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

Title	:	Reporting and Analysis Plan for: A randomized, double-blind, parallel group study, comparing the efficacy, safety and tolerability of two doses of umeclidinium bromide administered once-daily via a dry powder inhaler, versus placebo, in participants with asthma
Compound Number	:	GW685698+ GSK573719
Effective Date	:	25-JUN-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 205832
- 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.

RAP Author:

Author	Date	Approval Method
PPD Statistics Leader (Respiratory, Clinical Statistics)	25-JUN-2018	eSignature in CARS

RAP Team Approvals:

Approver	Date	Approval Method
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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 205832.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

The originally planned statistical analysis is specified in the protocol (dated: 15-NOV-2016), amendment 1 (dated: 09-DEC-2016) and amendment 2 (dated: 06-JUL-2017).

Changes to the planned analysis are:

- Region is added as a covariate to all statistical models (see Section 5.5.1). This is to ensure that the statistical analysis adjusts for possible region effect due to differences in local medical practices in the treatment of asthma.

- In addition to the protocol specified endpoints, the following will be analyzed in an exploratory manner:

    - Change from baseline in daily home PM FEV_1
    - Annualized rate of severe exacerbations
    - Time to first moderate/severe exacerbation
    - Time to first severe exacerbation

- A randomized population is defined in order to be included in the summary of analysis populations and so clearly show the flow of participants through the study, see Section 4.

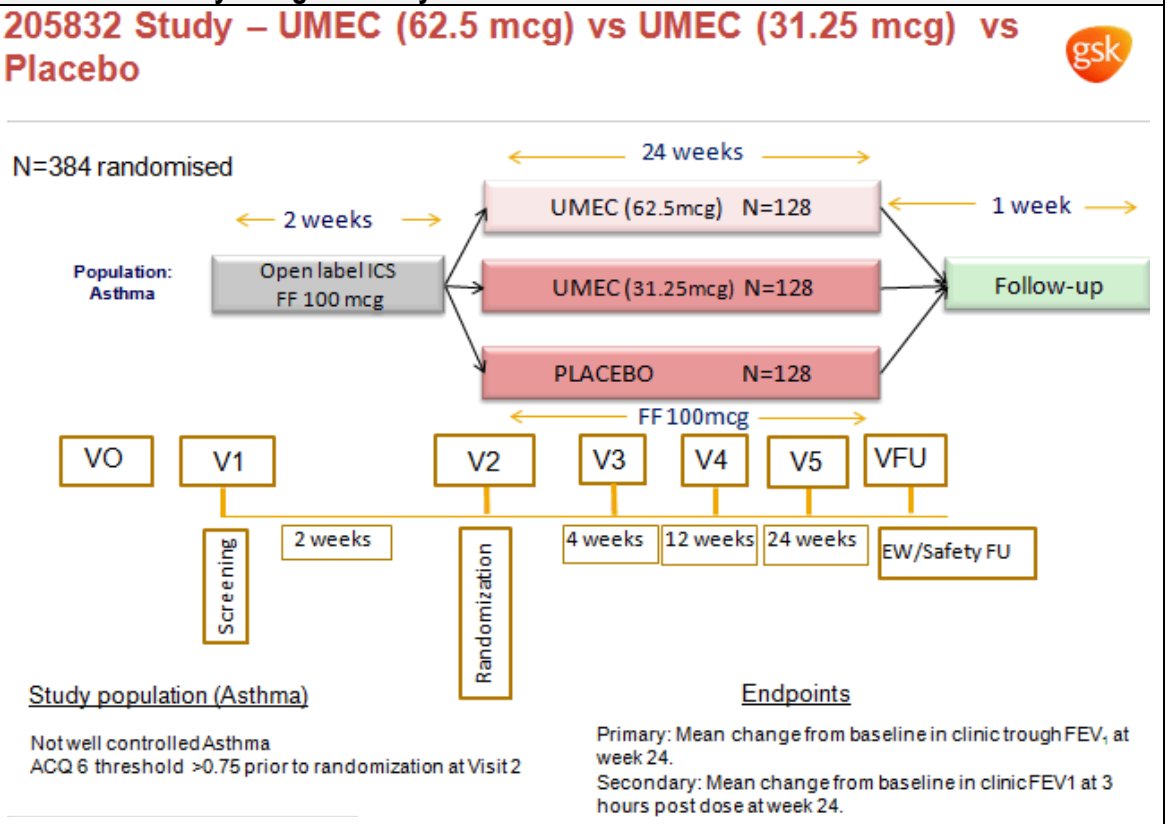
- Subgroups of gender, age, race and region have been defined, see Section 5.5.2.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• Evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function (trough FEV_1) versus placebo after 24 weeks of treatment.	• Mean change from baseline in clinic trough FEV_1 at Week 24
Secondary Objectives	**Secondary Endpoints**
• Evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function (3 hours post dose FEV_1) versus placebo after 24 weeks of treatment	• Mean change from baseline in clinic FEV_1 at 3 hours post dose at Week 24

Objectives	Endpoints
Safety Objectives	**Safety Endpoints**
• To evaluate the safety and tolerability of UMEC 62.5 mcg and UMEC 31.25 mcg compared to placebo	• Incidence and type of adverse events
	• ECG measurements
	• Vital signs
Other Objectives	**Other Endpoints**
• To evaluate other efficacy assessments of UMEC 62.5 mcg and UMEC 31.25 mcg compared to placebo	• Mean change from baseline in morning (AM) pre-dose Peak Expiratory Flow (PEF) over the 24-week treatment period
	• Mean change from baseline in evening (PM) PEF over the 24-week treatment period
	• Mean change from baseline in daily home trough FEV_1 over the 24-week treatment period
	• Mean change from baseline in daily rescue medication use over the 24-week treatment period
	• Mean change from baseline in SGRQ total score 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 SGRQ domain scores at Week 24
	• Mean change from baseline in the AQLQ total score at Week 24
	• Percent of patients meeting a responder threshold of ≥0.5 points improvement from baseline for the AQLQ total score at Week 24
	• Mean change from baseline in E-RS total score over the 24-week treatment period
	• Mean change from baseline in ACQ-5 total score at Week 24
	• Percent of patients meeting a responder threshold of ≥0.5 in change from baseline for the ACQ-5 at Week 24
	• Annualized rate of moderate/severe asthma exacerbations

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• This is a phase IIb, randomized, double-blind, 3-arm parallel group study, comparing the efficacy, safety and tolerability of UMEC (62.5 mcg and 31.25 mcg) administered once-daily in participants with asthma that is not well controlled (i.e. participants with an ACQ-6 total score >0.75 at Visit 2 [the Randomization Visit]) despite treatment with maintenance ICS. • The target total number of randomized participants is approximately 384, with 128 participants randomized to each of the 3 double-blind treatment arms. All participants will be on a background therapy of FF 100mcg administered daily. • 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 DPI once daily in the morning during the study treatment period. The open-label FF 100mcg will be delivered via an ELLIPTA DPI once daily following the double-blind treatment. • The duration of the treatment period is 24 weeks.

Overview of Study Design and Key Features	
Time & Events	• Refer to Appendix 2: Schedule of Activities

Treatment Assignment	• Eligible participants will enter a 2-week run-in period on fluticasone furoate [FF], 100 mcg daily via the ELLIPTA™ DPI.
	• At the end of the run-in period, eligible participants are to be randomized 1:1:1 to receive one of the following three double-blinded treatments:
	  ○ UMEC 62.5mcg
	  ○ UMEC 31.25mcg
	  ○ Placebo
	• The randomization code will be generated using GlaxoSmithKline (GSK) software (RAMOS NG). The study will use one central randomization schedule to allocate treatments for all randomized participants.
	• Participants will be randomized using an IWRS system (RAMOS NG).

Interim Analysis	• No interim is planned for this study.

2.4. Statistical Hypotheses

The primary objective of this study is to evaluate the efficacy of UMEC on top of a background therapy of FF 100 mcg in participants with not well controlled asthma over a 24-week treatment period. This is a superiority study to demonstrate the benefit of UMEC at two dosage strengths 62.5 mcg and 31.25 mcg when compared to Placebo. The primary efficacy endpoint is the mean change from baseline in trough FEV1 at Week 24.

The test for the primary efficacy endpoint is such that the null hypothesis is that there is no difference between treatment groups.

H0: $T1 - T2 = 0$

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

H1: $T1 - T2 \neq 0$

For the primary endpoint (and all other efficacy endpoints), the primary treatment comparisons of interest are:

- UMEC 62.5mcg vs Placebo
- UMEC 31.25mcg vs Placebo

For each comparison test on the primary endpoint, the null hypothesis is there is no difference between treatment groups. The alternative hypothesis is there is a difference between treatment groups. Therefore, T1 and T2 for these endpoints are the mean changes from baseline for the UMEC therapy and placebo, respectively, as listed above.

Other pairwise treatment comparisons of interest that aim to informally estimate any potential benefit of increasing the UMEC dose are given below for all efficacy endpoints.

- UMEC 62.5 mcg vs UMEC 31.25 mcg

For the multiple comparisons and multiplicity adjustment, please see Section 5.6.

3. PLANNED ANALYSES

3.1. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps for this Clinical Data Interchange Standards Consortium (CDISC) study:

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. Complete conversion of System Independent (SI) data to Study Data Tabulation Model (SDTM) data conversion has been completed by the 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 Data Management upon receipt of the final treatment un-blinded 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 • Safety
Randomized	• This population will comprise of all participants who were randomized (i.e. were assigned 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 recorded as a screen failure or run-in failure but is randomized and does not receive a dose of study treatment, is considered to be randomized	• Study population • Efficacy • Safety

Population	Definition / Criteria	Analyses Evaluated
	in error. This population will be based on the treatment the participant was randomized to receive.	

Refer to Appendix 9 : List of Data Displays which details the population used for each display.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
1	Placebo	Placebo	1
2	UMEC 31.25mcg	UMEC 31.25mcg	2
3	UMEC 62.5mcg	UMEC 62.5mcg	3

5.1. Study Treatment & Sub-group Display Descriptors

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

1. UMEC 62.5mcg vs Placebo
2. UMEC 31.25mcg vs Placebo
3. UMEC 62.5mcg vs UMEC 31.25mcg

5.2. Baseline Definitions

In general, the baseline value is the last assessment value, including unscheduled assessments (where stated), prior to randomized treatment start for the efficacy endpoints based on assessments at clinic visits, unless otherwise specified, and the average value over the last 14 days prior to randomized treatment start during the run-in period for the efficacy endpoints based on participants' diary data.

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

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Screening	Day 1 (Pre-Dose)	
Efficacy: Clinic Spirometry			
Trough FEV_1, FEV_1 3h post-dose, FVC, FEV_1/FVC Ratio, FEV_1 % predicted		X	Day 1 (pre-dose)

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Screening	Day 1 (Pre-Dose)	
Efficacy: Questionnaires			
ACQ-5, SGRQ, AQLQ, Global Assessment of Severity		X	Day 1
Efficacy: Diary Assessments			
	Baseline Period		
Home trough FEV_1, AM PEF	Last 14 AM assessments during the run-in period, including AM assessment on the day of first randomized treatment (i.e., treatment start date per protocol)		Baseline
PM FEV_1, PM PEF	Last 14 PM assessments immediately preceding the day of first randomized treatment during the run-in period		Baseline
Daily rescue medication use	Last 14 days during the run-in period, including AM assessments on the day of first randomized treatment (i.e., treatment start date per protocol).		Baseline
E-RS total score	Last 14 PM assessments immediately preceding first randomized treatment during the run-in period		Baseline
Safety			
ECGs	X		Screening
Vital signs		X	Day 1

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 scheduled baseline visit. Unscheduled visits will not be considered.

5.2.1. Clinic Assessments

Baseline value for clinic FEV_1 related endpoints is the last acceptable/borderline acceptable (pre-dose) FEV_1 value obtained prior to randomized treatment start date (either from pre-dose at Randomization Visit, from pre-bronchodilator at Run-in visit or from pre-bronchodilator at an unscheduled visit). This definition will also be used for the baseline value in the analysis of change from baseline in FEV_1 3 hours post dose.

For ACQ-5, SGRQ, and AQLQ, baseline value for each endpoint is the derived value based on the questionnaire administered at the Randomization visit.

For the global assessment of severity, baseline is defined as the response given at the Randomization Visit.

For the safety assessments (vital signs and ECGs) the baseline value is the latest value recorded prior to the randomized treatment start, including unscheduled visits. Specifically, the baseline value is based on Visit 1 for ECGs, and on Visit 2 for vital signs.

5.2.2. Diary Assessments

Efficacy endpoints based on diary assessments include E-RS total score, home AM (trough) and PM FEV_1, AM and PM PEF, and daily rescue medication use.

AM assessments include AM PEF, trough FEV_1, night-time asthma symptoms, and night-time puffs of rescue albuterol/salbutamol. PM assessments include PM PEF, PM FEV_1, daytime asthma symptoms, daytime puffs of rescue albuterol/salbutamol, and E-RS score.

For these endpoints, baseline period is the last 14 days during the run-in period prior to randomized treatment start date, including AM assessments on the first day of randomized treatment. For the AM assessments, baseline period includes the randomized treatment start date and the 13 days immediately preceding this during the run-in period. For the PM assessments, baseline includes the 14 days immediately preceding randomized treatment start date during the run-in period. For daily rescue medication use, the baseline period is PM on Day -14 to AM on treatment start date, inclusive. For a given endpoint, the baseline value will be calculated using available data as the average of non-missing daily values over the baseline period. If fewer than 7 days of data over the baseline period are available, the baseline value will be set as missing.

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 the 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 24 weeks with 4-weekly time intervals are defined as follows:

Weeks	AM assessment Days	PM assessment Days	Daily assessment 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
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. Multicentre 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.

Geographic Region	**Countries**	**Total # Randomized/Planned**
Russia	Russia	Russia 174/150
USA	United States	United States 69/100,
Rest of World	Canada, Poland, Romania	Canada 21/50, Poland 114/120, Romania 58/40

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 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 is 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.

5.5.2. Examination of Subgroups

The following definitions for subgroups will be used. Additional subgroups of clinical interest may also be considered.

Subgroup	Categories	Derivation
Gender	Male Female	N/A
Age (years)	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.
Race	Black White Asian Other	• Black includes African American/African Heritage • Other will include American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander or Multiple race.
Region	Russia USA Rest of World	Rest of World includes Canada, Poland and Romania
Eosinophils (G/L)	<0.15 ≥0.15	Based on labs performed at Screening Visit

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

- Descriptive statistics of FEV_1 and change from baseline in FEV_1 over time
- On-treatment adverse events during the study

5.6. Multiple Comparisons and Multiplicity

To account for multiple tests involving the two UMEC doses 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 test in the hierarchy.

A step-down procedure with the following hierarchy will be used for the primary comparisons in the primary endpoint.

- The contrast between UMEC 62.5 mcg vs Placebo
(two-sided, alpha = 0.05. Null hypothesis of no treatment difference)

- The contrast between UMEC 31.25 mcg vs Placebo
(two-sided, alpha = 0.05. Null hypothesis of no treatment difference)

The second hypothesis will be formally tested only if the first hypothesis has been rejected, thus maintaining the overall significance level at 5%. Specifically, if the defined treatment comparison for the primary efficacy endpoint at the highest dose of UMEC 62.5 mcg is significant at 0.05 level then the efficacy of UMEC 62.5 mcg is demonstrated, and the treatment comparison can be repeated on the UMEC 31.25 mcg dose. Note that, if the first hypothesis is not rejected a nominal p-value for the second hypothesis may be provided in the displays for descriptive purposes only and will not alter the conclusion of the step-down procedure.

No multiplicity adjustment will be made on these two treatment comparisons on the secondary endpoint. For all efficacy endpoints (primary, secondary and other), treatment comparisons between UMEC 62.5 vs UMEC 31.25 mcg informally investigating the benefit of increasing UMEC dose 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
10.3	Appendix 3: Assessment Windows
10.4	Appendix 4: Study Phases
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Reporting Standards for Missing Data

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the ITT population, unless otherwise specified. Displays which use the All Subject Enrolled population are identified below.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 9: List of Data Displays.

Table 1 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Study Populations	Y[1]		
Reasons for Screen Failures and Run-in Failures	Y[1]		Y[1]
Rescreen Subjects	Y[1]		Y[1]
Number of Subjects by Country and Site ID	Y[1], Y		
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		
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
ACQ Score	Y		Y
Concomitant Medications			
Asthma Medications	Y		Y
Non-Asthma Medications	Y		Y
Asthma Maintenance Therapy	Y		
Relationship between ATC Level1/Ingredient/Verbatim Text for Non-Asthma Medications			Y
Treatment Compliance			
Treatment Compliance	Y		Y
Randomized and Actual Treatments			Y
Treatment Blind Broken During Study			Y
Treatment Misallocations			Y
Inhaler Malfunctions			Y

NOTES:
Y = Yes display generated.
1. All Subjects Enrolled population

6.1.1. Disposition of Subjects

The study populations will be summarized based on the All Subjects Enrolled population, including the number and percentage of participants overall and in each treatment group (where appropriate), who were enrolled, screened (All Subjects Screened), randomized

and included in the ITT population. Additionally, the reasons for Screen Failure and Run-in Failure, will be summarized for the All Subjects Enrolled population. A similar summary will be produced for participants who were rescreened, presented by screening attempt. Listings of failures prior to randomization will be generated. A listing will also be generated for the rescreened subjects (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, randomized) under each subject id.

The number and percentage of participants at each centre and within each country will be summarized for both the All Subjects Enrolled population and the ITT population.

The number and percentage of participants who completed the double blinded 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. A Kaplan-Meier curve will be generated for time to early withdrawal from treatment. Time to early withdrawal from study treatment is measured from randomized treatment start date to randomized treatment stop date. Participants who complete the study treatment per protocol are censored at the date of end of study visit. For participants who are lost to follow up, the last study treatment date will be used, see Section 10.7.2.1 for details of handling missing dates.

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. A Kaplan-Meier curve will be generated for time to early withdrawal from study. Time to early withdrawal from study is measured from the randomized treatment start date to the date of early withdrawal from the study for participants who have an early withdrawal (EW) visit. Participants who complete the study per protocol are censored at the end of study visit date. Participants who are lost to follow up without an EW visit date will use the last date associated with any record for the participant.

The number and percentage of participants who failed the eligibility criteria (inclusion, exclusion, or randomization) will be summarized. The number and percentage of participants with any important protocol deviations determined by the study team prior to study treatment unblinding will also be summarized.

The number and percentage of participants by 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.

6.1.2. 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])
- Age ranges (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 with either oral/systemic corticosteroids and/or antibiotics, requiring hospitalization and total number)
- 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.
- Summary of pneumonia history
- Spirometry at Visit 1 and Visit 2: FEV_1, FVC, FEV_1/FVC, reversibility by albuterol/salbutamol (Visit 1 only), and associated percent predicted values. Note: Predicted values will be based upon the European Respiratory Society (ERS) Global Lung Function Initiative [Quanjer, 2012].
- Change in pre-bronchodilator / pre-dose clinic FEV_1 from Visit 1 to Visit 2, during the run-in period.
- Home spirometry during the run-in period.
- ACQ-6 scores at Visit 1 and ACQ-5 and ACQ-6 scores at Visit 2.
- Change in ACQ-6 scores from Visit 1 to Visit 2 during the run-in period.
- Summary of past and current medical histories

6.1.3. Concomitant Medications

Summaries will be provided for the asthma medications at:

- Study entry
- During the screening/run-in period
- On-treatment period
- Post-treatment period
- Post-study period

Asthma medication tables will be reported 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 and 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.

6.1.4. Treatment Compliance

Treatment compliance will be assessed for each treatment arm for:

- Open-label FF 100 mcg during the run-in period
- Open label FF 100 mcg during the randomized treatment period
- Double blind treatment during the randomized treatment period

Additional details on the derivations are provided in Section 10.6.2.

7. EFFICACY ANALYSES

To demonstrate the benefit of UMEC the primary comparisons of interest are:

- UMEC 62.5 mcg vs Placebo
- UMEC 31.25 mcg vs Placebo

Other pairwise treatment comparisons of interest that aim to informally estimate any potential benefit of increasing the UMEC dose are given below for all efficacy endpoints.

- UMEC 62.5 mcg vs UMEC 31.25 mcg

7.1. Primary Efficacy Analyses

Table 2 provides an overview of the planned efficacy analyses for the primary endpoint, with full details of data displays being presented in Appendix 9: List of Data Displays.

Table 2 Overview of Primary Efficacy Endpoint Analyses

Primary Efficacy Endpoint	Absolute						Change from Baseline					
	Stats Analysis		Summary		Individual		Stats Analysis		Summary		Individual	
	T	F	T	F	F	L	T	F	T	F	F	L
Clinic Trough FEV_1												
Trough FEV_1 (MMRM analysis, de facto type estimand, primary analysis)	Y		Y			Y	Y	Y	Y	Y		Y
Trough FEV_1 (MMRM analysis, de jure type estimand)	Y		Y				Y	Y	Y	Y		
Trough FEV_1 (Supportive/Sensitivity Analyses)	Y[1]						Y	Y				
Trough FEV_1 by subgroup			Y						Y			

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TF 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.
- [1] Not performed for tipping point analysis

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 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, temporary treatment interruption and temporary treatment switches.

Participants who discontinue study treatment prematurely are encouraged to return for all clinic visits as planned. Data collected on- or post treatment discontinuation will be included in the primary analysis, as well as data collected after rescue medication or treatment switches.

For the primary analysis, no imputation of missing data is planned. Missing data is assumed Missing at Random (MAR) and handled via Mixed Model Repeated Measures (MMRM) analysis, see Section 7.1.5.1 for details.

This analysis corresponds to the "de facto" analysis pre-specified in the protocol.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

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

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• Mean change from baseline in trough FEV_1 at Week 24
Model Specification
• FEV_1 and change from baseline will be summarized at each visit according to treatment status (on-treatment or post-treatment). Baseline FEV_1 will be summarized overall and split by participants who have an on-treatment FEV_1 value at week 24, participants who have a post-treatment FEV_1 value at week 24 and participants with missing FEV_1 data at Week 24. • The primary efficacy analysis will evaluate the treatment policy (de facto) type estimand in the ITT population, using a MMRM analysis. • Analyses will include the fixed, categorical effects of treatment, visit, treatment by visit interaction, sex, region. as well as continuous fixed covariates of age, baseline value and baseline value by visit interaction. Point estimates and 95% confidence intervals will be calculated for the primary comparisons of interest. See details in Section 2.4

- Clinic trough FEV1 data (both on- and post-treatment) collected at all scheduled clinic visits will be included in the analysis. These include the clinic visits at Weeks 4, 12 and 24.
- While missing data are not explicitly imputed in the MMRM analyses, there is an underlying assumption that any missing data are missing at random. All available data will be utilized via modelling 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
    - Continuous: age, baseline value for clinic FEV_1
    - Interaction: baseline*Visit, treatment*Visit
  - Repeated: Visit
- 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.
- Baseline is defined in Section 5.2.1
- Two models will be fitted; one with a response variable of change from baseline and one with the response variable as the raw value.

Model Checking & Diagnostics

- 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.
  - Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
  - If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data or non-parametric methods if appropriate.

Model Results Presentation

- 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 2.4 at Weeks 4, 12, and 24.
- The LS mean change from baseline and LS mean treatment differences (and associated 95% CIs) will also be presented graphically for each UMEC dose versus placebo at Weeks 4, 12, and 24.
- A forest plot will present the results from the primary analysis alongside the results from the supportive analyses and the jump to reference sensitivity analysis described below.
- A table and grid of p-values will be produced to display the results from the tipping point analysis described below. A heat plot of the results and a line plot of the results corresponding to the missing at random assumption in the placebo arm will also be produced.

Exploring interaction terms

- Interaction by treatment term will be added to the primary analysis model one at a time

for the following main effect covariates: age, baseline value for clinic trough FEV_1, region and sex.

- Summary of test results for main effect covariates from the primary analysis model will be presented along with the test results for the interaction terms mentioned above.

Supportive Analyses

- An "on-treatment" analysis will be performed, corresponding to the 'de jure' type estimand 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 7.1.1, Section 7.1.2 and Section 7.1.3 respectively.
    - 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, using the same model as for the primary analysis of the "treatment policy" estimand.

- During the study, there were concerns at several sites which lead to a lack of confidence in the data received from these sites. An analysis similar to the primary analysis (treatment policy estimand) will therefore be performed but excluding all data from all participants at these sites. The impacted sites will be identified and documented prior to unblinding.

Sensitivity Analyses

The primary analysis of the treatment policy estimand 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 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.

The following different algorithms are proposed to impute the post-study discontinuation missing data on the primary efficacy endpoint (change from baseline in trough FEV_1 at Week 24). All analyses include all FEV1 data collected both on and post-treatment:

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 UMEC and Placebo.

   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 tipping point.

   For each of the comparisons of UMEC vs. placebo the delta for the UMEC and placebo arms will be allowed to vary independently, while assuming MAR (delta=0mL) for the other UMEC treatment arm. The imputation model will contain the same terms as in the primary analysis MMRM model, modeled at each visit.

   For a given pair of 'delta comparison' as in the table below, complete sets of Week 24 data

for all 3 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. The imputed FEV_1 will then be analyzed using an ANCOVA model. The covariates in the analysis model will be the same as those in the primary efficacy analysis apart from the removal of the "visit" term and interactions. The results then will be combined across imputations using Rubin's method [Rubin 1978] and the treatment comparison of interest will be present.

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

			UMEC 62.5mcg								
			Delta (mL)								
			-3x	-2.5x	-2x	-1.5x	-x	-0.5x	0	0.5x	x
Placebo	Delta (mL)	Mean change post-with-drawal	-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 statistically significant evidence of a treatment effect, and clinical judgment will be applied as to the plausibility of the associated assumptions.

Repeat this process for both of the UMEC vs placebo treatment comparisons in turn.

2. Jump to Reference:

This method assumes that participants with post-treatment missing data in the test groups (UMEC 62.5mcg or UMEC 31.25mcg) would have provided data similar to those in the placebo treatment arm [Carpenter, 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, regardless of the UMEC dose in their randomized treatment. Post-treatment missing data in the placebo group are imputed under MAR.

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, modeled at each visit. For each of the multiple imputations, the complete data at Week 24 will then be analyzed using ANCOVA model, including the covariates in the primary efficacy analysis apart from the removal of the "visit" term and interactions. The estimates from multiple imputations will be combined across imputations using Rubin's method. The treatment comparisons of interest will be presented.
Subgroup Analyses
• Summaries of clinic trough FEV_1 at baseline and at each clinic visit, and the change from baseline at each clinic visit will be presented for each of the subgroups listed in Section 5.5.2.

7.2. Secondary Efficacy Analyses

Table 3 Overview of Secondary Efficacy Endpoint Analyses

Endpoint	Absolute						Change from Baseline					
	Stats Analysis		Summary		Individual		Stats Analysis		Summary		Individual	
	T	F	T	F	F	L	T	F	T	F	F	L
Secondary Endpoint												
Mean change from baseline in clinic FEV_1 at 3 hours post dose at Week 24	Y		Y			Y	Y	Y	Y	Y		Y

NOTES:
- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TF 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 secondary endpoint is the change from baseline in clinic FEV_1 at 3 hours post dose.

7.2.2. Summary Measure

The mean change from baseline in clinic FEV_1 at 3 hours post dose at Week 24 will be compared between treatment groups.

7.2.3. Population of Interest

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

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

An "on-treatment" strategy will be used to handle the intercurrent event of treatment discontinuation. Participants who discontinued treatment prior to Week 24 were not required to perform FEV_1 at 3 hours post dose, as they were no longer receiving a dose of

study drug at site. Therefore, this analysis uses only on-treatment data ("de-jure" type estimand) as the purpose of this efficacy endpoint is to evaluate the peak effect of UMEC at 3 hours post dose.

A "treatment policy" strategy will be used for the intercurrent events of use of rescue medication and treatment switches, i.e. the intercurrent event will be ignored and all data used in the analysis.

Participants who are missing a valid measurement at either baseline or Week 24 will be excluded from the analysis.

7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

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

7.2.5.1. Statistical Methodology Specification

Endpoint / Variables
• Mean change from baseline in clinic FEV_1 at 3 hours post dose at Week 24
Model Specification
• Change from baseline in clinic FEV_1 at 3 hours post study treatment at Week 24 will be summarized and analyzed using an Analysis of Covariance (ANCOVA) model adjusting for the covariates in a similar manner to that outlined in Section 7.1.5.1 (excluding visit terms). • Baseline value is defined in Section 7.2.1. • 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. 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 and region. ▪ Continuous: age, and baseline value. • The OM option in SAS will be used to derive the LS means based on the distribution of the covariates observed in the data • Two models will be fitted; one with a response variable of change from baseline and one with the response variable as the raw value.
Model Checking & Diagnostics
○ Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. If there are any departures from the distributional assumptions, alternative models will be explored

using appropriate transformed data or non-parametric methods if appropriate.
Model Results Presentation
• 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 2.4. • The LS mean change from baseline and LS mean treatment differences (and associated 95% CIs) for the comparisons of UMEC vs Placebo will also be presented graphically for each UMEC dose at Week 24

7.3. Exploratory Efficacy Analyses

Table 4 Overview of Exploratory Efficacy Analyses

Endpoint	Absolute						Change from Baseline					
	Stats Analysis		Summary		Individual		Stats Analysis		Summary		Individual	
	T	F	T	F	F	L	T	F	T	F	F	L
Other Exploratory Efficacy Endpoints												
Clinic spirometry parameters (FVC, FEV/FVC, Percent Predicted Normal FEV_1)			Y			Y			Y			Y
Mean change from baseline in morning (AM) pre-dose Peak Expiratory Flow (PEF) over the 24-weeks treatment period	Y		Y			Y	Y	Y	Y	Y		Y
Mean change from baseline in morning evening (PM) PEF over the 24-weeks treatment period	Y		Y			Y	Y	Y	Y	Y		Y
Mean change from baseline in home daily trough FEV_1 over the 24-weeks treatment period	Y		Y			Y	Y	Y	Y	Y		Y
Mean change from baseline in home daily PM FEV_1 over the 24-weeks treatment period	Y		Y			Y	Y	Y	Y			Y
Mean change from baseline in daily rescue medication use over the 24-weeks treatment period	Y		Y			Y	Y	Y	Y			Y
Mean change from baseline in SGRQ total score at Week	Y		Y			Y	Y	Y	Y			Y

Endpoint	Absolute						Change from Baseline					
	Stats Analysis		Summary		Individual		Stats Analysis		Summary		Individual	
	T	F	T	F	F	L	T	F	T	F	F	L
24												
Percent of patients meeting a responder threshold of ≥4 points improvement (decrease) from baseline for the SGRQ total score at Week 24	Y		Y	Y		Y						
Mean change from baseline in SGRQ domain scores at Week 24	Y		Y			Y	Y	Y	Y			Y
Mean change from baseline in the Asthma Quality of Life Questionnaire (AQLQ) total score at Week 24	Y		Y			Y	Y	Y	Y			Y
Percent of patients meeting a responder threshold of ≥0.5 points improvement from baseline for the AQLQ total score at Week 24	Y		Y	Y		Y						
Mean change from baseline in Asthma Control Questionnaire-5 (ACQ-5) total score at Week 24	Y		Y			Y	Y	Y	Y			Y
Percent of patients meeting a responder threshold of ≥0.5 in change from baseline for the ACQ-5 at Week 24	Y		Y	Y		Y						
Mean change from baseline in E-RS scores over the 24-	Y		Y			Y	Y	Y	Y			Y

Endpoint	Absolute						Change from Baseline					
	Stats Analysis		Summary		Individual		Stats Analysis		Summary		Individual	
	T	F	T	F	F	L	T	F	T	F	F	L
weeks treatment period												
Global Assessment of Severity			Y			Y						Y
Global Assessment of Response to Treatment			Y			Y						
Annualized rate of moderate/severe asthma exacerbations	Y	Y	Y	Y		Y						
Time to first moderate/severe asthma exacerbation	Y	Y	Y									
Annualized rate of severe asthma exacerbations	Y	Y	Y	Y		Y						
Time to first severe asthma exacerbation	Y	Y	Y									

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TF 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. Endpoints / Variables

As specified in the protocol, other efficacy endpoints/variables to be assessed in an exploratory manner are:

- Change from baseline in morning (AM) pre-dose Peak Expiratory Flow (PEF)
- Change from baseline in evening (PM) PEF
- Change from baseline in daily home trough FEV_1
- Change from baseline in daily rescue medications use
- Change from baseline in SGRQ total score
- Percent of patients meeting a responder threshold of ≥4 points improvement (decrease) from baseline for the SGRQ total score
- Change from baseline in SGRQ domain scores
- Change from baseline in AQLQ total score
- Percent of patients meeting a responder threshold of ≥0.5 points improvement from baseline in AQLQ total score

- Change from baseline in E-RS total score
- Change from baseline in ACQ-5 total score
- Percent of patients meeting a responder threshold of ≥0.5 in change from baseline for the ACQ-5
- Annualized rate of moderate/severe exacerbations

In addition, the following endpoints (which were not specified in the protocol) will also be assessed in an exploratory manner:

- Change from baseline in daily home PM FEV_1
- Annualized rate of severe exacerbations
- Time to first moderate/severe exacerbation
- Time to first severe exacerbation

7.3.2. Summary Measure

For the following endpoints, the mean change from baseline at 4-weekly intervals over the 24-Week post-baseline period and the mean over the 24-Week post-baseline period will be compared between treatment groups:

- Change from baseline in morning (AM) pre-dose Peak Expiratory Flow (PEF)
- Change from baseline in evening (PM) PEF
- Change from baseline in daily home trough FEV_1
- Change from baseline in daily home PM FEV_1
- Change from baseline in daily rescue medications use
- Change from baseline in E-RS total score
-

For the following endpoints, the mean change from baseline at Week 24 will be compared between treatment groups:

- Change from baseline in SGRQ total score
- Change from baseline in SGRQ domain scores
- Change from baseline in AQLQ total score
- Change from baseline in ACQ-5 total score

For the following endpoints, the proportion of responders at Week 24 will be compared between treatment groups:

- Percent of patients meeting a responder threshold of ≥4 points improvement (decrease) from baseline for the SGRQ total score
- Percent of patients meeting a responder threshold of ≥0.5 points improvement (increase) from baseline in AQLQ total score
- Percent of patients meeting a responder threshold of ≥0.5 in change (decrease) from baseline for the ACQ-5

For the following endpoints, the ratio of exacerbation rates will be used to compare the treatments:

- Annualized rate of moderate/severe exacerbations
- Annualized rate of severe exacerbations

For the following endpoints, the average hazard ratio over the post-baseline period will be used to compare the treatments:

- Time to first moderate/severe exacerbation
- Time to first severe exacerbation

7.3.3. Population of Interest

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

7.3.4. 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 and temporary treatment switches.

Participants who discontinue treatment prematurely are encouraged to return for all clinic visits as planned. Data collected post treatment discontinuation will be included in all analyses, as well as data collected after rescue medication or treatment switches.

This analysis corresponds to the "de facto" analysis.

For responder analyses, a composite strategy will be used to handle the intercurrent event of premature withdrawal from study. The endpoint analyzed will therefore essentially be the percent of participants who do not prematurely discontinue from the study and meet the responder threshold. This is the equivalent to handling participants with missing data as non-responders (see Section 10.7.2).

7.3.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

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

Data collected on global assessment of severity and response to treatment, the supplemental asthma items on wheeze and short of breath, data on night time awakenings and data on asthma symptoms and physical activity, along with data collected for 11-item E-RS, will be evaluated to support qualification of the E-RS as an endpoint for asthma. These exploratory analyses will be the participant of a separate RAP. E-RS and the global assessment of severity and response to treatment will also be summarized in the CSR.

7.3.5.1. Statistical Methodology Specification

Endpoint / Variables

- Change from baseline in morning (AM) pre-dose Peak Expiratory Flow (PEF)
- Change from baseline in evening (PM) PEF
- Change from baseline in daily home trough FEV_1
- Change from baseline in daily home PM FEV_1
- Change from baseline in daily rescue medications use
- Change from baseline in SGRQ total score
- Change from baseline in SGRQ domain scores
- Change from baseline in AQLQ total score
- Change from baseline in E-RS total score
- Change from baseline in ACQ-5 total score

Model Specification

- All analyses are based on the treatment policy (de facto) type estimand. Analyses are based on the ITT population.
- Both on- and post-treatment data collected during the study will be included in the displays.
- Baseline definitions are provided in Section 5.2

Diary data (Home Trough FEV_1, PM FEV_1, AM PEF, PM PEF, daily rescue medications use and E-RS)

- For each given endpoint based on diary data, the summary data will be provided over 4-week incremental periods. Details on derivations for the diary data can be found in Section 10.6.3.
- These endpoints will be summarized at baseline, over 4-week incremental periods and over Weeks 1-24, see Section 5.3.2.
- The changes from baseline over 4-weekly periods of the 24-week treatment period will be analyzed using a MMRM model, adjusting for treatment, age, sex, region, baseline value, period, treatment by period interaction, and baseline value by period interaction. The average treatment effect over the 24-week period will also be obtained from the model.
- Weekly mean change from baseline in trough FEV_1 over the first 8 weeks of the treatment period will also be analyzed using a repeated measures model. Week will be added to the model as a covariate, in addition to treatment group, age (years), sex, region, baseline home trough FEV_1. The model will also contain a week-by-treatment interaction term, and a week-by-baseline interaction term.
- Additionally, weekly mean absolute and changes from baseline in AM PEF, PM PEF and home trough FEV_1 will be summarized descriptively from Week 1 to 24.

Terms in the MMRM model - longitudinal analysis of mean change from baseline over 4-week incremental periods of the 24-weeks treatment period:

  - For each given parameter, the dependent variable is the period change from baseline
  - Period: Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24.
  - Covariates:
    - Categorical: treatment group, sex, region and period.
    - Continuous: age, baseline value
  - Interaction: baseline*period, treatment*period
  - Repeated: period
- 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

Terms in the MMRM model - longitudinal analysis of weekly mean change from baseline over the first 8 weeks of the treatment period:

- Dependent Variable: period change from baseline in home trough FEV_1
- Period: Week 1, Week 2, Week 3, up to and including Week 8.
- Covariates:
  - Categorical: treatment group, sex, region and period.
  - Continuous: age, baseline value
- Interaction: baseline*period, treatment*period
- Repeated: period

- 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

PROs (SGRQ, AQLQ and ACQ-5)

- PRO data (both on- and post-treatment) collected at baseline, Week 4, 12 and Week 24 will be included in the analysis. Data will be summarized by treatment group and by visit.
- For SGRQ, the total score and the individual domain scores will be analyzed.
- Change from baseline will be analyzed using a mixed model repeated measures (MMRM) analysis, adjusting for covariates appropriately.

Terms in the MMRM:

- For each parameter, the dependent variable is the change from baseline
- Covariates:
  - Categorical: treatment group, sex, region, visit.
  - Continuous: age, baseline value
  - Interaction: baseline*Visit, treatment*Visit
- Repeated: Visit

- 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

For Diary data and PROs, two models will be fitted; one with a response variable of change from baseline and one with the response variable as the raw value.

Model Checking & Diagnostics

- 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 that a model fails to run using the KR method, then the residual method will be used instead for that endpoint.
- An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line.
  - In the event that a model fails to converge, alternative correlation structures may be considered for the analysis of the endpoint.
  - Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
  - If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data or non-parametric

methods if appropriate.
Model Results Presentation
• 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 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. • The weekly descriptive mean AM PEF, PM PEF and home trough FEV_1 change from baseline over time will be plotted. • A forest plot will display the treatment estimate and 95% CI for the SGRQ total score and domain scores at Week 24.

Endpoint / Variables
• Percent of patients meeting a responder threshold of ≥4 points improvement (decrease) from baseline for the SGRQ total score • Percent of patients meeting a responder threshold of ≥0.5 points improvement (increase) from baseline in AQLQ total score • Percent of patients meeting a responder threshold of ≥0.5 in change (decrease) from baseline for the ACQ-5
Model Specification
• The analysis is based on the de-facto estimand and is based on the ITT population. • Percent of participants meeting the responder threshold will be summarized by visit, and analyzed using a generalized linear model that is applicable to binary outcome measures, adjusted for covariates appropriately. • Computation of confidence intervals for the odds ratios is based on the individual Wald tests. Terms in the GLMM: ○ Dependent Variable: Responder (Yes/No) ○ Covariates: ▪ Categorical: treatment group, sex, region and visit. ▪ Continuous: age, Baseline value ○ Interaction: Baseline*Visit, treatment*Visit ○ Link function: Logit ○ The model will be fitted with an unstructured variance-covariance matrix. ○ The OM option in SAS will be used.
Model Checking & Diagnostics
• 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. • Pearson residuals will be plotted by using PLOTS=PEARSONPANEL option for the model statement in SAS.
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 with associated 95% CI and p-value will be presented by visit. • A bar chart displaying the percentage of responders by treatment group will be presented. • Additionally, a shift table for ACQ-5 change from baseline to Week 24 in control categories will be produced (see Section 10.6.3).

Endpoint / Variables
• Annualized rate of moderate/severe exacerbations • Annualized rate of severe exacerbations
Model Specification
• Asthma exacerbations will be summarized, including number of participants with exacerbations, number of exacerbations and characteristics of exacerbations. • Analysis will be performed using a generalized linear model assuming a negative binomial distribution • The analysis is based on the treatment policy (de facto) type estimand, including all moderate/severe or severe (respectively) exacerbations observed during the study (both on- and post-treatment), based on the ITT population.

Terms in the model:

- Dependent variable: number of recorded (not imputed) exacerbations experienced per participant during the study (both on- and post-treatment).
- Covariates:
  - Categorical: treatment group, region, sex and severe asthma exacerbations in the previous year (0, ≥1).
  - Continuous: age.
- Offset: logarithm of time (year) on study
- The OM option in SAS will be used.

- Severe asthma exacerbations in the previous year is defined as the number of exacerbations that required either oral/systemic corticosteroids and/or antibiotics (not involving hospitalization) or those that required hospitalization as reported by participants at Visit 1.

Model Checking & Diagnostics

- 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 analysis fails to converge the covariate for severe asthma exacerbations in the previous year will be removed. If the analysis still fails to converge only summaries will be provided.

Model Results Presentation

- Treatment group mean annual exacerbation rates, treatment rate ratios and associated 95% confidence intervals (CI) and p-values will be presented. The treatment rate ratios and associated 95% CIs will also be presented graphically.
- Percentage reduction in annual exacerbation rates and associated 95% CIs will also be presented.

Endpoint / Variables

- Time to first moderate/severe exacerbations
- Time to first severe exacerbations

Model Specification

- Cox's proportional hazards model
- All asthma exacerbations observed during the study (on- or post-treatment) will be used in the analyses
- Participants who prematurely discontinue from the study will be censored at the date of their EW visit + 1 day.
- Terms in the model:
  - Response: time to first moderate/severe asthma exacerbation during the study (both on- and post-treatment) or time to first severe asthma exacerbation during the study (both on- and post-treatment)
  - Covariates:
    - Categorical: treatment group, sex, region, severe asthma exacerbations in the previous year (0, ≥1).
    - 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.

Model Checking & Diagnostics

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

Additionally, descriptive statistics, including all on- and post-treatment data, for the following parameters will be presented:

- Clinic FVC (L) at Baseline, Week 4, Week 12 and Week 24.
- Clinic FEV/FVC ratio at Baseline, Week 4, Week 12 and Week 24
- Clinic FEV_1 percent predicted of normal (%) at Baseline, Week 4, Week 12 and Week 24.
- Global Assessment of Severity and Response to Treatment at Baseline (Severity only), Week 4, Week 12 and Week 24

All baseline data will be presented in separate tables in order to present both by treatment group and for the overall analysis population.

8. SAFETY ANALYSES

The safety analyses will be based on the ITT population including all data collected during the study. Participants will be analyzed according to the treatment they were randomized to. On-treatment safety data collected at scheduled clinic visits will be summarized and analyzed by treatment and by visit, unless otherwise specified. Run-in adverse events, on-treatment adverse events and post-treatment adverse events will be summarized separately.

Table 5 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 9: List of Data Displays.

Table 5 Overview of Planned Safety Analyses

	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Exposure								
Summary of Exposure During the Run-in Period	Y			Y				
Summary of Treatment Exposure	Y			Y				
Summary of Post-Treatment Duration on Study	Y			Y				
Adverse Events (AEs)								
Relationship of AE System Organ Class, Preferred Term and Verbatim Text				Y				
Pre-treatment AEs								
AEs during the run-in period	Y			Y				
Overview of On-treatment AEs								
Overview of On-Treatment AEs	Y							
Overview of On-Treatment AEs during the study adjusted for exposure (per thousand person-years)	Y							
AEs								
On-Treatment AEs	Y			Y				
On-treatment AEs during the study adjusted for exposure (per thousand person-years)	Y							

	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Post-Treatment AEs	Y			Y				
Post-Study AEs	Y							
Drug-related AEs								
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							
SAEs								
On-Treatment SAEs	Y							
On-Treatment SAEs adjusted for exposure (per thousand person-years)	Y							
On-Treatment Fatal SAEs				Y				
Post-Treatment SAEs	Y							
Post-Treatment Fatal SAEs				Y				
Post-Study SAEs	Y							
Drug-related SAE								
On-Treatment Drug-Related SAEs	Y							
On-treatment Drug related SAEs adjusted for exposure (per thousand person-years)	Y							
On-Treatment Drug-Related Fatal SAEs				Y				
AEs leading to Withdrawal								
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				
AEs of Special Interest								
On-Treatment AEs of Special Interest	Y			Y				
On-treatment AEs of	Y							

	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Special Interest adjusted for exposure (per thousand person-years)								
On-Treatment SAEs of Special Interest	Y			Y				
On-treatment SAEs of Special Interest adjusted for exposure (per thousand person-years)	Y							
Post-Treatment AEs of Special Interest	Y							
Post Treatment SAEs of Special Interest	Y							
Common AEs								
Common on-treatment AEs (1% or More of Subjects in Any Treatment Group)	Y							
Common on-treatment AEs (3% or More of Subjects in Any Treatment Group)	Y							
10 Most Frequent On-treatment Adverse Events in Each Treatment Group	Y							
Subgroup analyses								
On-Treatment AEs by Age Subgroup	Y							
On-Treatment AEs by Gender	Y							
On-Treatment AEs by Race	Y							
On-Treatment AEs by Region	Y							
Subject numbers								
Subject Numbers for Individual on-treatment AEs				Y				
Subject Numbers for on-treatment AEs of Special Interest				Y				

	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
MACE								
On-Treatment Major Adverse Cardiac Events (Narrow Definition)	Y			Y				
On-Treatment Major Adverse Cardiac Events (Broad Definition)	Y			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)								
Summary of On-Treatment Pneumonia	Y			Y				
Liver Events								
Medical conditions for subjects 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	F	L	T	F	F	L
Laboratory Parameters								
Chemistry Data Outside the Normal Range				Y				
Hematology Data Outside the Normal Range				Y				
Vital Signs[1]								
Vital Sign Data (Pulse Rate, Sys BP, Dia BP)	Y			Y	Y			
12-Lead ECGs[1]								
ECG Values	Y				Y			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. Statistical analysis also performed for change from baseline in vital signs (pulse rate, SBP, DBP) and ECG parameters (PR interval and QTc(F) interval)

8.1. Extent of Exposure

Exposure will be summarized for the ITT population.

Exposure to open label FF 100mcg during the run-in period will be summarized and presented in the following categories: ≥1 day, ≥1week, ≥2weeks.

Overall extent of exposure to open label FF 100mcg and to double blind study treatment during the randomized treatment period will be summarized in increments of 4 weeks for ≥1 day, ≥4 weeks, ≥8 weeks, ≥12 weeks, ≥16 weeks, ≥20 weeks, ≥24 weeks. The category 24 weeks (-5/+2 days) will also be presented to capture the number of participants completing treatment per protocol, including permitted visit windows.

Post-treatment duration in study will also be summarized using the categories 0 weeks (i.e. participants who discontinued IP and withdrew from the study at the same time), >0 to 4 weeks, >4 to 12 weeks and >12 weeks for participants who prematurely discontinued from study treatment. 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 details of the planned displays are provided in Appendix 9: List of Data Displays.

The eCRF 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.

For each type of adverse events (e.g., AEs, drug-related AEs, serious AEs), where appropriate, three summary tables will be provided for the ITT population for the following treatment phases:

- On-treatment AEs
  - On-treatment AEs adjusted for exposure (per thousand person-years)
- Post-treatment AEs
- Post-study AEs.

For assignment of AEs to study phases see Section 10.4.1.

Adverse events will also be summarized by gender, age, race and region as defined in Section 5.5.2.

Adverse events during the run-in period will be summarized separately.

Adverse events for participants who received an incorrect treatment during the study will be listed.

8.3. Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. The details of the planned displays are provided in Appendix 9: List of Data Displays.

Adverse events of special interest have been defined as AEs which have specified areas of interest for one or more of the treatment groups (UMEC 31.25mcg and UMEC 62.5mcg). These consist in 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).

Table 6 presents the special interest AE groups for FF and UMEC, defined upon the release of version 20.1 of the MedDRA dictionary.

Table 6 AESI definitions

Special Interest AE Group	Special Interest AE Subgroup	PTs for Inclusion
Cardiovascular effects*	Cardiac arrhythmia	Cardiac arrhythmia (SMQ), excluding congenital and neonatal arrhythmias
	Cardiac failure	Cardiac Failure (SMQ)
	Cardiac ischaemia	Myocardial Infarction (SMQ) Other Ischaemic Heart Disease (SMQ)
	Stroke	Central nervous system haemorrhages and cerebrovascular conditions (SMQ)
	Hypertension	Hypertension (SMQ)
Pneumonia*	Pneumonia	Infective Pneumonia (Narrow SMQ)
LRTI (excluding pneumonia SMQ)*	LRTI (excluding pneumonia SMQ)	Selected PTs
Decreased bone mineral density and associated fractures	Decreased bone mineral density and associated fractures	Osteoporosis/Osteopenia (SMQ) Selected PTs
Hypersensitivity*	Hypersensitivity	Hypersensitivity (SMQ) Angioedema (SMQ) Anaphylactic reaction (SMQ)
Anticholinergic Syndrome*	Anticholinergic syndrome	Anticholinergic Syndrome SMQ
Gastrointestinal obstruction*	Gastrointestinal obstruction	Gastrointestinal obstruction SMQ
Adrenal Suppression	Adrenal Suppression	Selected PTs
Antimuscarinic ocular effects / Corticosteroid Associated Eye Disorders	Glaucoma (antimuscarinic / corticosteroid)	Glaucoma (SMQ)
	Cataracts (corticosteroids)	Lens disorder (SMQ)
Effects on Glucose	Effects on Glucose	Hyperglycaemia/new onset diabetes mellitus (SMQ)
Local steroid effects	Local steroid effects	Selected PTs
Urinary retention*	Urinary retention	Selected PTs
Dry mouth / Drying airway secretions*	Dry mouth / Drying airway secretions	Selected PTs (narrow and broad focus)
*: of interest for UMEC only.		

Adverse events of special interest will be summarized in the same manner outlined in Section 8.2 for overall AEs.

8.4. Major Adverse Cardiac Events (MACE)

The MACE endpoint will be analyzed using broad and narrow definitions.

The Broad MACE will be defined as follows:

- Cardiac Ischaemia Special Interest AE Subgroup (Myocardial Infarction SMQ and Other Ischaemic Heart Disease SMQ) including fatalities,

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

The narrow MACE definition will include only the PTs of "myocardial infarction" and "acute myocardial infarction" in place of the Cardiac Ischaemia Special Interest AE subgroup.

8.5. Clinical Laboratory Analyses

Laboratory (hematology, clinical chemistry, and urinalysis) tests are performed at Screening (Visit 1) only. For hematology and clinical chemistry, laboratory values will be classified as 'Low', 'Normal', or 'High' based on the provided normal ranges. Only laboratory data for participants with a least one value outside the 'Normal' range will be listed.

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. The details of the planned displays are presented in Appendix 9: List of Data Displays.

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.

For a given participant, the baseline value for each of the vital signs (pulse rate, diastolic blood pressure, and systolic blood pressure) is the last value recorded prior to randomized treatment start date, generally at Visit 2. Change from baseline value at post-randomization visits is the difference between the first recorded vital sign value at the clinic visit and the baseline value.

The 'maximum/minimum post-baseline' value will be derived as the maximum/minimum 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

12-lead ECGs are measured at Visit 1, and approximately 15-45 minutes after the administration of study treatment at Visits 3 and 5, and at Early Withdrawal visit. The ECG measurements of interest are QTc (F), heart rate, and PR interval. QTc(B) will also be summarized. All ECG data present in the database will be considered valid and will be reported (even if the ECG had a technical error).

For a given participant, the baseline value for each of the parameters is the last value recorded prior to randomized treatment start date, generally the assessment at Visit 1, but can be a repeat and/or unscheduled assessment. Change from baseline value at post-randomization visit is the difference between the first recorded ECG value at the clinic visit and the baseline value.

The 'maximum/minimum post-baseline' value will be derived as the maximum/minimum on-treatment value recorded at any scheduled, unscheduled, or Early Withdrawal (EW) visit after the start of study treatment. QTc (F) values (including 'maximum post-baseline') will be categorized as follows: ≤450msec, >450 to ≤ 480msec, >480 to ≤500msec, >500 to ≤530msec and >530msec. Change from baseline QTc (F) values (including change to 'maximum post baseline') will be categorized as follows: ≤-60msec, >-60 to ≤-30msec, >-30 to ≤0msec, >0 to ≤30msec, >30 to ≤60msec, and >60msec.

See Section 8.6.4 for details on the statistical analysis of QTc (F) and PR interval 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 worst case post-baseline is defined as:

- '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'

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

Statistical Analysis of Safety Endpoints
Endpoints
• Change from baseline in Systolic BP • Change from baseline in Diastolic BP • Change from baseline in Pulse rate • Change from baseline in PR interval; • Change from baseline in QTc (F) interval
Model Specification, Checking, Results Presentation and SAS code
• These endpoints will be analyzed using the same methodology as for the primary analysis of trough FEV_1 as outlined in Section 7.1. • All on-treatment data collected at scheduled clinic visits will be included.

9. REFERENCES

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10. APPENDICES

10.1. 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 prior to unblinding and freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- Participants who received an incorrect container will be captured as an important protocol deviation. The actual treatment in the incorrect container will be identified by S&P and, if applicable, recorded as incorrect treatment per randomization schedule and quality controlled prior to SDTM DBF.
- This dataset will be the basis for the summaries and listings of protocol deviations.

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.

No per-protocol analysis is planned for this study.

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Events

Protocol Activity	Pre-Screen	Screen Run-in	Treatment Period				Follow-up	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window				**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Informed consent (ICF) [a]	X							
Genetic ICF [b]	X							
Inclusion and exclusion criteria		X	X					
Demography [c]	X	X						
Medical history		X						
Asthma history [d]		X						
Exacerbation history		X						
Smoking History and status		X						
Concomitant medication review	X	X	X	X	X	X	X	X

Protocol Activity	Pre-Screen	Screen Run-in	Treatment Period				Follow-up	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window				**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Register visit in Interactive Web Response System (IWRS) (RAMOS NG) [e]	X	X	X	X	X	X	X	
Randomization [f]			X					
Laboratory Assessments								
Urinalysis		X						
Hematology and clinical chemistry [g]		X						
Hepatitis B and C		X [m]						
Genetic sample			X [n]					1.
Serum pregnancy test		X [o]				X [o]	X [o]	
Urine pregnancy test			X [o]	X [o]	X [o]			
Safety Assessments								
Physical exam including height and weight [h]		X				X	X	
12-lead Electrocardiogram (ECG) [i]		X		X		X	X	
Vital signs [j]		X	X	X	X	X	X	
Adverse Event (AE) review		X	X	X	X	X	X	X

Protocol Activity	Pre-Screen	Screen Run-in	Treatment Period				Follow-up	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window				**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Serious Adverse Event (SAE) review	X	X	X	X	X	X	X	X
Study Treatment								
Dispense Albuterol/Salbutamol, as required		X	X	X	X			
Collect Albuterol/Salbutamol, as required			X	X	X	X	X	
Dispense open label fluticasone furoate (FF) 100 mcg medication		X	X	X	X			
Administer open label FF 100 mcg		X	X	X	X	X		
Collect open label FF 100 mcg			X	X	X	X	X	
Dispense double-blind study treatment			X	X	X			
Administer double-blind study treatment			X[p]	X[p]	X[p]	X[p]		
Collect double-blind study treatment				X	X	X	X	
Assess FF 100 mcg run-in medication compliance			X					

Protocol Activity	Pre-Screen	Screen Run-in	Treatment Period				Follow-up	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window				**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Assess FF 100 mcg and double-blind study treatment compliance				X	X	X	X	
Efficacy Assessments								
Global Assessment of Severity [k]			X	X	X	X	X	
Global Assessment of Response to Treatment [k]				X	X	X	X	
Asthma Control Questionnaire (ACQ-6) [k]		X	X [q]					
Asthma Control Questionnaire (ACQ-5) [k]				X	X	X	X	
St. George's Respiratory Questionnaire (SGRQ) [k]			X	X	X	X	X	
Asthma Quality of Life Questionnaire (AQLQ) [k]			X	X	X	X	X	

Protocol Activity	Pre-Screen	Screen Run-in	Treatment Period				Follow-up	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window				**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Evaluating Respiratory Symptoms (E-RS) +Asthma symptoms + Peak Expiratory Flow (PEF) + Home Forced Expiratory Volume in 1 second (FEV)1 [k, l]		X						
eDiary Dispense		X						
eDiary Collect						X	X	
eDiary Review			X	X	X	X	X	
Dispense paper Medical Problems/Medications Taken worksheet	X	X	X	X	X			
Review paper Medical Problems/Medications Taken worksheet		X	X	X	X	X	X	
Reversibility		X [r]						
Exacerbation assessment			X	X	X	X	X	
Pre-dose spirometry (clinic)		X [s]	X [s]	X [s]	X [s]	X [s]	X [s]	
Post-dose spirometry (clinic)			X [t]			X [t]	X [t]	

a) The ICF must be signed before any study procedures, including medication cessation.
b) 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.
c) Demography may be captured at either the Pre-screen Visit or Screening Visit (for participants who do not have a Pre-screen Visit).
d) 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).
e) The IWRS will be used for randomization, emergency unblinding and study treatment supply management (Please refer to the RAMOS NG IWRS manual and SRM for more information).
f) Participants must not be randomized prior to confirming their eligibility to participate in the study.
g) If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required.
h) Physical Examination will include height and weight at Visit 1 only.
i) 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 9.4.3 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.
j) The vital signs assessment will include the measurement of blood pressure, heart rate.
k) Assessment(s) to be completed prior to the administration of study treatment.
l) 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.
m) Hepatitis C RNA is optional however a confirmatory negative Hepatitis C RNA test must be obtained, to be able to enrol participants with positive Hepatitis C antibody due to prior resolved disease. Hep B/C: If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required.
n) Pharmacogenetic sample may be drawn any time from Visit 2 onwards.
o) Assessments only to be conducted in females of reproductive potential.
p) Study treatment should be administered at approximately the same time of day at each applicable clinic visit.
q) Baseline ACQ-5 will be derived from items 1-5 of the Randomization (Visit 2) ACQ-6.
r) 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 or ipratropium aerosol. If airway reversibility is not demonstrated at Visit 1 then the assessment may be repeated within 7 days of Visit 1 (see Section 9.4.3 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 2-week run-in period.
s) Pre-dose spirometry should 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 and FF 100 mcg. After V2 pre-dose spirometry assessments should be performed within $\pm$ 1 hour of the V2 spirometry.
t) Post-dose spirometry is to be performed 3 hours ($\pm$ 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 within $\pm$ 1 hour of the V2 spirometry.

10.3. Appendix 3: Assessment Windows

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 has values recorded for the Week 4 visit that were actually made on the 23rd day of treatment, they will be presented as Week 4 values in the summary tables.

The post-randomization study data collected at early withdrawal (EW) 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 3/ Week 4
57 to 126	85	Visit 4/ Week 12
>=127	169	Visit 5/Week 24

Note:

- For 3 hrs post-dose FEV_1 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.

10.4. Appendix 4: Study Phases

10.4.1. Study Phases

Study phases for assessments scheduled at a set time will be defined according to 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 ≤ Assessment Date/Time < Date of randomization or randomized treatment start date, whichever is later.
On-Treatment during the Study	Randomized Treatment Start Date ≤ Event Onset Date or Assessment Date/Time ≤ Study Treatment Stop Date +1 day or any assessment with a missing or partial date unless there is evidence it was not on-treatment
Post-Treatment during the Study*	Randomized Treatment Stop Date +1 < Event Onset Date or Assessment Date/Time ≤ Last Scheduled Clinic Visit (i.e., Visit 5 (EOS Visit) or Early Withdrawal [EW] Visit) Note: if any participant does not receive a dose of randomized treatment then all post baseline data prior to early withdrawal or EOS visit is considered as post-treatment.
Post-Study	Event Onset Date > Last Scheduled Clinic Visit (i.e., Visit 5 (EOS Visit) or Early Withdrawal Visit) +1 day Note, for participants who continue in the study after IP discontinuation (i.e. where treatment discontinuation date < Visit 5 (EOS visit) date or EW visit date), the rule will be: Event Onset Date > Last Scheduled Clinic Visit (i.e. Visit 5 (EOS Visit) or EW Visit)
*Only applicable for participants who continue in the study after IP discontinuation	

Classification of a concomitant medication into study phases (pre-study period [at study entry], screening/run-in period, on-treatment during the study, post-treatment during the study, 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.

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Compound	: /arenv/arprod/gsk2834425/mid205832/final
QC Spreadsheet	: /arenv/arwork/gsk2834425/mid205832/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.	

10.5.2. Reporting Standards

General

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

Formats
• All data (including data collected post treatment discontinuation) 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%, 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 DP’s.

Planned and Actual Time	

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • 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 and/or figures 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.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principles 7.01 to 7.13.	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

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 subject 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 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 dose. Note: If any container (correct or incorrect) 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 30 possible doses from this container.
Participants excluded from ITT population
• A participant who is recorded as a screen failure or run-in 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.

10.6.2. Study Population

Demographics and Baseline Characteristics
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 the eCRF. Birth date will be imputed as follows: ○ Any participant with a missing day and month will have this imputed as '30th June'. ○ 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-duration of asthma • 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. • Age of onset will be presented in years. If the calculation results in a decimal due to duration of asthma being collected in years and months, the "floor" of the calculated value will be taken.
Body Mass Index (BMI)
• Calculated as Weight (kg) / Height $(m)^2$
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.
ACQ
• Details of how to score the ACQ are provided in the Asthma Control Questionnaire, Background, Administration and Analysis, April 2008. • At baseline, ACQ-5 will be derived from items 1-5 of ACQ-6 performed at the randomization visit (Visit 2). • For further information on ACQ, see Section 10.6.3.
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 are 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

Demographics and Baseline Characteristics
Age
• hypercholesterolemia.

Pneumonia History
• Pneumonia history will be assessed at Visit 1. Participants with pneumonia recorded as either current or past medical condition should also report the number of pneumonia episodes in the past 12 months and the number of pneumonia episodes requiring hospitalization over the past 12 months. This information will be summarized.

Treatment Compliance

- Treatment compliance will be assessed for the run-in period and double-blind treatment period.
- If a dose counter start count is missing then it will be assumed to be 30 for the Ellipta DPI (e.g., such as for the open-label therapy dispensed during double-blind treatment period). If a dose counter stop value is missing then number of doses received will be set to missing for that container.
- For the run-in phase (containers are to be returned prior to or on randomized study drug start date), percentage compliance to FF via ELLIPTA will be calculated as follows:

$$\frac{dose\ counter\ start\ value - dose\ counter\ stop\ value}{run\ in\ treatment\ stop\ date - run\ in\ treatment\ start\ date + 1} * 100$$

  If more than one container is dispensed during run-in and are returned prior to or on randomized treatment start date, the number of doses received by each participant will be calculated as the sum of (dose counter start value – dose counter stop value) over all inhalers dispensed. If the date of container returned is > date of randomized treatment start date then the number of FF doses received will be set to missing for that container. For participants who were not randomized or were randomized in error and not treated, containers should be returned prior to or on the date of Visit 2.

- For each of the FF and double-blind containers dispensed during the double-blind treatment period, the actual total number of doses received by each participant will be calculated as the sum of (dose counter start value – dose counter stop value) over all inhalers dispensed to the participant during the double-blind treatment period, and percentage treatment compliance will be calculated as follows:

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

  Treatment compliance calculations for FF during the double-blind treatment period will not be adjusted in the case where a patient has not returned their run-in medication prior to randomization and continue use into the double-blind treatment period. Treatment compliance will be based only on the returned devices prior to or at end of study/early

withdrawal visit that were dispensed during the double-blind treatment period.

- 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

10.6.3. Efficacy

Spirometry

Trough FEV1 and FVC

- The trough value for FEV_1 at Weeks 4, 12, and 24, visit is the value of the pre-dose (prior to taking the morning dose of study treatment) assessment in Liters (L).
- Predicted percent normal FEV_1: Predicted values will be based upon the European Respiratory Society (ERS) Global Lung Function Initiative Quanjer, 2012]

Post-dose FEV_1

- The post-dose value for FEV_1 at Week 24 or at the EW visit is the assessment value approximately 3 hours after administering the study medication and measured in Liters.

Asthma Exacerbations

- Each asthma exacerbation will be categorized based on severity as follows:
    - Moderate:
        - Deterioration in asthma symptoms, deterioration in lung function, or an increased rescue bronchodilator use lasting for at least 2 days or more, but will not be severe enough to warrant systemic corticosteroid use for 3 days or more and/or hospitalization.
        - An event that, when recognized, should result in a temporary change in treatment, in an effort to prevent the exacerbation from becoming severe.
    - Severe:
        - The deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension or injection) for at least 3 days, OR an inpatient hospitalization or emergency department visit because of asthma, requiring systemic corticosteroids
- 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.
- 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 up to and including the start date of their first exacerbation or up to and including the end of study (EOS) date (or early withdrawal date) + 1 day. Participants that have not experienced an exacerbation will be censored at EOS or early withdrawal + 1 day.

Asthma Control Questionnaire (ACQ)

General

- All 6 items of ACQ have response on 0-6 ordinal scale (0=no impairment/limitation, 6=total impairment/ limitation). The total score is calculated as the average of all non-missing item responses [Asthma Control Questionnaire, Background, Administration and Analysis,

Spirometry

April 2008].
• 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 differs between visits, the following rules will be applied:
  • If the language at Visit 1 and Visit 2 are the same, but the language at a post-randomization visit differs, all ACQ scores at the post-randomization visit and all subsequent visits will be set to missing.
  • If the language at Visit 2 is the same as the language at post-randomization visits, but this differs from the language at Visit 1, the Visit 1 ACQ scores will be set to missing and change during the screening/run-in period will not be calculated.
  • If the language at Visit 2 differs from both the language at Visit 1 and the language at post-randomization visits, all ACQ scores for all visits will be set to missing.
  • If the language is missing at any visit (including baseline) and is the same at all non-missing visits, the language at the missing visit will be assumed to be unchanged.
• ACQ-6 is performed at Visit 1 (screening) and Visit 2 (randomization) only and is primarily used for inclusion/exclusion criteria. ACQ-5 is derived at baseline from the ACQ-6 performed at Visit 2 and performed at all post randomization visits. ACQ-5 forms the basis of the efficacy evaluation.

Responder Status according to ACQ Total Score
• A participant will be considered a responder according to ACQ-5 total score if their ACQ-5 total score has decreased at least 0.5 units from the baseline ACQ-5 total score. • A participant will be considered a non-responder if their ACQ-5 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 10.7.2.
ACQ Control Category

• Control categories are defined as:
  • Well controlled: ≤ 0.75
  • Partially controlled: 0.75 < ACQ score < 1.5
  • Inadequately controlled: ≥ 1.5

St. George's Respiratory Questionnaire (SGRQ)
General
• Details for how to score the SGRQ, including handling of missing data, are outlined in the SGRQ manual (June 2009). • Changes from baseline in domain and total score will be calculated for the converted scores. • 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 is missing at any visit (including baseline) and is the same at all 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 10.7.2.
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 (June 2005). • Changes from baseline in total score will be calculated for the converted scores. • 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 is missing at any visit (including baseline) and is the same at all 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 10.7.2.

Calculation of Daily eDiary Endpoints
General
• Efficacy endpoints based on diary assessments include E-RS total score, home trough FEV_1 (L), PM FEV_1, AM and PM PEF (L/min), and daily rescue medication use. • The detailed derivations for diary data are provide in Section 5.2.2 for baseline value and Section 5.3.2 for post-baseline values. • For AM and PM endpoints, if more than one assessment is available on the same calendar day, all assessments will be used in the calculation of the average for a given period.
Daily rescue medication use (puffs/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 two morning assessments but no evening assessment or two evening assessments but no morning assessment then the daily rescue medication is the sum of the assessments • 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))
Evaluating Respiratory Symptoms (E-RS)
• The E-RS scoring instructions can be found in Appendix B of the User Manual [E-RS (Evaluating Respiratory Symptoms (E-RSTM) in COPD (E-RSTM: COPD) User Manual, Version 5.0. March 2016] • Changes from baseline in total score will be calculated. • 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. • If the language is missing at any timepoint (including baseline period) and is the same at all non-missing timepoints, the language at the missing timepoint will be assumed to be unchanged.

10.6.4. Safety

Extent of Exposure
Run-in Exposure, Treatment Exposure and Post-Treatment On-Study Duration
• Treatment exposure is calculated separately for run-in open label FF 100mcg, randomized double-blind treatment (Placebo, UMEC 31.25mcg or UMEC 62.5mcg) and open label FF100mcg treatment during the treatment period. • Duration of run-in exposure to open label FF100mcg is calculated as: ○ Run-in stop date – run-in start date + 1 • 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: • Last Scheduled Clinic Visit (i.e., Visit 5 (EOS Visit) or Early Withdrawal Visit) – treatment stop date.
Treatment Exposure Categories
• Duration of Treatment Exposure during the double-blind treatment period will be summarized for the following categories: ○ Exposure intervals (weeks): ≥1 day, ≥4 weeks, ≥8 weeks, ≥12 weeks, ≥16 weeks, ≥20 weeks, ≥24 weeks. The category 24 weeks (-5/+2 days) will also be displayed to give the number of participants completing the study per protocol.
Post-treatment On-Study Duration
• Post-treatment On-Study duration will be summarized for the following categories: ○ Duration intervals 0 weeks, >0 to4 weeks, >4 to 12 weeks, >12 weeks.

Adverse Events
Adverse Event Rate
• Event rate per thousand person-years will be displayed for most On-Treatment AE data in separate tables as listed in Section 10.9.8. 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.
AE's of Special Interest
Adverse events of special interest have been defined as AEs which have specified areas of interest for one or more of the treatment groups (FF and/or UMEC). These consist in 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). Table 6 (Section 8.3) presents the special interest AE groups for FF and UMEC, defined upon the release of version 20.1 of the MedDRA dictionary.

Pneumonia (AESI)
Pneumonia Event Rate
• Pneumonia events will be events classified in the pneumonia AESI group (rather than events

Pneumonia (AESI)
Pneumonia Event Rate
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 (including fatalities) • Other ischemic heart disease SMQ (including fatalities)	-Myocardial infarction PT -Acute myocardial infarction PT
Central nervous system haemorrhages and cerebrovascular conditions SMQ (including fatalities)	

10.7. Appendix 7: Reporting Standards for Missing Data

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Withdrawal from Study Prior to Randomization o Participants who are pre-screening failures, screening failures or run-in failures (see Protocol Section 5.5 for the definitions) will be reported to account for the subject disposition. • Withdrawal from Study Treatment o 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. • Participant study completion (i.e. as specified in the protocol) was defined as 'A participant will be considered to have completed the study when they have completed all phases of the study including pre-screening, screening, run-in, the randomized treatment phase, and safety follow-up.' • Withdrawn participants were not replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o 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 data is excluded from the table. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such. o 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).
Spirometry	• When spirometry has been performed but the reading was unacceptable, a record in the database will indicate that the spirometry was performed but all data will be missing and will not be included in listings or summary displays.
Responder analyses	• Participants with a missing baseline will have responder status as missing. • Participants with missing data at the analysis timepoint, regardless of treatment status, will be considered as a non-responder.

Element	Reporting Detail
	• For ACQ/SGRQ/AQLQ, participants that have withdrawn from study prior to the visit in question will be imputed as non-responders at all visits after early withdrawal visit where the assessment was expected to be performed.
Treatment compliance	• For the run-in phase, if date open-label FF 100 ELLIPTA™ DPI device returned is > randomized treatment start date (or Visit 2 for participants who are not treated) date then compliance is set to missing for that container. • 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 received will be set to missing for that container.

10.7.2.1. 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 2 (Day 1) date will be used.
	• If overall treatment stop date is missing, 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 Visit 5 (End of Study) 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
	• These rules will apply to both randomized double-blind treatment and open label FF100mcg for the treatment period.

Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event:
	  ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Study Phases
	  ○ Missing Stop Day: Last day of the month will be used.
	• Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
	  ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
	  ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day

Element	Reporting Detail
	(dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

10.8. Appendix 8: Abbreviations & Trade Marks

10.8.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
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
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IP	Investigational Product
ITT	Intent-To-Treat
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PDMP	Protocol Deviation Management Plan
PP	Per Protocol
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings

10.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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10.9. Appendix 9: List of Data Displays

10.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.1 to 2.n
Safety	3.1 to 3.n	3.1 to 3.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

10.9.2. Mock Example Shell Referencing

Displays will follow IDSL standards where possible. Example mock-up displays will be provided in separate documents and stored in the eTMF. 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.

10.9.3. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

10.9.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	ITT	ES1	Summary of Subject Disposition	ICH E3, FDAAA, EudraCT	SAC
1.2.	ITT	SD1	Summary of Treatment Status	ICH E3	SAC
1.3.	ITT	Study Specific	Summary of Treatment Status at Each Clinic Visit		SAC
1.4.	All Subjects Enrolled	ES6	Summary and Reason for Screen Failures and Run-in Failures	Journal Requirements	SAC
1.5.	All Subjects Enrolled	Study Specific	Summary of Rescreens in the Study and Failure Reasons		SAC
1.6.	All Subjects Enrolled	NS1	Summary of Subject Enrolment by Country and Site ID	EudraCT/Clinical Operations	SAC
1.7.	ITT	NS1	Summary of Subjects Included in the ITT Population by Country and Site ID		SAC
Protocol Deviation					
1.8.	ITT	IE2	Summary of Inclusion, Exclusion, or Randomization Criteria Deviations		SAC
1.9.	ITT	DV1	Summary of Important Protocol Deviations	ICH E3	SAC
Population Analyzed					
1.10.	All Subjects Enrolled	SP1	Summary of Study Populations	IDSL	SAC
Demographic and Baseline Characteristics					
1.11.	ITT	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC
1.12.	ITT	DM1	Summary of Demographic Characteristics by Country		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.13.	All Subjects Enrolled	DM11	Summary of Age Ranges	EudraCT	SAC
1.14.	ITT	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC
1.15.	ITT	DM6	Summary of Race and Racial Combination Details		SAC
1.16.	ITT	Study Specific	Summary of Disease Duration		SAC
1.17.	ITT	Study Specific	Summary of Asthma Medical History Questionnaire		SAC
1.18.	ITT	Study Specific	Summary of Exacerbation History		SAC
1.19.	ITT	SU1 (subset)	Summary of Smoking Status		SAC
1.20.	ITT	Study Specific	Summary of Cardiovascular History / Risk Factors		SAC
1.21.	ITT	FH1	Summary of Family History of Cardiovascular Risk Factors		SAC
1.22.	ITT	Study Specific	Summary of Pneumonia History		SAC
1.23.	ITT	Study Specific	Summary of Clinic Spirometry at Screening and Randomization		SAC
1.24.	ITT	Study Specific	Summary of Change in Clinic Pre-Bronchodilator / Pre-Dose FEV1 (L) during the Run-in Period		SAC
1.25.	ITT	Study Specific	Summary of Home Spirometry During the Run-in Period		SAC
1.26.	ITT	Study Specific	Summary of ACQ score at Screening and Randomization		SAC
1.27.	ITT	Study Specific	Summary of Change from Screening in ACQ-6 Score during the Run-in Period		SAC
1.28.	ITT	MH4	Summary of Current Medical Conditions	ICH E3	SAC
1.29.	ITT	MH4	Summary of Past Medical Conditions	ICH E3	SAC
Prior and Concomitant Medications					
1.30.	ITT	Study Specific	Summary of Asthma Maintenance Therapy at Study Entry		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.31.	ITT	Study Specific	Summary of Asthma Maintenance Therapy Following Treatment Discontinuation		SAC
1.32.	ITT	CM1	Summary of Asthma Concomitant Medications at Study Entry	ICH E3	SAC
1.33.	ITT	CM1	Summary of Asthma Concomitant Medications During the Screening/Run-in Period		SAC
1.34.	ITT	CM1	Summary of On-Treatment Asthma Concomitant Medications		SAC
1.35.	ITT	CM1	Summary of Post-Treatment Asthma Medications		SAC
1.36.	ITT	CM1	Summary of Post-Study Asthma Medications		SAC
1.37.	ITT	CM1	Summary of On-Treatment Non-Asthma Concomitant Medications		SAC
1.38.	ITT	CM1	Summary of Post-Treatment Non-Asthma Medications		SAC
1.39.	ITT	CM1	Summary of Post-Study Non-Asthma Medications		SAC
Treatment Compliance					
1.40.	ITT	TC1	Summary of Treatment Compliance (%)		SAC

10.9.5. Study Population Figures

Study Population Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	ITT	TTE10	Kaplan-Meier Plot of Time to Early Discontinuation from Study Treatment		SAC
1.2.	ITT	TTE10	Kaplan-Meier Plot of Time to Early Withdrawal from the Study		SAC

10.9.6. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Primary Efficacy Endpoint: Trough FEV_1					
2.1.	ITT	Study Specific	Summary of Baseline Clinic Trough FEV_1 (L)		SAC
2.2.	ITT	Study Specific	Summary of Clinic Trough FEV_1 (L) (On- and Post-Treatment)	On- and post-treatment data	SAC
2.3.	ITT	Study Specific	Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) (On- and Post-Treatment)	On- and post-treatment data	SAC
2.4.	ITT	Study Specific	Summary of Clinic Trough FEV1 (L) by Treatment Status (On- and Post-Treatment)	On- and post-treatment data (separately)	SAC
2.5.	ITT	Study Specific	Sensitivity Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) (Jump to Reference) (On- and Post-Treatment)	On- and post-treatment data. Multiple imputation using jump to reference.	SAC
2.6.	ITT	Study Specific	Sensitivity Analysis of Mean Change from Baseline in Clinic Trough FEV1 (L) (Tipping Point) UMEC 62.5mcg vs Placebo (On- and Post-Treatment)	On- and post-treatment data. Tipping point analysis	SAC
2.7.	ITT	Study Specific	Sensitivity Analysis of Mean Change from Baseline in Clinic Trough FEV1 (L) (Tipping Point p-value Grid) UMEC 62.5mcg vs Placebo (On- and Post-Treatment)	On- and post-treatment data. Tipping point analysis	SAC
2.8.	ITT	Study Specific	Sensitivity Analysis of Mean Change from Baseline in Clinic Trough FEV1 (L) (Tipping Point) UMEC 31.25mcg vs Placebo (On- and Post-Treatment)	On- and post-treatment data. Tipping point analysis	SAC
2.9.	ITT	Study Specific	Sensitivity Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) (Tipping Point p-value Grid) UMEC 31.25mcg vs Placebo (On- and Post-Treatment)	On- and post-treatment data. Tipping point analysis	SAC
2.10.	ITT	Study Specific	Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) (on-Treatment)	On-treatment data only	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.11.	ITT	Study Specific	Analysis of Mean Change from Baseline in Clinic Trough FEV_1 (L) excluding sites with data concerns (On- and Post-Treatment)	On- and post-treatment data	SAC
2.12.	ITT	Study Specific	Summary of Clinic Trough FEV_1 (L) by Gender (On- and Post-Treatment)	On- and post-treatment data	SAC
2.13.	ITT	Study Specific	Summary of Clinic Trough FEV_1 (L) by Age (On- and Post-Treatment)	On- and post-treatment data	SAC
2.14.	ITT	Study Specific	Summary of Clinic Trough FEV_1 (L) by Race (On- and Post-Treatment)	On- and post-treatment data	SAC
2.15.	ITT	Study Specific	Summary of Clinic Trough FEV1 (L) by Region (On- and Post-Treatment)	On- and post-treatment data	SAC
2.16.	ITT	Study Specific	Summary of Clinic Trough FEV_1 (L) by Eosinophils at Screening (On- and Post-Treatment)	On- and post-treatment data	SAC
2.17.	ITT	Study Specific	Significance Levels for All Covariates Included in the Analysis Model for Change from Baseline in Trough FEV1 (L) and Interactions with Treatment (On- and Post-Treatment)	On- and post-treatment data	SAC
Secondary Efficacy Endpoint: FEV1 at 3 hours post Dose					
2.18.	ITT	Study Specific	Summary of Change from Baseline in Clinic FEV_1 at 3 Hours Post Dose (On-Treatment)	On-treatment data only	SAC
2.19.	ITT	Study Specific	Analysis of Mean Change from Baseline in Clinic FEV_1 at 3 Hours Post Dose at Week 24 (On-Treatment)	On-treatment data only	SAC
Exploratory Efficacy Endpoints					
2.20.	ITT	Study Specific	Summary of Clinic Spirometry Data (On- and Post-Treatment)	On- and post-treatment data	SAC
2.21.	ITT	Study Specific	Summary of Home AM PEF (L/min) (On- and Post-Treatment)	On- and post-treatment data	SAC
2.22.	ITT	Study Specific	Analysis of Mean Change from Baseline in Home AM PEF (L/min) over the 24 Week Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.23.	ITT	Study Specific	Summary of Home PM PEF (L/min) (On- and Post-Treatment)	On- and post-treatment data	SAC
2.24.	ITT	Study Specific	Analysis of Mean Change from Baseline in Home PM PEF (L/min) over the 24-Week Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.25.	ITT	Study Specific	Summary of Home Trough FEV_1 (L) (On- and Post-Treatment)	On- and post-treatment data	SAC
2.26.	ITT	Study Specific	Analysis of Mean Change from Baseline in Home Trough FEV_1 (L) over the 24-week Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.27.	ITT	Study Specific	Analysis of Mean Change from Baseline in Home Trough FEV_1 (L) up to Week 8 by 1-Week Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.28.	ITT	Study Specific	Summary of Home PM FEV_1 (L) (On- and Post-Treatment)	On- and post-treatment data	SAC
2.29.	ITT	Study Specific	Analysis of Mean Change from Baseline in Home PM FEV_1 (L) over the 24-week Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.30.	ITT	Study Specific	Summary of Baseline Daily Rescue Medication use (Puffs/Day)		SAC
2.31.	ITT	Study Specific	Summary of Daily Rescue Medication Use (Puffs/Day) (On- and Post-Treatment)	On- and post-treatment data	SAC
2.32.	ITT	Study Specific	Analysis of Mean Change from Baseline in Daily Rescue Medication use (Puffs/Day) over the 24-week Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.33.	ITT	Study Specific	Summary of Baseline SGRQ Total Score		SAC
2.34.	ITT	Study Specific	Summary of SGRQ Total Score (On- and Post-Treatment)	On- and post-treatment data	SAC
2.35.	ITT	Study Specific	Analysis of Mean Change from Baseline in SGRQ Total Score (On- and Post-Treatment)	On- and post-treatment data	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.36.	ITT	Study Specific	Summary and Analysis of Percent of Patients Meeting a Responder Threshold of ≥4 Points Improvement (Decrease) from Baseline for the SGRQ Total Score (On- and Post-Treatment)	On- and post-treatment data	SAC
2.37.	ITT	Study Specific	Summary of Baseline SGRQ Domain Scores		SAC
2.38.	ITT	Study Specific	Summary of SGRQ Domain Scores (On- and Post-Treatment)	On- and post-treatment data	SAC
2.39.	ITT	Study Specific	Analysis of Mean Change from Baseline in SGRQ Domain Scores (On- and Post-Treatment)	On- and post-treatment data	SAC
2.40.	ITT	Study Specific	Summary of Baseline AQLQ Total Score		SAC
2.41.	ITT	Study Specific	Summary of AQLQ Total Score (On- and Post-Treatment)	On- and post-treatment data	SAC
2.42.	ITT	Study Specific	Analysis of Mean Change from Baseline in AQLQ Total Score (On- and Post-Treatment)	On- and post-treatment data	SAC
2.43.	ITT	Study Specific	Summary and Analysis of Percent of Patients Meeting a Responder Threshold of ≥0.5 Points Improvement (Increase) from Baseline for the AQLQ Total Score (On- and Post-Treatment)	On- and post-treatment data	SAC
2.44.	ITT	Study Specific	Summary of Baseline E-RS Total Score		SAC
2.45.	ITT	Study Specific	Summary of E-RS Total Score (On- and Post-Treatment)	On- and post-treatment data	SAC
2.46.	ITT	Study Specific	Analysis of Mean Change from Baseline in E-RS Total Score (On- and Post-Treatment) over the 24-week Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.47.	ITT	Study Specific	Summary of ACQ-5 Total Score (On- and Post-Treatment)	On- and post-treatment data	SAC
2.48.	ITT	Study Specific	Shift in ACQ-5 Control Category from Baseline to Week 24 (On- and Post-Treatment)	On- and post-treatment data	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.49.	ITT	Study Specific	Analysis of Mean Change from Baseline in ACQ-5 Total Score (On- and Post-Treatment)	On- and post-treatment data	SAC
2.50.	ITT	Study Specific	Summary and Analysis of Percent of Patients Meeting a Responder Threshold of ≥0.5 in change (decrease) from baseline for the ACQ-5 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.51.	ITT	Study Specific	Summary of Moderate and Severe Asthma Exacerbations (On- and Post-Treatment)	On- and post-treatment data	SAC
2.52.	ITT	Study Specific	Analysis of Moderate/Severe Asthma Exacerbations (On- and Post-Treatment)	On- and post-treatment data	SAC
2.53.	ITT	Study Specific	Summary and Analysis of Time to First Moderate/Severe Asthma Exacerbation (Days) (On- and Post-Treatment)	On- and post-treatment data	SAC
2.54.	ITT	Study Specific	Analysis of Severe Asthma Exacerbations (On- and Post-Treatment)	On- and post-treatment data	SAC
2.55.	ITT	Study Specific	Summary and Analysis of Time to First Severe Asthma Exacerbation (Days) (On- and Post-Treatment)	On- and post-treatment data	SAC
2.56.	ITT	Study Specific	Summary of Baseline Global Assessment of Severity		SAC
2.57.	ITT	Study Specific	Summary of Global Assessment of Severity and Response to Treatment (On- and Post-Treatment)	On- and post-treatment data	SAC

10.9.7. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Efficacy Endpoint					
2.1.	ITT	Study Specific	Box Plot of Change from Baseline in Clinic Trough FEV_1 (L) at Week 4, Week 12 and Week 24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.2.	ITT	Study Specific	Empirical Distribution Function Plot of Change from Baseline in Clinic Trough FEV_1 (L) at Week 4, Week 12 and Week 24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.3.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in Clinic Trough FEV_1 (L) up to Week 24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.4.	ITT	Study Specific	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)	On- and post-treatment data	SAC
2.5.	ITT	Study Specific	Box Plot of Change from Baseline in Clinic Trough FEV_1 (L) at Week 4, Week 12 and Week 24 (On-Treatment)	On-treatment data only	SAC
2.6.	ITT	Study Specific	Empirical Distribution Function Plot of Change from Baseline in Clinic Trough FEV1 (L) at Week 4, Week 12 and Week 24 (On-Treatment)	On-treatment data only	SAC
2.7.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in Clinic Trough FEV_1 (L) up to Week 24 (On-Treatment)	On-treatment data only	SAC
2.8.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Clinic Trough FEV_1 (L) up to Week 24 (On-Treatment)	On-treatment data only	SAC
2.9.	ITT	Study Specific	Forest Plot of Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Trough FEV1 (L) and Associated Supportive/Sensitivity Analyses at Week 24		SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.10.	ITT	Study Specific	Tipping Point Heat Plot for Mean Change from Baseline in Clinic Trough FEV1 (L) Difference UMEC 62.5mcg – Placebo (On- and Post-Treatment)		SAC
2.11.	ITT	Study Specific	Tipping Point Line Plot for Mean Change from Baseline in Clinic Trough FEV1 (L) Difference UMEC 62.5mcg – Placebo (On- and Post-Treatment)		SAC
2.12.	ITT	Study Specific	Tipping Point Heat Plot for Mean Change from Baseline in Clinic Trough FEV1 (L) Difference UMEC 31.25mcg – Placebo (On- and Post-Treatment)		SAC
2.13.	ITT	Study Specific	Tipping Point Line Plot for Mean Change from Baseline in Clinic Trough FEV1 (L) Difference UMEC 31.25mcg – Placebo (On- and Post-Treatment)		SAC
Secondary Efficacy Endpoint					
2.14.	ITT	Study Specific	Box Plot of Change from Baseline in Clinic FEV_1 (L) at 3 Hours post Dose at Week 24 (On-Treatment)	On-treatment data only	SAC
2.15.	ITT	Study Specific	Empirical Distribution Function Plot of Change from Baseline in Clinic FEV_1 (L) at 3 Hours post Dose at Week 24 (On-Treatment)	On-treatment data only	SAC
2.16.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in Clinic FEV_1 (L) at 3 Hours post Dose at Week 24 (On-Treatment)	On-treatment data only	SAC
2.17.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Clinic FEV_1 (L) at 3 Hours post Dose at Week 24 (On-Treatment)	On-treatment data only	SAC
Other Efficacy Endpoints					
2.18.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in Home AM PEF (L/min) over the 24-week Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.19.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home AM PEF (L/min) over the 24-week Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.20.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in Home AM PEF (L/min) over Weeks 1-24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.21.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in AM PEF (L/min) over Weeks 1-24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.22.	ITT	Study Specific	Descriptive Weekly Mean Change from Baseline in Home AM PEF (L/min) from Weeks 1-24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.23.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in Home PM PEF (L/min) over the 24-week Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.24.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home PM PEF (L/min) over the 24-week Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.25.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in Home PM PEF (L/min) over Weeks 1-24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.26.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home PM PEF (L/min) over Weeks 1-24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.27.	ITT	Study Specific	Descriptive Weekly Mean Change from Baseline in Home PM PEF (L/min) from Weeks 1-24 (On- and Post-Treatment)	On- and post-treatment data	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.28.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in Home Trough FEV1 (L) over the 24-week Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.29.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home Trough FEV1 (L) over the 24-week Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.30.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in Home Trough FEV1 (L) over Weeks 1-24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.31.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home Trough FEV1 (L) over Weeks 1-24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.32.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in Home Trough FEV1 (L) up to Week 8 by 1-Week Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.33.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home Trough FEV1 (L) over Weeks 1-8 by 1-Week Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.34.	ITT	Study Specific	Descriptive Weekly Mean Change from Baseline in Home Trough FEV1 (L) from Weeks 1-24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.35.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in Home PM FEV1 (L) over the 24-week Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.36.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home PM FEV1 (L) over the 24-week Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.37.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in Home PM FEV1 (L) over weeks 1-24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.38.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Home PM FEV1 (L) over weeks 1-24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.39.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in Daily Rescue Medication Use (puffs/day) over the 24-week Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.40.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Daily Rescue Medication Use (puffs/day) over the 24-week Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.41.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in Daily Rescue Medication Use (puffs/day) over weeks 1-24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.42.	ITT	Study Specific	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)	On- and post-treatment data	SAC
2.43.	ITT	Study Specific	Empirical Distribution Function Plot of Change from Baseline in SGRQ Total Score at Week 4, Week 12 and Week 24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.44.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in SGRQ Total Score at Week 4, Week 12 and Week 24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.45.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in SGRQ Total Score at Week 4, Week 12 and Week 24 (On- and Post-Treatment)	On- and post-treatment data	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.46.	ITT	Study Specific	Bar Chart of Percent of Subjects Meeting a Responder Threshold of ≥4 Points Improvement (Decrease) from Baseline for the SGRQ Total Score at Week 24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.47.	ITT	Study Specific	Forest plot of Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in SGRQ total score and SGRQ Domain Scores at Week 24	On- and post-treatment data	SAC
2.48.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in AQLQ Total Score at Week 4, Week 12 and Week 24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.49.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in AQLQ Total Score at Week 4, Week 12 and Week 24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.50.	ITT	Study Specific	Bar Chart of Percent of Subjects Meeting a Responder Threshold of ≥0.5 Points Improvement (Increase) from Baseline for the AQLQ Total Score at Week 24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.51.	ITT	Study Specific	Empirical Distribution Function Plot of Change from Baseline in E-RS Total Score over the 24 weeks Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.52.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in E-RS Total Score over the 24 weeks Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.53.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in E-RS Total Score over the 24 weeks Treatment Period by 4-Weekly Intervals (On- and Post-Treatment)	On- and post-treatment data	SAC
2.54.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in E-RS Total Score over Weeks 1-24 (On- and Post-Treatment)	On- and post-treatment data	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.55.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in E-RS Total Score over Weeks 1-24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.56.	ITT	Study Specific	Empirical Distribution Function Plot of Change from Baseline in ACQ-5 Total Score at Week 4, Week 12 and Week 24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.57.	ITT	Study Specific	Least Squares Mean (95% CI) Change from Baseline in ACQ-5 Total Score at Week 4, Week 12 and Week 24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.58.	ITT	Study Specific	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in ACQ-5 Total Score at Week 4, Week 12 and Week 24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.59.	ITT	Study Specific	Bar Chart of Percent of Subjects Meeting a Responder Threshold of ≥0.5 in Change (Decrease) from Baseline for the ACQ-5 Total Score at Week 24 (On- and Post-Treatment)	On- and post-treatment data	SAC
2.60.	ITT	Study Specific	Adjusted Moderate/Severe Asthma Exacerbations Rate Ratio (On- and Post-Treatment)	On- and post-treatment data	SAC
2.61.	ITT	Study Specific	Kaplan-Meier Plot of Time to First Moderate/Severe Asthma Exacerbation (On- and Post-Treatment)	On- and post-treatment data	SAC
2.62.	ITT	Study Specific	Adjusted Severe Asthma Exacerbations Rate Ratio (On- and Post-Treatment)	On- and post-treatment data	SAC
2.63.	ITT	Study Specific	Kaplan-Meier Plot of Time to First Severe Asthma Exacerbation (On- and Post-Treatment)	On- and post-treatment data	SAC

10.9.8. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Treatment Exposure					
3.1.	ITT	EX1	Summary of Exposure to Open-Label FF100mcg During the Run-in Period		SAC
3.2.	ITT	EX1	Summary of Treatment Exposure	ICH E3	SAC
3.3.	ITT	Study Specific	Summary of Post-Treatment Duration on Study		SAC
Adverse Events (AEs)					
3.4.	ITT	AE1	Summary of Adverse Events During the Screening/Run-in Period	ICH E3	SAC
3.5.	ITT	AE13	Overview of On-treatment Adverse Events		SAC
3.6.	ITT	Study Specific	Overview of On-treatment Adverse Events per Thousand Person-Years		SAC
3.7.	ITT	AE1	Summary of On-Treatment Adverse Events		SAC
3.8.	ITT	Study Specific	Summary of On-Treatment Adverse Events per Thousand Person-Years		SAC
3.9.	ITT	AE1	Summary of Post-Treatment Adverse Events		SAC
3.10.	ITT	AE1	Summary of Post-Study Adverse Events		SAC
3.11.	ITT	AE1	Summary of On-Treatment Drug-Related Adverse Events	ICH E3	SAC
3.12.	ITT	Study Specific	Summary of On-treatment Drug-Related Adverse Events per Thousand Person-Years		SAC
3.13.	ITT	AE1	Summary of Post-Treatment Drug-Related Adverse Events		SAC
3.14.	ITT	AE3	Summary of Common On-Treatment Adverse Events (1% or more of Subjects in Any Treatment Group)	ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.15.	ITT	AE3	Summary of Common On-Treatment Adverse Events (3% or more of Subjects in Any Treatment Group)	ICH E3	SAC
3.16.	ITT	Study Specific	Summary of the 10 Most Frequent On-Treatment Adverse Events in Each Treatment Group		SAC
3.17.	ITT	AE1_by	Summary of On-Treatment Adverse Events by Age Group		SAC
3.18.	ITT	AE1_by	Summary of On-Treatment Adverse Events by Gender		SAC
3.19.	ITT	AE1_by	Summary of On-Treatment Adverse Events by Race		SAC
3.20.	ITT	AE1_by	Summary of On-Treatment Adverse Events by Region		SAC
3.21.	ITT	AE1_by	Summary of On-Treatment Adverse Events by Eosinophils at Screening		SAC
3.22.	ITT	AE15	Summary of On-Treatment Common (≥3%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC
Serious and Other Significant Adverse Events					
3.23.	ITT	AE1	Summary of On-Treatment Serious Adverse Events		SAC
3.24.	ITT	Study Specific	Summary of On-treatment Serious Adverse Events per Thousand Person-Years		SAC
3.25.	ITT	AE1	Summary of Post-Treatment Serious Adverse Events		SAC
3.26.	ITT	AE1	Summary of Post-Study Serious Adverse Events		SAC
3.27.	ITT	AE1	Summary of On-Treatment Drug-Related Serious Adverse Events		SAC
3.28.	ITT	Study Specific	Summary of On-treatment Drug-Related Serious Adverse Events per Thousand Person-Years		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.29.	ITT	AE1	Summary of On-Treatment Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study		SAC
3.30.	ITT	AE1	Summary of Post-Treatment Adverse Events Leading to Withdrawal from Study		SAC
3.31.	ITT	AE1	Summary of On-Treatment Adverse Events of Special Interest		SAC
3.32.	ITT	Study Specific	Summary of On-Treatment Adverse Events of Special Interest per Thousand Person-Years		SAC
3.33.	ITT	AE1	Summary of Post-Treatment Adverse Events of Special Interest		SAC
3.34.	ITT	AE1	Summary of On-Treatment Serious Adverse Events of Special Interest		SAC
3.35.	ITT	Study Specific	Summary of On-Treatment Serious Adverse Events of Special Interest per Thousand Person-Years		SAC
3.36.	ITT	AE1	Summary of Post-Treatment Serious Adverse Events of Special Interest		SAC
3.37.	ITT	AE16	Summary of On-Treatment Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC
MACE					
3.38.	ITT	Study Specific	Summary of On-Treatment Major Adverse Cardiac Events (MACE) – Narrow Definition		SAC
3.39.	ITT	Study Specific	Summary of On-Treatment Major Adverse Cardiac Events (MACE) Per Thousand Person-Years – Narrow Definition		SAC
3.40.	ITT	Study Specific	Summary of On-Treatment Major Adverse Cardiac Events (MACE) – Broad Definition		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.41.	ITT	Study Specific	Summary of On-Treatment Major Adverse Cardiac Events (MACE) Per Thousand Person-Years – Broad Definition		SAC
Pneumonia and Radiography (Chest X-Rays)					
3.42.	ITT	Study Specific	Summary of On-Treatment Pneumonia, Including Chest X-ray Finding		SAC
ECG					
3.43.	ITT	EG2	Summary of ECG Values (On-Treatment)	IDSL	SAC
3.44.	ITT	EG2	Summary of Change from Baseline in ECG Values (On-Treatment)	IDSL	SAC
3.45.	ITT	EG1	Summary of ECG Findings (On-Treatment)	IDSL	SAC
3.46.	ITT	Study Specific	Summary of ECG Findings Shifts from Baseline (On-Treatment)		SAC
3.47.	ITT	Study Specific	Summary of ECG Abnormalities (On-Treatment)		SAC
3.48.	ITT	Study Specific	Analysis of Mean Change from Baseline in PR interval (msec) (On-Treatment)		SAC
3.49.	ITT	Study Specific	Analysis of Mean Change from Baseline in QTc(F) Interval (msec) (On-Treatment)		SAC
Vital Signs					
3.50.	ITT	VS1	Summary of Vital Signs (On-Treatment)	ICH E3	SAC
3.51.	ITT	VS1	Summary of Change from Baseline in Vital Signs (On-Treatment)	ICH E3	SAC
3.52.	ITT	Study Specific	Analysis of Mean Change from Baseline in Systolic Blood Pressure (mmHg) (On-Treatment)		SAC
3.53.	ITT	Study Specific	Analysis of Mean Change from Baseline in Diastolic Blood Pressure (mmHg) (On-Treatment)		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.54.	ITT	Study Specific	Analysis of Mean Change from Baseline in Pulse Rate (beats/min) (On-Treatment)		SAC

10.9.9. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
3.1.	ITT	Study Specific	Plot of Exposure to Study Treatment Over Time		SAC
ECG					
3.2.	ITT	EG7	Empirical Distribution Function Plot of Maximum Post-Baseline QTc(F) (msec) (On-Treatment)		SAC
3.3.	ITT	EG7	Empirical Distribution Function Plot of Change from Baseline in Maximum Post-Baseline QTc(F) (msec) (On-Treatment)		SAC
3.4.	ITT	Study Specific	Least Squares Means (95% CI) Change from Baseline in PR Interval (msec) (On-Treatment)		SAC
3.5.	ITT	Study Specific	Least Squares Means (95% CI) Change from Baseline in QTc(F) Interval (msec) (On-Treatment)		SAC
3.6.	ITT	Study Specific	Least Squares Means (95% CI) Change from Baseline in Systolic Blood Pressure (mmHg) (On-Treatment)		SAC
3.7.	ITT	Study Specific	Least Squares Means (95% CI) Change from Baseline in Diastolic Blood Pressure (mmHg) (On-Treatment)		SAC
3.8.	ITT	Study Specific	Least Squares Means (95% CI) Change from Baseline in Pulse Rate(beats/min) (On-Treatment)		SAC

10.9.10. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	All Subjects Screened	ES7	Listing of Reasons for Screen Failure, Run-in Failure or Randomization Failure	Journal Guidelines	SAC
2.	ITT	ES3	Listing of Reasons for Study Withdrawal	ICH E3	SAC
3.	ITT	SD3	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC
4.	ITT	BL2	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	SAC
5.	ITT	Study Specific	Listing of Randomized and Actual Treatments	ICH E3	SAC
6.	ITT	Study Specific	Listing of Study Treatment Misallocations	ICH E3	SAC
Protocol Deviations					
7.	All Subjects Enrolled	DV2	Listing of Important Protocol Deviations	ICH E3	SAC
8.	ITT	IE3	Listing of Subjects with Inclusion/Exclusion Criteria, or Randomization Deviations	ICH E3	SAC
Populations Analyzed					
9.	ITT	Study Specific	Listing of Subjects Excluded from the Primary Efficacy Analysis	ICH E3	SAC
10.	All Subjects Screened	Study Specific	Listing of Subjects Who Were Randomized in Error and Not Included in the Intent-To-Treat Population	ICH E3	SAC
Demographic and Baseline Characteristics					
11.	ITT	DM4	Listing of Demographic Characteristics	ICH E3	SAC
12.	ITT	DM10	Listing of Race	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Treatment Compliance					
13.	ITT	Study Specific	Listing of Treatment Compliance Data	ICH E3	SAC
Efficacy					
14.	ITT	Study Specific	Listing of Clinic Spirometry Data	ICH E3	SAC
Exposure					
15.	ITT	EX3 (modified)	Listing of Run-in Exposure, Treatment Exposure and Post-Treatment Study Duration	ICH E3	SAC
Adverse Events					
16.	All Subjects Enrolled	AE8	Listing of All Adverse Events for Subjects Not Included in the ITT Population	ICH E3	SAC
17.	ITT	AE8	Listing of All Adverse Events	ICH E3	SAC
18.	ITT	Study Specific	Listing of Adverse Events for Subjects Who Received an Incorrect Treatment	ICH E3	SAC
19.	ITT	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
20.	Not Applicable	AE2	Listing of Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC
Serious and Other Significant Adverse Events					
21.	ITT	AE8	Listing of Fatal Serious Adverse Events	ICH E3	SAC
22.	ITT	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	SAC
23.	ITT	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC
24.	ITT	AE8	Listing of Adverse Events Leading to Discontinuation of Study Treatment or Early Withdrawal from Study	ICH E3	SAC
25.	ITT	AE8	Listing of Serious Adverse Events of Special Interest	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Hepatobiliary (Liver)					
26.	ITT	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	IDSL	SAC
27.	ITT	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	IDSL	SAC
All Laboratory					
28.	ITT	LB5	Listing of Chemistry Values for Subjects with at Least One Value Outside the Normal Range	ICH E3	SAC
29.	ITT	LB5	Listing of Haematology Values for Subjects with at Least One Value Outside the Normal Range	ICH E3	SAC
ECG					
30.	ITT	EG3 (modified)	Listing of ECG Values for Subjects with any Abnormal ECG Finding	IDSL	SAC
31.	ITT	EG5	Listing of ECG Abnormalities	IDSL	SAC
Vital Signs					
32.	ITT	VS4 (modified)	Listing of Vital Signs	IDSL	SAC

10.9.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
33.	ITT	Study Specific	Listing of Rescreened Subjects		SAC
34.	ITT	MH2	Listing of Medical Conditions		SAC
35.	ITT	Study Specific	Listing of Pneumonia History		SAC
36.	ITT	Study Specific	Listing of Family History of Cardiovascular Risk Factors		SAC
37.	ITT	Study Specific	Listing of Asthma Duration and Exacerbation History		SAC
38.	ITT	SU2	Listing of Smoking History and Status		SAC
39.	ITT	CM3	Listing of Asthma Concomitant Medications		SAC
40.	ITT	CM3	Listing of Non-Asthma Concomitant Medications		SAC
41.	Not Applicable	CM6	Relationship between ATC Level 1, Ingredient and Verbatim Text for Non-Asthma Medications		SAC
42.	ITT	Study Specific	Listing of Inhaler Malfunctions		SAC
Efficacy					
43.	ITT	Study Specific	Listing of Derived FEV1 (L) Data		SAC
44.	ITT	Study Specific	Listing of Derived Diary Data		SAC
45.	ITT	Study Specific	Listing of SGRQ Scores		SAC
46.	ITT	Study Specific	Listing of AQLQ Scores		SAC
47.	ITT	Study Specific	Listing of E-RS Scores		SAC
48.	ITT	Study Specific	Listing of ACQ Scores		SAC
49.	ITT	Study Specific	Listing of Moderate/Severe Asthma Exacerbations		SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
50.	ITT	Study Specific	Listing of Moderate/Severe Asthma Exacerbations with an Onset Within 14 Days Prior to Early Withdrawal from Study or Discontinuation of Study Treatment		SAC
51.	ITT	Study Specific	Listing of Global Assessment of Severity and Response to Treatment		SAC
Safety					
52.	ITT	AE7	Listing of Subject Numbers for Individual Adverse Events of Special Interest	IDSL	SAC
53.	Not Applicable	Study Specific	Listing of Adverse Event of Special Interest Group, Subgroup, Sub-SMQ and Preferred Term		SAC
54.	ITT	AE8	Listing of MACE (Narrow and Broad Definition)	IDSL	SAC
55.	ITT	Study Specific	Listing of Pneumonia Data, including Chest X-ray Finding		SAC
56.	ITT	Study Specific	Listing of Bone Fracture Data		SAC
57.	ITT	LIVER5	Listing of Liver Event Results and Time of Event Relative to Treatment	IDSL	SAC
58.	ITT	LIVER6	Listing of Liver Event Information for RUCAM Score	IDSL	SAC
59.	ITT	LIVER7	Listing of Liver Biopsy Details	IDSL	SAC
60.	ITT	LIVER8	Listing of Liver Imaging Details	IDSL	SAC
61.	All Subjects Enrolled	IDSL	Patient Profile for Arrhythmias	IDSL	SAC
62.	All Subjects Enrolled	IDSL	Patient Profile for Congestive Heart Failure	IDSL	SAC
63.	All Subjects Enrolled	IDSL	Patient Profile for Cerebrovascular Events/Stroke	IDSL	SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
64.	All Subjects Enrolled	IDSL	Patient Profile for Deep Vein Thrombosis / Pulmonary Embolism	IDSL	SAC
65.	All Subjects Enrolled	IDSL	Patient Profile for Myocardial Infarction / Unstable Angina	IDSL	SAC
66.	All Subjects Enrolled	IDSL	Patient Profile for Hypertension	IDSL	SAC
67.	All Subjects Enrolled	IDSL	Patient Profile for Revascularization	IDSL	SAC
68.	All Subjects Enrolled	IDSL	Patient Profile for Valvulopathy	IDSL	SAC
69.	All Subjects Enrolled	IDSL	Patient Profile for All Cause Deaths	IDSL	SAC