1								
Trough FEV_1 (de facto type estimand, primary analysis)	Y	Y	Y	Y	Y	Y	Y	Y
Trough FEV_1 (de jure type estimand, supportive analysis)	Y	Y	Y	Y	Y	Y	Y	
Trough FEV_1 (de facto type estimand excluding sites with data concerns, supportive analysis)	Y	Y	Y	Y	Y	Y	Y	
Trough FEV_1 (Missing data imputations Sensitivity Analyses)	Y			Y	Y			
Trough FEV_1 (Pooled FF dose, de facto estimand, of other interest)	Y	Y		Y	Y	Y		
Trough FEV_1 by subgroup		Y				Y		

NOTES:

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

7.1.1. Endpoint / Variables

The primary efficacy endpoint is change from baseline in clinic trough FEV_1 at Week 24.

7.1.2. Summary Measure

The mean change from baseline in trough FEV_1 at Week 24 will be compared between treatment groups.

7.1.3. Population of Interest

The primary efficacy analyses will be based on the ITT population.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

A "treatment policy" strategy will be used to handle all intercurrent events, including treatment discontinuation, use of rescue medication provided for the study or for asthma exacerbations, temporary treatment interruption, or treatment switches.

Participants who discontinue study treatment prematurely are encouraged to stay in the study and return for all clinic visits as planned. Data collected on- or post-treatment discontinuation will be included in the primary analysis, regardless of the use of rescue medications or treatment switches. This analysis corresponds to the "de facto" analysis pre-specified in the protocol and thus referenced throughout this document.

For the primary analysis, no imputation of missing data are planned. Missing data are assumed Missing at Random (MAR) handled via Mixed Model Repeated Measures (MMRM) analysis. To examine the sensitivity of the results of the primary analysis to departures from this assumption, further sensitivity analyses will be performed using alternative assumptions on the missing data.

7.1.5. Statistical Analyses / Methods

The primary efficacy analysis will evaluate the "de facto" type estimand in the Intent-to-Treat population, using a mixed-model repeated measures (MMRM) analysis (see details in Section 7.1.6).

Supportive analysis based on the 'de jure' type estimand will be performed, including only on-treatment FEV_1 data collected prior to and at Week 24, using MMRM with the same covariates as in the 'de facto' primary analysis. Post-treatment data will not be utilized in the analysis, nor will imputation be made for any missing data.

A supportive analysis will be performed for the primary efficacy endpoint based on the "de facto" type estimand, excluding all randomized participants enrolled at Site No. PPD and Site No. PPD as a result of study non-compliance based on the GSK issue-investigation report, and the standard GSK monitoring and auditing practices. Additionally, subjects randomized at sites PPD and PPD will be excluded due to a lack of confidence in the data received.

The primary 'de facto' analysis includes all FEV_1 data collected following discontinuation of randomized treatment for participants who remain in the study and assumes that any remaining missing data due to early withdrawal from the study prior to Week 24 is missing at random (MAR). To examine the sensitivity of the results of the primary analysis to departures from this assumption, further sensitivity analyses will be performed using alternative assumptions. For each proposed imputation method, the sensitivity analysis will be performed, including both observed and imputed FEV_1 data.

The following different algorithms are proposed to impute the post-treatment missing data for the primary efficacy endpoint (change from baseline in trough FEV_1 at Week 24). Intermediate missing data will be imputed as MAR. All approaches will utilize all on and post-treatment data available.

1. Tipping Point:

   This method will explore the potential effect of missing data on the reliability of the results by using different assumptions regarding the primary endpoint outcome in participants who withdraw from study early. Participants who withdraw from study earlier than Week 24 will have missing data imputed first assuming a missing at random mechanism and then adding on a "marginal delta" prior to analyzing the imputed datasets and combining the results. The marginal deltas are to vary independently for FF/UMEC/VI and FF/VI.

   The deltas to be investigated are pre-selected multiples of the observed treatment effect. If the observed treatment effect from the primary analysis is x, the deltas to be investigated will range from -3x to +x mL for both active and placebo arms, in increments of 0.5x mL. The increment or range may be refined based on the analysis results and the location of the tipping point.

   For each of the four primary comparisons of triple vs. dual (a fixed dose of FF and a fixed dose of UMEC): the delta for these two relevant FF/UMEC/VI and FF/VI arms will be allowed to vary independently, while assuming MAR (delta=0mL) for the other four treatment arms. The imputation model will contain the same terms as in the primary analysis MMRM model.

   For a given pair of 'delta comparison' as in the table below, complete sets of Week 24 data for all 6 treatment arms will be produced with multiple imputation based on missing at random (MAR) assumption. For each of the multiple imputations, the relevant deltas (+ and/or -) will be added to the imputed FEV_1 under MAR for each respective treatment arm.

   For example, the grid for the comparison between FF/UMEC/VI 100/62.5/25 and FF/VI 100/25 is as follows: The mean change from baseline post-withdrawal from study is calculated as mean of delta + change under the MAR assumptions (FF/UMEC/VI 100/62/5/25 = z (mL), and FF/VI 100/25 = y (mL)) for each respective treatment group. Of the less interest for the sensitivity analysis are the greyed-out grid points for the deltas where FF/UMEC/VI performs relatively better than FF/VI.

			FF/UMEC/VI 100/62.5/25								
			Delta (mL)								
			-3x	-2.5x	-2x	-1.5x	-x	-0.5x	0	0.5x	x
FF/VI 100/25	Delta (mL)	Mean change post-withdrawal	-3x+z	-2.5x+z	-2x+z-	-1.5x+z	-x+z	-0.5x+z	z	0.5x+z	x+z
	-3x	-3x+y									
	-2.5x	-2.5x+y									
	-2x	-2x+y									
	-1.5x	-1.5x+y									

	-x	-x+y									
	-0.5x	-0.5x+y									
	0	y									
	0.5x	0.5x+y									
	x	x+y									

The analysis results will be used to evaluate the plausibility of the assumed difference from MAR for missing outcomes on each treatment arm under which (Tipping Point) the conclusions change, i.e., under which there is no longer evidence of a treatment effect, and clinical judgment will be applied as to the plausibility of the associated assumptions.

Repeat this process for each of the four primary treatment comparisons of interest as outlined in Section 7.

2. Jump to Reference:

   This method assumes that participants with post-treatment missing data in the test groups (FF/UMEC/VI) would have provided data similar to those in the reference group [Carpenter et al, 2013]. This approach represents the situation where the participant's expected mean change from baseline in Trough FEV_1 is shifted to that of the reference arm (FF/VI with the same FF dose), regardless of the UMEC dose in their randomized treatment. Post-treatment missing data in the reference groups (FF/VI 100/25 or 200/25 mcg) are imputed under MAR.

   The analysis will include data from all treatment arms and the primary treatment comparisons as outlined in Section 7 will be presented. For FF/UMEC/VI 100/62.5/25 & 100/31.25/25 the reference arm will be FF/VI 100/25. For FF/UMEC/VI 200/62.5/25 & 200/31.25/25 the reference arm will be FF/VI 200/25.

   Missing data prior to treatment discontinuation will be imputed assuming the participants are on their randomized treatment for that time point (MAR). The imputation model will contain the same terms as in the primary analysis MMRM model.

7.1.6. Statistical Methodology Specification

Primary Statistical Analyses
Endpoint
• Mean change from baseline in trough FEV_1 at Week 24
Primary Model Specification
• Mixed Models Repeated Measures (MMRM) model. • The analysis is based on 'de facto' type estimand, based on the ITT population. • Clinic trough FEV_1 (both on- and post-treatment) data collected prior to and at Week 24 will be included in the analysis. • No imputation is made on missing data.

Primary Statistical Analyses

• While missing data are not explicitly imputed in the MMRM analyses, there is an underlying assumption that the data are missing at random. All available data will be utilized via modeling of the within-participant correlation structure, the derived treatment differences will be adjusted to take into account the missing data.
• Terms in the model:
  ○ Dependent Variable: change from baseline in trough FEV_1 at each visit
  ○ Covariates:
  ▪ Categorical: treatment group, sex, region, visit, pre-study ICS dosage at screening,
  ▪ Continuous: age, baseline value for clinic FEV_1
  ○ Interaction: baseline*Visit, treatment*Visit
  ○ Repeated: Visit
• The model will be fit with an unstructured variance-covariance matrix.
• The LS mean trough FEV_1 and LS mean change from baseline in trough FEV_1 will be estimated using the observed marginal distributions of the study population covariates by inclusion of the OM (observed margins) dataset in SAS.

Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Baseline summaries will be presented for all participants, those who are on-treatment at week 24 and those who are off-treatment at week 24 and for those who are missing data at week 24. • Data collected at all scheduled clinic visits, both on- and post-treatment, will be summarized by visit (absolute value and change from baseline). • Boxplots of the change from baseline at each clinic visit will be presented. • Empirical distribution function plots of the change from baseline at each clinic visit will be presented. • Least-square (LS) means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors. The estimated treatment difference along with corresponding standard error, 95% CI and unadjusted p-value will be presented for all treatment comparisons specified in Section 7 at Weeks 4, 12, and 24. • LS mean change from baseline values and LS mean treatment differences (and associated 95% CIs) for the comparisons of the two FF/UMEC/VI vs. a FF/VI at a given FF dose will be will also be presented graphically at Weeks 4, 12, and 24, for each of the FF doses in two separate panels.
Exploring interaction terms
• Interaction by treatment terms will added to the main model one at a time for the following main effect covariates: age, baseline value for clinic FEV_1, region, sex and pre-study ICS dosage at screening. • Summary of test results for main effect covariates in main model will be presented along with the test results for the interaction terms mentioned above.

Primary Statistical Analyses

Supportive Statistical Analyses

- An 'on-treatment' analysis will be performed, corresponding to the 'de jure' type estimand analysis specified in the protocol.
    - The endpoint/variable, summary measure and population of interest will be the same as for the primary analysis, as outlined above.
    - The MMRM model fitted will be the same as stated above.
    - Strategy for Intercurrent (Post-Randomization) Events:
    - An "on-treatment" strategy will be used to handle the intercurrent event of treatment discontinuation. Data collected after treatment discontinuation will be excluded from the analysis and only on-treatment data will be used.
    - No imputation of missing data is planned. Missing data is assumed Missing at Random (MAR) and handled via Mixed Model Repeated Measures (MMRM) analysis.

The same outputs as for the on- and post-treatment (de facto) estimate will be produced

Supportive Statistical analysis - removing sites

The primary model will be repeated excluding participants from sites PPD and PPD
The results of the fitted model will be presented. Summaries and figures will not be produced.

Primary Statistical Analyses

Sensitivity analyses – imputation of missing data

- Imputation Model: Mixed Models Repeated Measures (MMRM) model
  - Dependent Variable: change from baseline in trough FEV_1 at each visit
  - Covariates:
    - Categorical: treatment group, sex, region, visit, pre-study ICS dosage at screening,
    - Continuous: age, baseline value for clinic FEV_1
  - Interaction: baseline*Visit, treatment*Visit, age*Visit, sex*Visit, region*visit, pre-study ICS treatment dosage*visit
  - Repeated: Visit
- Imputation methods:
  - Tipping Point
  - Jump to Reference
- For each of the multiple imputations, complete datasets of clinic trough FEV_1 at Week 24 (both observed and imputed) will be analysed using an ANCOVA model (on each imputation).
- Analysis model:
  - Dependent Variable: change from baseline in trough FEV_1 at each visit
  - Covariates:
    - Categorical: treatment group, sex, region, pre-study ICS dosage at screening
    - Continuous: age, baseline value for clinic FEV_1.
  - All 6-arm data are included in the model.
- Multiple imputation methods will be used with results from the ANCOVA combined across imputations using Rubin's method [Rubin 1987] as implemented in SAS PROC MIANALYZE.
- Details for the sensitivity analysis under each imputation method for post-study missing data are provided in Section 7.1.5.
- The LS mean and LS mean change (and 95% confidence intervals) will be presented as well as the primary comparison of interest detailed in Section 7.
- A forest plot of the LS mean treatment difference at week 24 will be presented for the primary de facto analysis, the supportive and sensitivity analyses and J2R analysis.
- For the tipping point analysis, a heat map of the p-values will be produced for each of the primary comparisons of interest for the different deltas applied.
- Model checking and diagnostics will not be performed for the imputed datasets.

Pooled FF doses

The primary 'de facto' analysis will be repeated for the pooled FF doses. The analysis model will be the same as specified above. Note:

- All 6-arm data are included in the model.
- LSMESTIMATE statement will be used with the treatment code as specified Section 7.
- The boxplots and empirical plots will not be produced for these analyses.

Subgroups

Summaries of the baseline and change from baseline will be presented for each of the subgroups listed in Section 5.5.2.

7.2. Key Secondary Analyses

An overview of the planned key secondary is provided below. The full details of data displays are presented in Appendix 10: List of Data Displays.

Key Secondary Endpoint	Absolute			
	Stats Analysis		Summary	Individual
	T	F	T	L
Annualized rate of moderate/severe asthma exacerbations using pooled FF doses (Negative Binomial, de facto type estimand, of primary interest)	Y	Y	Y	
Annualized rate of moderate/severe asthma exacerbations using pooled FF doses (de jure type estimand, supportive)	Y	Y	Y	
Annualized rate of moderate/severe asthma exacerbations using pooled FF doses (de facto type estimand excluding sites with data concerns, supportive analysis)	Y			
Annualized rate of moderate/severe asthma exacerbations (Sensitivity analyses, missing data imputations)	Y	Y		
Annualized rate of moderate/severe asthma exacerbations using unpooled doses (de facto type estimand, of other interest)	Y	Y	Y	Y
Annualized rate of moderate/severe asthma exacerbations by subgroup			Y	

NOTES:

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

7.2.1. Endpoint / Variables

The key secondary endpoint is the annualized rate of moderate/severe asthma exacerbations.

7.2.2. Summary Measure

The ratio of annualized moderate/severe exacerbation rates will be used to compare the treatments.

7.2.3. Population of Interest

Analyses will be based on the ITT population.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

The "treatment policy" strategy for the key secondary is the same as for the primary efficacy analysis outlined in Section 7.1.4.

To examine the sensitivity of the results of the key secondary endpoint analysis to departures from this assumption, further sensitivity analyses will be performed using alternative assumptions on the missing data, see details in Section 7.2.5.

7.2.5. Statistical Analyses / Methods

Asthma exacerbations will be summarized for the periods: Weeks 1-52, Weeks 1-24, and Weeks 25-52 (see Section 11.6.3), including the following details of the event:

- Number of participants contributing to the reporting period
- Duration of time in reporting period (days)
- Number and percent of participants with moderate / severe exacerbations (0, 1, 2, >2)
- Number of moderate / severe exacerbations
    - Number and percent of exacerbations that required hospitalization, emergency room visit, or the use of systemic corticosteroids.
    - Outcome and duration (days) of moderate/severe exacerbations
    - Number and percent of participants with severe exacerbations
        - Require hospitalization
        - Require visit to emergency room
        - Require the use of systemic corticosteroid
    - Number and percent of participants with moderate exacerbations
        - Number with deterioration in asthma symptoms, deterioration in lung function, increased rescue bronchodilator use (and all possible combinations of the three).
        - Number who took medication

Summaries for weeks 1-52 will also be provided by gender, age, race, region, pre-study ICS dosage at screening, BMI and CV History/Risk Factor at Screening.

The exacerbation rate will be analyzed using a generalized linear model, assuming the number of exacerbations has a negative binomial probability distribution and that its mean is related to covariate factors with a 'log link' function. The logarithm of time (year) on study will be used as an offset variable. Missing data due to early withdrawal from the study will not be imputed.

The exacerbation rate over the first 24 weeks of the study will also be analyzed in the same manner.

Supportive analysis for the pooled FF doses, based on 'de jure' type estimand will be performed, including all on-treatment moderate/severe exacerbation data collected during double-blind treatment period.

Sensitivity analysis will be performed for the key secondary efficacy endpoint based on the 'de facto' type estimand, excluding all randomized participants enrolled at Site No. PPD and Site No. PPD as a result of study non-compliance based on the GSK issue-investigation report, and the standard GSK monitoring and auditing practices. Additionally, subjects randomized at sites PPD and PPD will be excluded due to a lack of confidence in the data received.

The 'de facto' type estimand analysis for the key secondary endpoint includes all moderate/severe asthma exacerbations following discontinuation of randomized treatment for participants who remain in the study and assumes that any remaining missing data due to early withdrawal from study prior to the planned end of study visit is Missing at Random (MAR). To examine the sensitivity of the analysis result to departures from this assumption, further sensitivity analyses will be performed using alternative assumptions analogous to those used for the primary endpoint. For each proposed imputation method, the sensitivity analysis will include both observed (on and post-treatment) and imputed asthma exacerbation events. The following different algorithms are proposed to impute the post-treatment missing data.

These analyses will be performed for weeks 1-52 only.

For each approach, exacerbations in the unobserved period will be imputed only up to the participant's planned end of study visit date determined by participant's randomization date (see Section 11.3.2).

- Tipping Point:

  This method will explore the potential effect of missing data on the reliability of the results by using different assumptions regarding the moderate/severe asthma exacerbation rate in participants who withdraw from study early. Participants who withdrew from the study earlier than their planned end of study will have missing data imputed for the period of time between withdrawal from the study to the planned end of study visit first assuming missing at random (MAR) and then multiplying the estimated exacerbation rate under MAR by different deltas. The imputed exacerbation rates will vary independently for FF/UMEC/VI arms and FF/VI arms.

The deltas to be investigated are pre-selected multiples of the observed rate reduction. If the observed rate reduction from the key secondary analysis is x, the deltas to be investigated will range from 1-x to 1+3x for both active and placebo arms, in increments of 0.5x (For example, if the observed rate reduction is 20% (x=0.2) the imputed rates will be multiplied by deltas of 0.8 to 1.6 in increments of 0.1). The increment or range may be refined based on the analysis results and the location of tipping point.

For the comparison of FF/UMEC/VI UMEC 62.5 vs. FF/VI: a delta is applied to the two triple arms involving UMEC 62.5, and separately a delta is applied to the two FF/VI arms, and both deltas will be allowed to vary independently; the delta will be equal to 1 (i.e., under MAR assumption) for the triples involving UMEC 31.25. The same approach will be taken for the comparison of FF/UMEC/VI UMEC 31.25 vs FF/VI, this time varying the delta applied to the triple arms involving UMEC 31.25 and setting the delta for the triples involving UMEC 62.5 equal to 1. The imputation model will contain the same covariates as in the key secondary endpoint analysis (de facto) model (with MAR rates being delta-adjusted).

For a given pair of 'delta comparison' as in the table below, complete sets of exacerbation data (observed and imputed exacerbations) for all 6 treatment arms will be produced with multiple imputation based on missing at random (MAR) assumption. For each of the multiple imputations, the relevant deltas will be multiplied to the imputed exacerbation rates under MAR for the respective treatment arms.

For example, the grid for the comparison between triples at UMEC 62.5 and duals is as follows: The post-withdrawal mean rate is calculated as the delta *mean rate under the MAR assumption (triples at UMEC 62.5 = z, and duals = y). The greyed-out grid points for the deltas are of less interest in the sensitivity analysis where Triples FF/UMEC/VI at UMEC 62.5 performs relatively better than duals FF/VI when the imputed exacerbations for the post-withdrawal missing data are deviated from the estimates under MAR in the pooled (FF doses) analysis for the respective treatment arms. The cell with delta = 1 for both FF/UMEC/VI and FF/VI represents the key secondary analysis result under MAR.

			Triples at UMEC 62.5				
			Delta				
			0.8	1	1.2	1.4	1.6
Duals	Delta	Mean rate post-withdrawal	(1-x)*z	1*z	(1+x)*z	(1+2x)*z	(1+3x)*z
	1.6	(1+3x)*y					
	1.4	(1+2x)*y					
	1.2	(1+x)*y					
	1	1*y					
	0.8	(1-x)*y					

The analysis results will be used to evaluate the plausibility of the assumed difference from MAR for missing outcomes on each treatment arm under which (Tipping Point) the conclusions change, i.e., under which there is no longer evidence of a treatment effect, and clinical judgment will be applied as to the plausibility of the associated assumptions.

This process will be repeated for each of the primary treatment comparisons of FF/UMEC/VI vs. FF/VI as outlined in Section 7.

- Jump to Reference:

  This method assumes that participants in the test groups (FF/UMEC/VI) with missing data after study withdrawal would have provided post-treatment data similar to those in the respective reference group. This approach represents the situation where the participant's expected rate of exacerbations is shifted to that of the reference arm. The FF/VI 100/25 will be the reference arm for the FF/UMEC/VI 100/62.5/25 and FF/UMEC/VI 100/31.25/25 arms, and FF/VI 200/25 will be the reference arm for the FF/UMEC/VI 200/62.5/25 and FF/UMEC/VI 200/31.25/25 arms. Post-study missing data in the reference groups (FF/VI 100/25 or FF/VI 200/25) are imputed under MAR.

  This approach uses multiple imputation methods based on pattern mixture models [Keene, 2014]. The imputation model will contain the same covariates as in the key secondary efficacy analysis (de facto) model (exacerbation rates being constructed as though patients "jump to reference" in the unobserved period).

  The primary treatment comparisons as outlined in Section 7, based on pooled FF doses, will be presented.

A listing of exacerbations where the onset occurs within 14 days of study withdrawal or withdrawal from treatment will also be produced.

Further analysis details for asthma exacerbation related endpoints are provided in Section 7.2.6.

7.2.6. Statistical Methodology Specification

Secondary Statistical Analyses
Endpoint
• Annualized rate of moderate/severe asthma exacerbations
Model Specification

• Generalized linear model assuming a negative binomial distribution
• The analysis is based on 'de facto' type estimand, including all moderate/severe exacerbations observed during the study (both on- and post-treatment).
• Terms in the model:
  • Dependent variable: number of recorded moderate/severe asthma exacerbations experienced per participant during the study (both on- and post-treatment).
  • Covariates:

Secondary Statistical Analyses

- Categorical: treatment group, sex, region, pre-study ICS dosage at screening, severe asthma exacerbations in the previous year (0, 1, >=2).
- Continuous: age.
- Offset: logarithm of time (year) on study

- For the pooled analysis:
  - All 6-arm data are included in the model.
  - LSMESTIMATE statement will be used with the treatment code as specified Section 7.
- Mean annualized rate of moderate/severe asthma exacerbations will be estimated using the observed marginal distributions of the study population covariates by inclusion of the OM (obsmargins) option.

Model Checking & Diagnostics

- Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- Summary table of the number of events, and details of the events will be produced for the periods Weeks 1-24, 1-52 and 25-52 (See Section 11.6.3 for more details)
- Treatment group mean annualized moderate/severe exacerbation rates, treatment rate ratios and associated 95% confidence intervals (CI) and p-values will be presented for all treatment comparisons specified in Section 7. The treatment rate ratios and associated 95% CIs will also be presented graphically.
- Percentage reduction in annualized moderate/severe exacerbation rates and associated 95% CIs will also be presented.

Exploring Interaction Terms

- Interaction by treatment terms will added to the main model one at a time for the following main effect covariates: age, region, sex and pre-study ICS dosage at screening, severe exacerbations in the previous year.
- Summary of test results for main effect covariates in main model will be presented along with the test results for the interaction terms mentioned above.

Supportive Statistical Analyses

- An 'on-treatment' analysis will be performed, corresponding to the 'de jure' type estimand analysis specified in the protocol.
  - The endpoint/variable, summary measure and population of interest will be the same as for the primary analysis, as outlined in Section 7.2.1, Section 7.2.2 and Section 7.2.3 respectively.
  - The covariates will be included in the model as stated above.
  - Offset: logarithm of time (year) on treatment.
  - Strategy for Intercurrent (Post-Randomization) Events:
    - An "on-treatment" strategy will be used to handle the intercurrent event of treatment discontinuation. Data collected after treatment discontinuation will be excluded from the analysis and only on-treatment data will be used.
    - No imputation of missing data is planned. Missing data is assumed Missing at Random (MAR).

Sensitivity analysis - removing sites

The primary model will be repeated excluding participants from sites PPD and PPD using data from weeks 1-52.
The results of the fitted model will be presented. Summaries and figures will not be produced.

Secondary Statistical Analyses

Sensitivity Statistical Analyses – missing data imputation

- Generalized linear model assuming a negative binomial distribution
- Imputation methods:
  - Tipping Point
  - Jump to Reference
- For each of the multiple imputations, the complete datasets of moderate/severe asthma exacerbations (both recorded and imputed) will then be analysed using a negative binomial model (on each imputation).
- Imputation and analysis model:
  - Dependent variable:
    - Imputation model: Number of recorded moderate/severe asthma exacerbations experienced per participant.
    - Analysis model: Number of recorded and imputed moderate/severe asthma exacerbations experienced per participant.
  - Covariates:
    - Categorical: treatment group, sex, region, pre-study ICS dosage at screening, severe asthma exacerbations in the previous year (0, 1, >=2).
    - Continuous: age.
  - Offset: logarithm of time (year) on study (imputation: on- and post-treatment data, analysis: including imputed time on study up to EOS or planned EOS).
- All 6-arm data are included in the model.
- LSMESTIMATE statement will be used with the treatment code as specified Section 7.
- Multiple imputation methods will be used with results from the negative binomial model combined across imputations on the log-scale, using Rubin's method [Rubin 1987] as implemented in SAS PROC MIANALYZE before exponentiating to obtain the estimates for the rates and rate ratios
- Details for the sensitivity analysis under each imputation method for post-study missing data are provided in Section 7.2.1.
- The mean annualized exacerbation rate, rate ratio (and 95% CIs) for the primary comparison of interest detailed in Section 7 will be presented. For the J2R imputation, the percentage reductions (and 95% Cis) will also be presented.
- A forest plot of the rate ratios (and 95% CI) will be presented for the de facto, de jure, sensitivity and J2R analyses.
- For the tipping point analysis, a heat map of the p-values will be produced for each of the primary comparisons of interest for the different deltas applied. A line plot of the rate ratio and 95% CI will also be produced across the deltas applied to the UMEC/FF/VI arms, with the delta for the FF/VI arm set to 0 (MAR). The tipping point where the two-sided p-value rises above 0.05 will be included in the plot if possible.
- Model checking and diagnostics will not be performed for the imputed datasets.

Unpooled data

The 'de facto' summary outputs, analysis and figures will be repeated on the unpooled data.

Subgroups

Summaries will be presented for weeks 1-52 for each of the subgroups listed in Section 5.5.2.

7.3. Other Secondary Analyses

An overview of the planned secondary analyses is provided below. The full details of secondary efficacy analyses data displays are presented in Appendix 10: List of Data Displays.

Endpoint	Absolute			Change from Baseline				
	Stats Analysis	Summary	Individual	Stats Analysis		Summary		Individual
	T	T	L	T	F	T	F	L
Clinic FEV_1 at 3 hours post study treatment (de jure type estimand)	Y	Y	Y	Y	Y	Y	Y	Y
Clinic FEV_1 at 3 hours post study treatment (de jure type estimand, pooled FF doses)	Y	Y		Y	Y	Y	Y	
SGRQ total score using pooled FF doses (de facto type estimand)	Y	Y		Y	Y	Y	Y	
SGRQ total score (de facto type estimand)	Y	Y		Y	Y	Y	Y	
ACQ-7 total score using pooled FF doses (de facto type estimand)	Y	Y		Y	Y	Y	Y	
ACQ-7 total score (de facto type estimand)	Y	Y		Y	Y	Y	Y	
E-RS total score using pooled FF doses (de facto type estimand)	Y	Y		Y	Y	Y	Y	
E-RS total score (de facto type estimand)	Y	Y		Y	Y	Y	Y	

NOTES:

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

7.3.1. Endpoint / Variables

As specified in the protocol, other secondary endpoints are:

- Change from baseline in clinic FEV_1 at 3 hours post study treatment at Week 24
- Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 24
- Change from baseline in Asthma Control Questionnaire-7 (ACQ-7) total score at Week 24
- Change from baseline in Evaluating Respiratory Symptoms (E-RS) total score over Weeks 21-24 (inclusive)

7.3.2. Summary Measure

- Mean treatment difference on change from baseline in clinic FEV_1 at 3 hours post study treatment at Week 24
- Mean treatment difference on change from baseline in SGRQ total score at Week 24
- Mean treatment difference on change from baseline in ACQ-7 total score at Week 24
- Mean treatment difference on change from baseline in E-RS total score over Weeks 21-24 (inclusive).

7.3.3. Population of Interest

The secondary efficacy analyses will be based on the ITT population.

7.3.4. Strategy for Intercurrent (Post-Randomization) Events

No imputation will be made for missing data.

7.3.5. Statistical Analyses / Methods

7.3.5.1. Statistical Methodology Specification

Endpoint
• Mean change from baseline in clinic FEV_1 at 3 hours post study treatment at Week 24
Model Specification

• Baseline value is defined in Section 5.2.
• The analysis is based on the on-treatment (de jure) type estimand, including on-treatment data collected at Week 24. This is because those participants who withdraw from study treatment will not be able to provide the 3 hours post study treatment assessment in the remainder of the study and so a de facto analysis is not possible.
• Change from baseline in clinic FEV_1 at 3 hours post study treatment at Week 24 will be analyzed using an Analysis of Covariance (ANCOVA) model
• Terms in the model:
  ○ Dependent Variable: change from baseline in clinic FEV_1 at 3 hours post study treatment at Week 24.
  ○ Covariates:
  ▪ Categorical: treatment group, sex, region, pre-study ICS dosage at screening.
  ▪ Continuous: age, baseline value for clinic FEV_1
• The LS mean FEV_1 at 3 hours post study treatment and LS mean change from baseline in FEV_1 at 3 hours post study treatment will be estimated using the observed marginal distributions of the study population covariates by inclusion of the OM (observed margins) option in SAS.
• The analysis will be repeated for the pooled FF doses, LSMESTIMATE statement will be used with the treatment code as specified Section 7.

Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Absolute values, change from pre-dose FEV_1 and change from baseline in clinic FEV_1 at 3 hours post study treatment at Day 1, Weeks 24, 36 and 52 will be summarized. • For the unpooled data, box plots and empirical distribution function plots for the change from baseline in clinic FEV_1 at 3 hours post study treatment at Week 24 will be presented.

- Least-Squares (LS) means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors. The estimated treatment difference along with corresponding standard error, 95% CI and unadjusted p-value will be presented for all treatment comparisons specified in Section 7.
- The LS mean change from baseline and LS mean treatment differences (and associated 95% CIs) for the comparisons of the two FF/UMEC/VI vs. a FF/VI at a given FF dose will be will also be presented graphically at Week 24, for each of the FF doses in two separate panels.

Endpoints

- Change from baseline in SGRQ total score at Week 24
- Change from baseline in ACQ-7 total score at Week 24
- Change from baseline in E-RS total score at Week 24

Model Specification

- Analyses are based on the treatment policy (de facto) type estimand using the pooled FF doses.
- Baseline definitions are provided in Section 5.2.
- The change from baseline for each endpoint will be analyzed using a Mixed Models Repeated Measures (MMRM) model.
- Terms in the MMRM model
  - Period:
    - SGRQ: Clinic visits Week 12 and 24
    - ACQ-7: Clinic visits at Week 4, 12 and 24
    - E-RS: Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24.
  - Covariates:
    - Categorical: treatment group, sex, region, pre-study ICS dosage at screening and period.
    - Continuous: age, baseline value
  - Interaction: baseline*period, treatment*period
    - Repeated: period
  - All 6-arm data are included in the model.
  - LSMESTIMATE statement will be used with the treatment code as specified Section 7.
  - For the E-RS endpoint, the average treatment effect over the 24-week treatment period will also be obtained from the model and presented in the analysis output.
- The model will be fitted with an unstructured variance-covariance matrix.
- The OM option in SAS will be used to derive the LS means based on the distribution of the covariates observed in the data

Analyses of other interest:

- The summaries and analyses will be repeated for the 'de facto' type estimates using the unpooled data.

Model Checking & Diagnostics

Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

• Absolute values and change from baseline will be summarized by period.
• For the ACQ endpoint, the number and percentage of participants in each control category (see Section 11.6.3) and the change in control category will be presented. A shift table of the number and percentages of participants in each control category relative to baseline will also be presented.
• Boxplots of the change from baseline at each clinic visit will be presented.
• Empirical distribution function plots of the change from baseline at each clinical visit will be presented.
• Least-Squares (LS) means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors for the relevant periods. The estimated treatment difference along with corresponding standard error, 95% CI and unadjusted p-value will be presented for all treatment comparisons specified in Section 2.4 at each timepoint.
• The LS mean change from baseline and treatment differences (and associated 95% CIs) at each timepoint will also be presented graphically.
  ○ Where unpooled FF is presented the figures will present the comparisons of the two FF/UMEC/VI vs. FF/VI at a given FF dose at each timepoint, with the FF doses in two separate panels.
  ○ Where pooled FF is presented the figures will present the comparisons of the pooled FF/UMEC/VI vs. FF/VI at a given UMEC dose will be presented graphically at each time point.

7.4. Other Efficacy Analyses

An overview of the planned other efficacy analyses is provided below. The full details of data displays are presented in Appendix 10: List of Data Displays.

All analyses will use the de-facto type estimand, unless otherwise stated.

For all non-lung function endpoints, analyses will focus on pooled FF doses. In addition, analyses of exacerbation endpoints and responder rates for ACQ-7, SGRQ and E-RS will present unpooled treatment comparisons.

For the lung function related endpoints only the unpooled analyses will be performed.

The treatment comparisons that will be presented for each endpoint are detailed in Section 7.

Other Endpoint	Absolute					Change from Baseline				
	Stats Analysis		Summary		Individual	Stats Analysis		Summary		Individual
	T	F	T	F	L	T	F	T	F	L
Clinic trough FEV_1 over the first 24 weeks of the treatment period	Y		Y		Y	Y	Y	Y		Y
Home daily trough FEV_1	Y		Y		Y	Y	Y	Y	Y	Y
Home daily PM FEV_1	Y		Y		Y	Y	Y	Y	Y	Y
Annualized rate of severe asthma exacerbations	Y	Y	Y							
Time to first severe asthma exacerbation	Y	Y	Y							
Time to first moderate/severe asthma exacerbation	Y	Y	Y							
ACQ-7, ACQ-6 and ACQ-5 responder	Y		Y	Y						
ACQ-7, ACQ-6 and ACQ-5 Asthma Control	Y		Y	Y						
SGRQ domain scores	Y		Y		Y	Y	Y	Y		Y
SGRQ responder	Y		Y	Y						
E-RS domain scores	Y		Y		Y	Y	Y	Y		Y
E-RS responder	Y		Y	Y						
Asthma Quality of Life	Y		Y		Y	Y	Y	Y		Y

Other Endpoint	Absolute					Change from Baseline				
	Stats Analysis		Summary		Individual	Stats Analysis		Summary		Individual
	T	F	T	F	L	T	F	T	F	L
Questionnaire (AQLQ) total										
AQLQ responder	Y		Y	Y						
Home daily AM PEF	Y		Y		Y	Y	Y	Y	Y	Y
Home daily PM PEF	Y		Y		Y	Y	Y	Y	Y	Y
Symptom-free days	Y		Y		Y	Y	Y	Y		Y
Rescue medication-free days	Y		Y		Y	Y	Y	Y		Y
Daily rescue medication use	Y		Y		Y	Y	Y	Y		Y
Healthcare Outcomes										
Global assessment of severity and response to treatment			Y							
Work Productivity and Activity Impairment-Specific Health Problem			Y							
Unscheduled asthma related healthcare resource utilization			Y		Y					

NOTES:

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

7.4.1. Endpoint / Variables

As specified in the protocol, other efficacy endpoints are:

- Change from baseline in clinic trough FEV_1 over the first 24 weeks of the treatment period (weighted mean)
- Change from baseline in home daily trough FEV_1 over the first 24 weeks of the treatment period
- Change from baseline in home daily PM FEV_1 over the first 24 weeks of the treatment period
- Annualized rate of severe asthma exacerbations
- Time to first severe asthma exacerbation
- Time to first moderate/severe asthma exacerbation

- Percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-7 at Week 24
- Percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-6 at Week 24
- Percentage of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-5 at Week 24
- Percentage of patients that have achieved asthma control based on ACQ-7 (i.e. a total score ≤0.75) at both Week 12 and Week 24
- Percentage of patients that have achieved asthma control based on ACQ-6 (i.e. a total score ≤0.75) at both Week 12 and Week 24
- Percentage of patients that have achieved asthma control based on ACQ-5 (i.e. a total score ≤0.75) at both Week 12 and Week 24
- Change from baseline in SGRQ domain scores (symptoms, activity, impact) at Week 24
- Percent of patients meeting a responder threshold of ≥ 4 points improvement (decrease) from baseline for the SGRQ total score at Week 24
- Change from baseline in E-RS domain scores (breathlessness, cough and sputum, chest) over Weeks 21-24 (inclusive) of the treatment period
- Percent of patients meeting a responder threshold of ≥ 2 points improvement (decrease) from baseline for the E-RS total score over Weeks 21-24 (inclusive) of the treatment period
- Change from baseline in the Asthma Quality of Life Questionnaire (AQLQ) total score at Week 24
- Percent of patients meeting a responder threshold of ≥ 0.5 points improvement (increase) from baseline for the AQLQ total score at Week 24
- Change from baseline in morning (AM) pre-dose Peak Expiratory Flow (PEF) over the first 24 weeks of the treatment period
- Change from baseline in evening (PM) PEF over the first 24 weeks of the treatment period
- Change from baseline in the percentage of symptom-free days over the first 24 weeks of the treatment period
- Change from baseline in the percentage of rescue medication-free days over the first 24 weeks of the treatment period
- Change from baseline in daily rescue medication use over the first 24 weeks of the treatment period.
- Unscheduled asthma-related healthcare resource utilization over the first 24 weeks of the treatment period.

7.4.2. Summary Measure

- Mean treatment difference on change from baseline in clinic trough FEV_1 over the first 24 weeks of the treatment period (weighted mean)
- Mean treatment difference on change from baseline in home daily trough FEV_1 over the first 24 weeks of the treatment period
- Mean treatment difference on change from baseline in home daily PM FEV_1 over the first 24 weeks of the treatment period
- Rate ratio on annualized rate of severe asthma exacerbations
- Hazard Ratio on time to first severe asthma exacerbation
- Hazard Ratio on time to first moderate/severe asthma exacerbation
- Odds ratio on percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-7 at Week 24
- Odds ratio on percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-6 at Week 24
- Odds ratio on percentage of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-5 at Week 24
- Odds ratio on percentage of patients that have achieved asthma control based on ACQ-7 (i.e. a total score ≤0.75) at both Week 12 and Week 24
- Odds ratio on percentage of patients that have achieved asthma control based on ACQ-6 (i.e. a total score ≤0.75) at both Week 12 and Week 24
- Odds ratio on percentage of patients that have achieved asthma control based on ACQ-5 (i.e. a total score ≤0.75) at both Week 12 and Week 24
- Mean treatment difference on change from baseline in SGRQ domain scores (symptoms, activity, impact) at Week 24
- Odds ratio on percent of patients meeting a responder threshold of ≥ 4 points improvement (decrease) from baseline for the SGRQ total score at Week 24
- Mean treatment difference on change from baseline in E-RS domain scores (breathlessness, cough and sputum, chest) over Weeks 21-24 (inclusive) of the treatment period
- Odds ratio on percent of patients meeting a responder threshold of ≥ 2 points improvement (decrease) from baseline for the E-RS total score over Weeks 21-24 (inclusive) of the treatment period
- Mean treatment difference on change from baseline in the Asthma Quality of Life Questionnaire (AQLQ) total score at Week 24
- Odds ratio on percent of patients meeting a responder threshold of ≥ 0.5 points improvement (increase) from baseline for the AQLQ total score at Week 24
- Mean treatment difference on change from baseline in morning (AM) pre-dose Peak Expiratory Flow (PEF) over the first 24 weeks of the treatment period

- Mean treatment difference on change from baseline in evening (PM) PEF over the first 24 weeks of the treatment period
- Mean treatment difference on change from baseline in the percentage of symptom-free days over the first 24 weeks of the treatment period
- Mean treatment difference on change from baseline in the percentage of rescue medication-free days over the first 24 weeks of the treatment period
- Mean treatment difference on change from baseline in daily rescue medication use over the first 24 weeks of the treatment period.
- Unscheduled asthma-related healthcare resource utilization over the first 24 weeks of the treatment period.

7.4.3. Population of Interest

The Other efficacy analyses will be based on the Intent-To-Treat population

7.4.4. Strategy for Intercurrent (Post-Randomization) Events

No imputation will be made for missing data.

In general, a "treatment policy" strategy will be used to handle all intercurrent events, as described in Section 7.1.4, with the exception of the analyses of responders and asthma control.

For these analyses, a "treatment policy" strategy will be used to handle the intercurrent event of early discontinuation from study treatment, and a "composite" strategy will be used to handle the intercurrent event of premature withdrawal from study, where subjects who withdraw from the study prior to the timepoint of interest are considered non-responders at that timepoint. Participants with missing data at the timepoint of interest, regardless of treatment status, will be considered as non-responders. The endpoint analyzed will therefore essentially be the percent of participants who do not prematurely discontinue from the study, have data available at the timepoint and meet the responder threshold.

7.4.4.1. Statistical Methodology Specification

Endpoint
Mean change from baseline in clinic trough FEV_1 over the first 24 weeks of the treatment period
Model Specification
• Clinic trough FEV_1 over the first 24 weeks of the treatment period and the change from baseline will be summarized. • Baseline value is defined in Section 5.2. • The analysis is based the on- and post-treatment (de facto) type estimand, including all clinic trough FEV_1 data collected at all scheduled clinic visits prior to and on Week 24 (both on- and

post-treatment). The derivation of clinic trough FEV_1 AUC_{0-24w} will use all data collected at Baseline, Weeks 4, 12, and 24.

- Change from baseline in clinic trough FEV_1 over the first 24 Weeks will be analyzed using an ANCOVA model.
- Terms in the model:
  - Covariates:
    - Categorical: treatment group, sex, region, pre-study ICS dosage at screening,
    - Continuous: age, baseline value for clinic FEV_1
- The LS mean FEV_1 over the first 24 weeks and LS mean change from baseline over the first 24 weeks will be estimated using the observed marginal distributions of the study population covariates by inclusion of the OM (observed margins) option in SAS.

Model Checking & Diagnostics

- Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- Summary statistics of the absolute and change from baseline in FEV_1 over the first 24 weeks will be presented.
- Least-Squares (LS) means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors. The estimated treatment difference along with corresponding standard error, 95% CI and unadjusted p-value will be presented for all treatment comparisons specified in Section 7.
- The LS mean change from baseline and LS mean treatment differences (and associated 95% CIs) for the comparisons of the two FF/UMEC/VI vs. a FF/VI at a given FF dose will also be presented graphically at Week 24, for each of the FF doses in two separate panels.

Endpoints

- Mean change from baseline in home daily trough FEV_1 over the first 24 weeks of the treatment period
- Mean change from baseline in home daily PM FEV_1 over the first 24 weeks of the treatment period
- Mean change from baseline in home daily morning (AM) pre-dose PEF over the first 24 weeks of the treatment period
- Mean change from baseline in home daily evening (PM) PEF over the first 24 weeks of the treatment period
- Mean change from baseline in E-RS Breathlessness scores over Weeks 21-24 (inclusive) of the treatment period
- Mean change from baseline in E-RS Cough & Sputum scores over Weeks 21-24 (inclusive) of the treatment period
- Mean change from baseline in E-RS Chest Symptoms scores over Weeks 21-24 (inclusive) of the treatment period
- Mean change from baseline in the percentage of symptom-free days over the first 24 weeks of the treatment period
- Mean change from baseline in the percentage of rescue medication-free days over the first 24 weeks of the treatment period
- Mean change from baseline in daily rescue medication use over the first 24 weeks of the

treatment period.
Model Specification
• These analyses will be performed using an MMRM model as for the E-RS data detailed in Section 7.3.5.1, using the on- and post-treatment (de facto) type estimand. • The home daily trough FEV_1, PM FEV_1, AM PEF and PM PEF endpoints will be analyzed and presented using unpooled doses. • The E-RS domains, percentage of symptom free days, percentage of rescue medication free days and daily rescue medication use will be analyzed and presented using the pooled FF doses. • The home daily trough FEV_1, PM FEV_1, AM PEF and PM PEF endpoints will also be summarized in 1 weekly periods up to week 52. • To assess for time to maximal effect of UMEC when comparing FF/UMEC/VI to FF/VI, weekly changes from baseline in Home Daily Trough FEV_1 over the first 8 weeks of the treatment period will also be analyzed using the same MMRM detailed in Section 7.3.5.1. Here the period term is: ○ Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8 • The LS mean change from baseline and LS mean treatment difference in percentage of symptom-free days and percentage of rescue medication-free days will also be presented as the equivalent number of additional symptom-free/rescue medication-free days per week.
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Model Results Presentation
• These analyses will be presented as for the E-RS data detailed in Section 7.3.5.1. Box plots and empirical distribution plots will not be presented. • A plot of the LS mean change and LS mean treatment difference will be produced for the Home Daily Trough FEV_1 data for the 1-weekly intervals up to week 8 (in a similar manner to the 4-weekly data up to week 24). • A line plot of the unadjusted weekly mean change from baseline in home daily trough FEV_1, PM FEV_1, AM and PM PEF will be presented up to 24 weeks. • For the E-RS domain (Breathlessness, cough & sputum and chest symptom) scores, these will be included in the same summaries and presented by domain. A forest plot will display the treatment estimate and 95% CI for the E-RS total score and domain scores at Weeks 21- 24.

Endpoint
• Annualized rate of severe asthma exacerbations
Model Specification
• Data for weeks 1-52 will be analyzed using a generalized mixed model as specified in Section 7.2.6 based on the on- and post-treatment (de facto) type estimand, presenting both unpooled and pooled FF dose treatment comparisons.
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Model Results Presentation
• See Section 7.2.6

Endpoints
• Time to first severe asthma exacerbation • Time to first moderate/severe asthma exacerbation
Model Specification

• Cox's proportional hazards model
• All asthma exacerbations observed during the study (on- or post-treatment) will be used in the analyses
• Terms in the model:
  • Response: time to first severe (or moderate/severe) asthma exacerbation during the study (both on- and post-treatment)
  • Covariates:
  ○ Categorical: treatment group, sex, region, pre-study ICS dosage at screening, severe asthma exacerbations in the previous year (0, 1, >=2).
  ○ Continuous: age
• The 'exact' method will be used for handling ties. If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used instead.
• For the pooled analysis:
• All 6-arm data are included in the model.
• LSMESTIMATE statement will be used with the treatment code as specified Section 7.
• The analyses will be repeated using unpooled data.

Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Model Results Presentation
• Hazard ratios for pairwise treatment comparisons with associated 95% CIs and p-values will be presented. • Kaplan-Meier survivor functions will be obtained for each treatment group using PROC LIFETEST with a TIME statement.

Endpoints
• Percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-7 at Week 24 • Percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-6 at Week 24 • Percentage of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-5 at Week 24 • Percent of patients meeting a responder threshold of ≥ 4 points improvement (decrease) from baseline for the SGRQ total score at Week 24 • Percent of patients meeting a responder threshold of ≥ 2 points improvement (decrease) from baseline for the E-RS total score over Weeks 21-24 (inclusive) of the treatment period • Percent of patients meeting a responder threshold of ≥ 0.5 points improvement (increase) from baseline for the AQLQ total score at Week 24
Model Specification
• The analysis includes on-and post-treatment data and is based on the ITT population.

- For details of handling missing data, see Section 11.7.2.
- Analyses for the ACQ-7, SGRQ and E-RS total score will present unpooled and pooled FF doses treatment comparisons.
- Analyses for the ACQ-5, ACQ-6 and AQLQ will be carried out for the pooled FF doses.
- Percent of participants meeting the responder threshold will be summarized by period, and analyzed using a generalized linear model (logistic regression), including all data up to week 24.
- Computation of confidence intervals for the odds ratios is based on the individual Wald tests calculated on the log scale and then back transformed.
- Period:
    - ACQ-5, ACQ-6, ACQ-7, AQLQ: Clinic visits at Week 4, 12 and 24
    - SGRQ: Clinic visits Week 12 and 24
    - E-RS: Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24.
- Terms in the model:
    - Dependent Variable: Responder (Yes/No)
    - Covariates:
        - Categorical: treatment group, sex, region, pre-study ICS dosage at screening and period.
        - Continuous: age, Baseline value
    - Interaction: Baseline*period, treatment*period
- Link function: Logit
- All 6-arm data are included in the model.
- Where the output presents the pooled FF doses, LSMESTIMATE statement will be used with the treatment code as specified Section 7.
- The model will be fitted with an unstructured variance-covariance matrix.
- The OM option in SAS will be used.

Model Checking & Diagnostics

- Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses

Model Results Presentation

- Number and percentage of responders and non-responders for each treatment at each Week will be presented. The number of non-responders due to missing data will also be presented.
- The odds ratio for all treatment comparisons as specified in Section 7, with associated 95% CI and p-value will be presented by visit.
- A forest plot displaying the odds ratios (and 95% CI) for the primary treatment comparisons as specified in Section 7 at week 24 (weeks 21-24 for the E-RS endpoint) will be presented.

Endpoints

- Percentage of patients that have achieved asthma control based on ACQ-7 (i.e. a total score ≤0.75) at both Week 12 and Week 24
- Percentage of patients that have achieved asthma control based on ACQ-6 (i.e. a total score ≤0.75) at both Week 12 and Week 24
- Percentage of patients that have achieved asthma control based on ACQ-5 (i.e. a total score ≤0.75) at both Week 12 and Week 24

Model Specification

- The analysis includes on-and post-treatment data and is based on the ITT population.
- For details of handling missing data, see Section 11.7.2.
- Analysis for the ACQ-7 will present unpooled and pooled FF dose treatment comparisons.

• Analyses for the ACQ-5 and ACQ-6 will be carried out for the pooled FF doses.
• Percent of participants meeting the asthma control criterial will be summarized and analyzed using a generalized linear model (logistic regression).
• Computation of confidence intervals for the odds ratios is based on the individual Wald tests calculated on the log scale and then back transformed.
 	
• Terms in the model:
  ○ Dependent Variable: Asthma control (Yes/No)
  ○ Covariates:
  ▪ Categorical: treatment group, sex, region and pre-study ICS dosage at screening
  ▪ Continuous: age, Baseline value
• Link function: Logit
• All 6-arm data are included in the model.
• Where the output presents the pooled FF doses, LSMESTIMATE statement will be used with the treatment code as specified Section 7.
• The model will be fitted with an unstructured variance-covariance matrix.
• The OM option in SAS will be used.

Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Model Results Presentation
• Number and percentage of participants with and without asthma control for each treatment. The number of participants without asthma control due to missing data will also be presented. • Odds ratio for treatment comparison with associated 95% CI and p-value as specified Section 7. • A forest plot displaying the odds ratios (and 95% CI) for the primary treatment comparisons as specified in Section 7 at week 24 will be presented.

Endpoint
• Mean change from baseline in SGRQ domain scores at Week 24
Model Specification
• Change from baseline in SGRQ domain scores will be summarized and analyzed as for the SGRQ total score as specified in Section 7.3.5.1, for each domain separately. • Summaries and analyses will use the on- and post-treatment (de facto) type estimand and be presented for pooled FF doses.
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Model Results Presentation
• As for the SGRQ specified in Section 7.3.5.1. Summaries and analyses will be presented by domain. A forest plot will display the treatment estimate and 95% CI for the SGRQ total score and domain scores at Week 24.

Endpoint
• Mean change from baseline in AQLQ total score at Week 24
Model Specification
• Change from baseline in AQLQ total score will be summarized and analyzed as for the SGRQ endpoint as specified in Section 7.3.5.1. • Summaries and analyses will use the on- and post-treatment (de facto) type estimand and be presented for pooled FF.
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Model Results Presentation
• As for the SGRQ specified in Section 7.3.5.1.

Other Statistical Analyses
Endpoints
• Unscheduled asthma-related healthcare resource utilization over the first 24 weeks. • WPAI-SHP • Global assessment of severity • Global assessment of response to treatment
Model Specification
• Summaries will use the on- and post-treatment (de facto) type estimand and be presented for unpooled data. • No formal statistical analyses will be carried out. • Unscheduled asthma-related healthcare resource utilization will also be summarized by contact type (related to an exacerbation/not related to an exacerbation) and up to 52 weeks for subjects with ≥ 36 Weeks of planned treatment exposure.
Model Checking & Diagnostics
Not applicable
Model Results Presentation
• Summary statistics appropriate for the data collected at visits where data was collected.

8. SAFETY ANALYSES

All safety analyses will be based on the ITT population. On-treatment safety data collected at scheduled clinic visits will be summarized and analyzed by treatment and by visit, unless otherwise specified. On-treatment adverse events and post-treatment adverse events will be summarized separately. All data will be listed, unless otherwise specified.

An overview of the planned analyses is provided below. The full details of safety analysis data displays are presented in Appendix 10: List of Data Displays

	Absolute			Change from Baseline		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Exposure						
Extent of Treatment Exposure (unpooled and pooled FF doses)	Y					
Post-Treatment Duration on Study	Y					
Adverse Events (AEs)						
Relationship of AE System Organ Class, Preferred Term and Verbatim Text			Y[1]			
AEs during screening/ run-in period	Y		Y[1]			
AEs during stabilization period	Y		Y[1]			
Overview of On-Treatment AEs	Y					
On-Treatment AEs	Y		Y			
On-Treatment AEs adjusted for exposure (per thousand person-years)	Y					
On-Treatment AEs in the respiratory, thoracic and mediastinal disorders SOC	Y					
On-Treatment AEs in the respiratory, thoracic and mediastinal disorders SOC (per thousand person-years)	Y					
Post-Treatment AEs during the study	Y		Y			
Post-Study AEs	Y		Y			
On Treatment AEs during Weeks 1-24	Y					
On Treatment AEs during Weeks 1-36 for participants with ≥ 36 weeks of planned treatment exposure	Y					
On Treatment AEs during Weeks 1-52 for participants with 52 weeks of planned treatment	Y					

	Absolute			Change from Baseline		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
exposure						
On-Treatment Drug-Related AEs	Y					
On-Treatment Drug-Related AEs during the study adjusted for exposure (per thousand person-years)	Y					
Post-Treatment Drug-Related AEs	Y					
On-Treatment SAEs	Y					
On-Treatment SAEs adjusted for exposure (per thousand person-years)	Y					
Post-Treatment SAEs	Y					
Non-fatal SAEs			Y			
Fatal SAEs			Y			
On-Treatment Drug-Related SAEs	Y					
On-Treatment Drug-Related SAEs adjusted for exposure (per thousand person-years)	Y					
On-Treatment SAEs during Weeks 1-24	Y					
On-Treatment SAEs during Weeks 1-36 for participants with ≥ 36 weeks of planned treatment exposure	Y					
On-Treatment SAEs during Weeks 1-52 for participants with 52 weeks of planned treatment exposure	Y					
On-Treatment AEs Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study	Y		Y			
Post-Treatment AEs Leading to Withdrawal from Study	Y		Y			
On-Treatment AESIs	Y		Y			
On-Treatment AESIs adjusted for exposure (per thousand person-years)	Y					
Post-treatment AESIs	Y					
On-Treatment AESIs during Weeks 1-24	Y					
On-Treatment AESIs during Weeks 1-36 for participants with ≥ 36 weeks of planned treatment exposure	Y					
On-Treatment AESIs during Weeks 1-52 for participants with 52 weeks of planned treatment	Y					

	Absolute			Change from Baseline		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
exposure						
On-Treatment SAEs of Special Interest	Y		Y			
On-Treatment SAEs of Special Interest adjusted for exposure (per thousand person-years)	Y					
Post-treatment SAEs of special interest	Y					
On-treatment AEs (3% or More of Participants in Any Treatment Group)	Y					
The 10 Most Frequent On-treatment Adverse Events in Each Treatment Group	Y					
On-Treatment AEs during Study by Subgroups	Y					
Subject Numbers for Individual AEs			Y			
Subject Numbers for On-Treatment AEs of Special Interest			Y			
MACE						
On-Treatment Major Adverse Cardiac Events (Narrow Definition)	Y					
On-Treatment Major Adverse Cardiac Events (Broad Definition)	Y					
On-Treatment Major Adverse Cardiac Events (Narrow Definition) adjusted for exposure (per thousand person-years)	Y					
On-Treatment Major Adverse Cardiac Events (Broad Definition) adjusted for exposure (per thousand person-years)	Y					
Pneumonia and radiography (Chest X-rays)						
On-Treatment Pneumonia and radiography (Chest X-rays)	Y		Y			
Liver Events						
Medical conditions for participants with liver stopping events			Y			
Liver Event Results and Time of Event Relative to Treatment			Y			
Liver Event Substance Use			Y			
Liver Event Information for RUCAM Score			Y			
Liver Biopsy Details			Y			
Liver Imaging Details			Y			

	Absolute			Change from Baseline		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Laboratory Parameters						
Chemistry Values for Participants with at Least One Value Outside the Normal Range			Y			
Chemistry Data	Y	Y		Y	Y	
Chemistry Data Outside the Normal Range	Y					
Chemistry Changes from Baseline Relative to the Normal Range	Y					
Hematology Values for Participants with at Least One Value Outside the Normal Range			Y			
Hematology Data	Y	Y		Y	Y	
Hematology Data Outside the Normal Range	Y					
Hematology Changes from Baseline Relative to the Normal Range	Y					
Worst Case Urinalysis Results Post-Baseline Relative to Baseline				Y		Y
Vital Signs						
Vital Sign Data (Pulse Rate, Sys BP, Dia BP)[2]	Y		Y	Y	Y[2]	
12-Lead ECGs						
ECG Values[2]	Y			Y	Y[2]	Y
ECG Findings	Y		Y			
ECG Findings Shifts from Baseline	Y					
QTcF Categories	Y			Y		
ECG Abnormalities	Y		Y			Y
Maximum Post-Baseline QTcF	Y	Y		Y	Y	

NOTES:

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

1 – All Subjects Enrolled population

2 – Statistical analysis also performed for change from baseline in vital signs (pulse rate, SBP, DBP) and ECG parameters (PR interval, QTc(F) interval and heart rate)

8.1. Extent of Exposure

The extent of exposure to fluticasone/salmeterol [FSC], 250/50 mcg, via the DISKUS DPI during the run-in period, to FF/VI 100/25mcg, via the ELLIPTA DPI during the stabilization period, to randomised study treatment and post-treatment data will be summarized by the categories in Section 11.6.4. The number of days of post-treatment

data will also be summarized for all participants with at least one day of post-treatment data.

8.2. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards.

The CRF texts for adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be reported using the primary System Organ Class (SOC) and the Preferred Term.

Adverse events will be summarized and grouped by primary SOC and by adverse event (i.e., Preferred Term) within primary SOC. Results will be displayed in the order of decreasing frequency, both across primary SOC and within primary SOC. The number of participants with one or more events of any type will also be calculated. The relationship of primary SOC, Preferred Terms, and verbatim text will be listed.

The following summaries will be provided:

- AEs during screening/run-in.
- AEs during stabilization period.
- On-treatment AEs: All AEs, drug-related AEs, all SAEs, drug-related SAEs
  - Outputs will be repeated adjusted for exposure (per thousand persons years) to account for variable treatment duration
- Post-treatment AEs: All AEs, drug related AEs, all SAEs
- Post-study AEs.

Adverse events will also be summarized by gender, age, race, region, pre-study ICS dosage at screening, BMI and CV History/Risk Factor at Screening.

In addition, the on-treatment AEs and on-treatment SAEs will be presented (see Section 11.6.4 for more details on participants and reporting period included in each table):

- Up to week 24
- Up to week 36 for all participants whose EOS visit or planned EOS visit is after week 24
- Up to week 52 for all participants whose EOS visit or planned EOS visit is after week 36

In addition, common (3% or more participants in any treatment arm) on-treatment adverse will be presented. To support this, the 10 most frequent AEs in each treatment group will be presented.

8.3. Adverse Events of Special Interest Analyses

Adverse events of special interest have been defined as AEs which have specified areas of interest for one or more of the compounds (FF, VI and/or UMEC) or combination therapies (FF/UMEC/VI and/or FF/VI). These consist of groupings of preferred terms

based on the MedDRA dictionary version used in each reporting effort. Subgroups may be defined, based on relevant combination of preferred terms, or on Standardized MedDRA queries (SMQ).

The table below presents the special interest AE groups for FF, UMEC and VI, defined upon the release of version 21.1 of the MedDRA dictionary.

Special Interest AE Group		**Special Interest AE Subgroup**	**PTs/SMQs for Inclusion**
Cardiovascular effects*		Cardiac arrhythmia	Cardiac arrhythmia (SMQ), excluding congenital and neonatal arrhythmias
		Cardiac failure	Cardiac Failure (SMQ)
		Cardiac ischaemia	Ischaemic Heart Disease (SMQ)
		Stroke	Central nervous system haemorrhages and cerebrovascular conditions (SMQ)
		Hypertension	Hypertension (SMQ)
Pneumonia			Infective pneumonia (SMQ)
LRTI excluding infective pneumonia SMQ			Selected PTs
Decreased bone mineral density and associated fractures			Osteoporosis/Osteopenia (SMQ) Selected PTs
Hypersensitivity			Hypersensitivity (SMQ) Angioedema (SMQ) Anaphylactic reaction (SMQ)
Anticholinergic Syndrome*			Anticholinergic Syndrome SMQ
Gastrointestinal obstruction*			Gastrointestinal obstruction SMQ
Adrenal Suppression			Selected PTs
Antimuscarinic ocular effects / Corticosteroid Associated Eye Disorders		Glaucoma (antimuscarinic / corticosteroid)	Glaucoma (SMQ),
		Cataracts (corticosteroids)	Lens disorder (SMQ)
Effects on Glucose			Hyperglycaemia/new onset diabetes mellitus (SMQ)
Local steroid effects			Selected PTs
Urinary retention*			Selected PTs
Effects on potassium			Selected PTs
Tremor			Selected PTs
Asthma/Bronchospasm for Asthma-related intubations and deaths			Asthma/bronchospasm SMQ

Special Interest AE Group		Special Interest AE Subgroup	PTs/SMQs for Inclusion
Dry mouth / Drying of airway secretions*			Selected PTs (narrow and broad focus)
*: of interest for UMEC			

Adverse events of special interest will be summarized in the same manner outlined in Section 8.2 for overall AEs, and by the study population subgroups identified in Section 5.5.2.

In addition, the on-treatment AESIs will be summarized (see Section 11.6.4 for more details on participants and reporting period included in each table):

- Up to week 24
- Up to week 36 for all participants whose EOS visit or planned EOS visit is after week 24
- Up to week 52 for all participants whose EOS visit or planned EOS visit is after week 36

8.4. Major Adverse Cardiac Events

Major Adverse Cardiac Events (MACE) endpoint will be analyzed using broad and narrow definitions.

The broad MACE will be defined as:

- Cardiac Ischaemia Special Interest AE Subgroup (Ischaemic Heart Disease SMQ) excluding fatalities,

- Stroke Special Interest AE Subgroup (Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ) excluding fatalities

The narrow MACE will be defined as:

- PTs of “myocardial infarction” and “acute myocardial infarction” excluding fatalities,

- Stroke Special Interest AE Subgroup (Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ) excluding fatalities

The broad and narrow MACE tables will also be provided adjusted for exposure (per thousand persons years) to account for variable treatment duration.

CV deaths will be considered in the CSR, alongside the broad and narrow MACE defined above.

8.5. Clinical Laboratory Analyses

On-treatment laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 10: List of Data Displays

Laboratory values will be classified as 'Low', 'Normal', or 'High' based on the provided normal ranges.

Change from baseline values will be classified relative to the normal range as 'To Low', 'To Normal or No Change', or 'To High'. Participants who do not change categories or move from out-of-range to normal will be classified as 'To Normal or No Change'.

An 'any time post-baseline' change classification will be derived for each treatment in which participants will be counted in the 'To Low' or 'To High' categories if they reported a change from a 'Normal' baseline to a value below or above the normal range, respectively, at any on-treatment scheduled, unscheduled, or EW visit during the associated treatment. Participants who did not report a change to a value outside the normal range at any visit while taking the associated treatment will be counted in the 'To Normal or No Change' category.

8.6. Other Safety Analyses

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

8.6.1. Vital Signs

Vital signs (pulse rate, diastolic blood pressure, and systolic blood pressure) are measured at every clinic visit, starting at Visit 1, and prior to conducting spirometry.

The 'minimum post-baseline' and 'maximum post-baseline' value will be derived as the minimum and maximum on-treatment value recorded at any scheduled, unscheduled, or Early Withdrawal (EW) visit after the start of study treatment. See Section 8.6.4 for details on the statistical analysis of vital signs data.

8.6.2. ECG

The on-treatment ECG measurements of interest are QTc (F), QTc(B), heart rate, and PR interval. All ECG data present in the database will be considered valid and will be reported (even if the ECG had a technical error).

A 'maximum post-baseline' and 'minimum post-baseline' QTc (F), QTc(B), PR interval, and heart rate value will be derived as the maximum (or minimum) on-treatment value recorded at any scheduled, unscheduled, or EW visit after the start of study treatment.

Absolute and change from baseline QTc (F) values (including 'maximum post-baseline') will be categorized as detailed in Section 11.6.4.

See Section 8.6.4 for details on the statistical analysis of QTc (F), PR interval and heart rate data.

An 'any time post-baseline' ECG interpretation will be derived as the worst on-treatment interpretation recorded at a scheduled, unscheduled, or EW visit after the start of study treatment. The order of severity from worst to best for ECG interpretation is: abnormal, normal, unable to evaluate.

8.6.3. Pregnancy

Any pregnancies reported during the study will be summarized in case narratives. Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE and included in summaries and listings of AEs/SAEs.

8.6.4. Planned Statistical Analyses of Safety Endpoints

8.6.4.1. Vital Signs and ECGs

Statistical Analysis of Safety Endpoints
Endpoints
• Change from baseline in Pulse rate • Change from baseline in Systolic BP • Change from baseline in Diastolic BP • Change from baseline in QTc (F) • Change from baseline in PR Interval • Change from baseline in Heart Rate (ECG)
Model Specification, Checking, Results Presentation and SAS code
• Data up to Week 24 for these endpoints will be analyzed using the same methodology as trough FEV_1 in Section 7.1.6 using the on-treatment (de jure) type estimand and unpooled data. • Treatment comparisons 1) and 2) only as defined in Section 7 will be presented.

9. POP PK DATA SPECIFICATION

Population PK analysis will be the subject of a separate RAP and reported separately. Pop PK dataset preparation will be performed by Contract Research Organisation.

9.1. Pop PK Dataset Specification

General Description:

- Missing or unknown values in covariates, if not to be imputed, will be assigned -99;
- The dataset is sorted by STUDYID, SUBJID, DATETIME, EVID descending unless specify otherwise
- The data items (columns) in the analysis-ready data file will be provided the same order as follows.
- Non-numerical concentration values (such as missing samples, not assayed samples, or non-reportable samples) will not be included.

- Participants with no quantifiable concentration values will be included.
- Dosing events occurring prior to the subsequent PK sample(s) will be included (i.e., dosing events on the preceding day for pre-dose PK samples, and dosing events at the specified visit for post-dose samples)
- Liver event data will be retained in the dataset.

The dataset will be a comma delimited ASCII text file and will be named: NM.205715.PK.v1.csv.

Table 1 provides a list of variables required for the Pop PK dataset and format for the variables.

Table 1 Variables required in the Pop PK (*Mandatory variable name, included for traceability)

Variable	Label (Variable description)	Type	Units	Missing value	Codes/Derivation/Notes
ID	NONMEM subject identifier	Integer	None	Never	Sequential subject identifier to start at PP
STUDYID*	Unique identifier for a study	Char	None	Never	205715
USUBJID*	Unique subject identifier	Char	None	Never	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product. As in the SAS dataset.
SUBJID*	Subject identifier for study	Char	None	Never	Subject identifier, which must be unique within the study. As in the SAS dataset.
COUNTRY*	Country	Char	None	Never	Country of the investigational site in which the subject participated in the trial. e.g. USA
CNC	NONMEM Country code	Integer	None	Never	*As in SAS dataset if available, otherwise generate a numerical code for each country, e.g. 1, 2,…*
SITEID*	Unique identifier for a study site	Num	None	Never	e.g. PPD any lead zero should not be included.
DGRP	Actual Treatment group	Char	None	Never	As in SAS dataset e.g. FF/UMEC/VI 100/62.5/25
DOSEFF	Dose amount of FF	Num	*ug*	Never	Actual dose amount to be entered in all rows for each subject. e.g. DOSEFF=100 for FF/UMEC/VI 100/62.5/25
DOSEUMEC	Dose amount of UMEC	Num	*ug*	Never	Actual dose amount to be entered in all rows for each subject. e.g. DOSEUMEC=62.5 for FF/UMEC/VI 100/62.5/25; DOSEUMEC=0 for FF/VI 100/25

Variable	Label (Variable description)	Type	Units	Missing value	Codes/Derivation/Notes
DOSEVI	Dose amount of VI	Num	*ug*	Never	Actual dose amount to be entered in all rows for each subject. e.g. DOSEVI=25 for FF/UMEC/VI 100/62.5/25
VISIT	Planned Study visit	Char	none	Never	Scheduled visit, as in SAS dataset
VISITNUM	Planned study visit	Num	none	Never	Scheduled visit, as in SAS dataset, in numeric format
DAY	Study day number of record	Num	day	Never	Day of study relative to first IP dose
PTM	Planned Time	Char	*None*	Only for dosing records	Planned Time As in SAS dataset Blank for dosing records.
DATETIME	Date and time of dose and PK sample	MM/DD/YYYY HH:MM:SS	None	Never	Date and time of dose and PK measurement record
TIME	Relative time from LAST dose to sample	Num	*h*	Never	Actual time from last dose of IP prior to sample. **For pre-dose sample on a visit, TIME=relative time from the dose taken at the previous day.** For dosing records, set TIME = 0.
AMTFF	NONMEM Amount of FF administered	Num	*ug*	Never	AMTFF=DOSEFF for rows of dosing event AMT='0' for observation rows
AMTUMEC	NONMEM Amount of UMEC administered	Num	*ug*	Never	AMTFF=DOSEUMEC for rows of dosing event AMT='0' for observation rows
AMTVI	NONMEM Amount of VI administered	Num	*ug*	Never	AMTFF=DOSEVI for rows of dosing event AMT='0' for observation rows
ANALYTE	Analyte measured	char	None	Never	As in the SMS2000 e.g. FF, UMEC, VI
RESC	Conc for corresponding ANALYTE (char)	char	*pg/mL*	blank	As in the SMS2000. If measurement is below LLQ, it is populated as NQ, otherwise, it is populated as the actual measurement. No sample (NS), insufficient sample (IS) and no result (NR) records will be excluded from dataset.
CONC	Conc for corresponding ANALYTE (num)	Num	*pg/mL*	"."	Dosing row CONC=0. NQ will be included in the dataset but set as "."

Variable	Label (Variable description)	Type	Units	Missing value	Codes/Derivation/Notes
LNCONC	Natural log of CONC column	Num	None	Never	If CONC=0 or CONC=".", then LNCONC='.'
LLQ	Lower Limit of quantification	Num	pg/mL	Never	Lower limit of quantification of assay. LLQ=0 for dosing rows.
LNLLQ	Natural log of LLQ	Num	None	Never	If LLQ=0, then LNLLQ='.'
LABL	Label describing the record	Char	None	Never	LABL explains the type of measurement for CONC for the current record LABL=DOSE for dosing row, LABL=CONC for observation rows.
TYPE	For handling NQ values in NONMEM	Integer			If LABL=DOSE then TYPE = 0, If CONC value present TYPE = 1 If LABL=CONC and CONC value missing TYPE = 2
MDV1	Missing data variable	Integer			0 if LABL contains CONC; 1 if LABL contains DOSE
EVID	NONMEM Event ID	Integer	None	Never	*EVID=1 for LABL=DOSE,* *EVID=0 for LABL=CONC*
II	NONMEM Inter-dose interval	Integer	*Specify*	Never	II=24 for dosing rows, II=0 for PK observation rows.
SS	Steady-state data item	Integer	None	Never	SS=1 for dosing records SS=0 for PK observation rows
RATE	NONMEM Rate of drug infusion	Integer	None	Never	Rate = 0 For PK observation rows, Rate = -2 for dosing records
MDV	NONMEM Missing data value	Integer	None	Never	MDV=1 for dosing records MDV=0 for CONC >0 MDV=1 for CONC="."
OCC	Occasion	Integer	None	Never	*e.g. OCC=1 for Week 12* *OCC=2 for Week 24* *OCC=3 for Week 52* *OCC=4 for Early Withdrawal*
POPTEXT	Subject population text	Char	None	Never	*POPTEXT="ASTHMA"*
AGE	Subject Age	Num	*Specify*	-99	From source data.
SEX	Subject gender	Integer	None	Never	0=Male, 1=Female
SEXTEXT	Subject gender text	Char	None	Never	Text corresponding to code for SEX
BMI	Baseline Body Mass Index	Num	*Specify*	-99	From source data. Formula: Weight(kg)/(height(m)**2)
WT	Baseline Subject weight	Num	*Specify*	-99	From source data.
HT	Baseline Subject height	Num	*Specify*	-99	From source data.

Variable	Label (Variable description)	Type	Units	Missing value	Codes/Derivation/Notes
RACE	Subject race code1	Integer	None	-99	From source data e.g. 1=African American / African Heritage 2=American Indian or Alaska Native 3=Asian – Central / South Asian Heritage 4=Asian – East Asian Heritage 5=Asian – Japanese Heritage 6=Asian – South East Asian Heritage 7=Asian – Mixed Race 8=Native Hawaiian or other Pacific Islander 9=White – Arabic / North African Heritage 10=White – White / Caucasian / European Heritage 11=White – Mixed Race 12=Mixed Race
RACETXT	Subject race text	Char	None	Never	Text corresponding to code for RACE
ETHN	Subject ethnicity	Num	None	-99	From source data definition. E.g. 1=Hispanic or Latino, 2=Non-Hispanic
ETHNTEXT	Subject ethnicity text	Char	None	Never	Text corresponding to code for ETHN.
REGN	Region for subject	Num	None	-99	1 = Japan (All subjects recruited from study centres in Japan) 2 = Korea (All subjects recruited from study centres in South Korea) 3 = Rest of the World (to include all other countries)
SMOK	Subject smoking status	Integer	None	Never	0=Non-smoker, 1=Smoker, 2=Former smoker
SMOKTEXT	Subject smoking status text	Char	None	Never	Text corresponding to code for SMOK
FEV1	FEV_1 at baseline	Num	None	Never	As in the source dataset
FVC	FVC at baseline	Num	None	Never	As in the source dataset
FEV1FVC	Ratio of FEV_1 and FVC at baseline	Num	None	Never	As in the source dataset 0=>=0.7 (70%); 1=<0.7 (70%)
CRCL	Baseline Creatinine Clearance	Num	mL/min	-99	From source data. *formula e.g.* Creatinine Clearance will be calculated based on the Cockcroft-Gault equation. • CrCL (ml/min) = [140 – AGE (in

Variable	Label (Variable description)	Type	Units	Missing value	Codes/Derivation/Notes
					years)]*Weight(kg)*0.85 (for female patients) / [72* Serum Creatinine (micromol/L) * 0.0113]
ALT	Alanine aminotransferase	Num		-99	Baseline defined in the source dataset
AST	Aspartate aminotransferase	Num		-99	Baseline defined in the source dataset
ALB	Albumin	Num		-99	Baseline defined in the source dataset
TBIL	Total bilirubin	Num		-99	Baseline defined in the source dataset
SCR	Serum Creatinine	Num	micro mol/L	-99	Baseline defined in the source dataset
PKSUB	PK substudy indicator	Integer			1 – if subject is in PK subset (same for all rows for the subject) 0 – if subject is not in PK subset
ERRCONT	Incorrect container indicator	Integer			1 – if subject received an incorrect container and any of the PK sampling or dosing dates/times are between the treatment start and end date (inclusive) of the incorrect container (flag only those specific PK records) 0 – otherwise
EXCREC	Exception record	Char	None	Blank	Flag for records for which the date/time and other information was obtained from the PK Exceptions Document, via data management. These records were not entered into the CRF database and correspond to samples that may have been taken in error or at an incorrect visit.

10. REFERENCES

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GlaxoSmithKline Document Number 2016N271022_02 Study 205715, a Phase III, randomized, double-blind, active controlled, parallel group study, comparing the efficacy, safety and tolerability of the fixed dose combination FF/UMEC/VI with the fixed dose dual combination of FF/VI, administered once-daily via a dry powder inhaler in subjects with inadequately controlled asthma. Effective Date: 13-Dec-2016

GlaxoSmithKline Document Number 2016N271022_03 Study 205715, a Phase III, randomized, double-blind, active controlled, parallel group study, comparing the efficacy, safety and tolerability of the fixed dose combination FF/UMEC/VI with the fixed dose dual combination of FF/VI, administered once-daily via a dry powder inhaler in subjects with inadequately controlled asthma. Effective Date: 23-Jun-2017

GlaxoSmithKline Document Number 2016N271022_04 Study 205715, a Phase III, randomized, double-blind, active controlled, parallel group study, comparing the efficacy, safety and tolerability of the fixed dose combination FF/UMEC/VI with the fixed dose dual combination of FF/VI, administered once-daily via a dry powder inhaler in subjects with inadequately controlled asthma. Effective Date: 29-Sep-2017

GlaxoSmithKline Document Number 2016N271022_05 Study 205715, a Phase III, randomized, double-blind, active controlled, parallel group study, comparing the efficacy, safety and tolerability of the fixed dose combination FF/UMEC/VI with the fixed dose dual combination of FF/VI, administered once-daily via a dry powder inhaler in subjects with inadequately controlled asthma. Effective Date: 05-Dec-2017

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11. APPENDICES

11.1. Appendix 1: Protocol Deviation Management

Protocol deviations (PDs) will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed by source data lock to ensure all important deviations are captured and categorised on the protocol deviations dataset (except for the PD of taking incorrect treatment).
- Participants who received an incorrect container will be captured as an important protocol deviation. The actual treatment in the incorrect container will be identified and quality controlled by S&P either as incorrect treatment or unplanned treatment per randomization schedule prior to DBF.
- This dataset will be the basis for the summaries and listings of protocol deviations.

No per-protocol analysis is planned for this study.

11.2. Appendix 2: Protocol Defined Schedule of Events

11.2.1. Time and Events Table

Protocol Activity	Pre-Screen[1]	Screen Run-in	Enrolment Stabilization	Treatment Period						Follow-up	
				Fixed Treatment Period				Variable Treatment Period			
Visit	**0**	**1[1]**	**2[2]**	**3[3] Random-ization**	**4**	**5**	**6**	**7**	**8 End of Study (EOS)**	**Early Withdrawal (EW)[4]**	**Safety Follow-up Contact**
Study Day	**-49 to -36**	**-35**	**-14**	**1**	**29**	**85**	**169**	**253**	**365**		
Week	**-6 to -7**	**-5**	**-2**	**0**	**4**	**12**	**24**	**36**	**52**		**1 week after Visit 8/EOS or EW Visit**
Window			**-3/+5d[4]**		**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Written Informed Consent[5]	x										
Genetic Informed Consent[6]	x										
Demography	x										
Medical history		x									
Asthma History[7]		x									
Exacerbation History		x									
Concomitant Medication Assessment	x	x	x	x	x	X	x	x	x	x	x
Inclusion/Exclusion criteria		x	x								
Smoking History and status		x									
Randomization[8]				x							
Register visit in IRT (RAMOS NG)[9]	x	x	x	x	x	X	x	x	x	x	x
Efficacy Assessments											
Global Assessment of Severity[10]				x	x	X	x	x	x	x	

Protocol Activity	Pre-Screen[1]	Screen Run-in	Enrolment Stabilization	Treatment Period						Follow-up	
				Fixed Treatment Period				Variable Treatment Period			
Visit	**0**	**1[1]**	**2[2]**	**3[3] Random-ization**	**4**	**5**	**6**	**7**	**8 End of Study (EOS)**	**Early Withdrawal (EW)[4]**	**Safety Follow-up Contact**
Study Day	**-49 to -36**	**-35**	**-14**	**1**	**29**	**85**	**169**	**253**	**365**		
Week	**-6 to -7**	**-5**	**-2**	**0**	**4**	**12**	**24**	**36**	**52**		**1 week after Visit 8/EOS or EW Visit**
Window			**-3/+5d[4]**		**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Global Assessment of Response to Treatment[10]					x	X	x	x	x	x	
ACQ[10]		x	x	x	x	X	x	x	x	x	
SGRQ[10]				x		X	x	x	x	x	
AQLQ[10]				x	x	X	x	x	x	x	
Healthcare Resource Utilization[10]				x	x	X	x	x	x	x	
E-RS + asthma symptoms + PEF + home FEV_1[10, 11]		X									
eDiary/device training and registration		x									
Dispense eDiary		x									
Collect eDiary									x	x	
eDiary review			x	x	x	X	x	x	x	x	
Dispense paper Medical Problems/Medications Taken worksheet	x	x	x	x	x	X	x	x	x	x	

Protocol Activity	Pre-Screen[1]	Screen Run-in	Enrolment Stabilization	Treatment Period						Follow-up	
				Fixed Treatment Period				Variable Treatment Period			
Visit	**0**	**1[1]**	**2[2]**	**3[3] Random-ization**	**4**	**5**	**6**	**7**	**8 End of Study (EOS)**	**Early Withdrawal (EW)[4]**	**Safety Follow-up Contact**
Study Day	**-49 to -36**	**-35**	**-14**	**1**	**29**	**85**	**169**	**253**	**365**		
Week	**-6 to -7**	**-5**	**-2**	**0**	**4**	**12**	**24**	**36**	**52**		**1 week after Visit 8/EOS or EW Visit**
Window			**-3/+5d[4]**		**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Review paper Medical Problems/Medications Taken worksheet		x	x	x	x	X	x	x	x	x	x
Pre-dose spirometry (clinic)		x[12]	x[12]	x[13]	x[12]	x[12]	x[13]	x[12]	x[13]	x[13, 14]	
Post-dose spirometry (clinic)				x[13]			x[13]		x[13]	x[13, 14]	
Reversibility test		x[15]	x[16]								
Exacerbation assessment			x	x	x	X	x	x	x	x	x
Health Outcomes											
WPAI-SHP[10]				x		X	x		x	x	
Safety Assessments											
Physical Examination		x					x		x	x	
Vital Signs		x[17]	x	x	x	X	x	x	x	x	
ECG[18]		x			x		x		x	x	
Adverse Events		x	x	x	x	x	x	x	x	x	

Protocol Activity	Pre-Screen[1]	Screen Run-in	Enrolment Stabilization	Treatment Period						Follow-up	
				Fixed Treatment Period				Variable Treatment Period			
Visit	**0**	**1[1]**	**2[2]**	**3[3] Random-ization**	**4**	**5**	**6**	**7**	**8 End of Study (EOS)**	**Early Withdrawal (EW)[4]**	**Safety Follow-up Contact**
Study Day	**-49 to -36**	**-35**	**-14**	**1**	**29**	**85**	**169**	**253**	**365**		
Week	**-6 to -7**	**-5**	**-2**	**0**	**4**	**12**	**24**	**36**	**52**		**1 week after Visit 8/EOS or EW Visit**
Window			**-3/+5d[4]**		**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Serious Adverse Events	X	x	x	x	x	x	x	x	x	x	x
FeNO[19]				x							
Laboratory Assessments											
Hematology and clinical chemistry		x				x	x		x	x	
Total Serum IgE		x									
Urinalysis		x				x	x		x	x	
Pharmacogenetic sample[20]				x							
Serum pregnancy test		x[21]					x[21]		x[21]	x[21]	
Urine pregnancy test[21]			x	x	x	x		x			
PK samples						x[22]	x[23]		x[23, 24]	x[23]	
Study Treatment											
Dispense ICS/LABA run-in medication		x[25]									

Protocol Activity	Pre-Screen[1]	Screen Run-in	Enrolment Stabilization	Treatment Period						Follow-up	
				Fixed Treatment Period				Variable Treatment Period			
Visit	**0**	**1[1]**	**2[2]**	**3[3] Random-ization**	**4**	**5**	**6**	**7**	**8 End of Study (EOS)**	**Early Withdrawal (EW)[4]**	**Safety Follow-up Contact**
Study Day	**-49 to -36**	**-35**	**-14**	**1**	**29**	**85**	**169**	**253**	**365**		
Week	**-6 to -7**	**-5**	**-2**	**0**	**4**	**12**	**24**	**36**	**52**		**1 week after Visit 8/EOS or EW Visit**
Window			**-3/+5d[4]**		**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Assess run-in medication compliance			x								
Collect ICS/LABA run-in medication			x								
Dispense ICS/LABA stabilization medication			x								
Assess stabilization medication compliance				x							
Collect ICS/LABA stabilization medication				x							
Administer double-blind study treatment[26]				x	x	x	x	x	x	x[27]	
Dispense double-blind study treatment (Scheduled)				x	x	x	x	x			
Dispense double-blind study treatment (Unscheduled)				x[28]							
Assess double-blind study treatment compliance					x	x	x	x	x	x	

Protocol Activity	Pre-Screen[1]	Screen Run-in	Enrolment Stabilization	Treatment Period						Follow-up	
				Fixed Treatment Period				Variable Treatment Period			
Visit	**0**	**1[1]**	**2[2]**	**3[3] Random-ization**	**4**	**5**	**6**	**7**	**8 End of Study (EOS)**	**Early Withdrawal (EW)[4]**	**Safety Follow-up Contact**
Study Day	**-49 to -36**	**-35**	**-14**	**1**	**29**	**85**	**169**	**253**	**365**		
Week	**-6 to -7**	**-5**	**-2**	**0**	**4**	**12**	**24**	**36**	**52**		**1 week after Visit 8/EOS or EW Visit**
Window			**-3/+5d[4]**		**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Collect double-blind study treatment (Scheduled)					x	x	x	x	x	x	
Collect double-blind study treatment (Unscheduled)				x[29]							
Dispense albuterol/salbutamol, as required		x	x	x	x	x	x	x			
Collect albuterol/salbutamol, as required			x	x	x	x	x	x	x	x	
Dispense FP, as required[30]		x	x	x	x	x	x	x			
Collect FP, as required			x	x	x	x	x	x	x	x	

Notes:

1. Visit 1 must be completed ≥1 day but ≤14 days after Visit 0; however, if it is local and routine medical practice to request that a participant withhold their ICS at least 24 hours prior to a clinic visit then, provided that the participant has complied with the request, Visit 0 and Visit 1 can occur on the same day.
2. Visit 2 may be conducted up to 3 days before the scheduled date of Visit 2. The duration of the run-in period (i.e. the time period between Visits 1 and 2) must be ≥18 days but ≤26 days.
3. Visit 3 must always be conducted ≥14 days but ≤17 days after Visit 2.
4. EW Visit should be conducted if double-blind study treatment is discontinued AND the participant discontinues from participating in the study.
5. The ICF must be signed before any study procedures, including medication cessation.

6. Genetics research consent may be obtained at the same time as the study IC and must be obtained prior to obtaining a genetic blood sample.
7. The assessment of asthma history will include: the age of the participant when they were first provided with an inhaler for asthma; completion of an asthma medical history questionnaire (a copy of this questionnaire and instructions for its use can be found in the SRM).
8. Participants must not be randomized prior to confirming their eligibility to participate in the study.
9. The IRT will be used for randomization, emergency unblinding and study treatment supply management (Please refer to the RAMOS NG IRT manual and SRM for more information).
10. Assessment(s) to be completed prior to the administration of study treatment.
11. To be completed using the provided combined spirometer/eDiary device. Assessments should be completed in the morning upon wakening and in the evening immediately prior to going to bed.
12. Spirometry to be performed between 6am and 11am after withholding rescue medication for at least 6 hours and prior to taking the morning dose of study treatment. Pre-dose spirometry assessments should be performed at the same time of day at each applicable visit.
13. Pre-dose spirometry to be performed between 6am and 11am, prior to taking the morning dose of study treatment. Post-dose spirometry is to be performed 3 hours (± 15 minutes) after taking the morning dose of study treatment. Rescue medication should be withheld for at least 6 hours prior to the pre-dose spirometry assessments until after completion of the 3-hour post-dose spirometry assessments. Pre- and post-dose spirometry assessments should be performed at the same time of day at each applicable visit.
14. In the event that double-blind study treatment is not administered at this visit, spirometry assessments should be performed at the same time of day as the pre- and post-dose spirometry assessments at the preceding on-treatment clinic visits.
15. Following completion of the pre-dose spirometry assessments, the reversibility test will be conducted between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol. If airway reversibility is not demonstrated at Visit 1 then the assessment may be repeated within 7 days of Visit 1 (see Section 7.3.4.1.1. of the protocol for details of the criteria to be met before a repeat of the reversibility assessment is permitted). If airway reversibility is successfully demonstrated at the second attempt and all other eligibility criteria assessed at Visit 1 are met then the participant may enter the 3-week run-in period (starting on the date that airway reversibility was successfully demonstrated at the second attempt).
16. Following completion of the pre-dose spirometry assessments, the reversibility test will be conducted between 60 and 90 minutes following 4 inhalations of ipratropium aerosol (see Section 7.3.4.1 of the protocol)
17. The vital signs assessment will include the measurement of height and weight at this visit only.
18. At the Screening Visit (Visit 1), the ECG is to be obtained after the vital signs assessment but prior to performing the pre-bronchodilator spirometry assessment (see Section 7.5.6 of the protocol). At all post-randomization visits the ECG is to be obtained 15 minutes to 45 minutes after the administration of study treatment.
19. Exhaled Nitric Oxide is widely accepted as a non-invasive marker for airway inflammation and will be assessed to characterise the study participant population. Details on performing the FeNO assessment, including information on the equipment provided and its use, are documented in the SRM and the third-party vendor manual.
20. Pharmacogenetic sample may be drawn any time from Visit 3 onwards.
21. Assessments only to be conducted in females of reproductive potential.
22. Pharmacokinetic (PK) subset: In a subset of approximately 20% of all randomized participants, PK samples will be obtained at pre-dose on the visit day, and 1 sample in each of the following three time windows: 5min-30min, 45min-90min, and 2-3h post-dose on the visit day. NOTE: the date and time of study treatment administration on the day prior to the visit must be recorded in the eCRF. See Appendix 7 of the protocol for country-specific requirements.
23. PK sample to be obtained at pre-dose on the visit day (This PK sample is to be obtained from ALL study participants). NOTE: the date and time of study treatment administration on the day prior to the visit must be recorded in the eCRF.
24. PK sample to be obtained at this visit ONLY in the event that Visit 8/EOS assessments are conducted at Week 24.

25. In the event that the reversibility assessment needs to be repeated within 7 days of Visit 1 (see Section 7.3.4.1.1 of the protocol) then the medication for the 3-week run-in period must not be dispensed until airway reversibility is successfully demonstrated at the second attempt and all other eligibility criteria assessed at Visit 1 are confirmed as met.
26. Study treatment should be administered at the same time of day at each applicable clinic visit.
27. The administration of study treatment at this visit is optional. If study treatment is not administered at this visit then those assessments which are scheduled based on the time of study treatment administration should be performed at approximately the same time of day as performed at the preceding post-randomization visits
28. Between scheduled visits, unscheduled visits to the study clinic to re-supply the participant with double-blind study treatment is permitted after Visit 3 but before Visit 8/EOS. The IRT will be used for study treatment supply management (Please refer to the RAMOS NG IRT manual and SRM for more information).
29. In the event that the participant attends the study clinic for the unscheduled dispensing of double-blind study treatment, previously dispensed study treatment should be collected for drug accountability purposes.
30. FP may be used temporarily to treat the symptoms of a moderate asthma exacerbation, at the Investigator's discretion. However, please note that a participant's use of the provided FP prior to randomization at Visit 3 would meet the enrolment or randomization concomitant medication exclusion criteria (see Section 5.3.2 and Section 5.4.2 of the protocol)

11.3. Appendix 3: Assessment Windows

11.3.1. General

In general, data will be reported according to the nominal time of clinic visits and assessments as specified in the protocol. For example, if a participant had recorded values for the Week 4 visit on the 22nd day of treatment, the data will be presented as Week 4 values in the summary tables.

The post-randomization clinic data collected at EW/ End of Study (EOS) visits in the eCRF and SDTM data will be mapped based on study day as follows:

Study days	Target date for visit	Visit/Week
15 to 56	29	Visit 4/ Week 4
57 to 126	85	Visit5/ Week 12
127 to 210	169	Visit 6/Week 24
211 to 308	253	Visit 7/Week 36
>=309	365	Visit 8/ Week 52

If a participant has an EW visit on or before day 14 then the data collected at this study visit will be listed but excluded from visit-based summaries, figures and analyses.

Note:

- For SGRQ, WPAI-SHP, laboratory and PK endpoints there is no planned assessment at week 4 and so data that slots to week 4 will be excluded from summaries and analyses.

- For ECG there is no planned assessment at week 12, and so data that slots to week 12 will be excluded from summaries and analyses.

- For FEV_1 3 hrs post study treatment there are no planned assessments at weeks 4 and 12, and so data that slots to weeks 4 and 12 will be excluded from summaries and analyses.

Multiple assessments slotting to the same visit

If there is more than one non-missing value within an assessment window for a given analysis or summary, the measure from the scheduled visit will take priority.

All data will be listed.

11.3.2. Variable Duration

The duration of the treatment period is variable but will be a minimum of 24 weeks and a maximum of 52 weeks.

For participants with an EOS visit, the visit will be mapped to the windows as specified in Section 11.3.1.

For participants who are lost to follow up or withdraw from the study early, then their planned EOS visit will be:

- if randomized date is on or after the 27th August 2017 then a participant's planned EOS visit is week 24.
- if randomized date is on or between the 7th May 2017 and the 26th August 2017 then a participant's planned EOS visit is week 36
- if randomization date is on or prior to the 6th May 2017 then a participant's planned EOS is week 52

If a participant has a EW visit past their planned EOS visit as defined above, then their planned EOS date become the next scheduled clinic visit (i.e. if a participant has a planned EOS visit of week 24 with an EW visit at week 28, then their planned EOS visit will become week 36). Similarly, if a participant is reported as lost to follow up after attending their planned EOS visit, then their planned EOS visit will become the next scheduled clinic visit. Thus,

- If a participant has a planned EOS visit of week 24, attends this visit and then is subsequently lost to follow up (for example, at week 28 based on study conclusion date), then their planned EOS visit will become week 36).

- If a participant has a planned EOS visit of week 24, does not attend this visit, and is lost to follow up at a later time point (for example, week 25 based on study conclusion date), then their planned EOS visit will remain as week 24.

The study completion date will be set at 181 days (i.e. 25 weeks and 6 days) post the final participant's randomization date.

11.4. Appendix 4: Study Phases

Study phases for assessments scheduled at a set time will be defined in accordance with the planned relative time of the assessment.

Any events/assessments for participants not in the ITT population will be assigned a Pre-treatment phase.

For all events and assessments, the study phases will be defined as follows:

Study Phase	Definition
Screening/Run-In period	Visit 1 date ≤ Event Onset Date or Assessment Date/Time < Visit 2 date or date of first dose of Stabilization treatment, whichever is later
Stabilization period	Date of first dose of Stabilization treatment ≤ Event Onset Date or Assessment Date/Time < Randomized treatment start date. Note: if baseline assessment and done on treatment start date then assumed to be done prior to treatment start.
On-Treatment	Randomized treatment start date ≤ Event Onset Date or Assessment Date/Time ≤ Study Treatment Stop Date +1 or any assessment with a missing or partial date unless there is evidence it was not on-treatment
Post-Treatment [1]	Randomized Treatment Stop Date +1 < Event Onset Date or Assessment Date/Time ≤ Last Scheduled Clinic Visit (i.e., Visit 8 [EOS Visit] or Early Withdrawal Visit [EW])[2] Note: if any participant does not receive a dose of randomized treatment then all post-baseline data prior to EW or EOS visit is considered as post-treatment.
Post-Study	Event Onset Date > Last Scheduled Clinic Visit (i.e., Visit 8 (EOS Visit) or Early Withdrawal Visit)[2] +1 day Note, for participants who continue in the study after IP discontinuation (i.e. where treatment discontinuation date < Visit 8 (EOS visit) date or EW visit date), the rule will be: Event Onset Date > Last Scheduled Clinic Visit (i.e. Visit 8 (EOS Visit) or EW Visit)[2]
[1]: Applicable only for participants who continue in the study after IP discontinuation. [2] If a subject is lost to follow up and does not have an EoS or EW visit, their study conclusion date will be used if available. If no study conclusion date is available, the last contact date will be used.	

Classification of a concomitant medication into study phase (at study entry, screening/run-in period, stabilization period, on-treatment, post-treatment, or post-study) will be made with reference to the study phase as defined above. A medication will be classified into every period in which it was taken. For medications with partial start and stop dates, the medication will be classified into every period in which it could have been taken.

11.5. Appendix 5: Data Display Standards & Handling Conventions

11.5.1. Reporting Process

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Area	: /arenv/arprod/gsk2834425/mid205715/final
QC Spreadsheet	: /arenv/arwork/gsk2834425/mid205715/final/documents
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM Implementation Guide Version 3.1.3 or higher & ADaM Implementation Guide Version 1.0 or higher. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• Rich Text Format (RTF) files will be generated for the final reporting efforts to be used for the CSR writing.	

11.5.2. Reporting Standards

Reporting Standards
General

• Displays will use the term “Subjects” to refer to “Participants”.
• The current GSK Pooled Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated:
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• All data (including data collected following study treatment discontinuation [post-treatment]) will be reported according to the treatment to which the participant was randomized unless otherwise stated. However, there may be additional adhoc displays for individual participants using the actual treatment received. • The reported precision of data will follow IDSL statistical principles but may be adjusted to a clinically interpretable number of decimal places. • In most cases, percentages between 1% and 99%, inclusive, will be rounded to integers. Percentages greater than 0%, but less than 1%, will be reported as <1%, and percentages greater than 99%, but less than 100%, will be reported as >99%. For some rare events, percentages may be reported in 1 decimal point. In this case, percentages greater than 0%,

Reporting Standards	
but less than 0.1%, will be reported as <0.1%. • 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 decimal places.	
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.
  • If an assessment is reported for a scheduled visit regardless of assessment date/time relative to protocol T&E, the data will be used for that visit.
• 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 participant's listings.	

Unscheduled Visits	
• Unscheduled visits will not be included in summary tables except as part of a 'worst case post-baseline' assessment. • All unscheduled visits will be included in listings. • Unscheduled visits may be used for baseline where specified in Section 5.2.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

11.6. Appendix 6: Derived and Transformed Data

11.6.1. General

Study Day

• Calculated as the number of days from randomization date:
  • Reference Date = Missing → Study Day = Missing
  • Reference Date < Treatment Start Date → Study Day = Reference Date – Treatment Start Date
  • Reference Date ≥ Treatment Start Date → Study Day = Reference Date – Treatment Start + 1

Treatment Period Completion/Withdrawal and Study Completion/Withdrawal

• A participant is considered to have completed the treatment period if the answer to the question "Was the study treatment stopped permanently before the scheduled end of the treatment period?" on the Study Treatment Discontinuation eCRF page is "No". Date of completion of treatment period will be the treatment stop date.
• A participant is considered to have completed the study if the answer to the question "Was the participant withdrawn from the study?" on the Study Conclusion eCRF page is "No". Otherwise, if the answer is "Yes" then the participant is considered to have withdrawn early from study. The date of study completion/withdrawal as entered on the eCRF will be used as the study completion/withdrawal date.
• If a participant prematurely discontinues IP, according to the CRF instructions participants should be reported as continuing in the study if they attend either normal visits, or the safety follow-up visit after the early withdrawal visit (DSCONT='Y'). To identify participants who are continuing in the study per the normal visit schedule and providing post-treatment data, the following will be implemented:
  ○ If a participant prematurely discontinues IP and study at the same time, they are not considered to be continuing in the study (i.e. DSCONT will be "N").
  ○ If a participant prematurely discontinues IP and only has an EW visit and a safety follow up visit on or after the date of IP discontinuation they are not considered to be continuing in the study (DSCONT will be "Y"). Note, if a participant initially continues in the study following IP discontinuation but then discontinues study prior to the next scheduled clinic visit they will be considered as not continuing in the study as they will not be providing post-treatment data.
  ○ If a participant prematurely discontinues IP and has a scheduled visit (not EW or safety follow-up visit) on or after the date of IP discontinuation then the participant is continuing in the study (DSCONT will be "Y").

Planned and Actual Randomized Treatment
For participants who received the correct treatment throughout the study, the actual treatment will be the same as the planned treatment. For participants who received an incorrect treatment, the actual treatment will be derived as follows: • If the number of doses on an incorrect treatment is less than the number of doses on the planned treatment, then the actual treatment is assigned as planned treatment. • If the number of doses on an incorrect treatment is greater than the number of doses on the planned treatment, then the actual treatment is assigned as the incorrect treatment. • If the number of doses on an incorrect treatment and planned treatment are the same, the actual treatment is assigned as the treatment with the highest UMEC and/or FF dose. • If an incorrect container was dispensed and not returned, such that it is not possible to ascertain whether or not any doses were taken from the incorrect container, it will be assumed that the participant took all possible doses from this container (i.e., 30 doses in total).
Participants excluded from ITT population
• A participant who is recorded as a screen failure, run-in failure, or stabilization failure, but is randomized and does not receive a dose of study treatment, is considered to be randomized in error and will be excluded from the ITT population • These participants will be identified using the deviations dataset where the term “Randomized in Error:” is reported.

11.6.2. Study Population

Demographics
Age
• Age will be calculated based on the Pre-Screening Visit date (or Screening, if pre-screening not performed). • Only year of birth is collected on eCRF. Day and Month of birth are imputed as 30 June. Age is derived using the date of the pre-screening visit. • All participants with imputed age of 17 or 18 years will be source data verified, and presence / absence of protocol deviation on the inclusion criteria #1 will be taken into consideration in the derivation for the analysis variable age. • Birth date will be presented in listings as 'YYYY'.
Age at onset
• This will be derived as age at pre-screening visit (or screening, if pre-screening not performed)-disease duration. • If a participant has age of onset of <0 this will be queried by data management. • As we do not collect date of birth to the exact date negative values could occur. In these cases, the age of onset will be set to 0.
Body Mass Index (BMI)
• Calculated as weight (kg) / [height (m)]^2 • BMI will be presented as for summary statistics with 1 decimal place.
Clinic Spirometry Assessment
• At Visit 1, if the spirometry assessment is repeated for a given participant to meet the eligibility criteria on the reversibility, the repeated spirometry data will be used for that visit.
Cardiovascular History and Risk Factor

Cardiovascular history and risk factors will be assessed at Visit 1. Participants with one or more of the following terms recorded as either current or past medical conditions at Visit 1 is considered to have cardiovascular history/risk factors:
• Cardiovascular history
  ○ arrhythmia,
  ○ congestive heart failure,
  ○ coronary artery disease,
  ○ myocardial infarction,
  ○ cerebrovascular accidents,
• Cardiovascular risk factors
  ○ hypertension,
  ○ diabetes mellitus,
  ○ hypercholesterolemia.

Treatment Compliance
• If a dose counter start count is missing, then it will be assumed to be 30 for the ELLIPTA DPI. If any dose counter stop is missing, then the number of doses taken will be set to missing for that inhaler. • Number of doses of study drug taken by each participant from each inhaler = Dose

Demographics

counter start value – dose counter stop value.

- The derivation for treatment compliance during the double-blind treatment period is defined as the sum of (dose counter start value – dose counter stop value) over all inhalers dispensed to the participant and returned during the double-blind treatment period (i.e. from randomization to EOS/EW visit) and percentage compliance will be calculated as follows:

$$\text{Treatment compliance} = \frac{\text{Total number of doses received}}{\text{Treatment stop date – treatment start date +1}} \text{ X } 100$$

If a participant is lost to follow up (without EOS/EW visit) then their treatment stop date will be handled in accordance to Section 11.7.2 and doses received will be calculated for inhalers dispensed and returned from randomization to treatment stop date.

- The derivation of the treatment compliance during the first 24 weeks is as follows:
  - For participants who withdraw from IP prior to week 24 or with End of Study visit at Week 24 is the same as the treatment compliance during the double-blind treatment period.
  - For participants who continue the double-blind study treatment beyond Week 24 is defined as the sum of (dose counter start value – dose counter stop value) over all inhalers dispensed to the participant prior to Visit 6 (Week 24) and returned by the participant on or before Visit 6 (Week 24) during the double-blind treatment period divided by the treatment duration covered by these inhalers, i.e., Week 24 clinic visit date – treatment start date Note: participants received first dose of the newly dispensed inhaler in clinic per protocol.
- Overall compliance will be categorized as follows:
  - < 50 %
  - ≥50 % to < 80%
  - ≥80 % to < 95 %
  - ≥95 % to ≤105 %
  - >105 % to ≤120 %
  - >120 %.
- If a participant receives a treatment other than the randomized treatment during the study, the compliance will still be calculated using data from all containers received and overall exposure start and stop dates.

Severe exacerbation in the previous year

The number of severe exacerbations in the previous year is defined as:

Number of exacerbations in the last 12 months that required oral/systemic corticosteroids (not involving hospitalisation) + Number of exacerbations in the last 12 months that required hospitalisation

11.6.3. Efficacy

Spirometry

Trough FEV_1 and FVC

- The trough value for FEV_1 at Weeks 4, 12, 24, 36 and 52 visits is the value of the pre-dose (prior to taking the morning dose of study treatment) assessment.

Post study treatment FEV_1

- The post study treatment value for FEV_1 at Week 24 and at the End of Study visit is the assessment value approximately 3 hours after administering the study medication.

Trough FEV_1 over time

To evaluate the effect of UMEC over the first 24 weeks of the treatment period, the (weighted) mean trough FEV_1 over the first 24 weeks of the treatment period will be calculated as the FEV_1 area under the curve ($AUC_{0\text{-}24w}$) normalized for time. Specifically, FEV_1 weighted mean $AUC_{0\text{-}24w}$ will be calculated based on all non-missing data as area under the curve from day 1 to week 24 using the linear trapezoidal rule divided by the observation time (24 weeks) to report in liter (L) units. If one or more observations are missing between two non-missing observations, the value(s) will be linearly interpolated between the two non-missing values.

The weighted mean $AUC_{0\text{-}24w}$ will be calculated over the nominal assessment time per protocol as follows:

$$\text{WM } FEV_1 \text{ } AUC_{0\text{-}24w} = \frac{\frac{1}{2}\sum_{i=0}^{3}(FEV_1(t_i) + FEV_1(t_{i+1})) * (t_{i+1} - t_i)}{24w}$$

Where, t_0 = 0 (week), t_1= 4 (week), t_2=12 (week), and t_3=24 (week); FEV_1 (t_0) = baseline trough FEV_1, and for i>0, FEV_1 (t_i) = trough FEV_1 reading at planned week t_i.

If baseline, week 24 or any two timepoints are missing the AUC will not be calculated.

Asthma Exacerbations

General

- Exacerbations will be presented based on onset date relative to the period being summarized. i.e. if the onset date occurs within the study period then it will be reported within that study period)

The following data will be included in the exacerbation analyses and summaries

Analysis	Time point	Data to be included (i.e. from participants first dose up to date/study day specified)
On- and post-	1-52	- Up to EOS/ EW/study conclusion date*/date of death

Asthma Exacerbations		
treatment	1-24	- If participants planned EOS visit is week 24: EOS/EW visit/study conclusion date*/date of death - If participants planned EOS visit is later than week 24 use data up to the minimum of study day 169, EW, lost to follow up*, date of death.
	25-52	- If participants planned EOS visit is later than week 24 and they have not withdrawn from the study before study day 170, then data from day 170 to EW/EOS /study conclusion date*/date of death will be included in the analysis. - Data from participants who have withdrawn from study before study day 170 or whose planned EOS visit was week 24 will be excluded from these summaries.
On- and post-treatment sensitivity analysis	1-52	- For participants with an EOS visit, all data up to the EOS visit will be included - For participants without an EOS visit, all data available plus imputed data up to the participants planned EOS visit will be included.
On-treatment	1-52	- If a participant does not withdraw from treatment prior to withdrawing from/completing the study (or being lost to follow up or dying) then up to last treatment date. - If a participant withdraws from treatment prior to withdrawing/completing the study (or being lost to follow up or dying) then up to last treatment date+1
	1-24	- If a participant's planned EOS visit is week 24 and the participant does not withdraw from treatment prior to withdrawing from/completing the study (or being lost to follow up or dying): Last date of treatment - If a participant's planned EOS visit is week 24 and the participant withdraws from treatment prior to withdrawing from/completing the study (or being lost to follow up or dying)): Last date of treatment +1 - If a participant's planned EOS is later than week 24 and participant does not withdraw from treatment prior to withdrawing from/completing the study (or being lost to follow up or dying): use the minimum of (169, Last treatment date) - If a participant's planned EOS is later than week 24 and participant withdraws from treatment prior to withdrawing from/completing the study (or being lost to follow up or dying): use the minimum of (169, Last treatment date+1)
	25-52	- If participants planned EOS visit is later than week 24 and they have not withdrawn from the treatment before study day 170 then data from day 170 up to the following timepoint will be used: o If the participant does not withdraw from treatment

Asthma Exacerbations		
		prior to withdrawing from/completing the study (or being lost to follow up or dying): Last date of treatment ○ If the participant withdraws from treatment prior to withdrawing from/completing the study (or being lost to follow up or dying): Last date of treatment+1 - Data from participants who have withdrawn from treatment before study day 170 or whose planned EOS visit was week 24 will be excluded from these summaries.
*if no study conclusion date, then use last contact date.		

- Denominators will be based on the number of participants with data available for the period being summarized.
- Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation
- The duration of an exacerbation will be calculated as exacerbation resolution date or date of death - exacerbation onset date + 1.

Time to First Exacerbation

- On- and Post-Treatment Exacerbations: The time to first exacerbation will be calculated as exacerbation onset date of first exacerbation – date of start of treatment+1. Participants will be represented from their Day 1 date to the start date of their first exacerbation up to and including the end of study date/early withdrawal date day. Participants that have not experienced an exacerbation on or before the end of study date/early withdrawal/ lost to follow up study/ date of death day are censored at the end of study date/early withdrawal date /study conclusion date (or date of last contact if no study conclusion date)/ date of death.

Asthma Control Questionnaire (ACQ)

General

Scoring instructions can be found Asthma Control Questionnaire: Background, Administration and Analysis, *May, 2012*.

The ACQ consists of seven attributes of asthma control (denoted as ACQ-7), and is to be administrated on all scheduled clinic visits. Six attributes (ACQ-6), to be self-completed by the participant in a 6-item questionnaire, enquire about the frequency and/or severity of symptoms over the previous week in the following sequential order on: nocturnal awakening, symptoms on waking in the morning, activity limitation, shortness of breath, wheeze, and rescue medication use. ACQ-5 consists of the first five questions of ACQ, measuring asthma symptoms. The seventh attribute measures the lung function, which will be included via study visit spirometry assessment on pre-bronchodilator FEV_1 % predicted value using Quanjer equation [Quanjer 2012]. The score for ACQ-5, ACQ-6, or ACQ-7 is the mean of the 5, 6 or 7 items, respectively.

- All 7 items of ACQ have response on 0-6 ordinal scale (0=no impairment/limitation, 6=total impairment/ limitation). For each version of ACQ (5, 6, 7), the total score is calculated as the

Asthma Control Questionnaire (ACQ)
average of all non-missing item responses [Asthma Control Questionnaire, Background, Administration and Analysis, May, 2012]. • Only one of the first five item responses are allowed to be missing in calculating the total scores for all versions of ACQ. • If the language of the ACQ conducted at a post-baseline visit is different to the language used at Day 1 baseline, all ACQ scores at that visit and all subsequent visits will be set to missing. • If the language of the ACQ changes during the run-in phase, stabilization phase and randomization, the change in these periods will only be calculated where the language remained consistent. • If the language of the ACQ is missing at any visit (including Baseline) and is the same at all remaining non-missing visits, the language at the missing visit will be assumed to be unchanged
ACQ control categories
ACQ total scores at each visit will be summarized by the following asthma control categories: a) well controlled, i.e., ACQ total score ≤ 0.75, b) partially controlled i.e., 0.75 < ACQ total score <1.5, c) inadequately controlled, i.e., ACQ total score ≥1.5. Shift from baseline at each visit in ACQ total score will also be summarized by the following categories: a) Improved (defined as from inadequately controlled at baseline to partially or well controlled at visit, or from partially controlled at baseline to well controlled at visit) b) Unchanged (defined as same asthma control category at visit and baseline) c) Worsening (defined as from well controlled at baseline to partially or inadequately controlled at visit, or from partially controlled at baseline to inadequately controlled at visit)
Responder Status according to ACQ Total Score
• A participant will be considered a responder according to ACQ total score if their ACQ total score has decreased at least 0.5 units from the baseline ACQ total score. • A participant will be considered a non-responder if their ACQ total score has decreased by less than 0.5 units, has not changed, or has increased compared to baseline. • Missing data will be handled as detailed in Section 11.7.2.

St. George's Respiratory Questionnaire (SGRQ)
General
• Details for how to score the SGRQ, including handling of missing data, are outlined in the

St. George's Respiratory Questionnaire (SGRQ)
SGRQ manual (June, 2009). • Changes from baseline in domain and total score will be calculated. • If the language of the SGRQ conducted at a post-treatment visit is different to the language used at Day 1 baseline, all SGRQ scores at that visit and all subsequent visits will be set to missing. • If the language of the SGRQ is missing at any visit (including Baseline) and is the same at all remaining non-missing visits, the language at the missing visit will be assumed to be unchanged
Responder Status according to SGRQ Total Score
• A participant will be considered a responder according to SGRQ total score if their SGRQ total score has decreased at least 4 units from the baseline SGRQ total score. • A participant will be considered a non-responder if their SGRQ total score has decreased by less than 4 units, has not changed, or has increased compared to baseline. • Missing data will be handled as detailed in Section 11.7.2.

Asthma Quality of Life Questionnaire (AQLQ)
General
• Details for how to score the AQLQ, including handling of missing data, are outlined in the AQLQ manual (May, 2012). • Changes from baseline in total score will be calculated. • If the language of the AQLQ conducted at a post-treatment visit is different to the language used at Day 1 baseline, all AQLQ scores at that visit and all subsequent visits will be set to missing. • If the language of the AQLQ is missing at any visit (including Baseline) and is the same at all remaining non-missing visits, the language at the missing visit will be assumed to be unchanged
Responder Status according to AQLQ Total Score
• A participant will be considered a responder according to AQLQ total score if their AQLQ total score has increased at least 0.5 from the baseline AQLQ total score. • A participant will be considered a non-responder if their AQLQ total score has increased by less than 0.5 units, has not changed, or has decreased compared to baseline. • Missing data will be handled as detailed in Section 11.7.2.

Calculation of Daily eDiary Endpoints

General

- Efficacy endpoints based on diary assessments include E-RS total score and subscale scores (breathlessness, cough & sputum, chest symptoms), Home Daily AM (trough) and PM FEV_1, AM and PM PEF, percentage of symptom-free days, percentage of rescue medication-free days, and daily rescue medication use.
- The detailed derivations for diary data are provide in Section 5.2 for baseline value and Section 5.3.2 for post-baseline values.
- If the language of the E-RS conducted post-randomization is different to the language used during the baseline period, all E-RS scores post-randomization will be set to missing.
- The E-RS scoring instructions can be found in Appendix B of the User Manual [E-RS (Evaluating Respiratory Symptoms (E-RS™) in COPD (E-RS™: COPD) User Manual, *Version 5.0.* March, 2016].

Symptom-free days

- For a given day, a participant has a symptom-free day if the responses to both the evening (measures symptoms during the day) and following morning's (measures nocturnal symptoms from the previous night) assessments indicate no symptoms.
- A participant has a symptom-free day if the participant has no asthma symptoms AND the participant's activities are not at all limited AND the participant has no nocturnal awakenings due to asthma symptoms, per diary data as in the table below:

Assessment Time	Question	Outcome
Morning	Did you wake up due to asthma symptoms (i.e. wheezing, coughing, shortness of breath, or chest tightness)?	No
Evening	Please describe the severity of your asthma symptoms today (i.e. cough, wheeze, chest tightness, shortness of breath)	No asthma symptoms
	How limited were you in your activities today because of your asthma	Not at all limited

- If any of these outcomes is missing the symptom free day status will be set to missing
- If there is more than one morning or evening assessment assigned to a study day, then all records need to concur that no symptoms occurred for it to be considered a symptom free day
- Percentage of symptom free days will be calculated as the (number of symptom free days/total

number of days with non-missing symptom free day status)*100 within a given reporting period.
- If >50% of days within a reporting period have missing symptom free day status, the percentage of symptom free days will be considered missing for that period.

Rescue Medication free days

- For a given day, a participant has a rescue medication-free day if the responses to both the evening (measures rescue medication use during the day) and following morning's (measures rescue medication use during the previous night) assessments indicate no use of rescue medication.

- If either the evening and following morning's assessment is missing then the days rescue medication use is set to missing.
- If there is more than one morning or evening assessment assigned to a study day, then all records need to concur that no rescue medication was taken for it to be considered a rescue medication free day
- Percentage of rescue medication free days will be calculated as the (number of rescue medication free days/total number of days with non-missing rescue medication free day status)*100 within a given reporting period.
- If >50% of days within a reporting period have missing rescue medication free day status, the percentage of rescue medication free days will be considered missing for that period.

Number of puffs per day

- For a given day, the number of puffs will be the sum of the evening number of puffs (measures rescue medication use during the day) and following morning's number of puffs (measures rescue medication use during the previous night).

- If a participant only has one of these assessments, then the number of puffs will be set to missing.
- If a participant has both an evening and a morning assessment and > 1 assessment at either of those timepoint, use the maximum value reported for the timepoint (i.e. number of puffs=max(morning) + max(evening))

Healthcare Resource Utilization

- The total number of unscheduled asthma related healthcare resource utilization, including telephone contacts, specialist nurse visits, visits to a physician's office, home visits (day and night time), outpatient visits, visits to urgent care, visits to the emergency department, and hospitalizations associated with the participant's worsening of symptoms will be calculated.

The following data will be included in the summaries

Analysis	Time point	Data to be included (i.e. from participants first dose up to date/study day specified)
On- and post-treatment	1-24	- If participants planned EOS visit is week 24: EOS/EW visit/study conclusion date*/date of death - If participants planned EOS visit is later than week 24 use data up to the minimum of study day 169, EW study conclusion date*, date of death.
	1-52	- All health utilization data for participants with planned

	with >=36 planned exposure	EOS visit at Week 36 or Week 52.
*if no study conclusion date then use last contact date		

11.6.4. Safety

Extent of Exposure
Treatment Exposure During the Run-in and Stabilization Periods

• Duration of exposure to FSC during the run-in period is calculated as:
  • Run-in treatment stop date – Run-in treatment start date +1
• Duration of exposure to FF/VI 100/25 during the stabilization period is calculated as:
  • Stabilization treatment stop date – Stabilization treatment start date +1
• Exposure during the run-in and stabilization phase will be summarized as continuous and using the following categories:
  o ≥1 day, ≥1 weeks, ≥2 weeks, ≥3 weeks (Run-in period only)
In case of missing dates, no imputation will be performed. Exposure will be considered missing.

Randomized Treatment Exposure and Post-Treatment On-Study Duration

• Duration of treatment exposure to study treatment is calculated as:
  • treatment stop date – treatment start date +1
• Duration of Post-treatment time spent on study is calculated as:
  o Last Scheduled Clinic Visit (i.e., Visit 8 (EOS Visit) or Early Withdrawal Visit) – (treatment stop date+1).

Randomized Treatment Exposure Categories

• Treatment Exposure will be summarized as continuous, and using the following categories:
  o ≥1 day, ≥4 weeks, ≥8 weeks, ≥12 weeks, ≥16 weeks, ≥20 weeks, ≥24 weeks, ≥28 weeks, ≥32 weeks, ≥36 weeks, ≥40 weeks, ≥44 weeks, ≥48 weeks and ≥52 week, 24 weeks (-5/+2 days), 36 weeks (-5/+2 days), 52 weeks (-5/+2 days)
  o 24 weeks (-5/+2 days) will be based on Day 169. 36 weeks (-5/+2 days) will be based on Day 253. 52 weeks (-5/+2 days) will be based on Day 365.
  o Subjects whose planned End of Study visit is Week 36 or 52, are included if their Week 24 visit falls within the protocol permitted visit window and they are still on study treatment at this visit.
  o Subjects whose planned End of Study visit is Week 52, are included if their Week 36 visit falls within the protocol permitted visit window and they are still on study treatment at this visit.

Post-treatment On-Study Duration
• Post-treatment On-Study duration will be summarized as continuous and using the following categories: o Duration (Week): (0, 4], (4, 12], (12, 24], (24, 36], > 36

Adverse Events

Adverse Event Rate

- Event rate per thousand person-years will be displayed on most On-Treatment AE data displays listed in Section 11.10.8. Event rate per thousand person-years will be calculated as the number of events x 1000 divided by the total participant exposure during the time-period of interest.

On-treatment adverse events by time in study

The following data/participants with data will be included in the AE summaries for specific time periods. Exposure for the time periods will also be calculated as defined below to allow the presentation of rates.

Time point	Data to be included
Up to 24 weeks	- If participants planned EOS visit is week 24: up to last treatment date +1 - If participants planned EOS visit is later than week 24 use data up to the minimum (169, last treatment date+1)
Up to 36 weeks	- If participants planned EOS visit is week 24: exclude from summary table - If participants planned EOS visit is week 36: up to last treatment date +1 - If participants planned EOS visit is week 52 use data up to the minimum (253, last treatment date+1)
Up to 52 weeks	- If participants planned EOS visit is week 24: exclude from summary table - If participants planned EOS visit is week 36: exclude from summary table - If participants planned EOS visit is week 52 use data up to last treatment date+1

Maximum/Minimum Post-Baseline and Worst-Case Post-Baseline

Definition	Reporting Details
Maximum post-baseline	Maximum value over all on-treatment timepoints
Minimum post-baseline (Assessments that do not have a lower limit = 0)	Minimum value over all on-treatment timepoints
Worst case post-baseline (ECG findings)	• 'Abnormal' if any on-treatment assessment is evaluated as 'Abnormal' • 'Unable to evaluate' if all on-treatment assessments are 'Unable to evaluate' • 'Normal' if any on-treatment assessment is evaluated as 'Normal' and there are no on-treatment assessments evaluated as 'Abnormal'

Note: Assessment of minimum/maximum/worst-case post-baseline will include on-treatment data from scheduled, unscheduled and study discontinuation visits (if applicable).

Laboratory Parameters

- Non-quantifiable laboratory results will be treated as missing in summary displays. However, the results will be listed as received (e.g. '<x' or '>x').
- An 'any visit post-baseline' classification will be derived, in which participants will be counted in the 'low' and 'high' categories if they reported a low or high value at any scheduled or unscheduled on-treatment visit during the study.
- Change from baseline values will be classified relative to the normal range as 'to low', 'to normal or no change' or 'to high'. Participants who do not change categories or move from out-of-range to normal will be classified as 'to normal or no change'.
- An 'any visit post-baseline' change classification will be derived, in which participants will be counted in the 'to low' and 'to high' categories if they reported a change from a 'normal' baseline to a value below or above the normal range (respectively) at any on-treatment scheduled or unscheduled visit during the study. Participants who did not report a change to a value outside the normal range at any visit after the start of study treatment will be counted in the 'to normal or no change' category.

Multiple Measurements for Post-Baseline Visits for Safety

- Participants having both high and low values relative to normal ranges at post-baseline on-treatment visits for safety parameters will be counted in both the high and low categories of the "any visit post-baseline" row of related summary tables.

Urinanalysis

Potential Clinical Importance is defined as an increase in Protein or Occult Blood post-baseline relative to Baseline (Screening), or if microscopy is performed.

ECG

QTcF and QTcF change from baseline results will be reported in categories as below

ECG Parameter	Units	Ranges	
		Lower	Upper
Absolute			
Absolute QTcF Interval	msec	0	≤ 450
		> 450	≤ 480
		> 480	≤ 500
		> 500	≤ 530
		> 530	
Change from Baseline			
Change from Baseline QTcF	msec		≤-60
		>-60	≤-30
		>-30	≤0
		>0	≤ 30
		> 30	≤60
		> 60	

Pneumonia (AESI)
Pneumonia Event Rate
• Pneumonia events will be events classified in the pneumonia AESI group (rather than events recorded on the Pneumonia Details eCRF page). • Pneumonia event rate will be calculated as the number of events x 1000 divided by the total participant exposure during the time period of interest.
Association of Chest X-Ray with Pneumonia Event
• A chest X-ray is considered associated with pneumonia if it is performed within -7 to +14 days of the date of onset of pneumonia. Pneumonia is considered to be supported by a chest X-ray if the finding of the associated X-ray is consistent with the diagnosis of pneumonia, as recorded on eCRF page for chest X-ray.

MACE	
Broad MACE criteria	**Narrow MACE criteria**
Ischaemic heart disease SMQ: • Myocardial infarction SMQ (excluding fatalities) • Other ischemic heart disease SMQ (excluding fatalities) Central nervous system haemorrhages and cerebrovascular conditions SMQ (excluding fatalities)	-Myocardial infarction PT (excluding fatalities) -Acute myocardial infarction PT (excluding fatalities) Central nervous system haemorrhages and cerebrovascular conditions SMQ (excluding fatalities)

11.7. Appendix 7: Reporting Standards for Missing Data

11.7.1. Premature Withdrawals

Element	Reporting Detail

General	• Withdrawal from Study Prior to Randomization
	  • Participants who are pre-screening failures, screening failures, run-in failures, or stabilization failures (see Protocol Section 5.5 for the definitions) will be reported to account for the participant disposition.
	• Withdrawal from Study Treatment
	  • Randomized participants who withdraw from double-blind study treatment prematurely (for any reason) should, where possible, continue to be followed-up as per protocol until the end of the study, after returning to the appropriate asthma therapy per investigator's discretion. Post-treatment data will be included in the statistical analyses.
	• Withdrawal from Study
	  • See Appendix 2 for details on data collected at the Early Withdrawal visit.
	• Participant study completion (i.e. as specified in the protocol) was defined as 'A participant will be considered to have completed the study upon completion of all assessments and procedures for Visit 8/EOS and including a successful follow-up contact/visit.'

11.7.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument:
	  ○ These data will be indicated by the use of a "blank" in participant listing displays unless all data for a specific visit are missing in which case the visit is not displayed in the listing.
	  ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
	  ○ No imputation will be made for any missing numerical data, except in the sensitivity analysis of primary endpoints to assess the impact of missing data on study results. Missing data will generally not be considered in the calculation of percentages (i.e., the denominator will not include participants who have missing data at a given time point).

Responder Analysis	• Participants with a missing baseline will have responder status as missing. • Participants with missing data at scheduled clinic visit, regardless of treatment status, will be considered as non-responders. • For ACQ/SGRQ/AQLQ, participants that have withdrawn from study prior to the visit Week 24 will be imputed as non-responders at all visits after early

Element	Reporting Detail
	withdrawal visit where the assessment was expected to be performed, up to Week 24. • For E-RS and subscales, participants that have withdrawn from study prior Week 24 in question will be imputed as non-responders at time periods post-study withdrawal. This includes time periods up to and including Weeks 21-24.
Asthma Control Based on ACQ	• Participants with missing data at Week 12 or Week 24 will be classified as not achieving asthma control regardless of reasons in the summaries and analyses. • Participants with missing data at baseline will be excluded from the analysis, due to the inclusion of baseline as a covariate.

11.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays. • Dates which are completely missing will not be imputed, with the exception of the treatment stop date. Details for imputation of the treatment stop date are provided below.

Study treatment start and stop date	• If the study treatment start date is missing, the Visit 3 (Day 1) date will be used.
	• If overall treatment stop date is missing or partial, it will be imputed as follows:
	  • For participants who attended an Early Withdrawal visit, use the date of the Early Withdrawal visit
	  • For participants who attended the last on-treatment visit, use the End of Study Visit date
	  • For participants who died and did not attend the last on-treatment visit, use the date of death
	  • For all other participants, use the last recorded exposure stop date

Adverse Events	• Partial dates were not permitted to be entered in the eCRF for AEs, therefore no imputation of AE dates will be performed. •

Concomitant Medications	• Partial dates for any concomitant medications 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.

11.7.2.2. Handling of Missing Data for Statistical Analysis

The utilization of efficacy data in the statistical analyses are summarized in the table below:

Treatment / Study status	Data status	Data Inclusion for Analysis		
		Primary analysis 'de facto' estimand, without imputation	Supportive analysis 'de Jure' estimand, without imputation	Sensitivity Analysis 'de facto' estimand with imputation
on-treatment	have data	Yes	Yes	Yes: not imputed
post-treatment	have data	Yes	No	Yes: not imputed
post-treatment	missing data	No	No	Yes: imputed

Imputed post-treatment missing data will be imputed from early withdrawal visit date + 1 to planned end of study visit.

See Section 7.1.5 and Section 7.2.5 on the details for the proposed sensitivity analyses.

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

Endpoints	• Change from baseline in Trough FEV_1 • Change from baseline in ACQ total score • Change from baseline in SGRQ total score and domain scores • Change from baseline in AQLQ total score • Change from baseline in home daily trough FEV_1 over the first 24 weeks of the treatment period • Change from baseline in morning (AM) pre-dose PEF over the first 24 weeks of the treatment period • Change from baseline in evening (PM) PEF over the first 24 weeks of the treatment period • Change from baseline in E-RS Breathlessness scores over Weeks 21-24 (inclusive) of the treatment period • Change from baseline in E-RS Cough & Sputum scores over Weeks 21-24 (inclusive) of the treatment period • Change from baseline in E-RS Chest Symptoms scores over Weeks 21-24 (inclusive) of the treatment period • Change from baseline in the percentage of symptom-free days over the first 24 weeks of the treatment period • Change from baseline in the percentage of rescue medication-free days over the first 24 weeks of the treatment period • Change from baseline in daily rescue medication use over the first 24 weeks of the treatment period. • Change from baseline in Pulse rate • Change from baseline in Systolic BP • Change from baseline in Diastolic BP • Change from baseline in QTcF • Change from baseline in PR Interval • Change from baseline in Heart rate (ECG)
Analysis	• MMRM

- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
    - In the event the model fails to run using the KR method, then the residual method will be used instead.
- An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line.
    - In the event that this model fails to converge, alternative correlation structures may be considered such as CSH or CS.
    - Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of

the model respectively) to gain confidence that the model assumptions are reasonable].

Endpoints	• Mean change from baseline in clinic FEV_1 at 3 hours post study treatment at Week 24 • Mean change from baseline in clinic trough FEV_1 over the first 24 weeks of the treatment period
Analysis	• ANCOVA
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable].	

Endpoints	• Annualized rate of moderate/severe asthma exacerbations • Annualized rate of severe asthma exacerbations
Analysis	• Negative binomial regression
• The fit of the regression models will be examined using "Q-Q" plots of the standardized residuals. Interpretation of these plots will be aided by the addition of simulated envelopes as proposed by Atkinson (Atkinson, 1985). • If the model fails to converge, then the number of severe exacerbations will be fitted as a binary (0, >=1) variable. If the model still vails to converge removal of the covariate for number of severe exacerbations in the previous year will be considered.	

Endpoints	• Time to first moderate/severe asthma exacerbation • Time to first severe asthma exacerbation
Analysis	• Cox's proportional hazard model
• The proportional hazards assumption will be examined by obtaining the Kaplan-Meier estimates of the survival function S(t) over time separately for each treatment group. Under the assumption of proportional hazards between the treatment groups, ln{−ln[S(t)]} for two groups should be parallel to each other and the distance between them constant. If the curves are approximately parallel, then the proportional hazards assumption is not violated. If these curves cross each other or diverge greatly from the assumption of parallel lines, then the assumption is not met. • The 'exact' method for handling ties will be used. If the analysis will not run using the 'exact' method, the 'Efron' method for handling ties will be used instead.	

Endpoints	• Percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-7 at Week 24 • Percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease)from baseline for the ACQ-6 at Week 4 • Percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-5 at Week 24 • Percentage of patients that have achieved asthma control based on ACQ-7 (i.e. a total score ≤0.75) at both Week 12 and Week 24

	• Percentage of patients that have achieved asthma control based on ACQ-6 (i.e. a total score ≤0.75) at both Week 12 and Week 24 • Percentage of patients that have achieved asthma control based on ACQ-5 (i.e. a total score ≤0.75) at both Week 12 and Week 24 • Percent of patients meeting a responder threshold of ≥ 4 points improvement (decrease) from baseline for the SGRQ total score at Week 24 • Percent of patients meeting a responder threshold of ≥ 0.5 points improvement (increase) from baseline for the AQLQ total score at Week 24
Analysis	• Generalized linear model

- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
    - In the event the model fails to run using the KR method, then the residual method will be used instead.
- Computation of confidence intervals for the odds ratios is based on the individual Wald tests.
- Pearson residuals will be plotted by using PLOTS=PEARSONPANEL option for the model statement in SAS.

11.9. Appendix 9: Abbreviations & Trade Marks

11.9.1. Abbreviations

Abbreviation	Description
ACQ	Asthma Control Questionnaire
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
ALT	Alanine Transaminase
AM	Morning
AQLQ	Asthma Quality of Life Questionnaire
AST	Aspartate Transaminase
AUC	Area Under the Curve
BID	Twice Daily
BMI	Body Mass Index
BPM	Beats Per Minute
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DM	Data Management
DOB	Date of Birth
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EMA	European Medicines Agency
EOS	End of Study
E-RS[1]	Evaluating Respiratory Symptoms
EU	European Union
EW	Early Withdrawal
FDA	Food and Drug Administration
FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced expiratory volume in 1 second
FF	Fluticasone Furoate
FP	Fluticasone Propionate
FSC	Fluticasone Salmeterol Combination
FVC	Forced Vital Capacity
GSK	GlaxoSmithKline
ICH	International Conference on Harmonization

Abbreviation	Description
ICS	Inhaled Corticosteroids
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
kg	Kilogram
GUI	Guidance
L	Liters
L/min	Liters per minute
LABA	Long-Acting Beta-2-Agonist
LAMA	Long-Acting Muscarinic Antagonist
LRTI	Lower Respiratory Tract Infection
LTRA	Leukotriene Receptor Antagonist
m	Meter
MACE	Major Adverse Cardiac Event
MedDRA	Medicinal Dictionary for Regulatory Activities
mcg (μg)	Microgram
min	Minute
MMRM	Mixed Model Repeated Measures
msec	Millisecond
OCS	Oral Corticosteroid
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PM	Afternoon
QC	Quality Control
QD	Once daily
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RTF	Rich Text Format
SABA	Short-Acting Beta-2-Agonists
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
S&P	Statistics and Programming
SDTM	Study Data Tabulation Model
SGRQ	Saint George's Respiratory Questionnaire
SI	System Independent
SMQ	Standardized MedDRA Query
SOP	Standard Operation Procedure
TA	Therapeutic Area

Abbreviation	Description
TFL	Tables, Figures & Listings
UMEC	Umeclidinium
US	United States
VI	Vilanterol

[1] E-RS is now renamed Evaluating Respiratory Symptoms in COPD (E-RS: COPD). The term E-RS is used throughout this document for consistency with the study protocol

11.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
DISKUS
ELLIPTA

Trademarks not owned by the GlaxoSmithKline Group of Companies
E-RS: COPD
SAS

11.10. Appendix 10: List of Data Displays

11.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.54	1.1 to 1.2
Efficacy	2.1 to 2.138	2.1 to 2.118
Safety	3.1 to 3.90	3.1 to 3.18
Section	**Listings**	
ICH Listings	1 to 37	
Other Listings	38 to 74	

11.10.2. Mock Example Shell Referencing

Displays will follow IDSL standards where possible. Example mock-up displays will be provided in separate documents. Modifications and additional specifications for IDSL outputs will also be detailed in these documents, therefore where the mock displays differ from IDSL, the mock display should be followed.

11.10.3. Deliverables

Delivery [Priority]	Description
SAC [1]	Headline results
SAC	Statistical Analysis Complete

11.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Subjects Enrolled	SP1	Summary of Subject Populations		SAC [1]
1.2.	All Subjects Enrolled	ES6	Summary of Screen Failures, Run-in Failures, and Stabilization Failures		SAC [1]
1.3.	All Subjects Enrolled	SP_T1	Summary of Rescreens in the Study and Failure Reasons		SAC
1.4.	All Subjects Enrolled	NS1	Summary of Subject Enrolment by Country and Site ID		SAC
1.5.	ITT	NS1	Summary of Subject Included in the ITT population by Country and Site ID		SAC
1.6.	ITT	SD1	Summary of Treatment Status		SAC [1]
1.7.	ITT	ES1	Summary of Subject Disposition		SAC [1]
1.8.	ITT	IE2	Summary of Inclusion, Exclusion, Enrolment, or Randomization Criteria Deviations		SAC
1.9.	ITT	DV1	Summary of Important Protocol Deviations		SAC
1.10.	ITT	SP_T2	Summary of Treatment Status at Each Clinic Visit		SAC
1.11.	ITT	SP_T3	Summary of Planned and Actual End of Study Visit		SAC
Demography and Baseline Characteristics					
1.12.	ITT	DM1	Summary of Demographic Characteristics		SAC [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.13.	ITT	DM1	Summary of Demographic Characteristics – Pooled FF Doses		SAC
1.14.	All Subjects Enrolled	DM11	Summary of Age Ranges		SAC
1.15.	ITT	DM5	Summary of Race and Racial Combinations		SAC
1.16.	ITT	DM5	Summary of Race and Racial Combinations – Pooled FF		SAC
1.17.	ITT	DM6	Summary of Race and Racial Combination Details		SAC
1.18.	ITT	SP_T20	Summary of Pre-Study ICS Dosage at Screening		SAC [1]
1.19.	ITT	SP_T4	Summary of Disease Duration		SAC
1.20.	ITT	SP_T4	Summary of Disease Duration – Pooled FF Doses		SAC
1.21.	ITT	SP_T5	Summary of Asthma Medical History Questionnaire		SAC
1.22.	ITT	SP_T6	Summary of Exacerbation History		SAC [1]
1.23.	ITT	SP_T6	Summary of Exacerbation History – Pooled FF Doses		SAC
1.24.	ITT	SU1 (subset)	Summary of Smoking Status		SAC
1.25.	ITT	SP_T7	Summary of Cardiovascular History / Risk Factors		SAC [1]
1.26.	ITT	FH1	Summary of Family History of Cardiovascular Risk Factors		SAC
1.27.	ITT	SP_T8	Summary of Clinic Spirometry at Screening, Enrolment, and Randomization (Day 1)		SAC [1]
1.28.	ITT	SP_T8	Summary of Clinic Spirometry at Screening, Enrolment, and Randomization (Day 1) – Pooled FF Doses		SAC [1]
1.29.	ITT	SP_T9	Summary of Change in Clinic Pre-Bronchodilator / Pre-Dose FEV_1 (L) during Run-In and Stabilization Periods		SAC [1]
1.30.	ITT	SP_T10	Summary of Home Daily Spirometry During Run-in and Stabilization Periods		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.31.	ITT	SP_T11	Summary of Fractional Exhaled Nitric Oxide (ppb) at Baseline		SAC
1.32.	ITT	SP_t12	Summary of Total Serum IgE (KU/L) at Baseline		SAC
1.33.	ITT	SP_T13	Summary of ACQ Scores at Screening, Enrolment, and Randomization (Day 1)		SAC [1]
1.34.	ITT	SP_T14	Summary of Change in Pre-Treatment ACQ Scores		SAC [1]
1.35.	ITT	MH1	Summary of Current Medical Conditions		SAC
1.36.	ITT	MH1	Summary of Past Medical Conditions		SAC
1.37.	ITT	SP_T15	Summary of Pneumonia History		SAC
Concomitant Medications					
1.38.	ITT	SP_T16	Summary of Asthma Maintenance Therapy at Study Entry		SAC
1.39.	ITT	SP_T16	Summary of Asthma Maintenance Therapy at Study Entry – Pooled FF Doses		SAC
1.40.	ITT	CM1	Summary of Asthma Concomitant Medications at Study Entry		SAC
1.41.	ITT	CM1	Summary of Asthma Concomitant Medications During the Screening/Run-in Period		SAC
1.42.	ITT	CM1	Summary of Asthma Concomitant Medications During the Stabilization Period		SAC
1.43.	ITT	CM1	Summary of On-Treatment Asthma Concomitant Medications		SAC
1.44.	ITT	CM1	Summary of Post-Treatment Asthma Medications		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.45.	ITT	SP_T17	Summary of Asthma Maintenance Therapy Following Treatment Discontinuation		SAC
1.46.	ITT	CM1	Summary of Post-Study Asthma Medications		SAC
1.47.	ITT	SP_T21	Summary of Concomitant Medications Used for the Treatment of Moderate/Severe Asthma Exacerbations		SAC
1.48.	ITT	CM1	Summary of On-Treatment Non-Asthma Concomitant Medications		SAC
1.49.	ITT	CM1	Summary of Post-Treatment Non-Asthma Medications		SAC
1.50.	ITT	CM1	Summary of Post-Study Non-Asthma Medications		SAC
Treatment Compliance					
1.51.	ITT	SP_T18	Summary of Treatment Compliance (%)		SAC
1.52.	ITT	SP_T18	Summary of Treatment Compliance (%) – Pooled FF Doses		SAC
1.53.	ITT	SP_T19	Summary of Treatment Compliance (%) up to Week 24		SAC
1.54.	ITT	SP_T19	Summary of Treatment Compliance (%) up to Week 24 – Pooled FF Doses		SAC

11.10.5. Study Population Figures

Study Population Figures					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	ITT	SP_T1	Kaplan-Meier Plot of Time to Early Discontinuation from Study Treatment		SAC
1.2.	ITT	SP_T1	Kaplan-Meier Plot of Time to Early Withdrawal from Study		SAC

11.10.6. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Efficacy Endpoint					
2.1.	ITT	EFF_T1	Summary of Baseline Clinic Trough FEV_1 (L)		SAC [1]
2.2.	ITT	EFF_T2	Summary of Clinic Trough FEV_1 (L) (On- and Post-Treatment)	Weeks 4, 12, 24,36, 52	SAC [1]
2.3.	ITT	EFF_T4	Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) up to Week 24 (On- and Post-Treatment)	Weeks 4, 12, 24	SAC [1]
2.4.	ITT	EFF_T5	Summary of Test Results for all Covariates and Interactions Included in the MMRM Analysis Model for Change from Baseline in Clinic Trough FEV_1 (L)	Week 24	SAC
2.5.	ITT	EFF_T3	Summary of Clinic Trough FEV_1 (L) by Treatment Status (On- and Post-Treatment)	Weeks 4, 12, 24,36, 52	SAC
2.6.	ITT	EFF_T4	Supportive Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) up to Week 24 (On-Treatment)	Weeks 4, 12, 24	SAC
2.7.	ITT	EFF_T4	Supportive Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) up to Week 24 Excluding Sites with Data Concerns (On- and Post-Treatment)	Weeks 4, 12, 24	SAC
2.8.	ITT	EFF_T7	Sensitivity Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) at Week 24 (Jump to Reference) (On- and Post-Treatment)	Present Week 24 only	SAC
2.9.	ITT	EFF_T9	Sensitivity Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) at Week 24 (Tipping Point): FF/UMEC/VI 100/62.5/25 v FF/VI 100/25 (On- and Post-Treatment)	Present Week 24 only	SAC
2.10.	ITT	EFF_T8	Sensitivity Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) at Week 24 (Tipping Point p-value Grid): FF/UMEC/VI 100/62.5/25 v FF/VI 100/25 (On- and Post-	Present Week 24 only	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			Treatment)		

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.11.	ITT	EFF_T9	Sensitivity Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) at Week 24 (Tipping Point): FF/UMEC/VI 200/62.5/25 v FF/VI 200/25 (On- and Post-Treatment)	Present Week 24 only	SAC
2.12.	ITT	EFF_T8	Sensitivity Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) at Week 24 (Tipping Point p-value Grid): FF/UMEC/VI 200/62.5/25 v FF/VI 200/25 (On- and Post-Treatment)	Present Week 24 only	SAC
2.13.	ITT	EFF_T9	Sensitivity Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) at Week 24 (Tipping Point): FF/UMEC/VI 100/31.25/25 v FF/VI 100/25 (On- and Post-Treatment)	Present Week 24 only	SAC
2.14.	ITT	EFF_T8	Sensitivity Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) at Week 24 (Tipping Point p-value Grid): FF/UMEC/VI 100/31.25/25 v FF/VI 100/25 (On- and Post-Treatment)	Present Week 24 only	SAC
2.15.	ITT	EFF_T9	Sensitivity Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) at Week 24 (Tipping Point): FF/UMEC/VI 200/31.25/25 v FF/VI 200/25 (On- and Post-Treatment)	Present Week 24 only	SAC
2.16.	ITT	EFF_T8	Sensitivity Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) at Week 24 (Tipping Point p-value Grid): FF/UMEC/VI 200/31.25/25 v FF/VI 200/25 (On- and Post-Treatment)	Present Week 24 only	SAC
2.17.	ITT	EFF_T1	Summary of Baseline Clinic Trough FEV_1 (L) – Pooled FF Doses		SAC
2.18.	ITT	EFF_T2	Summary of Clinic Trough FEV_1 (L) (On- and Post-Treatment) – Pooled FF Doses	Weeks 4, 12, 24,36, 52	SAC
2.19.	ITT	EFF_T6	Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) up to Week 24 (On- and Post-Treatment) – Pooled FF Doses	Weeks 4, 12, 24	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.20.	ITT	EFF_10	Summary of Baseline Clinic Trough FEV_1 (L) by Gender		SAC
2.21.	ITT	EFF_T2	Summary of Clinic Trough FEV_1 (L) by Gender (On- and Post-Treatment)	Weeks 4, 12, 24,36, 52	SAC
2.22.	ITT	EFF_T10	Summary of Baseline Clinic Trough FEV_1 (L) by Age (<18, 18 to <65, 65 to <75, 75 to <85, ≥85 years)		SAC
2.23.	ITT	EFF_T2	Summary of Clinic Trough FEV_1 (L) by Age (<18, 18 to <65, 65 to <75, 75 to <85, ≥85 years) (On- and Post-Treatment)	Weeks 4, 12, 24,36, 52	SAC
2.24.	ITT	EFF_T10	Summary of Baseline Clinic Trough FEV_1 (L) by Age (<65, ≥65 years)		SAC
2.25.	ITT	EFF_T2	Summary of Clinic Trough FEV_1 (L) by Age (<65, ≥65 years) (On- and Post-Treatment)	Weeks 4, 12, 24,36, 52	SAC
2.26.	ITT	EFF_T10	Summary of Baseline Clinic Trough FEV_1 (L) by Race		SAC
2.27.	ITT	EFF_T2	Summary of Clinic Trough FEV_1 (L) by Race (On- and Post-Treatment)	Weeks 4, 12, 24,36, 52	SAC
2.28.	ITT	EFF_T10	Summary of Baseline Clinic Trough FEV_1 (L) by Region		
2.29.	ITT	EFF_T2	Summary of Clinic Trough FEV_1 (L) by Region (On- and Post-Treatment)	Weeks 4, 12, 24,36, 52	SAC
2.30.	ITT	EFF_T10	Summary of Baseline Clinic Trough FEV_1 (L) by Pre-Study ICS Dosage at Screening		SAC
2.31.	ITT	EFF_T2	Summary of Clinic Trough FEV_1 (L) by Pre-Study ICS Dosage at Screening (On- and Post-Treatment)	Weeks 4, 12, 24,36, 52	SAC
2.32.	ITT	EFF_T10	Summary of Baseline Clinic Trough FEV_1 (L) by BMI		
2.33.	ITT	EFF_T2	Summary of Clinic Trough FEV_1 (L) by BMI (On- and Post-Treatment)	Weeks 4, 12, 24,36, 52	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.34.	ITT	EFF_T10	Summary of Baseline Clinic Trough FEV_1 (L) by CV History/Risk Factor at Screening		
2.35.	ITT	EFF_T2	Summary of Clinic Trough FEV_1 (L) by CV History/Risk Factor at Screening (On- and Post-Treatment)	Weeks 4, 12, 24,36, 52	SAC
Key Secondary Efficacy Endpoint					
2.36.	ITT	EFF_T11	Summary of Moderate and Severe Asthma Exacerbations (On- and Post-Treatment) – Pooled FF Doses	Weeks 1-52, 1-24, 25-52	SAC [1]
2.37.	ITT	EFF_T12	Analysis of Moderate/Severe Asthma Exacerbations (On- and Post-Treatment) – Pooled FF Doses	Weeks 1-52, 1-24	SAC [1]
2.38.	ITT	EFF_T5	Summary of Test Results for all Covariates and Interactions Included in the the Negative Binomial Analysis Model for Moderate/Severe Asthma Exacerbations (On-and Post-Treatment) – Pooled FF Doses	Weeks 1-52, 1-24	SAC
2.39.	ITT	EFF_T11	Summary of Moderate and Severe Asthma Exacerbations (On-Treatment) – Pooled FF Doses	Weeks 1-52, 1-24, 25-52	SAC
2.40.	ITT	EFF_T12	Supportive Analysis of Moderate/Severe Asthma Exacerbations (On-Treatment) – Pooled FF Doses	Weeks 1-52, 1-24	SAC
2.41.	ITT	EFF_T12	Supportive Analysis of Moderate/Severe Asthma Exacerbations (On- and Post-Treatment) Excluding Sites with Data Concerns – Pooled FF Doses	Weeks 1-52	SAC
2.42.	ITT	EFF_T12	Sensitivity Analysis of Moderate/Severe Asthma Exacerbations (Jump to Reference) (On- and Post-Treatment) – Pooled FF Doses	Weeks 1-52	SAC
2.43.	ITT	EFF_T14	Sensitivity Analysis of Moderate/Severe Asthma Exacerbations (Tipping Point): FF/UMEC/VI UMEC 62.5 vs. FF/VI over Week 1-52 (On- and Post-Treatment)– Pooled FF Doses	Weeks 1-52	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.44.	ITT	EFF_T15	Sensitivity Analysis of Moderate/Severe Asthma Exacerbations (Tipping Point p-value Grid): FF/UMEC/VI UMEC 62.5 vs. FF/VI over Week 1-52 (On- and Post-Treatment) – Pooled FF Doses	Weeks 1-52	SAC
2.45.	ITT	EFF_T14	Sensitivity Analysis of Moderate/Severe Asthma Exacerbations (Tipping Point): FF/UMEC/VI UMEC 31.25vs. FF/VI over Week 1-52 (On- and Post-Treatment) – Pooled FF Doses	Weeks 1-52	SAC
2.46.	ITT	EFF_T15	Sensitivity Analysis of Moderate/Severe Asthma Exacerbations (Tipping Point p-value Grid): FF/UMEC/VIUMEC 31.25 vs. FF/VI over Week 1-52 (On- and Post-Treatment) – Pooled FF Doses	Weeks 1-52	SAC
2.47.	ITT	EFF_T11	Summary of Moderate and Severe Asthma Exacerbations (On- and Post-Treatment)	Weeks 1-52, 1-24, 25-52	SAC [1]
2.48.	ITT	EFF_T13	Analysis of Moderate/Severe Asthma Exacerbations (On- and Post-Treatment)	Weeks 1-52, 1-24	SAC [1]
2.49.	ITT	EFF_T11	Summary of Moderate and Severe Asthma Exacerbations by Gender (On- and Post-Treatment) - Pooled FF Doses	Weeks 1-52	SAC
2.50.	ITT	EFF_T11	Summary of Moderate and Severe Asthma Exacerbations by Age (<18, 18 to <65, 65 to <75, 75 to <85, ≥85 years) (On- and Post-Treatment) - Pooled FF Doses	Weeks 1-52	SAC
2.51.	ITT	EFF_T11	Summary of Moderate and Severe Asthma Exacerbations by Age (<65, ≥65 years) (On- and Post-Treatment) - Pooled FF Doses	Weeks 1-52	SAC
2.52.	ITT	EFF_T11	Summary of Moderate and Severe Asthma Exacerbations by Race (On- and Post-Treatment) - Pooled FF Doses	Weeks 1-52	SAC
2.53.	ITT	EFF_T11	Summary of Moderate and Severe Asthma Exacerbations by Region (On- and Post-Treatment) - Pooled FF Doses	Weeks 1-52	SAC
2.54.	ITT	EFF_T11	Summary of Moderate and Severe Asthma Exacerbations by	Weeks 1-52	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			Pre-Study ICS Dosage at Screening (On- and Post-Treatment) - Pooled FF Doses		
2.55.	ITT	EFF_T11	Summary of Moderate and Severe Asthma Exacerbations by BMI (On- and Post-Treatment) - Pooled FF Doses	Weeks 1-52	SAC
2.56.	ITT	EFF_T11	Summary of Moderate and Severe Asthma Exacerbations by CV History/Risk Factor at Screening (On- and Post-Treatment) - Pooled FF Doses	Weeks 1-52	SAC
Other Secondary Efficacy Endpoints					
2.57.	ITT	EFF_T16	Summary of Change from Baseline in Clinic FEV_1 (L) at 3 Hours Post Study Treatment (On-Treatment)	Day 1, Weeks 24and 52	SAC
2.58.	ITT	EFF_T4	Analysis of Mean Change from Baseline in Clinic FEV_1 (L) at 3 Hours Post Study Treatment at Week 24 (On-Treatment)	Week 24	SAC
2.59.	ITT	EFF_T16	Summary of Change from Baseline in Clinic FEV_1 (L) at 3 Hours Post Study Treatment (On-Treatment) - Pooled FF Doses	Day 1, Weeks 24 and 52	SAC
2.60.	ITT	EFF_T6	Analysis of Mean Change from Baseline in Clinic FEV_1 (L) at 3 Hours Post Study Treatment at Week 24 (On-Treatment) - Pooled FF Doses	Week 24	SAC
2.61.	ITT	EFF_T20	Summary of Baseline SGRQ Scores – Pooled FF Doses	Includes baseline total score and domain scores for symptoms, activity, and impact.	SAC [1]
2.62.	ITT	EFF_T2	Summary of SGRQ Total Score (On- and Post-Treatment) – Pooled FF Doses	Weeks 12, 24,36, 52	SAC [1]
2.63.	ITT	EFF_T6	Analysis of Mean Change from Baseline in SGRQ Total Score up to Week 24 up to Week 24 (On- and Post-Treatment) – Pooled FF Doses	Weeks 12, 24	SAC [1]
2.64.	ITT	EFF_T20	Summary of Baseline SGRQ Scores	Includes baseline total score and	SAC [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
				domain scores	
2.65.	ITT	EFF_T2	Summary of SGRQ Total Score (On- and Post-Treatment)	Weeks 12, 24,36, 52	SAC [1]
2.66.	ITT	EFF_T4	Analysis of Mean Change from Baseline in SGRQ Total Score up to Week 24 (On- and Post-Treatment)	Weeks 12, 24	SAC [1]
2.67.	ITT	EFF_T17	Summary of Baseline ACQ-7 Total Score – Pooled FF Doses		SAC [1]
2.68.	ITT	EFF_T18	Summary of ACQ-7 Total Score (On- and Post-Treatment) – Pooled FF Doses	Weeks 4, 12, 24,36, 52	SAC [1]
2.69.	ITT	EFF_T19	Shift in ACQ-7 Total Score Control Category from Baseline (On- and Post-Treatment) – Pooled FF Doses	Baseline to Weeks 4, 12, 24,36, 52	SAC
2.70.	ITT	EFF_T6	Analysis of Mean Change from Baseline in ACQ-7 Total Score up to Week 24 (On- and Post-Treatment) – Pooled FF Doses	Weeks 4, 12, 24	SAC [1]
2.71.	ITT	EFF_T18	Summary of ACQ-7 Total Score (On- and Post-Treatment)	Weeks 4, 12, 24,36, 52	SAC [1]
2.72.	ITT	EFF_T19	Shift in ACQ-7 Total Score Control Category from Baseline (On- and Post-Treatment)	Baseline to Weeks 4, 12, 24,36, 52	SAC
2.73.	ITT	EFF_T4	Analysis of Mean Change from Baseline in ACQ-7 Total Score up to Week 24 (On- and Post-Treatment)	Weeks 4, 12, 24	SAC [1]
2.74.	ITT	EFF_T20	Summary of Baseline E-RS Scores – Pooled FF Doses	Includes baseline total score and domain scores for breathlessness, cough and sputum, and chest	SAC
2.75.	ITT	EFF_T21	Summary of E-RS Total Score (On- and Post-Treatment) – Pooled FF Doses	4 weekly up to 52 weeks and weeks 1 to 24	SAC
2.76.	ITT	EFF_T6	Analysis of Mean Change from Baseline in E-RS Total Score up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment) – Pooled FF Doses	4 weekly up to 24 weeks, weeks 1 to 24	SAC
2.77.	ITT	EFF_T20	Summary of Baseline E-RS Scores	Includes baseline total score and	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
				domain scores for breathlessness, cough and sputum, and chest	
2.78.	ITT	EFF_T21	Summary of E-RS Total Score (On- and Post-Treatment)	4 weekly up to 52 weeks and weeks 1 to 24	SAC
2.79.	ITT	EFF_T4	Analysis of Mean Change from Baseline in E-RS Total Score up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment)	4 weekly up to 24 weeks, weeks 1 to 24	SAC
2.80.	ITT	EFF_T22	Summary of Analyses in Testing Hierarchy (On- and Post-Treatment)		SAC
Other Efficacy Endpoints					
2.81.	ITT	EFF_T2	Summary of Clinic Spirometry Data (On- and Post-Treatment)	Week 4, 12, 24, 36 and 52. Include FVC, FEV/FVC ratio and % predicted. Include pre- and post-dose where applicable.	SAC
2.82.	ITT	EFF_T23	Summary of Clinic Trough FEV_1 (L) Over the First 24 Weeks of the Treatment Period (On- and Post-Treatment)	AUC_{0-24w}	SAC
2.83.	ITT	EFF_T4	Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) Over the First 24 Weeks of the Treatment Period (On- and Post-Treatment)	AUC_{0-24w}	SAC
2.84.	ITT	EFF_T21	Summary of Home Daily Trough FEV_1 (L) (On- and Post-Treatment)	4 weekly up to 52 weeks and weeks 1 to 24	SAC
2.85.	ITT	EFF_T21	Summary of Home Daily Trough FEV_1 (L) by 1-Week Intervals (On- and Post-Treatment)	1-week up to 52 weeks	SAC
2.86.	ITT	EFF_T4	Analysis of Mean Change from Baseline in Home Daily Trough FEV_1 (L) up to Week 24 by 4-Weekly intervals (On- and Post-Treatment)	4 weekly up to 24 weeks, weeks 1 to 24	SAC
2.87.	ITT	EFF_T4	Analysis of Mean Change from Baseline in Home Daily Trough	1-week up to 8 weeks	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			FEV_1 (L) up to Week 8 by 1-Week Intervals (On- and Post-Treatment)		
2.88.	ITT	EFF_T21	Summary of Home Daily PM FEV_1 (L) (On- and Post-Treatment)	4 weekly up to 52 weeks and weeks 1 to 24	SAC
2.89.	ITT	EFF_T21	Summary of Home Daily PM FEV_1 (L) by 1-Week Intervals (On- and Post-Treatment)	1-week up to 52 weeks	SAC
2.90.	ITT	EFF_T4	Analysis of Mean Change from Baseline in Home Daily PM FEV_1 (L) up to Week 24 by 4-Weekly intervals (On- and Post-Treatment)	4 weekly up to 24 weeks, weeks 1 to 24	SAC
2.91.	ITT	EFF_T21	Summary of Home Daily AM PEF (L/min) (On- and Post-Treatment)	4 weekly up to 52 weeks and weeks 1 to 24	SAC
2.92.	ITT	EFF_T21	Summary of Home Daily AM PEF (L/min) by 1-Week Intervals (On- and Post-Treatment)	1-weekly intervals to week 52	SAC
2.93.	ITT	EFF_T4	Analysis of Mean Change from Baseline in Home Daily AM PEF (L/min) up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment)	4 weekly up to 24 weeks, weeks 1 to 24	SAC
2.94.	ITT	EFF_T21	Summary of Home Daily PM PEF (L/min) (On- and Post-Treatment)	4 weekly up to 52 weeks and weeks 1 to 24	SAC
2.95.	ITT	EFF_T21	Summary of Home Daily PM PEF (L/min) by 1-Week Intervals (On- and Post-Treatment)	1 weekly intervals to week 52	SAC
2.96.	ITT	EFF_T4	Analysis of Mean Change from Baseline in Home Daily PM PEF (L/min) up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment)	4 weekly up to 24 weeks, weeks 1 to 24	SAC
2.97.	ITT	EFF_T12	Analysis of Severe Asthma Exacerbations (On- and Post-Treatment) – Pooled FF Doses	Weeks 1-52	SAC
2.98.	ITT	EFF_T13	Analysis of Severe Asthma Exacerbations (On- and Post-	Weeks 1-52	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			Treatment)		
2.99.	ITT	EFF_T28	Summary and Analysis of Time to First Moderate/Severe Asthma Exacerbation (Days) (On- and Post-Treatment) – Pooled FF Doses	Weeks 1-52	SAC
2.100.	ITT	EFF_T29	Summary and Analysis of Time to First Moderate/Severe Asthma Exacerbation (Days) (On- and Post-Treatment)	Weeks 1-52	SAC
2.101.	ITT	EFF_T28	Summary and Analysis of Time to First Severe Asthma Exacerbation (Days) (On- and Post-Treatment) – Pooled FF Doses	Weeks 1-52	SAC
2.102.	ITT	EFF_T29	Summary and Analysis of Time to First Severe Asthma Exacerbation (Days) (On- and Post-Treatment)	Weeks 1-52	SAC
2.103.	ITT	EFF_T24	Summary and Analysis of Percent of Patients Meeting a Responder Threshold of ≥0.5 points improvement (decrease) from Baseline for ACQ-7 Total Score up to Week 24 (On- and Post-Treatment) – Pooled FF Doses	Weeks 4, 12, 24	SAC
2.104.	ITT	EFF_T25	Summary and Analysis of Percent of Patients Meeting a Responder Threshold of ≥0.5 points improvement (decrease) from Baseline for ACQ-7 Total Score up to Week 24 (On- and Post-Treatment)	Weeks 4, 12, 24	SAC
2.105.	ITT	EFF_T24	Summary and Analysis of Percent of Patients Meeting a Responder Threshold of ≥0.5 points improvement (decrease) from Baseline for ACQ-6 Total Score up to Week 24 (On- and Post-Treatment) – Pooled FF Doses	Weeks 4, 12, 24	SAC
2.106.	ITT	EFF_T24	Summary and Analysis of Percent of Patients Meeting a Responder Threshold of ≥0.5 points improvement (decrease) from Baseline for ACQ-5 Total Score up to Week 24 (On- and Post-Treatment) – Pooled FF Doses	Weeks 4, 12, 24	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.107.	ITT	EFF_T26	Summary and Analysis of Percent of Patients Who Have Achieved Asthma Control Based on ACQ-7 (i.e. a Total Score ≤0.75) at Both Week 12 and Week 24 (On- and Post-Treatment) – Pooled FF Doses	Includes data from weeks 12, 24	SAC
2.108.	ITT	EFF_T27	Summary and Analysis of Percent of Patients Who Have Achieved Asthma Control Based on ACQ-7 (i.e. a Total Score ≤0.75) at Both Week 12 and Week 24 (On- and Post-Treatment)	Includes data from weeks 12, 24	SAC
2.109.	ITT	EFF_T26	Summary and Analysis of Percent of Patients Who Have Achieved Asthma Control Based on ACQ-6 (i.e. a Total Score ≤0.75) at Both Week 12 and Week 24 (On- and Post-Treatment) – Pooled FF Doses	Includes data from weeks 12, 24	SAC
2.110.	ITT	EFF_T26	Summary and Analysis of Percent of Patients Who Have Achieved Asthma Control Based on ACQ-5 (i.e. a Total Score ≤0.75) at Both Week 12 and Week 24 (On- and Post-Treatment) – Pooled FF Doses	Includes data from weeks 12, 24	SAC
2.111.	ITT	EFF_T2	Summary of SGRQ Domain Scores (On- and Post-Treatment) – Pooled FF Doses	Includes domain scores for symptoms, activity, and impact. Weeks 12, 24, 36, 52	SAC
2.112.	ITT	EFF_T6	Analysis of Mean Change from Baseline in SGRQ Domain Scores up to Week 24 (On- and Post-Treatment) – Pooled FF Doses	Weeks 12, 24	SAC
2.113.	ITT	EFF_T24	Summary and Analysis of Percent of Patients Meeting a Responder Threshold of ≥ 4 Points Improvement (Decrease) from Baseline for the SGRQ Total Score up to Week 24 (On- and Post-Treatment) – Pooled FF Doses	Weeks 12, 24	SAC
2.114.	ITT	EFF_T25	Summary and Analysis of Percent of Patients Meeting a Responder Threshold of ≥ 4 Points Improvement (Decrease) from Baseline for the SGRQ Total Score up to Week 24 (On-	Weeks 12, 24	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			and Post-Treatment)		

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.115.	ITT	EFF_T21	Summary of E-RS Domain Scores (On- and Post-Treatment) – Pooled FF Doses	Includes domain scores for breathlessness, cough and sputum, and chest. 4 weekly up to week 52 and weeks 1-24	SAC
2.116.	ITT	EFF_T6	Analysis of Mean Change from Baseline in E-RS Domain Scores up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment) – Pooled FF Doses	Includes domain scores for breathlessness, cough and sputum, and chest 4 weekly up to week 24, and weeks 1-24	SAC
2.117.	ITT	EFF_T24	Summary and Analysis of Percent of Patients Meeting a Responder Threshold of ≥ 2 Points Improvement (Decrease) from Baseline for the E-RS Total Score up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment) – Pooled FF Doses	4 weekly up to week 24	SAC
2.118.	ITT	EFF_T25	Summary and Analysis of Percent of Patients Meeting a Responder Threshold of ≥ 2 Points Improvement (Decrease) from Baseline for the E-RS Total Score up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment)	4 weekly up to week 24	SAC
2.119.	ITT	EFF_T20	Summary of Baseline AQLQ Total Score– Pooled FF Doses		SAC
2.120.	ITT	EFF_T2	Summary of AQLQ Total Score (On- and Post-Treatment) – Pooled FF Doses	Weeks 4, 12, 24, 36 and 52	SAC
2.121.	ITT	EFF_T6	Analysis of Mean Change from Baseline in AQLQ Total Score up to Week 24 (On- and Post-Treatment) – Pooled FF Doses	Weeks 4, 12 and 24	SAC
2.122.	ITT	EFF_T24	Summary and Analysis of Percent of Patients Meeting a Responder Threshold of ≥ 0.5 Points Improvement (Increase) from Baseline for the AQLQ Total Score up to Week 24 (On- and Post-Treatment) - Pooled FF Doses	Weeks 4, 12, 24	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.123.	ITT	EFF_T20	Summary of Baseline Percentage of Symptom-Free Days – Pooled FF Doses		SAC
2.124.	ITT	EFF_T21	Summary of Percentage of Symptom-Free Days (On- and Post-Treatment) – Pooled FF Doses	4 weekly up to 52 weeks and weeks 1 to 24	SAC
2.125.	ITT	EFF_T34	Analysis of Mean Change from Baseline in the Percentage of Symptom-Free Days up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment) – Pooled FF Doses	4 weekly up to 24 weeks, weeks 1 to 24	SAC
2.126.	ITT	EFF_T20	Summary of Baseline Percentage of Rescue Medication-Free Days– Pooled FF Doses		SAC
2.127.	ITT	EFF_T21	Summary of Percentage of Rescue Medication-Free Days (On- and Post-Treatment) – Pooled FF Doses	4 weekly up to 52 weeks and weeks 1 to 24	SAC
2.128.	ITT	EFF_T34	Analysis of Mean Change from Baseline in the Percentage of Rescue Medication-Free Days up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment) – Pooled FF Doses	4 weekly up to 24 weeks, weeks 1 to 24	SAC
2.129.	ITT	EFF_T20	Summary of Baseline Daily Rescue Medication Use (Puffs/Day) – Pooled FF Doses		SAC
2.130.	ITT	EFF_T21	Summary of Daily Rescue Medication Use (Puffs/Day) (On- and Post-Treatment) – Pooled FF Doses	4 weekly up to 52 weeks and weeks 1 to 24	SAC
2.131.	ITT	EFF_T6	Analysis of Mean Change from Baseline in Daily Rescue Medication Use (Puffs/Day) up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment) – Pooled FF Doses	4 weekly up to 24 weeks, weeks 1 to 24	SAC
2.132.	ITT	EFF_T31	Summary of Baseline Global Assessment of Severity		SAC
2.133.	ITT	EFF_T32	Summary of Global Assessment of Severity and Response to Treatment (On- and Post-Treatment)	Weeks 4, 12, 24, 36 and 52	SAC
2.134.	ITT	EFF_T33	Summary of Work Productivity and Activity Impairment-Specific Health Problem (On- and Post-Treatment)	Day 1, Week 12, Week 24, and Week 52	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.135.	ITT	EFF_T30	Summary of Unscheduled Asthma-Related Healthcare Resource Utilization up to Week 24 (On- and Post-Treatment)		SAC
2.136.	ITT	EFF_T30	Summary of Unscheduled Asthma-Related Healthcare Resource Utilization up to Week 52 for Subjects with ≥ 36 Weeks of Planned Treatment Exposure (On- and Post-Treatment)		SAC
2.137.	ITT	EFF_T30	Summary of Unscheduled Asthma-Related Healthcare Resource Utilization up to Week 24 (On- and Post-Treatment) by Contact Type		SAC
2.138.	ITT	EFF_T30	Summary of Unscheduled Asthma-Related Healthcare Resource Utilization up to Week 52 for Subjects with ≥ 36 Weeks of Planned Treatment Exposure (On- and Post-Treatment) by Contact Type		SAC

11.10.7. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Efficacy Endpoint					
2.1.	ITT	EFF_F1	Box Plot of Change from Baseline in Clinic Trough FEV_1 (L) (On- and Post-Treatment)	Page per time point. Weeks 4, 12, 24, 36 and 52	SAC [1]
2.2.	ITT	EFF_F2	Empirical Distribution Function Plot of Change from Baseline in Clinic Trough FEV_1 (L) (On- and Post-Treatment)	Weeks 4, 12, 24, 36 and 52	SAC
2.3.	ITT	EFF_F3	Least Squares Mean (95% CI) Change from Baseline in Clinic	weeks 4, 12, 24	SAC [1]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			Trough FEV_1 (L) up to Week 24 (On- and Post-Treatment)		
2.4.	ITT	EFF_F4	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Clinic Trough FEV_1 (L) up to Week 24 (On- and Post-Treatment)	weeks 4, 12, 24	SAC [1]
2.5.	ITT	EFF_F1	Box Plot of Change from Baseline in Clinic Trough FEV_1 (L) (On-Treatment)	Weeks 4, 12, 24, 36 and 52	SAC
2.6.	ITT	EFF_F2	Empirical Distribution Function Plot of Change from Baseline in Clinic Trough FEV_1 (L) (On-Treatment)	Weeks 4, 12, 24, 36 and 52	SAC
2.7.	ITT	EFF_F3	Least Squares Mean (95% CI) Change from Baseline in Clinic Trough FEV_1 (L) up to Week 24 (On-Treatment)	Weeks 4, 12, 24	SAC
2.8.	ITT	EFF_F4	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Clinic Trough FEV_1 (L) up to Week 24 (On-Treatment)	Weeks 4, 12, 24	SAC
2.9.	ITT	EFF_F7	Forest Plot of Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Clinic Trough FEV_1 (L) and Associated Supportive/Sensitivity Analyses at Week 24	Forest plot at Week 24	SAC
2.10.	ITT	EFF_F5	Tipping Point Heat Plot for Mean Change from Baseline in Clinic Trough FEV_1 (L) Difference FF/UMEC/VI 100/62.5/25 v FF/VI 100/25 at Week 24 (On- and Post-Treatment)	Week 24	SAC
2.11.	ITT	EFF_F6	Tipping Point Line Plot for Mean Change from Baseline in Clinic Trough FEV_1 (L) Difference FF/UMEC/VI 100/62.5/25 v FF/VI 100/25 at Week 24 (On- and Post-Treatment)	Week 24	SAC
2.12.	ITT	EFF_F5	Tipping Point Heat Plot for Mean Change from Baseline in Clinic Trough FEV_1 (L) Difference FF/UMEC/VI 200/62.5/25 v FF/VI 200/25 at Week 24 (On- and Post-Treatment)	Week 24	SAC
2.13.	ITT	EFF_F6	Tipping Point Line Plot for Mean Change from Baseline in Clinic	Week 24	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			Trough FEV_1 (L) Difference FF/UMEC/VI 200/62.5/25 v FF/VI 200/25 at Week 24 (On- and Post-Treatment)		
2.14.	ITT	EFF_F5	Tipping Point Heat Plot for Mean Change from Baseline in Clinic Trough FEV_1 (L) Difference FF/UMEC/VI 100/31.25/25 v FF/VI 100/25 at Week 24 (On- and Post-Treatment)	Week 24	SAC
2.15.	ITT	EFF_F6	Tipping Point Line Plot for Mean Change from Baseline in Clinic Trough FEV_1 (L) Difference FF/UMEC/VI 100/31.25/25 v FF/VI 100/25 at Week 24 (On- and Post-Treatment)	Week 24	SAC
2.16.	ITT	EFF_F5	Tipping Point Heat Plot for Mean Change from Baseline in Clinic Trough FEV_1 (L) Difference FF/UMEC/VI 200/31.25/25 v FF/VI 200/25 at Week 24 (On- and Post-Treatment)	Week 24	SAC
2.17.	ITT	EFF_F6	Tipping Point Line Plot for Mean Change from Baseline in Clinic Trough FEV_1 (L) Difference FF/UMEC/VI 200/31.25/25 v FF/VI 200/25 at Week 24 (On- and Post-Treatment)	Week 24	SAC
2.18.	ITT	EFF_F3	Least Squares Mean (95% CI) Change from Baseline in Clinic Trough FEV_1 (L) up to Week 24 (On- and Post-Treatment) - Pooled FF Doses	Weeks 4, 12, 24	SAC
2.19.	ITT	EFF_F4	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Clinic Trough FEV_1 (L) up to Week 24 (On- and Post-Treatment) - Pooled FF Doses	Weeks 4, 12, 24	SAC
Key Secondary Efficacy Endpoint					
2.20.	ITT	EFF_F8	Forest Plot of Adjusted Moderate/Severe Asthma Exacerbations Rate Ratio (On- and Post-Treatment) - Pooled FF Doses	Weeks 1-24 and 1-52	SAC [1]
2.21.	ITT	EFF_F8	Forest Plot of Adjusted Moderate/Severe Asthma Exacerbations Rate Ratio (On-Treatment) - Pooled FF Doses	Weeks 1-24 and 1-52	SAC
2.22.	ITT	EFF_F9	Forest Plot of Adjusted Moderate/Severe Asthma Exacerbations	Weeks 1-52	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			Rate Ratio and Associated Supportive/Sensitivity Analyses over Weeks 1-52 - Pooled FF Doses		
2.23.	ITT	EFF_F5	Tipping Point Heat Plot for Adjusted Moderate/Severe Asthma Exacerbations Rate Ratio over Weeks 1-52 FF/UMEC/VI UMEC 62.5 vs. FF/VI (On- and Post-Treatment) - Pooled FF Doses	Weeks 1-52	SAC
2.24.	ITT	EFF_F6	Tipping Point Line Plot Adjusted Moderate/Severe Asthma Exacerbations Rate Ratio over Weeks 1-52 FF/UMEC/VI UMEC 62.5 vs. FF/VI (On- and Post-Treatment) - Pooled FF Doses	Weeks 1-52	SAC
2.25.	ITT	EFF_F5	Tipping Point Heat Plot for Adjusted Moderate/Severe Asthma Exacerbations Rate Ratio over Weeks 1-52 FF/UMEC/VI UMEC 31.25 vs. FF/VI (On- and Post-Treatment) - Pooled FF Doses	Weeks 1-52	SAC
2.26.	ITT	EFF_F6	Tipping Point Line Plot Adjusted Moderate/Severe Asthma Exacerbations Rate Ratio over Weeks 1-52 FF/UMEC/VI UMEC 31.25 vs. FF/VI (On- and Post-Treatment) - Pooled FF Doses	Weeks 1-52	SAC
2.27.	ITT	EFF_F9	Forest Plot of Adjusted Moderate/Severe Asthma Exacerbations Rate Ratio (On- and Post-Treatment)	Weeks 1-24 and 1-52	SAC [1]
Other Secondary Efficacy Endpoints					
2.28.	ITT	EFF_F1	Box Plot of Change from Baseline in Clinic FEV_1 (L) at 3 Hours Post Study Treatment at Week 24 (On-Treatment)	At week 24	SAC
2.29.	ITT	EFF_F2	Empirical Distribution Function Plot of Change from Baseline in Clinic FEV_1 (L) at 3 Hours Post Study Treatment at Week 24 (On-Treatment)	At week 24	SAC
2.30.	ITT	EFF_F10	Least Squares Mean (95% CI) Change from Baseline in Clinic FEV_1 (L) at 3 Hours Post Study Treatment at Week 24 (On-Treatment)	At week 24	SAC
2.31.	ITT	EFF_F11	Least Squares Mean (95% CI) Treatment Difference in Change	At week 24	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			from Baseline in Clinic FEV_1 (L) at 3 Hours Post Study Treatment at Week 24 (On-Treatment)		
2.32.	ITT	EFF_F10	Least Squares Mean (95% CI) Change from Baseline in Clinic FEV_1 (L) at 3 Hours Post Study Treatment at Week 24 (On-Treatment) - Pooled FF Doses	At week 24	SAC
2.33.	ITT	EFF_F11	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Clinic FEV_1 (L) at 3 Hours Post Study Treatment at Week 24 (On-Treatment) - Pooled FF Doses	At week 24	SAC
2.34.	ITT	EFF_F1	Box Plot of Change from Baseline in SGRQ Total Score (On- and Post-Treatment) - Pooled FF Doses	At weeks 12, 24, 36 and 52	SAC
2.35.	ITT	EFF_F2	Empirical Distribution Function Plot of Change from Baseline in SGRQ Total Score (On- and Post-Treatment) - Pooled FF Doses	At weeks 12, 24, 36 and 52	SAC
2.36.	ITT	EFF_F3	Least Squares Mean (95% CI) Change from Baseline in SGRQ Total Score up to Week 24 (On- and Post-Treatment) - Pooled FF Doses	At weeks 12, and 24	SAC
2.37.	ITT	EFF_F4	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in SGRQ Total Score up to Week 24 (On- and Post-Treatment) - Pooled FF Doses	At weeks 12, and 24	SAC
2.38.	ITT	EFF_F1	Box Plot of Change from Baseline in SGRQ Total Score (On- and Post-Treatment)	At weeks 12, 24, 36 and 52	SAC
2.39.	ITT	EFF_F2	Empirical Distribution Function Plot of Change from Baseline in SGRQ Total Score (On- and Post-Treatment)	At weeks 12, 24, 36 and 52	SAC
2.40.	ITT	EFF_F3	Least Squares Mean (95% CI) Change from Baseline in SGRQ Total Score up to Week 24 (On- and Post-Treatment)	At weeks 12, and 24	SAC
2.41.	ITT	EFF_F4	Least Squares Mean (95% CI) Treatment Difference in Change	At weeks 12, and 24	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			from Baseline in SGRQ Total Score up to Week 24 (On- and Post-Treatment)		
2.42.	ITT	EFF_F1	Box Plot of Change from Baseline in ACQ-7 Total Score (On- and Post-Treatment) - Pooled FF Doses	At weeks 4, 12, 24, 36 and 52	SAC
2.43.	ITT	EFF_F2	Empirical Distribution Function Plot of Change from Baseline in ACQ-7 Total Score (On- and Post-Treatment) - Pooled FF Doses	At weeks 4, 12, 24, 36 and 52	SAC
2.44.	ITT	EFF_F3	Least Squares Mean (95% CI) Change from Baseline in ACQ-7 Total Score up to Week 24 (On- and Post-Treatment) - Pooled FF Doses	At weeks 4, 12, and 24	SAC
2.45.	ITT	EFF_F4	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in ACQ-7 Total Score up to Week 24 (On- and Post-Treatment) - Pooled FF Doses	At weeks 4, 12, and 24	SAC
2.46.	ITT	EFF_F1	Box Plot of Change from Baseline in ACQ-7 Total Score (On- and Post-Treatment)	At weeks 4, 12, 24, 36 and 52	SAC
2.47.	ITT	EFF_F2	Empirical Distribution Function Plot of Change from Baseline in ACQ-7 Total Score (On- and Post-Treatment)	At weeks 4, 12, 24, 36 and 52	SAC
2.48.	ITT	EFF_F3	Least Squares Mean (95% CI) Change from Baseline in ACQ-7 Total Score up to Week 24 (On- and Post-Treatment)	At weeks 4, 12, and 24	SAC
2.49.	ITT	EFF_F4	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in ACQ-7 Total Score up to Week 24 (On- and Post-Treatment)	At weeks 4, 12, and 24	SAC
2.50.	ITT	EFF_F1	Box Plot of Change from Baseline in E-RS Total Score by 4-Weekly Intervals (On- and Post-Treatment) - Pooled FF Doses	4-weekly intervals up to week 52	SAC
2.51.	ITT	EFF_F2	Empirical Distribution Function Plot of Change from Baseline in E-RS Total Score by 4-Weekly Intervals (On- and Post-	4-weekly intervals up to week 52	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			Treatment) - Pooled FF Doses		
2.52.	ITT	EFF_F12	Least Squares Mean (95% CI) Change from Baseline in E-RS Total Score up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment) - Pooled FF Doses	4-weekly intervals up to week 24	SAC
2.53.	ITT	EFF_F13	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in E-RS Total Score up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment) - Pooled FF Doses	4-weekly intervals up to week 24	SAC
2.54.	ITT	EFF_F10	Forest Plot of Least Squares Mean (95% CI) Change from Baseline in E-RS Total Score over Weeks 1-24 (On- and Post-Treatment) – Pooled FF Doses	Forest plot of week 1-24 analysis	SAC
2.55.	ITT	EFF_F11	Forest Plot of Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in E-RS Total Score over Weeks 1-24 (On- and Post-Treatment) – Pooled FF Doses	Forest plot of week 1-24 analysis	SAC
2.56.	ITT	EFF_F1	Box Plot of Change from Baseline in E-RS Total Score by 4-Weekly Intervals (On- and Post-Treatment)	4-weekly intervals up to week 52	SAC
2.57.	ITT	EFF_F2	Empirical Distribution Function Plot of Change from Baseline in E-RS Total Score by 4-Weekly Intervals (On- and Post-Treatment)	4-weekly intervals up to week 52	SAC
2.58.	ITT	EFF_F12	Least Squares Mean (95% CI) Change from Baseline in E-RS Total Score up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment)	4-weekly intervals up to week 24	SAC
2.59.	ITT	EFF_F13	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in E-RS Total Score up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment)	4-weekly intervals up to week 24	SAC
2.60.	ITT	EFF_F10	Forest Plot of Least Squares Mean (95% CI) Change from Baseline in E-RS Total Score over Weeks 1-24 (On- and Post-	Forest plot of week 1-24 analysis	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			Treatment)		
2.61.	ITT	EFF_F11	Forest Plot of Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in E-RS Total Score over Weeks 1-24 (On- and Post-Treatment)	Forest plot of week 1-24 analysis	SAC
Other Efficacy Endpoints					
2.62.	ITT	EFF_F10	Least Squares Mean (95% CI) Change from Baseline in Clinic Trough FEV_1 (L) over the First 24 Weeks (On- and Post-Treatment)	AUC_{0-24w}	SAC
2.63.	ITT	EFF_F11	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Clinic Trough FEV_1 (L) over the First 24 Weeks (On- and Post-Treatment)	AUC_{0-24w}	SAC
2.64.	ITT	EFF_F12	Least Squares Mean (95% CI) Change from Baseline in Home Daily Trough FEV_1 (L) up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment)	4-weekly intervals up to week 24	SAC
2.65.	ITT	EFF_F13	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home Daily Trough FEV_1 (L) up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment)	4-weekly intervals up to week 24	SAC
2.66.	ITT	EFF_F10	Forest Plot of Least Squares Mean (95% CI) Change from Baseline in Home Daily Trough FEV_1 (L) over Weeks 1-24 (On- and Post-Treatment)	Forest plot of week 1-24 analysis	SAC
2.67.	ITT	EFF_F11	Forest Plot of Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home Daily Trough FEV_1 (L) over Weeks 1-24 (On- and Post-Treatment)	Forest plot of week 1-24 analysis	SAC
2.68.	ITT	EFF_F3	Least Squares Mean (95% CI) Change from Baseline in Home Daily Trough FEV_1 (L) up to Week 8 by 1-Week Intervals (On- and Post-Treatment)	weekly intervals up to week 8	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.69.	ITT	EFF_F4	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home Daily Trough FEV_1 (L) up to Week 8 by 1-Week Intervals (On- and Post-Treatment)	weekly intervals up to week 8	SAC
2.70.	ITT	EFF_F12	Descriptive Weekly Mean Change from Baseline in Home Daily Trough FEV_1 (L) up to Week 24 (On- and Post-Treatment)	weekly intervals up to week 24	SAC
2.71.	ITT	EFF_F12	Least Squares Mean (95% CI) Change from Baseline in Home Daily PM FEV_1 (L) up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment)	4-weekly intervals up to week 24	SAC
2.72.	ITT	EFF_F13	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home Daily PM FEV_1 (L) up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment)	4-weekly intervals up to week 24	SAC
2.73.	ITT	EFF_F10	Forest Plot of Least Squares Mean (95% CI) Change from Baseline in Home Daily PM FEV_1 (L) over Weeks 1-24 (On- and Post-Treatment)	Forest plot of week 1-24 analysis	SAC
2.74.	ITT	EFF_F11	Forest Plot of Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home Daily PM FEV_1 (L) over Weeks 1-24 (On- and Post-Treatment)	Forest plot of week 1-24 analysis	SAC
2.75.	ITT	EFF_F12	Descriptive Weekly Mean Change from Baseline in Home Daily PM FEV_1 (L) up to Week 24 (On- and Post-Treatment)	weekly intervals up to week 24	SAC
2.76.	ITT	EFF_F12	Least Squares Mean (95% CI) Change from Baseline in Home Daily AM PEF (L/min) up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment)	4-weekly intervals up to week 24	SAC
2.77.	ITT	EFF_F13	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home Daily AM PEF (L/min) up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment)	4-weekly intervals up to week 24	SAC
2.78.	ITT	EFF_F10	Forest Plot of Least Squares Mean (95% CI) Change from Baseline in Home Daily AM PEF (L/min) over Weeks 1-24 (On-	Forest plot of week 1-24 analysis	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			and Post-Treatment)		
2.79.	ITT	EFF_F11	Forest Plot of Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home Daily AM PEF (L/min) over Weeks 1-24 (On- and Post-Treatment)	Forest plot of week 1-24 analysis	SAC
2.80.	ITT	EFF_F12	Descriptive Weekly Mean Change from Baseline in Home Daily AM PEF (L/min) up to Week 24 (On- and Post-Treatment)	Weekly up to 24 weeks	SAC
2.81.	ITT	EFF_F12	Least Squares Mean (95% CI) Change from Baseline in Home Daily PM PEF (L/min) up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment)	4-weekly intervals up to week 24	SAC
2.82.	ITT	EFF_F13	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home Daily PM PEF (L/min) up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment)	4-weekly intervals up to week 24	SAC
2.83.	ITT	EFF_F10	Forest Plot of Least Squares Mean (95% CI) Change from Baseline in Home Daily PM PEF (L/min) over Weeks 1-24 (On- and Post-Treatment)	Forest plot of week 1-24 analysis	SAC
2.84.	ITT	EFF_F11	Forest Plot of Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home Daily PM PEF (L/min) over Weeks 1-24 (On- and Post-Treatment)	Forest plot of week 1-24 analysis	SAC
2.85.	ITT	EFF_F12	Descriptive Weekly Mean Change from Baseline in Home Daily PM PEF (L/min) up to Week 24 (On- and Post-Treatment)	Weekly up to 24 weeks	SAC
2.86.	ITT	EFF_F14	Kaplan-Meier Plot of Time to First Moderate/Severe Asthma Exacerbation (On- and Post-Treatment) - Pooled FF Doses	Weeks 1-52	SAC
2.87.	ITT	EFF_F14	Kaplan-Meier Plot of Time to First Moderate/Severe Asthma Exacerbation (On- and Post-Treatment)	Weeks 1-52	SAC
2.88.	ITT	EFF_F14	Kaplan-Meier Plot of Time to First Severe Asthma Exacerbation (On- and Post-Treatment) - Pooled FF Doses	Weeks 1-52	SAC
2.89.	ITT	EFF_F14	Kaplan-Meier Plot of Time to First Severe Asthma Exacerbation (On- and Post-Treatment)	Weeks 1-52	SAC
2.90.	ITT	EFF_F8	Odds Ratio for Percent of Patients Meeting a Responder	Week 24	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			Threshold of ≥0.5 Improvement (Decrease) from Baseline for the ACQ-7 Total Score at Week 24 (On- and Post-Treatment) - Pooled FF Doses		
2.91.	ITT	EFF_F8	Odds Ratio for Percent of Patients Meeting a Responder Threshold of ≥0.5 Improvement (Decrease) from Baseline for the ACQ-6 Total Score at Week 24 (On- and Post-Treatment) - Pooled FF Doses	Week 24	SAC
2.92.	ITT	EFF_F8	Odds Ratio for Percent of Patients Meeting a Responder Threshold of ≥0.5 Improvement (Decrease) from Baseline for the ACQ-5 Total Score at Week 24 (On- and Post-Treatment) - Pooled FF Doses	Week 24	SAC
2.93.	ITT	EFF_F8	Odds Ratio for Percent of Patients Meeting a Responder Threshold of ≥0.5 Improvement (Decrease) from Baseline for the ACQ-7 Total Score at Week 24 (On- and Post-Treatment)	Week 24	SAC
2.94.	ITT	EFF_F8	Odds Ratio for Percent of Patients that Have Achieved Asthma Control Based on ACQ-7 (i.e. a Total Score ≤0.75) at both Week 12 and Week 24 (On- and Post-Treatment) - Pooled FF Doses		SAC
2.95.	ITT	EFF_F8	Odds Ratio for Percent of Patients that Have Achieved Asthma Control Based on ACQ-6 (i.e. a Total Score ≤0.75) at both Week 12 and Week 24 (On- and Post-Treatment) - Pooled FF Doses		SAC
2.96.	ITT	EFF_F8	Odds Ratio for Percent of Patients that Have Achieved Asthma Control Based on ACQ-5 (i.e. a Total Score ≤0.75) at both Week 12 and Week 24 (On- and Post-Treatment) - Pooled FF Doses		SAC
2.97.	ITT	EFF_F8	Odds Ratio for Percent of Patients that Have Achieved Asthma Control Based on ACQ-7 (i.e. a Total Score ≤0.75) at both Week 12 and Week 24 (On- and Post-Treatment)		SAC
2.98.	ITT	EFF_F15	Forest Plot of Least Squares Mean Treatment Difference in	Forest plot at week 24	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			Change from Baseline in SGRQ Total and Domain Scores at Week 24 (On- and Post-Treatment) – Pooled FF Doses		
2.99.	ITT	EFF_F8	Odds Ratio for Percent of Patients Meeting a Responder Threshold of ≥ 4 Points Improvement (Decrease) from Baseline for the SGRQ Total Score at Week 24 (On- and Post-Treatment) - Pooled FF Doses	Week 24	SAC
2.100.	ITT	EFF_F8	Odds Ratio for Percent of Patients Meeting a Responder Threshold of ≥ 4 Points Improvement (Decrease) from Baseline for the SGRQ Total Score at Week 24 (On- and Post-Treatment)	Week 24	SAC
2.101.	ITT	EFF_F15	Forest Plot of Least Squares Mean Treatment Difference in Change from Baseline in E-RS Total and Domain Scores over Weeks 21-24 (Inclusive) of the Treatment Period (On- and Post-Treatment) – Pooled FF Doses	Forest plot at weeks 21-24	SAC
2.102.	ITT	EFF_F8	Odds Ratio for Percent of Patients Meeting a Responder Threshold of ≥ 2 Points Improvement (Decrease) from Baseline for the E-RS Total Score Over Weeks 21-24 (Inclusive) of the Treatment Period (On- and Post-Treatment) - Pooled FF Doses	Weeks 21-24	SAC
2.103.	ITT	EFF_F8	Odds Ratio for Percent of Patients Meeting a Responder Threshold of ≥ 2 Points Improvement (Decrease) from Baseline for the E-RS Total Score Over Weeks 21-24 (Inclusive) of the Treatment Period (On- and Post-Treatment)	Weeks 21-24	SAC
2.104.	ITT	EFF_F3	Least Squares Mean (95% CI) Change from Baseline in AQLQ Total Score up to Week 24 (On- and Post-Treatment) - Pooled FF Doses	Weeks 4,12,24,26 and 52	SAC
2.105.	ITT	EFF_F4	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in AQLQ Total Score up to Week 24 (On- and Post-Treatment) - Pooled FF Doses	Weeks 4,12,24,26 and 52	SAC
2.106.	ITT	EFF_F8	Odds Ratio for Percent of Patients Meeting a Responder Threshold of ≥ 0.5 Points Improvement (Increase) from Baseline	Week 24	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			for the AQLQ Total Score at Week 24 (On- and Post-Treatment) - Pooled FF Doses		
2.107.	ITT	EFF_F12	Least Squares Mean (95% CI) Change from Baseline in Percentage of Symptom-Free Days up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment) - Pooled FF Doses	4-weekly intervals up to week 24	SAC
2.108.	ITT	EFF_F13	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Percentage of Symptom-Free Days up to Week 24 by 4-Weekly Intervals On- and Post-Treatment) - Pooled FF Doses	4-weekly intervals up to week 24	SAC
2.109.	ITT	EFF_F10	Forest Plot of Least Squares Mean (95% CI) Change from Baseline in Percentage of Symptom-Free Days over Weeks 1-24 (On- and Post-Treatment) - Pooled FF Doses	Forest plot of week 1-24 analysis	SAC
2.110.	ITT	EFF_F11	Forest Plot of Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Percentage of Symptom-Free Days over Weeks 1-24 (On- and Post-Treatment) - Pooled FF Doses	Forest plot of week 1-24 analysis	SAC
2.111.	ITT	EFF_F12	Least Squares Mean (95% CI) Change from Baseline in Percentage of Rescue Medication-Free Days up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment) - Pooled FF Doses	4-weekly intervals up to week 24	SAC
2.112.	ITT	EFF_F13	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Percentage of Rescue Medication-Free Days up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment) - Pooled FF Doses	4-weekly intervals up to week 24	SAC
2.113.	ITT	EFF_F10	Forest Plot of Least Squares Mean (95% CI) Change from Baseline in Percentage of Rescue Medication-Free Days over Weeks 1-24 (On- and Post-Treatment) - Pooled FF Doses	Forest plot of week 1-24 analysis	SAC
2.114.	ITT	EFF_F11	Forest Plot of Least Squares Mean (95% CI) Treatment	Forest plot of week 1-24 analysis	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			Difference in Change from Baseline in Percentage of Rescue Medication-Free Days over Weeks 1-24 (On- and Post-Treatment) - Pooled FF Doses		
2.115.	ITT	EFF_F12	Least Squares Mean (95% CI) Change from Baseline in Daily Rescue Medication Use (Puffs/Day) up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment) - Pooled FF Doses	4-weekly intervals up to week 24	SAC
2.116.	ITT	EFF_F13	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Daily Rescue Medication Use (Puffs/Day) up to Week 24 by 4-Weekly Intervals (On- and Post-Treatment) - Pooled FF Doses	4-weekly intervals up to week 24	SAC
2.117.	ITT	EFF_F10	Forest Plot of Least Squares Mean (95% CI) Change from Baseline in Daily Rescue Medication Use (Puffs/Day) over Weeks 1-24 (On- and Post-Treatment) - Pooled FF Doses	Forest plot of week 1-24 analysis	SAC
2.118.	ITT	EFF_F11	Forest Plot of Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Daily Rescue Medication Use (Puffs/Day) over Weeks 1-24 (On- and Post-Treatment) - Pooled FF Doses	Forest plot of week 1-24 analysis	SAC

11.10.8. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
3.1.	ITT	EX1	Summary of Exposure to Fluticasone/Salmeterol 250/50 via the DISKUS DPI During the Run-in Period		SAC
3.2.	ITT	EX1	Summary of Exposure to FF/VI 100/25 via the ELLIPTA DPI During the Stabilization Period		SAC
3.3.	ITT	EX1	Summary of Exposure		SAC [1]
3.4.	ITT	EX1	Summary of Exposure – Pooled FF Doses		SAC
3.5.	ITT	SAFE_T1	Summary of Post-Treatment Duration		SAC
Adverse Events					
3.6.	ITT	AE1	Summary of Adverse Events During Screening/Run-in Period	Include total column	SAC
3.7.	ITT	AE1	Summary of Adverse Events During Stabilization Period	Include total column	SAC
3.8.	ITT	AE13	Overview of On-Treatment Adverse Events		SAC [1]
3.9.	ITT	SAFE_T2	Overview of On-Treatment Adverse Events per Thousand Person-Years		SAC
3.10.	ITT	AE1	Summary of On-Treatment Adverse Events		SAC [1]
3.11.	ITT	SAFE_T3	Summary of On-Treatment Adverse Events per Thousand Person-Years		SAC
3.12.	ITT	AE1	Summary of On-Treatment Adverse Events in the Respiratory, Thoracic and Mediastinal Disorders System Organ Class (Primary or Secondary)		SAC
3.13.	ITT	SAFE_T3	Summary of On-Treatment Adverse Events in the Respiratory, Thoracic and Mediastinal Disorders System Organ Class (Primary or Secondary) per Thousand Person-Years		SAC

Safety: Tables					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.14.	ITT	AE1	Summary of Post-Treatment Adverse Events		SAC
3.15.	ITT	AE1	Summary of Post-Study Adverse Events		SAC
3.16.	ITT	AE1	Summary of On-Treatment Adverse Events Up to Week 24		SAC
3.17.	ITT	SAFE-T3	Summary of On-Treatment Adverse Events Up to Week 24 per Thousand Person-Years		SAC
3.18.	ITT	AE1	Summary of On-Treatment Adverse Events Up to Week 36 for Subjects with ≥ 36 Weeks of Planned Treatment Exposure		SAC
3.19.	ITT	SAFE-T3	Summary of On-Treatment Adverse Events Up to Week 36 for Subjects with ≥ 36 Weeks of Planned Treatment Exposure per Thousand Person-Years		SAC
3.20.	ITT	AE1	Summary of On-Treatment Adverse Events for Subjects with 52 Weeks of Planned Treatment Exposure		SAC
3.21.	ITT	SAFE-T3	Summary of On-Treatment Adverse Events for Subjects with 52 Weeks of Planned Treatment Exposure per Thousand Person-Years		SAC
3.22.	ITT	AE1	Summary of On-Treatment Drug-Related Adverse Events		SAC [1]
3.23.	ITT	SAFE_T3	Summary of On-Treatment Drug-Related Adverse Events per Thousand Person-Years		SAC
3.24.	ITT	AE1	Summary of Post-Treatment Drug-Related Adverse Events		SAC
3.25.	ITT	AE1	Summary of On-Treatment Serious Adverse Events		SAC [1]
3.26.	ITT	SAFE_T3	Summary of On-Treatment Serious Adverse Events per Thousand Person-Years		SAC
3.27.	ITT	AE1	Summary of Post-Treatment Serious Adverse Events		SAC
3.28.	ITT	AE1	Summary of On-Treatment Serious Adverse Events Up to Week 24		SAC
3.29.	ITT	SAFE-T3	Summary of On-Treatment Serious Adverse Events Up to Week 24 per Thousand Person-Years		SAC

Safety: Tables					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.30.	ITT	AE1	Summary of On-Treatment Serious Adverse Events Up to Week 36 for Subjects with ≥ 36 Weeks of Planned Treatment Exposure		SAC
3.31.	ITT	SAFE-T3	Summary of On-Treatment Serious Adverse Events Up to Week 36 for Subjects with ≥ 36 Weeks of Planned Treatment Exposure per Thousand Person-Years		SAC
3.32.	ITT	AE1	Summary of On-Treatment Serious Adverse Events for Subjects with 52 Weeks of Planned Treatment Exposure		SAC
3.33.	ITT	SAFE-T3	Summary of On-Treatment Serious Adverse Events for Subjects with 52 Weeks of Planned Treatment Exposure per Thousand Person-Years		SAC
3.34.	ITT	AE1	Summary of On-Treatment Drug-Related Serious Adverse Events		SAC
3.35.	ITT	SAFE_T3	Summary of On-Treatment Drug-Related Serious Adverse Events per Thousand Person-Years		SAC
3.36.	ITT	AE1	Summary of On-Treatment Non-Serious Drug-Related Adverse Events	Required for Plain Language Summary	SAC
3.37.	ITT	SAFE_T3	Summary of On-Treatment Non-Serious Drug-Related Adverse Events per Thousand Person-Years	Required for Plain Language Summary	SAC
3.38.	ITT	AE1	Summary of On-Treatment Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study		SAC [1]
3.39.	ITT	AE1	Summary of Post-Treatment Adverse Events Leading to Withdrawal from the Study		SAC
3.40.	ITT	SAFE_T4	Summary of On-Treatment Adverse Events of Special Interest		SAC [1]
3.41.	ITT	SAFE_T5	Summary of On-Treatment Adverse Events of Special Interest per Thousand Person-Years		SAC

Safety: Tables					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.42.	ITT	AE1	Summary of On-Treatment Adverse Events of Special Interest Up to Week 24		SAC
3.43.	ITT	SAFE-T5	Summary of On-Treatment Adverse Events of Special Interest Up to Week 24 per Thousand Person-Years		SAC
3.44.	ITT	AE1	Summary of On-Treatment Adverse Events of Special Interest Up to Week 36 for Subjects with ≥ 36 Weeks of Planned Treatment Exposure		SAC
3.45.	ITT	SAFE-T5	Summary of On-Treatment Adverse Events of Special Interest Up to Week 36 for Subjects with ≥ 36 Weeks of Planned Treatment Exposure per Thousand Person-Years		SAC
3.46.	ITT	AE1	Summary of On-Treatment Adverse Events of Special Interest for Subjects with 52 Weeks of Planned Treatment Exposure		SAC
3.47.	ITT	SAFE-T5	Summary of On-Treatment Adverse Events of Special Interest for Subjects with 52 Weeks of Planned Treatment Exposure per Thousand Person-Years		SAC
3.48.	ITT	AE1	Summary of On-Treatment Serious Adverse Events of Special Interest		SAC
3.49.	ITT	SAFE_T6	Summary of On-Treatment Serious Adverse Events of Special Interest per Thousand Person-Years		SAC
3.50.	ITT	AE1	Summary of Post-Treatment Adverse Events of Special Interest		SAC
3.51.	ITT	AE1	Summary of Post-Treatment Serious Adverse Events of Special Interest		SAC
3.52.	ITT	AE3	Summary of Common On-Treatment Adverse Events (3% or More of Subjects in Any Treatment Group)		SAC

Safety: Tables					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.53.	ITT	AE3	Summary of the 10 Most Frequent On-Treatment Adverse Events in Each Treatment Group		SAC
3.54.	ITT	AE1	Summary of On-Treatment Adverse Events by Gender		SAC
3.55.	ITT	AE1	Summary of On-Treatment Adverse Events by Age (<18, 18 to <65, 65 to <75, 75 to <85, ≥85 years)		SAC
3.56.	ITT	AE1	Summary of On-Treatment Adverse Events by Age (<65, ≥65 years)		SAC
3.57.	ITT	AE1	Summary of On-Treatment Adverse Events by Race		SAC
3.58.	ITT	AE1	Summary of On-Treatment Adverse Events by Region		SAC
3.59.	ITT	AE1	Summary of On-Treatment Adverse Events by Pre-Study ICS Dosage at Screening		SAC
3.60.	ITT	AE1	Summary of On-Treatment Adverse Events by BMI		SAC
3.61.	ITT	AE1	Summary of On-Treatment Adverse Events by CV History/Risk Factor at Screening		SAC
MACE					
3.62.	ITT	SAFE_T6	Summary of On-Treatment Major Adverse Cardiac Events (MACE) – Narrow Definition		SAC
3.63.	ITT	SAFE_T6	Summary of On-Treatment Major Adverse Cardiac Events (MACE) – Broad Definition		SAC
3.64.	ITT	SAFE_T7	Summary of On-Treatment Major Adverse Cardiac Events (MACE) per Thousand Person-Years – Narrow Definition		SAC
3.65.	ITT	SAFE_T7	Summary of On-Treatment Major Adverse Cardiac Events (MACE) per Thousand Person-Years – Broad Definition		SAC

Safety: Tables					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pneumonia and Radiography (Chest X-Rays)					
3.66.	ITT	SAFE_T8	Summary of On-Treatment Pneumonia	Include the results of chest X-ray	SAC
Laboratory Parameters					
3.67.	ITT	LB1	Summary of Chemistry Data (On-Treatment)		SAC
3.68.	ITT	LB1	Summary of Change from Baseline in Chemistry Data (On-Treatment)		SAC
3.69.	ITT	SAFE_T9	Summary of Chemistry Data Outside the Normal Range (On-Treatment)		SAC
3.70.	ITT	LB3	Summary of Chemistry Shifts from Baseline Relative to Normal Range (On-Treatment)		SAC
3.71.	ITT	LB1	Summary of Hematology Data (On-Treatment)		SAC
3.72.	ITT	LB1	Summary of Change from Baseline in Hematology Data (On-Treatment)		SAC
3.73.	ITT	SAFE_T9	Summary of Hematology Data Outside the Normal Range (On-Treatment)		SAC
3.74.	ITT	LB3	Summary of Hematology Shifts from Baseline Relative to Normal Range (On-Treatment)		SAC
3.75.	ITT	LB16	Summary of Worst Case Urinalysis Results Post-Baseline Relative to Baseline (On-Treatment)		SAC
Vital Signs					
3.76.	ITT	VS1	Summary of Vital Signs (On-Treatment)	Present BMI as if calculated to 1 decimal place.	SAC
3.77.	ITT	VS1	Summary of Change from Baseline in Vital Signs (On-Treatment)	Present BMI as if calculated to 1 decimal place.	SAC

Safety: Tables					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.78.	ITT	EFF_T4	Analysis of Mean Change from Baseline in Systolic Blood Pressure (mmHg) up to Week 24(On-Treatment)		SAC
3.79.	ITT	EFF_T4	Analysis of Mean Change from Baseline in Diastolic Blood Pressure (mmHg) up to Week 24 (On-Treatment)		SAC
3.80.	ITT	EFF_T4	Analysis of Mean Change from Baseline in Pulse Rate (beats/min) up to Week 24 (On-Treatment)		SAC
12-Led ECGs					
3.81.	ITT	EG2	Summary of ECG Values (On-Treatment)		SAC
3.82.	ITT	EG2	Summary of Change from Baseline in ECG Values (On-Treatment)		SAC
3.83.	ITT	SAFE_T10	Summary of ECG Findings (On-Treatment)		SAC
3.84.	ITT	SAFE_T11	Summary of ECG Findings Shifts from Baseline (On-Treatment)		SAC
3.85.	ITT	SAFE_T12	Summary of ECG Abnormalities (On-Treatment)		SAC
3.86.	ITT	EFF_T4	Analysis of Mean Change from Baseline in Heart Rate as Measured by ECG (beats/min) up to Week 24 (On-Treatment)		SAC
3.87.	ITT	EFF_T4	Analysis of Mean Change from Baseline in PR Interval (msec) up to Week 24 (On-Treatment)		SAC
3.88.	ITT	EFF_T4	Analysis of Mean Change from Baseline in QTc(F) (msec) up to Week 24 (On-Treatment)		SAC
EudraCT/FDAAA					
3.89.	ITT	AE16	Summary of On-Treatment Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC

Safety: Tables					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.90.	ITT	AE15	Summary of Common (≥ 3%) On-Treatment Non-Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC

11.10.9. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
3.1.	ITT	SAFE_F1	Exposure to Study Treatment over Time		SAC
3.2.	ITT	SAFE_F2	Trellis Display of Maximum Post-Baseline Liver Function Test Values, Versus Baseline Liver Function Test Values (On-Treatment)		SAC
3.3.	ITT	SAFE_F3	Scatter Plots of Maximum Post-Baseline Versus Baseline for Chemistry Data (On-Treatment)		SAC
3.4.	ITT	SAFE_F4	Box Plots of Change from Baseline to Maximum Post-Baseline Values for Chemistry Data (On-Treatment)		SAC
3.5.	ITT	SAFE_F3	Scatter Plots of Minimum Post-Baseline Versus Baseline for Chemistry Data (On-Treatment)		SAC
3.6.	ITT	SAFE_F4	Box Plots of Change from Baseline to Minimum Post-Baseline Values for Chemistry Data (On-Treatment)		SAC
3.7.	ITT	SAFE_F3	Scatter Plots of Maximum Post-Baseline Versus Baseline for Hematology Data (On-Treatment)		SAC
3.8.	ITT	SAFE_F4	Box Plots of Change from Baseline to Maximum Post-Baseline Values for Hematology Data (On-Treatment)		SAC
3.9.	ITT	SAFE_F3	Scatter Plots of Minimum Post-Baseline Versus Baseline for Hematology Data (On-Treatment)		SAC

Safety: Figures					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.10.	ITT	SAFE_F4	Box Plots of Change from Baseline to Minimum Post-Baseline Values for Hematology Data (On-Treatment)		SAC
3.11.	ITT	SAFE_F5	Least Squares Mean (95% CI) Change from Baseline in Systolic Blood Pressure (mmHg) up to Week 24 (On-Treatment)		SAC
3.12.	ITT	SAFE_F5	Least Squares Mean (95% CI) Change from Baseline in Diastolic Blood Pressure (mmHg) up to Week 24 (On-Treatment)		SAC
3.13.	ITT	SAFE_F5	Least Squares Mean (95% CI) Change from Baseline in Pulse Rate (beats/min) up to Week 24 (On-Treatment)		SAC
3.14.	ITT	EG7	Empirical Distribution Function Plot of Maximum Post-Baseline QTc(F) (msec) (On-Treatment)		SAC
3.15.	ITT	EG7	Empirical Distribution Function Plot of Change from Baseline in Maximum Post-Baseline QTc(F) (msec) (On-Treatment)		SAC
3.16.	ITT	SAFE_F5	Least Squares Mean (95% CI) Change from Baseline in Heart Rate as Measured by ECG (beats/min) up to Week 24 (On-Treatment)		SAC
3.17.	ITT	SAFE_F5	Least Squares Mean (95% CI) Change from Baseline in PR Interval (msec) up to Week 24 (On-Treatment)		SAC
3.18.	ITT	SAFE_F5	Least Squares Mean (95% CI) Change from Baseline in QTc(F) (msec) up to Week 24 (On-Treatment)		SAC

11.10.10. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
1.	All Subjects Screened	ES7	Listing of Reasons for Screen Failure, Run-in Failure, or Stabilization Failure		SAC
2.	ITT	SD3	Listing of Reasons for Study Treatment Discontinuation		SAC
3.	ITT	ES3	Listing of Reasons for Study Withdrawal		SAC
4.	ITT	TA1	Listing of Randomized and Actual Treatments		SAC
5.	ITT	TA1	Listing of Randomized and Actual Strata	Change 'Randomized Treatment' to 'Randomized Strata' and 'Actual Treatment' to 'Actual Strata;	SAC
6.	ITT	LIST1	Listing of Study Treatment Misallocations		SAC
7.	ITT	LIST2	Listing of Subjects for Whom the Treatment Blind was Broken		SAC
Protocol Deviations					
8.	All Subjects Enrolled	DV2	Listing of Important Protocol Deviations		SAC
9.	ITT	IE3	Listing of Subjects with Inclusion, Exclusion, Enrolment, or Randomization Criteria Deviations		SAC
Population Analyzed					
10.	ITT	LIST3	Listing of Subjects Excluded from the Primary Efficacy Analysis	Include randomized subjects who had missing data either at baseline or post-baseline	SAC

ICH: Listings					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
11.	All Subjects Screened	LIST4	Listing of Subjects Who Were Randomized in Error and Not Included in the Intent-To-Treat Population		SAC
Demographic and Baseline Characteristics					
12.	ITT	DM4	Listing of Demographic Characteristics		SAC

ICH: Listings					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
13.	ITT	DM10	Listing of Race		SAC
Treatment compliance					
14.	ITT	LIST5	Listing of Study Treatment Compliance Data		SAC
Efficacy					
15.	ITT	LIST6	Listing of Clinic Spirometry Data		SAC
16.	ITT	LIST7	Listing of Moderate/Severe Asthma Exacerbations		SAC
17.	ITT	LIST8	Listing of Asthma Exacerbations With Onset Within 14 Days Prior to Early Withdrawal From Study or Discontinuation of Study Treatment		SAC
Exposure					
18.	ITT	EX3 (modified)	Listing of Exposure and Post-Treatment Study Duration		SAC
Adverse Events					
19.	All Subjects Enrolled	AE8	Listing of All Adverse Events for Subjects Not Included in the Intent-To-Treat Population		SAC
20.	ITT	AE8	Listing of All Adverse Events		SAC [1]
21.	ITT	AE8	Listing of Adverse Events for Subjects Who Received an Incorrect Treatment		
22.	ITT	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC
23.	ITT	AE8	Listing of Non-Fatal Serious Adverse Events		SAC
24.	ITT	AE8	Listing of Fatal Serious Adverse Events		SAC
25.	ITT	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC
26.	ITT	AE8	Listing of Serious Adverse Events of Special Interest		SAC

ICH: Listings					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
27.	ITT	AE8	Listing of Adverse Events Leading to Discontinuation of Study Treatment or Early Withdrawal from Study		SAC
28.	ITT	AE8	Listing of Non-Serious Adverse Events Leading to Discontinuation of Study Treatment or Early Withdrawal from Study		SAC
29.	All Subjects Enrolled	AE2	Listing of Adverse Event System Organ Class, Preferred Term and Verbatim Text		SAC
Hepatobiliary (Liver)					
30.	ITT	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	IDSL	SAC
31.	ITT	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	IDSL	SAC
All Laboratory					
32.	ITT	LB5	Listing of Chemistry Values for Subjects with at Least One Value Outside the Normal Range	Include data of the form '<X' or '>X'	SAC
33.	ITT	LB5	Listing of Hematology Values for Subjects with at Least One Value Outside the Normal Range	Include data of the form '<X' or '>X'	SAC
34.	ITT	LB5	Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance		SAC
ECG					
35.	ITT	EG3	Listing of All ECG Values for Subjects with an Abnormal ECG Finding	IDSL	SAC
36.	ITT	EG5	Listing of All ECG Findings for Subjects with an Abnormal Finding	IDSL	SAC

ICH: Listings					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
37.	ITT	VS4	Listing of Vital Signs		SAC

11.10.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
38.	All Subjects Enrolled	LIST9	Listing of Rescreened Subjects		SAC
39.	ITT	MH2	Listing of Medical Conditions		SAC
40.	ITT	LIST10	Listing of Pneumonia History		SAC
41.	ITT	LIST11	Listing of Family History of Cardiovascular Risk Factors		SAC
42.	ITT	LIST12	Listing of Asthma Duration and Exacerbation History		SAC
43.	ITT	SU2	Listing of Smoking History and Status		SAC
44.	ITT	CM3	Listing of Asthma Concomitant Medications		SAC
45.	ITT	CM3	Listing of Non-Asthma Concomitant Medications		SAC
46.	Not Applicable	CM6	Relationship between ATC Level 1, Ingredient and Verbatim Text for Non-Asthma Medications		SAC
47.	ITT	LIST13	Listing of Inhaler Malfunctions		SAC
Efficacy					
48.	ITT	LIST14	Listing of Derived Clinic FEV_1 (L) Data		SAC
49.	ITT	LIST15	Listing of Derived Diary Data		SAC
50.	ITT	LIST16	Listing of ACQ Scores		SAC
51.	ITT	LIST17	Listing of SGRQ Scores		SAC
52.	ITT	LIST18	Listing of E-RS Scores		SAC
53.	ITT	LIST19	Listing of AQLQ Scores		SAC

Non-ICH: Listings					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
54.	ITT	LIST20	Listing of Global Assessment of Severity and Response to Treatment		SAC
55.	ITT	LIST21	Listing of Unscheduled Healthcare Resource Utilization		SAC
Safety					
56.	ITT	AE7	Listing of Subject Numbers for Individual Adverse Events of Special Interest		SAC
57.	Not Applicable	LIST22	Listing of Adverse Event of Special Interest Group, Subgroup, Sub-SMQ, and Preferred Term	Include all pre-specified preferred terms regardless of whether they occurred	SAC
58.	ITT	AE8	Listing of MACE (Narrow and Broad Definition)		SAC
59.	ITT	LIST23	Listing of Pneumonia Data=		SAC
60.	ITT	LIST24	Listing of Bone Fracture Data		SAC
61.	ITT	LIVER5	Listing of Liver Event Results and Time of Event Relative to Treatment		SAC
62.	ITT	LIVER6	Listing of Liver Event Information for RUCAM Score		SAC
63.	ITT	LIVER7	Listing of Liver Biopsy Details		SAC
64.	ITT	LIVER8	Listing of Liver Imaging Details		SAC
65.	All Subjects Enrolled	IDSL	Patient Profile for Arrhythmias		SAC
66.	All Subjects Enrolled	IDSL	Patient Profile for Congestive Heart Failure		SAC
67.	All Subjects Enrolled	IDSL	Patient Profile for Cerebrovascular Events/Stroke		SAC
68.	All Subjects Enrolled	IDSL	Patient Profile for Deep Vein Thrombosis / Pulmonary Embolism		SAC

Non-ICH: Listings					
No.	**Population**	**IDSL ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
69.	All Subjects Enrolled	IDSL	Patient Profile for Myocardial Infarction /Unstable Angina		SAC
70.	All Subjects Enrolled	IDSL	Patient Profile for Peripheral Arterial Thromboembolism		SAC
71.	All Subjects Enrolled	IDSL	Patient Profile for Pulmonary Hypertension		SAC
72.	All Subjects Enrolled	IDSL	Patient Profile for Revascularization		SAC
73.	All Subjects Enrolled	IDSL	Patient Profile for Valvulopathy		SAC
74.	All Subjects Enrolled	IDSL	Patient Profile for All Cause Deaths		SAC