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

Title	:	Reporting and Analysis Plan for A 6-month, open label, randomised, efficacy study to evaluate fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) Inhalation Powder delivered once daily via the Dry Powder Inhaler Ellipta™ compared with usual ICS/LABA maintenance therapy delivered by Dry Powder Inhaler in subjects with Persistent Asthma
Compound Number	:	GW685698+GW642444
Effective Date	:	21-AUG-2017

Description:

The purpose of this document is to describe the final planned analyses and output to be included in the Clinical Study Report for Protocol HZA116492.

This RAP is intended to describe the planned efficacy and safety analyses required for the study.

This RAP will be provided to the study team members to convey the content of the final Statistical Analysis Complete (SAC) deliverable.

Author's Name and Functional Area:

PPD Principal Statistician (Clinical Statistics)	05-DEC-2016
PPD Statistics Leader (Clinical Statistics)	16-AUG-2017

Approved by:

PPD Director, Statistics & Programming (Clinical Statistics)	18-AUG-2017
PPD Programming Manager (Clinical Programming)	21-AUG-2017

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	This RAP details all planned analyses and output required for the final Clinical Study Report of study HZA116492.
Protocol	This RAP is based on the protocol amendment 02 (Dated: 28-APR-2016) of study HZA116492 (GSK Document No.: 2014N190259_02).
Primary Objective	To compare the efficacy of fluticasone furoate (FF)/vilanterol(VI) 92 mcg/22 mcg or FF 184 mcg/22 mcg with usual fixed combinations inhaled corticosteroid / long-acting beta agonist (ICS/LABA) for asthma maintenance therapy at Week 12 (Visit 4).
Primary Endpoint	Change from baseline in the Asthma Control Test (ACT) total score at Week 12 (Visit 4).
Study Design	This is a Phase IIIb multi-center randomised open label, parallel group study performed in subjects in primary and in respiratory specialist care / research sites who have a diagnosis of asthma and a regular treatment for asthma. Subjects with unsatisfactorily controlled asthma (defined as an ACT < 20) and intended to be treated by usual ICS/LABA maintenance therapy to seek a better control of their asthma will be randomised to receive either FF/VI (FF/VI 92 mcg/22 mcg or FF/VI 184 mcg/22 mcg) once daily or another usual ICS/LABA combination therapy in inhalation powder twice daily (fluticasone propionate[FP]/salmeterol [S] or budesonide[BUD]/formoterol [F]) decided by the physician. Physicians will be allowed during the treatment period to adapt prescription to different doses if necessary as well as to adapt doses of any comparative treatment according to products label.
Planned Analyses	No interim analysis is planned for this study. All decisions regarding final analysis for the reporting effort, as defined in this RAP document, will be made prior to Database Freeze (DBF) (unblinding) of the study data. All planned analyses will be carried out once DBF has taken place. Once this has been achieved, unblinding will occur and the analyses will be performed. The open-label study design and the method of recording study medication data in the datasets means that extra steps must be taken to ensure that Statistics and Programming (S&P) remain blinded to study investigator prescribing of study medication until the formal unblinding takes place at DBF. See Section 12.13 for more details.

Overview	Key Elements of the RAP
Analysis Populations	**All Subjects Enrolled (ASE) population:** All subjects screened (provided consent) and for whom a record exists on the study database. Note, this population is not identified in the protocol, but is needed for displays that include subjects screened but not in the intent-to-treat (ITT) population (e.g. tabulation of reasons for withdrawal before randomisation). **Intent-to-treat (ITT) population:** All randomized subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy). The ITT population will be used to analyze the primary efficacy endpoint analysis, the secondary efficacy endpoint and other efficacy endpoints. Subjects will be assigned to the treatment group as randomized for the ITT population. **Per protocol (PP) population**: all ITT subjects without any protocol deviations specifically defined in this RAP. Protocol deviations will be reviewed and will be classified as important or not important during data review meetings that will be held before DBF. Deviations classified as important will be further defined according to whether they require the patient to be excluded from the PP population. Deviations that exclude a patient from the PP population are defined in this RAP (see Section 12.1.2). Subjects will be assigned to the treatment group as treated for the PP population. **Safety population:** All enrolled subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy) and considered as-treated. The Safety population will be the basis for safety analyses. Subjects will be assigned to the treatment group as treated for the Safety population.
Hypothesis	The primary analysis is designed to determine whether the fixed combination FF/VI is non-inferior to any other ICS/LABA combinations in inhalation powder assuming a non-inferiority margin of 1.5. Non-inferiority will be claimed if the 95% two-sided confidence interval (CI) on the difference in mean primary efficacy endpoints (FF/VI versus ICS/LABA comparator) precludes the non-inferiority margin of -1.5. If (and only if) non-inferiority is significantly achieved at Week 12 (Visit 4) with regard to the primary endpoint, then non-inferiority of the fixed combination FF/VI to any other ICS/LABA combinations will be tested at Week 24 (Visit 6) considering the same non-inferiority margin of 1.5. Non-inferiority will be claimed if the 95% two-sided CI on the difference in mean primary efficacy endpoints (FF/VI versus ICS/LABA comparator) at Week 24 (Visit 6) precludes the non-inferiority margin of -1.5. This step-down testing procedure strongly controls the overall type I error of the non-inferiority endpoints at the 0.05 two-sided level.
Primary Analyses	The primary endpoint will be analysed using a mixed model repeated measures (MMRM) approach. The model will include factors and covariates as follows: randomised treatment, scheduled visit time point (Week 6 and Week 12), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient will be fitted as a random factor. The Restricted Maximum Likelihood (REML) estimation approach will be used, and the default covariance structure will be unstructured. Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point will be performed. The adjusted means for each treatment and the estimated treatment differences for the treatment comparisons will be presented together with the 95% CIs for the differences (FF/VI versus ICS/LABA comparator) and p-values at Week 12 (Visit 4). If non-inferiority is statistically achieved at Week 12 (Visit 4), then superiority of FF/VI to any other comparator will be tested at the usual 0.05 two-sided nominal level of significance.

Overview	Key Elements of the RAP
	The same models and analyses mentioned above will be used to assess the superiority hypothesis.
Secondary Analyses	**Key secondary analysis** The key secondary endpoint assessed at Week 24 (Visit 6) will also be analyzed using a MMRM approach where data up to and including Week 24 (Visit 6) will be used in the model. The model will include factors and covariates as follows: randomised treatment, scheduled visit time point (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient will be fitted as a random factor. The REML estimation approach will be used, and the default covariance structure will be unstructured. Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point will be performed. The adjusted means for each treatment and the estimated treatment difference for the treatment comparison will be presented together with the 95% CI for the difference (FF/VI versus ICS/LABA comparator) and p-value at Week 24 (Visit 6). If non-inferiority is statistically achieved at Week 24 (Visit 6), then superiority of FF/VI versus any other comparator will be tested at the usual 0.05 two-sided nominal level of significance. The same models and analyses mentioned above will be used to assess the superiority hypothesis. **Other secondary analyses** The other key secondary endpoint will be the correct use of the inhaler device assessed at randomisation (Visit 2), at Week 12 (Visit 4) and at Week 24 (Visit 6). The device will be considered as correctly used if the patient didn't make any critical or non-critical errors at the corresponding visits (randomisation [Visit 2], Week 12 [Visit 4] and Week 24 [Visit 6]). Percentages of subjects correctly using the device will be calculated within each group. A corresponding 95% CI of the difference in percentages will also be provided. An exploratory analysis of the categorised data will be performed using logistic regression models with covariates as follows: randomised treatment, correct use of inhaler device at baseline, randomised treatment-by-visit interaction, gender, age and country. The estimated treatment differences will be displayed as odds ratios together with 95% CIs and p-values.

2. RAP AMENDMENTS

A summary of the amendments made to the RAP are listed here.

Amendment Details
RAP-HZA116492 [05-DEC-2016]
GSK2285997-116492 Statistical Analysis Plan Reporting and Analysis Plan (Amendment 1) Version 001 [21-AUG-2017]
Subjects with a missed or out of window Visit 4 will no longer lead to exclusion from the PP population.
Treatment compliance calculation now covers changes in dose.
Clarified age range to be used, multiple sections
Updated standard shell references in Section 12.15
Added time since last dose derivation.
Resolved discrepancies between main body and example shells for terms included in subgroup analyses
Clarified labelling: “Day 0” to be labelled as “Randomisation (Day 0)”
Clarified labelling for MARS-A subgroups
Other label ordering clarifications
Removed references to PCI values for Vital Signs and updated tables accordingly

3. SUMMARY OF KEY PROTOCOL INFORMATION

3.1. Changes to the Protocol Defined Statistical Analysis Plan

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

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• N/A	• The open-label study design and the method of recording study medication data in the datasets means that extra steps must be taken to ensure that S&P remain blinded to study investigator prescribing of study medication until the formal unblinding takes place at DBF. See Section 12.13 for more details.	• To preserve the integrity of the analyses, S&P will remain blinded prior to formal unblinding at DBF. All planned analyses will be carried out after this point.
• N/A	• **All Subjects Enrolled (ASE) Population:** All subjects screened (provided consent) and for whom a record exists on the study database. Note, this population is not identified in the protocol, but is needed for displays that include subjects screened but not in the ITT Population (e.g. tabulation of reasons for withdrawal before randomisation).	• Population needed for displays that include subjects screened but not in the ITT population.
• Continuous variables will be summarized using descriptive statistics (number of observed and missing data, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum). • Categorical variables will be summarized as numbers of observed and missing data, counts and percentage for each category (reported to the number of non-missing values). For binary variables, 95% confidence	• See Appendix 16: Example Mock Shells for Data Displays for example mock shells for data displays	• Continuous and categorical variables will be summarized in line with GSK Integrated Data Standards Library (IDSL) data standards

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
intervals for proportions will be estimated based on the Clopper-Pearson method.		
• If treatment is withdrawn, then the missing ACT score at the nearest visit after treatment withdrawal will be replaced by the ACT score assessed at withdrawal time. If no ACT score is assessed at withdrawal time, then the ACT missing score at the nearest visit after treatment withdrawal will not be replaced.	• Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point will be performed.	• The protocol inconsistently describes whether or not missing scores will be imputed. Consistent with MMRM models and the MAR assumption they are based upon, no missing data will be imputed for the primary efficacy analysis. Sensitivity analyses for the primary endpoint are proposed in Section 8.1.2 and will consider imputation of missing data.
• The primary endpoint will be analysed using a mixed model repeated measures (MMRM) approach. The model will include factors and covariates as follows: treatment, scheduled visit time point (Week 6 and Week 12), baseline ACT, treatment by visit interaction, baseline ACT by visit interaction, gender, age and patient will be fitted as a random factor.	• The primary endpoint will be analysed using a MMRM approach. The model will include factors and covariates as follows: randomised treatment, scheduled visit time point (Week 6 and Week 12), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient will be fitted as a random factor.	• Clarified that *randomised* treatment and baseline ACT *total score* will be included. Additionally country will be included in the model due to the addition of Germany, and separate randomisation schedules for France and Germany achieving stratification by country • Same changes for secondary and other analyses
• Sensitivity analyses (for the primary endpoint)	• Text changed and clarified	• The text from the protocol regarding sensitivity analyses has been updated and clarified where necessary. Description of the multiple imputation (MI) process has been brought in line with GSK standard text.
• Usual ICS/LABA maintenance therapy	• Usual ICS/LABA	• The comparator arm is described as “Usual ICS/LABA” for consistency with reporting of the HZA115150 study (GSK Document No.: 2011N129785_02).

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• EQ-5D	• EQ-5D-5L	• Clarity as to which version of the EuroQol questionnaire is being used
• Binary response defined as an ACT score ≥ 20 at a given visit OR a 3 point increase from baseline in ACT change. • The responder analyses will be conducted using a logistic regression model at a given Visit or Phone Call adjusting for treatment and stratification factors (baseline ACT score categorized into two classes, baseline asthma therapy, and potentially season at randomization). Treatment by stratification factors interaction effects will be further investigated in additional logistic models adjusting for these specific effects.	• This endpoint will be analysed using a logistic regression model adjusting for randomised treatment, gender, country, baseline ACT total score, baseline ACT total score squared and age	• Clarified that *randomised* treatment will be included. • Country will be included in the model due to the addition of Germany, and separate randomisation schedules for France and Germany achieving stratification by country • Due to this being a composite endpoint, a quadratic relationship is expected between baseline score and probability of response. Baseline ACT total score and baseline ACT total score squared will be included (instead of "baseline ACT score categorised into two classes") to account for this • All patients are on the same baseline asthma therapy class (ICS), therefore this will not be included as a covariate • Season at randomisation will not be included; this is only considered as sensitivity analysis for the primary efficacy endpoint
• N/A	• ≥ 3 point increase from baseline in ACT total score at Week 12 (Visit 4) and Week 24 (Visit 6) • Time to first severe asthma exacerbation	• These endpoints have been added for consistency with the HZA115150 study (GSK Document No.: 2011N129785_02).

3.2. Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
• To compare the efficacy of FF/VI 92 mcg/ 22 mcg or FF 184 mcg/22 mcg with usual fixed combinations ICS/LABA for asthma maintenance therapy at Week 12 (Visit 4).	• Change from baseline in the ACT total score at Week 12 (Visit 4).
Secondary Objectives	**Secondary Endpoints**
• To assess effect of FF/VI on asthma control compared with usual ICS/LABA fixed combination at Week 24 (Visit 6).	• Change from baseline in ACT score at Week 24 (Visit 6).
• To assess Ellipta™ inhaler correct use compared with other dry powder inhaler (DPI) (Diskus and Turbuhaler) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).	• Percentage of subjects with correct use of device (defined as not making any critical error or non-critical error) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).
Other Objectives	**Other Endpoints**
• To assess effect of FF/VI on trough (pre-dose) forced expiratory volume in 1 second (FEV1) compared with usual ICS/LABA fixed combination at Week 12 (Visit 4)	• Change from baseline in trough (pre-dose) FEV1 at Week 12 (Visit 4).
• To assess the effect of FF/VI on response to treatment at Week 12 (Visit 4) and Week 24 (Visit 6)	• ACT score ≥ 20 or ≥ 3 point increase from baseline in ACT at Week 12 (Visit 4) and Week 24 (Visit 6). Note: A 3 point increase in ACT total score was suggested as the Minimal Clinically Important Difference (MCID) in the literature (Schatz, 2009). • ACT score ≥ 20 at Week 12 (Visit 4) and Week 24 (Visit 6). • ≥ 3 Point Increase from Baseline in ACT Total Score at Week 12 (Visit 4) and Week 24 (Visit 6) • Change from baseline in individual question scores for ACT at Weeks 12, 24
• To assess the compliance with study medication and self-reported adherence to study medication at Week 12 (Visit 4) and Week 24 (Visit 6)	• Compliance with study medication from Randomisation (Day 0) to Week 12 (Visit 4), from Week 12 (Visit 4) to Week 24 (Visit 6) and from randomisation (Day 0) to Week 24 (Visit 6). • Score of the Medication Adherence Report Scale for Asthma (MARS-A) questionnaire at Randomisation (Day 0), Week 12 (Visit 4) and Week 24 (Visit 6).
• To assess the effect of FF/VI on severe asthma exacerbation over the study period	• Number of subject with at least 1 severe asthma exacerbation*, number of severe asthma exacerbation and annual severe exacerbation rate over the study period.

Objectives	Endpoints
	• Time to first severe asthma exacerbation
• To assess the effect of FF/VI on Health Related Quality of Life at Week 24 (Visit 6)	• Change from baseline in total score and domain scores of standardised Asthma Quality of Life Questionnaire (AQLQ[S]) at Week 24 (Visit 6). • An increase from baseline of ≥ 0.5 in AQLQ(s) total score at Week 24 (Visit 6). • An increase from baseline of ≥ 0.5 in AQLQ(s) environmental stimuli domain score at Week 24 (Visit 6). • Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) individual domain scores at Week 24 (Visit 6). • Change from baseline in total score and domain scores of AQLQ(S) at Week 24 (Visit 6). • Health status using the EuroQol Questionnaire (EQ-5D-5L) at Week 24 (Visit 6).
• To assess Patient Satisfaction and Preference assessment with different inhalers at Week 12 (Visit 4)	• Score of Patient Satisfaction and Preference Questionnaire (PASAP-Q) at Week 12 (Visit 4).
• To evaluate the Safety of FF/VI compared with usual ICS/LABA (FP/S and BUD/F).	• Serious Adverse Events (SAE) and non-serious Adverse Drug Reactions (ADR): o Frequency and type of SAEs, o Frequency and type of non-serious ADRs related to treatment.

* A severe asthma exacerbation will be defined as deterioration of asthma requiring the use of systemic corticosteroids[2] (tablets, suspension, or injection) for at least 3 days or an inpatient hospitalisation, or emergency department visit due to asthma that required systemic corticosteroids [1,2,3].

Notes defining endpoints:

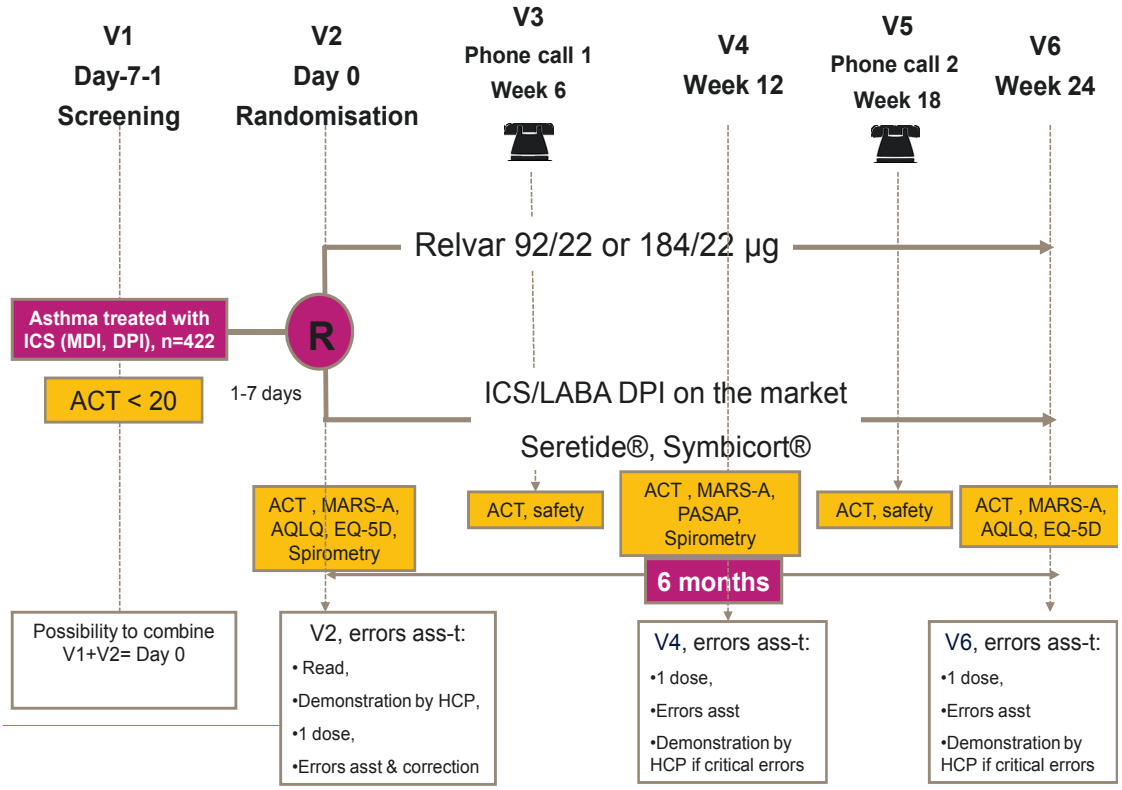
1. Contacts with a doctor or hospitalisation are defined as exacerbation-related contacts if these contacts were a direct result of an acute worsening of asthma symptoms.

2. A prescription of systemic corticosteroid is defined as exacerbation-related if the reason the drug was given, in whole or in part, was to treat an acute worsening of asthma symptoms.

3. Exacerbation-related hospitalisation includes hospitalisation that is prolonged as a result of an asthma exacerbation.

Overview of Study Design and Key Features

HZA 116492: study design



- A phone call is provided at Week 6 and Week 18 in order to check whether the subject has experienced any AEs and then the Investigator calling the patient must determine whether the event is related to study medication (either arm) and whether the event is serious. At these telephone calls subjects will also be asked to complete the ACT questionnaire and to send it back to the Investigator.

- Week 12 (Visit 4) should be scheduled at the same time of day as the randomisation visit (Visit 2).

Design Features	• This is a Phase IIIb multi-center randomised open label, parallel group study performed in subjects in primary and respiratory specialist care / research sites who have a diagnosis of asthma and a regular treatment for asthma. • Subjects with unsatisfactorily controlled asthma (defined as ACT total score < 20) and intended to be treated by usual ICS/LABA maintenance therapy to seek a better control of their asthma will be randomised to receive either FF/VI once daily or another usual ICS/LABA combination therapy in inhalation powder twice daily (FP/S or BUD/F) decided by the physician.

Overview of Study Design and Key Features

Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomisation schedule.

Subjects will be randomised in a 1:1 ratio to one of the 2 following treatment groups:

FF/VI (as per dose guidance below)

Initiate on usual inhaled dry powder ICS/LABA fixed combination for asthma maintenance therapy (i.e. Seretide Diskus or Symbicort Turbuhaler) according to usual physician's prescription.

Dose Guidance:

For subjects randomised to FF/VI, Investigator can make dosing decision based on the guidance below:

- FF/VI 92 mcg/22mcg dose once a day is approximately equivalent to FP/S medium dose (250 mcg/50mcg) and BUD/F medium dose (200 mcg/6 mcg) twice a day. See Table 2 for further guidance for doses conversion for other corticosteroids.
- FF/VI 184 mcg/22 mcg dose once a day is approximately equivalent to FP/S high dose (500 mcg/50 mcg) and to BUD/F high dose (400 mcg/12 mcg) twice a day. See Table 2 for guidance for dose conversion for other corticosteroids.
- Starting doses are: 92 mcg/22 mcg once daily for FF/VI; 250 mcg/50 mcg twice daily for FP/S and 200 mcg/6 mcg twice daily for BUD/F.

Table 2 ICS/LABA Daily Dose (SmPC Seretide Diskus; Symbicort Turbuhaler)

Formulation	Inhaler Devices	Doses Available (mcg) ICS/LABA and Inhalations/day
Fluticasone propionate/salmeterol	DPI (Diskus)	1 inhalation x 2 Medium-dose 250/50 High-dose 500/50
Budesonide/formoterol	DPI (Turbuhaler)	1-2 inhalations x 2 Medium-dose 200/6 High-dose 400/12

Information extracted from Global Initiative for Asthma (GINA, 2012).

For patients with moderate to severe hepatic impairment, the 92/22 micrograms dose of FF/VI should be used and patients should be monitored for systemic corticosteroid-related adverse reactions.

Overview of Study Design and Key Features	
	Planned Dose Adjustments Subjects for whom it is considered appropriate/necessary to adjust treatment can have their dose increased from the starting dose as would be normal clinical practice at the Investigator's discretion. This will not require the subject to be withdrawn from the study. It is not permitted for patients to be switched to a different treatment i.e. patients randomised to the usual ICS/LABA arm cannot change to a different ICS/LABA or receive FF/VI. Patients randomised to the FF/VI arm cannot receive usual ICS/LABA. If a switch between products is required, the patient should be withdrawn from the study.
Interim Analysis	No interim analysis is planned for this study.

From this point onwards in the RAP, usual ICS/LABA maintenance therapy will be referred to as usual ICS/LABA.

3.3. Statistical Hypotheses

The primary endpoint is defined as the change from baseline in the ACT total score assessed at Week 12 (Visit 4). The primary analysis will assess the non-inferiority of fixed combination FF/VI to usual ICS/LABA in inhalation powder assuming a non-inferiority margin of 1.5. Non-inferiority will be claimed if the 95% two-sided confidence interval on the difference in mean primary efficacy endpoints (FF/VI versus usual ICS/LABA) precludes the non-inferiority margin of -1.5.

If (and only if) non-inferiority is significantly achieved at Week 12 (Visit 4) with regard to the primary endpoint, then non-inferiority of the fixed combination FF/VI to usual ICS/LABA will be tested at Week 24 (Visit 6) considering the same non-inferiority margin of 1.5. Non-inferiority will be claimed if the 95% two-sided confidence interval on the difference in mean primary efficacy endpoints (FF/VI versus usual ICS/LABA) at Week 24 (Visit 6) precludes the non-inferiority margin of -1.5.

Of note, as the two tests for non-inferiority are sequentially performed, the closure principle holds and there is no need to adjust the two-sided nominal level of significance (i.e. 0.05) for each test.

3.4. Sample Size Assumptions

Results based on the HZA106829 study have shown that the estimated SD of the change in ACT score was 3.7. Unpublished data have shown that the standard deviation of change of ACT ranged from 3.8 to 4.8. Therefore, a somewhat conservative choice of SD of 4.5 point is retained.

Based on the literature (Schatz, 2009), the Minimally Important Difference (MID) of the ACT could be considered as 3 points. Half this MID (i.e. 1.5) could therefore be used to define the non-inferiority margin.

Assuming a 4.5 point standard deviation for the change in ACT total score at Week 12 (Visit 4), a 1.5 point non-inferiority margin, and a two-sided nominal significance level of 0.05, the sample size needed per group to achieve at least a 90% power is 191 (i.e. a total of 382 subjects).

Assuming a 10% dropout rate, around 422 subjects must be randomized either to FF/VI or to usual ICS/LABA in 1:1 ratio to achieve at least a 90% power.

4. PLANNED ANALYSES

4.1. Interim Analyses

Not applicable.

4.2. Data Look

At a date agreed by the study team and the contract research organisation (CRO) (selected to execute the statistical analyses specified in this RAP), a data look will be performed using blinded treatment codes on a subset of the data. The aim of the data look is solely to ensure that all of the required tables, figures and listings are being produced and formatted correctly, such that the output produced on unblinded data at the end of the study is correct and complete. This data look will be performed when sufficient data are available, but early enough to leave time for changes to be made to the planned outputs and methods prior to database release (DBR). Any changes will be documented before DBR.

4.3. Final Analyses

All planned analyses will be performed after the completion of the following sequential steps:

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

5. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	• Comprise of all subjects screened (provided consent) and for whom a record exists on the study database. • Note, this population is not identified in the protocol, but is needed for displays that include subjects screened but not in the ITT Population (e.g. tabulation of reasons for withdrawal before randomisation)	• Subject disposition tables
Intent-to-Treat (ITT)	• Comprise of all randomized subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA) • Subjects will be assigned to the treatment group as randomized for the ITT population	• Study Population • Efficacy
Per Protocol (PP)	• Comprise of all randomized subjects who receive at least one dose of study treatment and who comply with the protocol. • Protocol deviations that would exclude subjects from the PP population are defined in Section 5.1 (Protocol Deviations) and Appendix 1 (Protocol Deviation Management and Definition for Per-Protocol Population).	• This population will be used for summaries and re-analyses of the primary efficacy secondary efficacy endpoints.
Safety	• Comprise of all enrolled subjects having received at least one dose of study medication (either FF/VI or usual ICS/LABA) and considered as-treated. • Subjects will be assigned to the treatment group as treated for the Safety population	• Safety

NOTES:

- Please refer to Appendix 15: List of Data Displays which details the population to be used for each displays being generated.

5.1. Protocol Deviations

All PDs (any deviation from the protocol) are tracked and monitored during the study. Important PDs are those deviations that may compromise subject rights, safety, or well-being, and/or data integrity, and/or study end-points, and are defined in the protocol deviation management plan (PDMP). Apart from any incorrect treatment deviations, all protocol deviations will be agreed upon prior the unblinding and the freezing of the database. All deviations from the inclusion/exclusion criteria, and important PDs will be summarised. A listing of treatment misallocations will be produced.

6. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 3 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 3 Overview of Appendices

Section	Component
12.1	Appendix 1: Protocol Deviation Management and Definitions for PP Population
12.2	Appendix 2: Time & Events
12.3	Appendix 3: Assessment Windows
12.4	Appendix 4: Treatment States and Phases
12.5	Appendix 5: Data Display Standards & Handling Conventions
12.6	Appendix 6: Derived and Transformed Data
12.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
12.8	Appendix 8: Values of Potential Clinical Importance
12.9	Appendix 9: Multicenter Studies
12.10	Appendix 10: Examination of Covariates, Subgroups & Other Strata
12.11	Appendix 11: Multiple Comparisons & Multiplicity
12.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses
12.13	Appendix 13: Blinding Strategy
12.14	Appendix 14: Abbreviations & Trade Marks
12.15	Appendix 15: List of Data Displays
12.16	Appendix 16: Example Mock Shells for Data Displays

7. STUDY POPULATION ANALYSES

7.1. Overview of Planned Analyses

The study population analyses will be based on the ITT population, unless otherwise specified.

Table 4 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 15: List of Data Displays.

Table 4 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Populations	Y[1]		Y
Inclusion/exclusion Criteria Failures for Subjects Not Starting Treatment	Y[1]		
End of Study Record	Y[2]		Y
Attendance at Each Clinic Visit and Phone Call Visit	Y		
Number of Subjects by Country and Centre	Y[2,3]		
Randomised and Actual Treatments			Y
Protocol Deviations			
Deviations from the Inclusion/Exclusion Criteria	Y		Y
Important Protocol Deviations	Y		Y
Important Protocol Deviations Resulting in Exclusion from the PP Population	Y		Y
Treatment Misallocations			Y
Demographic and Baseline Characteristics			
Demographic Characteristics	Y[2,4]		Y
Race and Racial Combinations	Y		Y
Race and Racial Combinations Details	Y		
Current and Past Medical Conditions	Y		
Asthma Duration at Baseline	Y[2]		Y
Asthma Exacerbation History at Baseline	Y[2]		Y
Lung Function at Baseline	Y		
Smoking History at Baseline	Y[2]		Y
Concomitant Medications			
Pre-Treatment Concomitant Medications	Y		Y
On-Treatment Concomitant Medications	Y		Y
On-Treatment Asthma Concomitant Medications	Y		
Relationship between Ingredient and Verbatim Text			Y
Exposure and Medication Modifications			
Study Medication Dosage Modification	Y		
Extent of Exposure to Study Medication (Regardless of Modification to Study Medication Dosage)	Y	Y	Y
Extent of Exposure to Study Medication (up to First Modification of Study Medication Dosage)	Y		
Extent of Exposure to Study Medication by Medication and Dosage	Y		
Number of Subjects by Subgroup	Y		

NOTES:

- Y = Yes display generated.
- [1] Display will be based on ASE population
- [2] Display will be repeated for the PP population
- [3] Display will be repeated for the ASE population
- [4] Display will be repeated for the Safety population

8. PRIMARY STATISTICAL ANALYSES

8.1. Efficacy Analyses

8.1.1. Overview of Planned Efficacy Analyses

The primary efficacy analyses will be based on the ITT population and repeated for the PP population, unless otherwise specified.

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

Table 5 Overview of Planned Efficacy Analyses

Endpoint	Data displays generated						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
ACT Total Score							
Change from Baseline in the ACT Total Score at Week 12 (Visit 4)	Y[1,2,3,4,5,6,7]			Y[1,2,3,4,5,7]	Y[1]		Y[8]

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- Display will be repeated for the following subgroups (ITT only) (see Section 12.10 for more details):
  - [1]: Country
  - [2]: Number of severe asthma exacerbations in the previous year prior to randomisation
  - [3]: Smoking status at baseline
  - [4]: Age group
  - [5]: Gender
- [6] Sensitivity analyses will be produced for the following approaches:
  - Last observation carried forward (LOCF) (ITT only)
  - MI analyses utilizing covariates (ITT only)
  - Semi-parametric Hodges-Lehmann (HL) approach (ITT only)
  - Worst observation carried forward (WOCF) for treatment withdrawals (ITT only)
  - Adjusting for seasonal effect
- [7] Display will be repeated for:
  - FF/VI versus the subset of Usual ICS/LABA subjects prescribed FP/S at randomisation (only if ≥25% of Usual ICS/LABA patients are prescribed FP/S at randomisation)
  - FF/VI versus the subset of Usual ICS/LABA subjects prescribed BUD/F at randomisation (only if ≥25% of Usual ICS/LABA patients are prescribed BUD/F at randomisation)
- [8] Display will be produced for the ITT population only.

8.1.2. Planned Efficacy Statistical Analyses

Primary Statistical Analyses

Endpoint(s)

- Change from Baseline in the ACT Total Score at Week 12 (Visit 4)

Model Specification

- The primary endpoint will be performed on both the ITT and the PP populations, and analysed using an MMRM model utilizing the REML estimation approach and a default covariance structure of unstructured
- Terms fitted in the model will include:

Response	: Change from Baseline in ACT Total Score
Fixed Categorical	: Randomised treatment, visit (Week 6 and Week 12), gender, country
Fixed Continuous	: Baseline ACT total score, age
Interaction terms	: Randomised treatment-by-visit, baseline ACT total score-by-visit
Random effect	: Subject

SAS Code to Perform Analysis

```
proc mixed data=input_data;
        class trtcd gender country visit subjid ;
        model ACT = trtcd gender country age baseline
                        visit visit*baseline visit*trtcd / ddfm=kr ;
        repeated visit / subject=subjid type=un ;
        random intercept / subject=subjid ;
        lsmeans visit*trtcd / cl diff e om=OMdset at (baseline age)=(&blm. &agem.) ;
run ;
```

where OMdset is a dataset with a row for every visit-subject combination that contains all of the covariates and blm and agem are macro variables containing the means for baseline and age for the subjects used in the analysis. These are used to derive the adjusted means using coefficients which are based on the subjects used in the analysis.

Model Checking & Diagnostics

- Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- For Week 12 (Visit 4), the adjusted (least squares [LS]) mean change from baseline for each treatment and the estimated treatment difference for FF/VI versus Usual ICS/LABA (i.e. the difference in LS mean change from baseline) will be presented together with the associated 95% CI and p-value.
- Summary statistics will be produced for absolute value of and change from baseline in ACT total score at each post-baseline visit (Week 6 [Visit 3], Week 12 [Visit 4], Week 18 [Visit 5] and Week 24 [Visit 6]).
- A listing of ACT total and change from baseline scores will be provided.
- Mean ACT total score ± SD will be plotted by visit.

Subgroup Analyses

- For the analyses by country (France, Germany) and gender (male, female), the model will additionally include the randomised treatment-by-subgroup and randomised treatment-by-subgroup-by-visit interactions as a covariate.
    - For the analyses by number of severe asthma exacerbations in the previous year prior to randomisation (0, >1) and smoking status at baseline (Current smoker, Former smoker and Never smoked), the model will additionally include the subgroup, randomised treatment-by-subgroup interaction and randomised treatment-by-subgroup-by-visit interaction as covariates.
- For the analysis by age group (≤50 years, >50 years), the continuous covariate age will be replaced by age group, randomised treatment-by-age group interaction and randomised treatment-by-age group-by-visit interaction.

Sensitivity and Supportive Statistical Analyses

Justification for Sensitivity Analyses Handling Missing Data

- While subjects missing Week 12 (Visit 4) data but having earlier data will be included in the MMRM primary analysis, the interpretability of the results from the primary model will depend on the missing data satisfying the Missing at Random (MAR) assumption. To support the validity of the conclusions drawn from this analysis, several sensitivity analyses will be performed to explore the dropout pattern and its possible impact on treatment comparisons. These sensitivity analyses will be performed on the ITT population only.

Last Observation Carried Forward

- Missing values at Week 12 (Visit 4) will be replaced by the last available post-randomization value (either the Week 6 (Visit 2) ACT score or the ACT score at treatment withdrawal time, if applicable), i.e. based on the LOCF method. The change from baseline in ACT at Week 12 (Visit 4) will be analyzed using an analysis of covariance (ANCOVA) model adjusting for randomised treatment, baseline ACT score, gender, country and age. For Week 12 (Visit 4), the LS mean change from baseline for each treatment and estimated LS mean change from baseline difference for FF/VI versus Usual ICS/LABA will be presented together with the associated 95% CI and p-value.

Multiple Imputation

- Sensitivity analyses will be performed using MI methods based on pattern mixture models. First, a repeated measures Normal model will be fitted to the data using a Bayesian approach, with non-informative priors for the mean and variance-covariance matrix to provide a joint posterior for the parameters in this model. The repeated measures Normal model will include separate mean profiles for each treatment group and the same covariates as those in the primary efficacy analysis.
- Independent samples will then be drawn from the posterior distributions for the mean and variance-covariance matrix to provide inputs into an imputation model. For each subject with missing data, these sampled values of the parameters for mean vectors and the variance-covariance matrices specify a joint distribution for their observed and unobserved outcome data.
- The post-withdrawal part of each pattern-specific distribution will be modelled using the approach discussed below. This imputation model will have the same covariates as those in the primary efficacy analysis.
- Based on this imputation model, a single set of data will be sampled for the missing data based on the distribution for the subject's missing data conditional upon their observed data. Each imputed data set will then be analysed using simple ANCOVA at Week 12 (Visit 4) and the resulting treatment differences and their standard errors combined using Rubin's rules.
- The post-withdrawal part of each pattern-specific distribution will be modelled using these two approaches:
    - MAR Approach. The means and variance-covariances following withdrawal are chosen to reflect the subject's own treatment group. This approach will provide similar results to using a mixed effects model where the unstructured covariance matrix is estimated separately for each arm, and all covariates are crossed with treatment. As such it is not truly a sensitivity analysis as we expect to get very similar results. Like the MMRM this answers an on-treatment question.
    - Copy Differences from Reference Approach. This approach addresses a potential pattern of informative missingness, in which subjects withdrawn from the test groups would have followed the same trend over time (difference in mean value between time-points) as those in the reference group, had they continued in the study. Therefore, this approach may be considered conservative because it will assume that following withdrawal from a test treatment arm, imputation for their missingness will be derived from observed reference data. The intention is to represent an ITT-like approach.
- For each method, the LS mean change from baseline at Week 12 (Visit 4) for each treatment and estimated LS mean change from baseline difference for FF/VI versus Usual ICS/LABA will be presented together with the associated 95% CI and p-value.

Sensitivity and Supportive Statistical Analyses
Hodges-Lehmann Approach
• A sensitivity analysis based on the semi parametric HL approach will be proposed to assess the robustness of the MMRM Model-based non-inferiority results. The HL difference between groups at Week 12 (Visit 4) and corresponding 95% CI will be provided.
Worst Observation Carried Forward
• When treatment withdrawal occurs, an alternative method for imputing the missing value at the nearest visit after withdrawal time will be proposed: the primary endpoint missing value will be estimated by the worst ACT score observed between baseline visit and withdrawal time, inclusive – i.e. using the WOCF method. An ANCOVA model adjusting for randomised treatment, baseline ACT score, gender, country and age will be used to analyse this imputed data, with the LS mean change from baseline for each treatment presented at Week 12 (Visit 4) together with the estimated LS mean change from baseline difference and associated 95% CI
Summary of Sensitivity Statistical Analyses
• A plot will be produced displaying the treatment differences and 95% CIs for the primary analysis and each of the sensitivity analyses described above.
Seasonal effect
• A sensitivity analysis adjusting for seasonal effect will be performed by repeating the primary efficacy analysis with the addition of season at randomisation, season-by-visit, randomised treatment-by-season at randomisation interaction and randomised treatment-by-season at randomisation-by-visit interaction. See Section 12.10.3 for the definition of season at randomisation. The LS mean change from baseline at Week 12 (Visit 4) for each treatment and estimated LS mean change from baseline difference will be displayed for each season at randomisation together with the associated 95% CI and p-value, and the interaction p-value.

9. SECONDARY STATISTICAL ANALYSES

9.1. Efficacy Analyses

9.1.1. Overview of Planned Efficacy Analyses

The secondary efficacy analyses will be based on the ITT population, unless specified otherwise.

Table 6 provides an overview of the planned efficacy analyses, with further details of data displays being presented in Appendix 15: List of Data Displays.

Table 6 Overview of Planned Efficacy Analyses

Endpoint	Data displays generated						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
ACT Total Score							
Change from Baseline in the ACT Total Score at Week 24 (Visit 4)	Y[1,2,3,4]	Y		Y[1,2,4,5,6,7,8]	Y[1,2]		
Correct Use of Device							
Percentage of Subjects with Correct Use of Inhaler Device at Week 12 (Visit 4) and at Week 24 (Visit 6) Independently of the Use at Week 12 (Visit 4)	Y[1]			Y[1]			Y

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1] Display will be repeated for the PP population
- [2] Display will be repeated by Country (ITT only)
- [3] Sensitivity analyses will be produced for the following approaches:
  - LOCF (ITT only)
  - MI analyses utilizing covariates (ITT only)
  - Semi-parametric HL approach (ITT only)
  - WOCF for treatment withdrawals (ITT only)
  - Adjusting for seasonal effect
- [4] Display will be repeated for:
  - FF/VI versus the subset of Usual ICS/LABA subjects prescribed FP/S at randomisation (only if ≥25% of Usual ICS/LABA patients are prescribed FP/S at randomisation)
  - FF/VI versus the subset of Usual ICS/LABA subjects prescribed BUD/F at randomisation (only if ≥25% of Usual ICS/LABA patients are prescribed BUD/F at randomisation)
- Display will be repeated for the following subgroups (ITT only) (see Section 12.10 for more details):
  - [5]: Number of severe asthma exacerbations in the previous year prior to randomisation
  - [6]: Smoking status at baseline
  - [7]: Age group
  - [8]: Gender

9.1.2. Planned Efficacy Statistical Analyses

Secondary Statistical Analyses
Endpoint(s)
• Change from Baseline in the ACT Total Score at Week 24 (Visit 6)
Model Specification
• This endpoint will be performed on both the ITT and the PP populations, and analysed using an MMRM model utilizing the REML estimation approach and a default variance-covariance structure of unstructured • Terms fitted in the model will include: Response : Change from Baseline in ACT Total Score Fixed Categorical : Randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), gender, country Fixed Continuous : Baseline ACT total score, age Interaction terms : Randomised treatment-by-visit, baseline ACT total score-by-visit Random effect : Subject
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• For Week 24 (Visit 6), the LS mean change from baseline for each treatment and the estimated difference in LS mean change from baseline for FF/VI versus Usual ICS/LABA will be presented together with the associated 95% CI and p-value. • Summary statistics, a listing and plots of mean ACT total score ± SD will be produced as part of the primary efficacy endpoint analysis (see Section 8.1.2).
Subgroup Analysis
• For the analysis by country (France, Germany), the model will additionally include the randomised treatment-by-country, country-by-visit and randomised treatment-by-country-by-visit interactions as a covariate.

Sensitivity and Supportive Statistical Analyses
• The same sensitivity analyses as those described for the primary endpoint will be performed for the key secondary endpoint of change from baseline in the ACT total score at Week 24 (Visit 6) .

Secondary Statistical Analyses
Endpoint(s)
• Percentage of subjects with correct use of inhaler device at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4)
Model Specification
• These endpoints will be analysed for both the ITT and the PP populations using logistic regression models • Terms fitted in the model will include: Response : Endpoint Fixed Categorical : Randomised treatment, correct use of inhaler device at baseline, gender, country Fixed Continuous : Age
SAS Code to Perform Analysis

proc logistic data=input_data plots=(all);
class trtcd country baseline gender / ref=first param=ref;
model corr_use (event="Y") = trtcd baseline age gender country;
contrast "Trt_effect" trtcd 1 / estimate=exp;
run;

Secondary Statistical Analyses
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• The number and percentage of subjects with correct use within each randomised treatment group will be presented by visit, together with the adjusted odds ratio comparing FF/VI with Usual ICS/LABA, associated p-value and 95% CI. • A summary and listing of correct use / errors of inhaler use will be produced.

9.2. Safety Analyses

9.2.1. Overview of Planned Analyses

The safety analyses will be based on the Safety population.

Table 7 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 15: List of Data Displays.

Table 7 Overview of Planned Safety Analyses

Endpoint	Data displays generated					
	Stats Analysis		Summary		Individual	
	T	F	T	F	F	L
Adverse Events						
SAEs and ADRs Overview			Y			
Non-Serious ADRs			Y			Y
Serious ADRs			Y			
All ADRs			Y			
SAEs			Y			Y
SAEs and ADRs Leading to Permanent Discontinuation of Study Medication or Withdrawal from Study			Y			Y
SAEs Leading to Permanent Discontinuation of Study Medication or Withdrawal from Study			Y			
ADRs Leading to Permanent Discontinuation of Study Medication or Withdrawal from Study			Y			
Non-Serious ADRs Leading to Permanent Discontinuation of Study Medication or Withdrawal from Study						Y
Most Frequent Non-Serious ADRs, Reported by ≥1% or More of Subjects in Any Treatment Group			Y			
Non-Serious ADRs of Special Interest			Y			
Serious ADRs of Special Interest			Y			
All ADRs of Special Interest			Y			
SAEs of Special Interest			Y			
Fatal SAEs			Y			Y
Fatal Serious ADRs			Y			
Fatal SAEs of Special Interest			Y			
Non-Fatal SAEs			Y			Y
Non-Fatal SAEs of Special Interest			Y			
AE terms of Special Interest						Y
Top Ten Most Commonly Reported On-treatment ADRs per Treatment Group			Y			
Vital Signs						
Vital Signs			Y			Y

Endpoint	Data displays generated					
	Stats Analysis		Summary		Individual	
	T	F	T	F	F	L
Inhaler Device Malfunctions						
Inhaler Device Malfunctions						Y
Liver chemistry						
Liver event						Y
Liver biopsy						Y
Liver imaging						Y
Other						
Pregnancy						Y

NOTES:

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

9.2.2. Benefit:Risk analyses

Benefit:Risk analyses will be based on the ITT population for Benefit, and Safety population for Risk.

Table 8 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 15: List of Data Displays.

Table 8 Overview of Planned Benefit:Risk Analyses

Endpoint	Data displays generated				
	Stats Analysis		Summary		Individual
	T	F	T	F	L
Summary of Benefit:Risk		Y			

NOTES:

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

Benefit Risk Statistical Safety Analyses
Endpoint(s)
• Summary of Benefit:Risk: various endpoints analyses in the context of safety and effectiveness analyses
Model Specification
• Estimates and their 95% CIs obtained from selected safety and effectiveness analyses will be presented for the ITT population on a multiple panel forest plot which will display effectiveness and safety data. • For certain endpoints, the x-axis may be reversed to ensure benefit/risk to either FF/VI or Usual ICS/LABA is shown accurately. • Due to endpoints being presented using different scales, the forest plot will be split into additional panels to allow better visibility of the results.

Benefit Risk Statistical Safety Analyses
Model Checking & Diagnostics
• Model checking and diagnostics are described in each endpoint analysis section.
Model Results Presentation
• The top panel ("Benefits") of the forest plot will display: o difference in LS mean change from baseline from the MMRM analysis of the primary efficacy endpoint, defined as the change from baseline in ACT total score at Week 12 (Visit 4), as described in Section 8.1.2 o difference in LS mean change from baseline from the MMRM analysis of the change from baseline in ACT total score at Week 24 (Visit 6), as described in Section 9.1.2 o adjusted odds ratio from the logistic regression analysis of percentage of subjects with correct use of inhaler device at Week 12 (Visit 4), as described in Section 9.1.2 o adjusted odds ratio from the logistic regression analysis of percentage of subjects with correct use of inhaler device at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4), as described in Section 9.1.2 • The bottom panel ("Risks") of the forest plot will display the risk difference for FF/VI vs. usual ICS/LABA of the incidence of the following SAEs of special interest: o Asthma/bronchospasm, cardiovascular effects, decreased bone mineral density and associated fractures, hypersensitivity, local steroid effects, lower respiratory tract infection (LRTI) excluding pneumonia, pneumonia, adrenal suppression, ocular effects, effects on glucose, effects on potassium, tremor

10. OTHER STATISTICAL ANALYSES

10.1. Other Analyses

10.1.1. Overview of Planned Other Analyses

The other statistical analyses will be based on the ITT population, unless otherwise specified.

Table 9 provides an overview of the planned other analyses, with full details of data displays being presented in Appendix 15: List of Data Displays.

Table 9 Overview of Planned Other Analyses

Endpoint	Absolute						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Trough (Pre-dose) FEV1							
Change from Baseline in Trough (Pre-dose) FEV1 at Week 12 (Visit 4)	Y			Y			Y
ACT							
ACT Total Score ≥ 20 or ≥ 3 Point Increase from Baseline in ACT Total Score at Week 12 (Visit 4) and Week 24 (Visit 6)	Y			Y	Y		
ACT Total Score ≥ 20 at Week 12 (Visit 4) and Week 24 (Visit 6)				Y	Y		
≥ 3 Point Increase from Baseline in ACT Total Score at Week 12 (Visit 4) and Week 24 (Visit 6)				Y	Y		
Change from Baseline in Individual ACT Questions at Week 12 (Visit 4) and Week 24 (Visit 6)				Y			
Compliance with Study Medication							
Compliance with Study Medication from Randomisation (Day 0) to Week 12 (Visit 4), from Week 12 (Visit 4) to Week 24 (Visit 6) and from Randomisation (Day 0) to Week 24 (Visit 6)				Y[1]	Y		Y

Endpoint	Absolute						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
MARS-A Score at Randomisation (Day 0), Week 12 (Visit 4) and Week 24 (Visit 6).				Y[2]	Y[2]		Y
Severe asthma exacerbations							
Number of Subjects With at Least 1 Severe Asthma Exacerbation and Number of Severe Asthma Exacerbations				Y[3]			Y
Annual Severe Asthma Exacerbation Rate over the Study Period	Y	Y					
Time to First Severe Asthma Exacerbation	Y	Y					
Asthma Quality of Life Questionnaire (AQLQ[S])							
Change from Baseline in Total Score and Domain Scores of AQLQ(S) at Week 24 (Visit 6)				Y			Y
An Increase from Baseline of ≥ 0.5 in AQLQ(s) Total Score at Week 24 (Visit 6)	Y			Y			
An Increase from Baseline of ≥ 0.5 in AQLQ(s) Environmental Stimuli Domain Score at Week 24 (Visit 6)	Y			Y			
An Increase from Baseline of ≥ 0.5 in AQLQ(S) Individual Domain Scores (Symptoms, Activity limitations and Emotional Function) at Week 24 (Visit 6)				Y			
EQ-5D-5L							
EQ-5D-5L Descriptive System Dimensions at Week 24 (Visit 6)	Y			Y			Y
EQ-5D-5L Utility Score at Week 24 (Visit 6)	Y			Y			Y
EQ-5D-5L Visual Analogue Scale (VAS) Score at Week 24 (Visit 6)	Y			Y			Y

Endpoint	Absolute						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
PASAP-Q							
PASAP-Q Scores at Week 12 (Visit 4)				Y			Y

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1] Display will be repeated for the PP population
- [2] A reminder was sent to centres in France instructing that the MARS-A questionnaire refers to the patient's preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study). See Section 12.6.3 for further details. Display will be repeated split by:
  - Patients in France, all MARS-A assessments completed pre-reminder
  - Patients in France, some MARS-A assessments completed pre-reminder, some post-reminder
  - Patients in France, all MARS-A assessments completed post-reminder
  - Patients in Germany
- [3] Display will be repeated by season.

10.1.2. Planned Other Statistical Analyses

Other Statistical Analyses

Endpoint(s)

- Change from baseline in trough (pre-dose) FEV1 at Week 12 (Visit 4)
- Change from baseline in EQ-5D-5L Utility Score at Week 24 (Visit 6)
- Change from baseline in EQ-5D-5L VAS Score at Week 24 (Visit 6)

Model Specification

- These endpoints will be analysed for the ITT population using ANCOVA models
- Terms fitted in the model will include:

Response	: Endpoint
Fixed Categorical	: Randomised treatment, gender, country
Fixed Continuous	FEV1 endpoint: Baseline trough (pre-dose) FEV1 and age EQ-5D-5L Utility Score endpoint: Baseline EQ-5D-5L Utility Score and age EQ-5D-5L VAS Score endpoint: Baseline EQ-5D-5L VAS Score and age

Model Checking & Diagnostics

- Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.

SAS Code to Perform Analysis

```
proc mixed data=input_data;
        class trtcd gender country;
        model FEV1 = trtcd gender country age baseline  / ddfm=kr ;
        lsmeans trtcd / cl diff e;
run ;
```

Model Results Presentation

- The LS mean change from baseline for each treatment and the difference in estimated LS mean change from baseline for FF/VI versus Usual ICS/LABA will be presented together with the associated 95% CI and p-value.
- Summary statistics.
- Listings will be provided.

Other Statistical Analyses	
Endpoint(s)	
• Percentage of subjects who had either an ACT total score ≥ 20 or ≥ 3 point increase from baseline in ACT total score at Week 12 (Visit 4) and Week 24 (Visit 6) • Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) total score at Week 24 (Visit 6) • Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) environmental stimuli domain score at Week 24 (Visit 6) • Percentage of subjects with 'no problems' in each dimension of the EQ-5D-5L questionnaire at Week 24 (Visit 6)	
Model Specification	
• These endpoints will be analysed for the ITT population using logistic regression models • Terms fitted in the model will include:	
Response	: Endpoint
Fixed Categorical	: Randomised treatment, gender, country
Fixed Continuous	ACT endpoints: Baseline ACT total score, baseline ACT total score squared and age AQLQ(S) endpoints: Baseline AQLQ(S) score and age EQ-5D-5L endpoints: Baseline EQ-5D-5L dimension score and age
Model Checking & Diagnostics	
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.	
Model Results Presentation	
• The number and percentage of subjects with a response within each randomised treatment group will be presented by visit, together with the adjusted odds ratio comparing FF/VI with Usual ICS/LABA, associated 95% CIs and p-values. • The number and percentage of subjects with ACT total score ≥20 or ≥3 point increase from baseline in ACT total score will be summarized by visit to include the tabulations of frequencies together and separately. • The number and percentage of subjects with an increase from baseline of ≥ 0.5 in AQLQ(S) total and individual domain scores at Week 24 (Visit 6) will be summarized. • The responses to each EQ-5D-5L dimension will be descriptively summarised	

Other Statistical Analyses	
Endpoint(s)	
• Annual severe asthma exacerbation rate over the study period	
Model Specification	
• This endpoint will be analysed for the ITT population using a generalised linear model (GLM), assuming the Negative Binomial distribution • Terms fitted in the model will include:	
Response	: Annual severe asthma exacerbation rate over the study period
Fixed Categorical	: Randomised treatment, gender, country, number of severe asthma exacerbations in the previous year prior to randomisation (0, ≥1)
Fixed Continuous	: Age
Offset variable	: Logarithm of time on treatment
Model Checking & Diagnostics	
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.	

Other Statistical Analyses
SAS Code to Perform Analysis

proc genmod data=input_data;
class trtcd gender country;
model no_exac = trtcd exacbl gender country age / dist=negbin link=log offset=log_tm type3;
lsmeans trtcd /cl diff=control("0") om exp;
run;

Model Results Presentation
• The LS mean number / annual rate, adjusted treatment ratio and associated 95% CI and p-value will be presented. • Percentage reduction in mean number / annual rate and associated 95% CI will also be presented. • The severe asthma exacerbation data will be summarized to include the tabulations of exacerbation frequencies, exacerbation duration (days) and the outcome, the prescription of oral corticosteroids and/or antibiotics to treat exacerbations, hospitalisations and emergency department visits due to an exacerbation, intubations due to an exacerbation and withdrawal of IP or withdrawal from the study as a result of an exacerbation. • A listing of severe exacerbations will be provided. • Box plots will be provided for the severe annual exacerbation rates.

Other Statistical Analyses
Endpoint(s)
• Time to first severe asthma exacerbation
Model Specification
• The cumulative distribution of this endpoint will be illustrated for the ITT population using Kaplan-Meier estimates and evaluated using the Wald Chi-Square test based on a Cox proportional hazards model. • The analyses and summaries will include on-treatment exacerbations, from start date of exposure to min(stop date of exposure + 1 day, date of study discontinuation). • The exact method for handling ties in times will be used. • Terms fitted in the model will include: Response : Time to first severe asthma exacerbation Fixed Categorical : Randomised treatment, gender, country Fixed Continuous : Age
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• The hazard ratio for FF/VI versus Usual ICS/LABA with associated 95% CI and p-value will be presented. • Cumulative incidence curves of time to first severe asthma exacerbation will be presented. • Summary statistics will also be presented.

11. REFERENCES

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12. APPENDICES

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12.1. Appendix 1: Protocol Deviation Management and Definitions for PP Population

12.1.1. Protocol Deviations

All PDs (any deviation from the protocol) are tracked and monitored during the study. Important PDs are those deviations that may compromise subject rights, safety, or well-being, and/or data integrity, and/or study end-points, and are defined in the PDMP. Apart from any incorrect treatment deviations, all protocol deviations will be agreed upon prior the unblinding and the freezing of the database. All deviations from the inclusion/exclusion criteria, and important PDs will be summarised. A listing of treatment misallocations will be produced.

12.1.2. Exclusions from PP Population

Important PDs that will result in exclusion from the PP population are specified in Table 10, and will be summarised in a data display.

Table 10 PDs resulting in exclusion from the PP population

Deviation Category	Deviation Subcategory
Informed consent	• Signed informed consent/assent not available on site[1] • Wrong informed consent/assent version signed[1] • Informed consent/assent not signed and/or dated by subject (parent/Legally Acceptable representative, if applicable) • Informed consent/assent not signed and/or dated by appropriate site staff. [1] • Informed consent/assent not signed prior to any study procedure[1] • Other informed consent/assent deviations[1]
Eligibility criteria not met – inclusion criteria	• Informed consent • Gender and Age[2] • Type of subject • Current Asthma Therapy • Inability of subject to complete questionnaires
Eligibility criteria not met – exclusion criteria	• History of Life-threatening asthma • Subjects having a severe and unstable asthma • COPD Respiratory Disease • Other diseases/abnormalities[1] • Subjects with a history of adverse reaction to any intranasal, inhaled, or systemic corticosteroid and LABA therapy and to components of the inhalation powder[1] • Investigational Medications used within 30 days or five half-lives of prior study[1] • Chronic user of systemic corticosteroids • Subjects treated by the monoclonal antibody omalizumab (Xolair) or mepolizumab (Nucala™) • Subjects involved in other clinical trials[1]

Deviation Category	Deviation Subcategory
Not withdrawn after developing withdrawal criteria	• Not withdrawn from study[1] • Not discontinued from study treatment[1] • Other deviation of not being withdrawn after developing withdrawal criteria[1]
Excluded medication, vaccine or device	• Medication, excluded by the protocol, was administered[3] • Other excluded medication, vaccine or device deviation[3]
Wrong study treatment / administration / dose	• Study treatment not administered per protocol[1] • Wrong study treatment or assignment administered • Expired study treatment administered[1] • Use of study treatment impacted by a temperature excursion which was not reported or approved or which was disapproved for further use.[1] • Study treatment not available at site for administration[1] • Other deviations related to wrong study treatment/administration/dose[1]
Study procedures	• Non study treatment supply procedures[1] • Equipment procedures[1] • Other deviations from study procedures[1]

[1] To be reviewed on a case-by-case basis
[2] Patients < 18 years will be excluded from PP population, others will be reviewed on a case-by-case basis
[3] To be judged by the medical monitor

12.2. Appendix 2: Time & Events

12.2.1. Protocol Defined Time & Events

Study Visits	Visit 1* Screening	Visit 2* Randomisation	Visit 3 Phone call 1	Visit 4**	Visit 5 Phone call 2	Visit 6	Early Withdrawal
Study Week (± specified no. of days)	Day -7 to -1	Day 0	Week 6 (±3 days)	Week 12 (±7 days)	Week 18 (±3 days)	Week 24 (±14 days)	**Early Withdrawal**
Visit	x	x		x		x	x
Phone interview			x		x		
Assessments							
Informed Consent	x						
Eligibility criteria	x	x					
Demography	x						
Smoking status	x						
Medical/Family history of consented subjects including CV Risk factors and exacerbation history	x						
PGx (saliva sample)***		x					
Physical examination	x	x		x		x	x
Safety Assessments							
Urine Pregnancy Test¥		x		x		x	x
Exacerbation Assessment		x	x	x	x	x	x
Vital signs	x	x		x		x	x
Serious Adverse Event and Adverse Drug Reaction Assessment[1]		x	x	x	x	x	x
Efficacy Assessments							
Spirometry Testing (Pre-dose trough FEV1)		x		x			x ****
Subject Questionnaires							
Asthma Control Test	x	x	x	x	x	x	x
EQ-5D		x				x	x
Asthma Quality of Life Questionnaire		x				x	x
MARS-A questionnaire		x		x		x	x
Patient Satisfaction and Preference				x			x

Study Visits	Visit 1* Screening	Visit 2* Randomisation	Visit 3 Phone call 1	Visit 4**	Visit 5 Phone call 2	Visit 6	Early Withdrawal
Study Week (± specified no. of days)	Day -7 to -1	Day 0	Week 6 (±3 days)	Week 12 (±7 days)	Week 18 (±3 days)	Week 24 (±14 days)	**Early Withdrawal**
Visit	**x**	**x**		**x**		**x**	**x**
Phone interview			**x**		**x**		
(PASAP-Q)							
Inhaler correct use assessment							
Type A/overall errors record		**x**		**x**		**x**	
Medication Assessments							
Concomitant Medication Assessment	**x**	**x**		**x**		**x**	**x**
Dispense Study Medication[2]		**x**		**x**			
Collect Study Medication[2]				**x**		**x**	**x**
RAMOS/eCRF							
RAMOS NG		**x**		**x**			
eCRF	**x**	**x**	**x**	**x**	**x**	**x**	**x**

1. SAE and ADR monitoring will occur from Day 1. SAE related to study participation should begin from signing of informed consent form (ICF). An additional safety and ACT check is provided by phone at Week 6 and 18.
2. Throughout the study the study medication will be dispensed and collected by the investigator site.

* Visit 1 and Visit 2 can be combined if the subject did not take his usual asthma medication before coming on site. Then this visit will be Randomisation (Day 0) and all baseline characteristics will be collected at this visit. Written Informed Consent must be obtained prior to initiation of study procedures or initiating changes in medications.

** Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation visit).

***PGx saliva sample collected at Visit 2 (Randomisation) or any scheduled clinic visit thereafter.

**** Only if early withdrawal occurs before Week 12.

¥ Only for childbearing women.

12.3. Appendix 3: Assessment Windows

Clinic visits/phone calls are scheduled to take place as specified in the protocol. For the ACT and MARS-A questionnaires, measurements that are not within ±7 days of the visit target day for Week 6 (Visit 3) and Week 18 (Visit 5), or ±14 days for Week 12 (Visit 4) and Week 24 (Visit 6) will be excluded from the analyses. For EQ-5D-5L and AQLQ(S), measurements that are not within ±14 days of the visit target day of Week 24 (Visit 6) will be excluded from the summaries. For PASAP-Q, measurements that are not within ±14 days of the visit target day of Week 12 (Visit 4) will be excluded from the summaries.

Table 11 Visit slotting rules for ACT and MARS-A

Days relative to randomisation *	Target Study Day	Visit Slot
35 – 49	42	Week 6 (Visit 3)
70 – 98	84	Week 12 (Visit 4)
119 – 133	126	Week 18 (Visit 5)
154 – 182	168	Week 24 (Visit 6)
* Date of assessment – Randomisation date + 1		

Table 12 Visit slotting rules for EQ-5D-5L and AQLQ(S)

Days relative to randomisation *	Target Study Day	Visit Slot
154 – 182	168	Week 24 (Visit 6)
* Date of assessment – Randomisation date + 1		

Table 13 Visit slotting rules for PASAP-Q

Days relative to randomisation *	Target Study Day	Visit Slot
70 – 98	84	Week 12 (Visit 4)
* Date of assessment – Randomisation date + 1		

For all other endpoints, individual measurements collected outside of the assessment window for scheduled visits will be included in the ITT and PP analyses without adjustment.

All available data will be assigned to an assessment window where possible, including Early Withdrawal visits. If multiple measurements are collected within the same assessment window, the last valid value prior to randomisation will be used as the baseline value and the value closest to the target day for that window will be used for all post-randomisation visits. If values are the same distance from the target, then the earlier value will be taken.

12.4. Appendix 4: Treatment States and Phases

12.4.1. Treatment Phases

In general, assessments and events will be classified according to the time of occurrence relative to study treatment, unless otherwise specified. Endpoint/measurement specific definitions are defined in Section 12.4.2.

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

NOTES:

- If it is not possible to determine the treatment phase of an assessment or event, it will be considered as On-Treatment.

12.4.2. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of the study treatment. The earliest and latest exposure treatment start and stop dates will be used to determine whether an assessment or event was pre-treatment, on-treatment or post-treatment. If it is not possible to tell whether an assessment or event was on-treatment or not, it will be considered as on-treatment.

12.4.2.1. Treatment States for Concomitant Medications

Treatment State	Definition
Pre-Treatment	(Start Date of Medication < Study Treatment Start Date) and (End Date of Medication < Study Treatment Start Date)
On-Treatment	[(Start Date of Medication < Study Treatment Start Date) and (End Date of Medication ≥ Study Treatment Start Date)] or (Study Treatment Start Date ≤ Start Date of Medication ≤ Study Treatment Stop Date + 1)
Post-Treatment	Start Date of Medication > Study Treatment Stop Date +1

12.4.2.2. Treatment States for Efficacy Measurements

Treatment State	Definition
Pre-Treatment	Date of Measurement ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date of Measurement ≤ Study Treatment Stop Date + 1
Post-Treatment	Date of Measurement > Study Treatment Stop Date +1

12.4.2.3. Treatment States for Exacerbation Data

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

NOTES:

- If the study treatment stop date is missing, then the exacerbation will be considered to be On-Treatment
- See Section 12.6.3 for details on missing onset and/or resolution dates.

12.4.2.4. Treatment States for AE Data

Treatment states for adverse events are described below. Severe asthma exacerbations will be treated in the same way, with the exacerbation start date used in place of the AE start date.

Treatment State	Definition
Pre-Treatment	AE Onset Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ AE Onset Date ≤ Study Treatment Stop Date + 1
Post-Treatment	AE Onset Date > Study Treatment Stop Date + 1
Onset Time Since 1st Dose (Days)	If Study Treatment Start Date > AE Onset Date = AE Onset Date - Study Treatment Start Date If Study Treatment Start Date ≤ AE Onset Date = AE Onset Date - Study Treatment Start Date +1 Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' or is missing on the AE case report form (CRF) page.

NOTES:

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

12.5. Appendix 5: Data Display Standards & Handling Conventions

12.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	Fluticasone furoate /vilanterol inhalation Powder delivered once daily	FF/VI	2
B	Usual ICS/LABA maintenance therapy delivered by Dry Powder Inhaler	Usual ICS/LABA	1

NOTES:

1. Order represents treatments being presented in data displays, as appropriate.

12.5.2. Baseline Definition & Derivations

12.5.2.1. Baseline Definitions

For all endpoints the baseline value will be the last assessment prior to randomisation.

12.5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]
Maximum Change from Baseline	= Calculate the change from baseline at each given timepoint and determine the maximum change

NOTES:

- Unless otherwise specified, the baseline definitions specified in Section 12.5.2.1 will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

12.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area	: /arenv/arprod/gw685698_gw642444/hza116492/final
QC Spreadsheet	: /arenv/arwork/gw685698_gw642444/hza116492/final/qc
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards.	

Reporting Process
• For creation of ADaM datasets (e.g. ADCM, ADAE) the same version of dictionary datasets will be implemented for conversion from SI to SDTM.
Generation of RTF Files
• RTF files will be generated for all tables in the final reporting effort.

Reporting Standards	
General	
• The current GSK IDSL will be applied for reporting, unless otherwise stated: ○ 4.03 to 4.23: General Principles ○ 5.01 to 5.08: Principles Related to Data Listings ○ 6.01 to 6.11: Principles Related to Summary Tables ○ 7.01 to 7.13: Principles Related to Graphics	
Formats	
• All data will be reported according to the treatment the subject was randomised to unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DPs) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the electronic case report form (eCRF) or recorded in the raw dataset if from non eCRF sources. • 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 Times	
• Reporting for tables, figures and formal statistical analyses: • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). • Unscheduled or unplanned readings will be presented within the subject's listings. • For visits outside the time-windows, please see Section 12.3.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables or figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

12.6. Appendix 6: Derived and Transformed Data

12.6.1. General

Multiple Measurements at One Time Point
• If there are multiples values within a time window the last valid value prior to randomisation will be used as the baseline value and the value closest to the target day for that window will be used for all post-randomisation visits. If values are the same distance from the target, then for efficacy outputs where visit slotting is used the earlier record will be used. For all other cases of multiple valid measurements the mean will be taken. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

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

Time Since First Dose

• Calculated as the number of days from the date of first dose:
  • Ref Date = Missing → Time Since First Dose = Missing
  • Ref Date < First Dose Date → Time Since First Dose = Ref Date – First Dose Date
  • Ref Date ≥ First Dose Date → Time Since First Dose = Ref Date – (First Dose Date) + 1

Time Since Last Dose

• Calculated as the number of days from the date of last dose:
  • Ref Date = Missing → Time Since Last Dose = Missing
  • Ref Date < Last Dose Date → Time Since Last Dose = Ref Date – Last Dose Date
  • Ref Date ≥ Last Dose Date → Time Since Last Dose = Ref Date – Last Dose Date) + 1

Study Treatment Discontinuation
• In this study, subjects who are intentionally and permanently withdrawn from study medication may not continue in the study attending the remaining visits (excluding the Follow-up contact) and completing the scheduled assessments.

12.6.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ Any subject with a missing day will have this imputed as day '15'.
  ○ Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.
• Completely missing dates of birth will remain as missing, with no imputation applied. Consequently, the

Demographics
age of the subject will not be calculated and will remain missing. • Age, in whole years, will be calculated with respect to the date of screening (Visit 1).
Body Mass Index
• Calculated as Weight (kg) / [Height (m)]^2
Race
• In the demographic summary table race will be summarised as follows; White is defined as those subjects who chose only the White (Arabic/North African Heritage) and/or White (White/Caucasian/European Heritage) categories on the CRF, Black is defined as those subjects who chose only the African American/African Heritage category on the CRF, and Other is defined as those subjects who chose any of the other races on the CRF.

Extent of Exposure
Subjects for whom it is considered appropriate/necessary to adjust treatment can have their dose increased from the starting dose, and will be recorded in the eCRF. Treatment sequence identifier will be incremented by 1 each time the study medication is modified, and recorded on eCRF. Extent of exposure will be presented in three different ways: • The extent of exposure to study medication, regardless of study medication dosage modifications during the study, will be defined as the number of days on study medication and will be calculated for each subject as follows: Exposure = (study medication stop date – study medication start date) + 1 If medication start date is missing, then the randomisation date (i.e. date of Visit 2) of the subject will be used for medication start date. If the medication stop date is missing, the Visit 6 date or early withdrawal visit date will be used instead. If all these dates are missing, then the extent of exposure will be set to missing. • The extent of exposure to study medication, up to first study medication dosage modification • The extent of exposure to each dose of study medication, presented separately for FF/VI 92 mcg/22 mcg, FF/VI 184 mcg/22mcg, FP/S 250 mcg/50 mcg, FP/S 500 mcg/50 mcg, BUD/F 200 mcg/6 mcg, BUD/F 400 mcg/12 mcg Note: do not split by dose frequency

12.6.3. Efficacy

Primary Endpoint
ACT
The ACT is a validated self-administered questionnaire utilising 5 questions to assess asthma control during the past 4 Weeks on a 5-point categorical scale (1 to 5). By answering all 5 questions, a subject with asthma can obtain a score that may range between 5 and 25, with higher scores indicating better control. An ACT score of 5 to 19 suggests that the subject's asthma is unlikely to be well controlled. A score of 20 to 25 suggests that the subject's asthma is likely to be well controlled. The MID for ACT is 3 (Schatz, 2009).

Primary Endpoint

The total score is calculated as the sum of the scores from all 5 questions, provided all scores are non-missing; if any individual scores are missing then the overall score will be set to missing.

Secondary Endpoint

Correct Use of Device

Inhaler use will be assessed at Randomisation (Visit 2), Week 12 (Visit 4) and Week 24 (Visit 6). Correct use of device is defined as making no critical or non-critical errors.

Critical and Non-Critical Errors for Ellipta

Critical errors:

- Failed to open cover
- Shook the device upside down after dose preparation
- Exhaled directly into mouthpiece
- No seal by the lips around the mouthpiece during the inhalation

Non-critical errors:

- No exhalation before an inhalation
- Inhalation manoeuvre was not:
  - long
  - steady
  - deep
- Blocked air inlet during inhalation manoeuvre
- Did not hold breath
- Did not close the device (Note: this is an error but one which does not affect the medication that is inhaled)

Critical and Non-Critical Errors for Diskus

Critical errors:

- Failed to open cover
- Lever is not pushed back
- Shook the device after dose preparation
- Exhaled directly into mouthpiece
- No seal by the lips round the mouthpiece during the inhalation

Non-critical errors:

- No exhalation before an inhalation
- Inhalation manoeuvre was not:
  - steady
  - deep
- Did not hold breath
- Did not close the device (Note: this is an error but one which does not affect the medication that is inhaled)

Critical and Non-Critical Errors for Turbuhaler

Critical errors:

- Failed to remove cap
- Did not hold device upright (±45° OK) during dose preparation
- Base not twisted fully backwards and forwards, no click heard

Primary Endpoint

- Shook the device after dose preparation
- Exhaled directly into mouthpiece
- No seal by the lips round the mouthpiece during the inhalation

Non-critical errors:

- Device tipped downwards after dose preparation
- No exhalation before an inhalation
- Inhalation manoeuvre was not:
  - forceful
  - deep
- Blocked air inlet during inhalation manoeuvre
- Did not hold breath
- Did not close the device (Note: this is an error but one which does not affect the medication that is inhaled)

Other Endpoints

FEV1

FEV1 will be measured to assess lung function at Randomisation (Visit 2) and Week 12 (Visit 4). Visit 4 should be scheduled at the same time of day as Visit 2, FEV1 measurements should be taken pre-dose and subjects should be instructed not to take their asthma medication/study drug prior to coming into the clinic at these visits. Subjects should also withhold from using their rescue medication for at least 4 hours prior to Visit 2 and Visit 4.

All sites will use standardised spirometry equipment provided by GSK. For each observation, at least 3 (with no more than 8) efforts will be obtained. At least two of the spirometry efforts should be acceptable and repeatable. The best FEV1 value will be recorded in the eCRF.

MARS-A

The MARS-A questionnaire is a 10-item questionnaire. The response to all ten questions will be presented and included in the calculation of the MARS-A 10-score.

The responses to the MARS-A questions will be scored as follows: Always=1, Often=2, Sometimes=3, Rarely=4, Never=5. The MARS-A 10-Score will be calculated for each subject as the sum of scores for each of the ten questions divided by the number of non-missing responses to the ten questions.

If some responses are missing the MARS-A 10-score is calculated as follows for each subject:

- If eight or more of the questions have been answered, the missing responses for that subject will be imputed to the average score
- If less than eight of the questions have been answered, the overall MARS-A 10-score for that subject will be set to missing

The French translation of the MARS-A questionnaire did not go through cognitive debriefing; therefore, while the study was ongoing it was determined that there is no word for “preventer” in French. “Preventer inhaler” was translated as “dispositif d’inhalation” (i.e., “inhalation device”). A reminder was sent to centres in France instructing that the MARS-A questionnaire refers to the patient’s preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study) as opposed to their reliever inhaler. The German translation went through cognitive debriefing and was correctly translated. The MARS-A data

Other Endpoints

displays will therefore be repeated split by:

- Patients in France, all MARS-A assessments completed pre-reminder
- Patients in France, some MARS-A assessments completed pre-reminder, some post-reminder
- Patients in France, all MARS-A assessments completed post-reminder
- Patients in Germany

The reminder was sent on 17OCT2016, and it was assumed that the centres started implementing the instructions two days after this, i.e. on 19OCT2016. If a visit occurs on the 19OCT2016 then it will be categorised as having happened before the reminder.

Severe Asthma Exacerbations

Missing onset or resolution dates will be handled as follows:

- Single event with missing onset and/or resolution dates:
  - (a) Missing onset date: set onset date = study treatment start date
  - (b) Missing resolution date: set resolution date = study treatment stop date
  - (c) Both missing: imputed per both (a) and (b)
- Multiple events, one event with some missing onset/resolution dates; on the assumption any partial date information does not occur during the other events:
  - (a) Missing onset date: set onset date = max[(resolution date of the nearest previous event) + 1 day, study treatment start date]
  - (b) Missing resolution date: set resolution date = min[(onset date of the nearest subsequent event) - 1 day, study treatment stop date]
  - (c) Both missing: determine the largest gap between study treatment start date and first event onset date, between first event resolution date and next event(s) onset dates (if any), between last event resolution date and study treatment stop date. If there is more than one gap which is the largest, then take the first occurrence. Then impute as follows:

    onset date = (onset date of largest gap) + 1 day

    resolution date = (resolution date of largest gap) + 1 day

Time to First Severe Asthma Exacerbation

The date of a severe asthma exacerbation is defined as the exacerbation onset date. Subjects who complete the study without a severe asthma exacerbation will be censored. Time to first severe asthma exacerbation is measured from the date of randomisation (i.e., study treatment start date) to the onset date of first severe asthma exacerbation, as recorded on eCRF, or study treatment stop date (Visit 6 or early withdrawal visit) for subject who complete the study without any severe asthma exacerbations (censored). Analyses of time to first severe asthma exacerbation will be censored at Day 168.

AQLQ(S) Domain and Total Scores

The AQLQ(S) contains 32 items in four domains: activity limitation (11 items), symptoms (12 items), emotional function (5 items) and environmental stimuli (4 items). The following items are included in each of the 4 domains:

- Symptoms: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
- Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
- Emotional Function: 7, 13, 15, 21, 27
- Environmental Stimuli: 9, 17, 23, 26

The response format consists of a seven-point scale where a value of 1 indicates “total impairment” and a value of 7 indicates “no impairment”. The total AQLQ(S) score is the mean of all 32 items in the questionnaire and each individual domain score is calculated as the mean of the items within that domain. Hence, the total and domain scores are also each defined on a range from 1 to 7 with higher scores

Other Endpoints

indicating a higher quality of life. The MID for AQLQ(S) is 0.5 (Juniper, 1993).

For the total AQLQ(S) score, the score for a subject at any time point will only be calculated if at least 90% of the questions were answered (calculated as the mean of those non-missing questions). If fewer than 90% of the questions were answered, then the mean score for that subject at that time point will be considered missing.

For each individual domain of the AQLQ(S) score, the score for a subject at any time point will only be calculated if at least 90% of the questions for that domain were answered (calculated as the mean of those non-missing questions). If fewer than 90% of the questions were answered for that domain, then the mean score for that subject and domain at that time point will be considered missing.

EQ-5D-5L Utility and VAS Scores

The EQ-5D-5L is administered at randomisation (Visit 2), Week 24 (Visit 6) and Early Withdrawal. The EQ-5D-5L consists of 2 parts: the EQ-5D-5L descriptive system and the EQ VAS.

The EQ-5D-5L descriptive system comprises the following 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression. Each dimension has 5 levels, where Level 1 (coded as '1') = 'No problems', Level 2 (coded as '2') = 'Slight problems', Level 3 (coded as '3') = 'Moderate problems', Level 4 (coded as '4') = 'Severe problems' and Level 5 (coded as '5') = 'Extreme problems'. Subjects indicate their health state for each dimension by ticking (or placing a cross) in the box of the most appropriate level for that dimension. Ambiguous values (e.g. 2 boxes are ticked for a single dimension) will be considered missing. Missing values will be coded as '9'. The responses (1, 2, 3, 4 or 5) to the five questions will be converted into a single utility score using the developer's instructions (EuroQol, 2013): the responses (1, 2, 3, 4 or 5) to the five questions in the descriptive system can be represented as one of 5^5=3125 possible health states (11111, 11112, ... , 55555). These will be converted into a single summary index (y) that attaches value to each of the levels in each dimension by applying the formula below, which is based on the EQ-5D-5L value set for England (Devlin, 2016).

$$\begin{aligned} y = 1 - 0.9675 \times (&0.051M_2 + 0.063M_3 + 0.212M_4 + 0.275M_5 + 0.057S_2 + 0.076S_3 \\ &+ 0.181S_4 + 0.217S_5 + 0.051U_2 + 0.067U_3 + 0.174U_4 + 0.190U_5 + 0.060P_2 \\ &+ 0.075P_3 + 0.276P_4 + 0.341P_5 + 0.079A_2 + 0.104A_3 + 0.296A_4 \\ &+ 0.301A_5) \end{aligned}$$

where variables with subscript n are indicator variables equal to 1 when the corresponding level for the dimension is 'n' and equal to 0 otherwise, M_n variables represent responses for the mobility domain, S_n variables represent responses for the self-care domain, U_n variables represent responses for the usual activities domain, P_n variables represent responses for the pain / discomfort domain, and A_n variables represent responses for the anxiety / depression domain.
For example, health state where domains MSUPA = 11223 would be equal to:

$$1 - 0.9675 \times (0.051 + 0.060 + 0.104) \approx 0.7920$$

The EQ VAS records the subject's self-rated health state on a vertical, VAS where 0='worst imaginable health state' and 100='best imaginable health state'. Subjects indicate their own health state by drawing a line from the box on the left of the scale to whichever point on the scale indicates how good or bad their own health state is that day. Ambiguous values (e.g. the line crosses the VAS twice) will be considered missing. Missing values will be coded as '999'.

Only validated EuroQoLs completed in the same language as that completed at Baseline (Visit 2) will be

Other Endpoints

summarised.

PASAP-Q Domain and Total Scores

The PASAP-Q is a self-administered 16-item questionnaire measuring satisfaction and preference with inhaler devices (Kozma, 2005). Two domains (performance and convenience) are calculated from 13 satisfaction items, measured on a Likert-type scale where a value of 1 indicates "very dissatisfied" and 7 indicates "very satisfied". The performance and convenience domains together form the total score. The other items include an overall satisfaction question (again measured from 1 to 7), a preference question (not applicable and so not asked for this study) and a question on willingness to continue using the device in the future, measured on a scale of 0 (not willing) to 100 (definitely willing).

The performance and convenience domains include the following items:

- Performance: 1, 2, 3, 4, 5, 10, 11
- Convenience: 6, 7, 8, 9, 12, 13

If the patient completes at least half of the items in a domain, values for missing items are imputed using the mean of the completed items in that domain. The domain score is then transformed to a scale from 0 (least) to 100 (most) as follows:

$$\text{Domain Score} = [\text{Mean}(\text{responses for items in domain}) - 1] \times \frac{100}{6}$$

If the patient completes less than half of the items in a domain, then the missing items are not imputed and the domain score is set to missing. The total score can be calculated only when both domain scores are computable and substitution for missing items at the domain level has taken place, and is calculated on the same scale as:

$$\text{Total Score} = [\text{Mean}(\text{responses for all 13 items}) - 1] \times \frac{100}{6}$$

The overall satisfaction and willingness questions are summarised on their original scales of 1 to 7 and 0 to 100 respectively.

Other Endpoints

Treatment Compliance

Overall percentage treatment compliance for every subject will be calculated for each type of inhaler (Diskus, Turbuhaler and Ellipta) separately.

Compliance for Diskus, Turbuhaler and Ellipta will be based on the total number of inhalations taken from each type of inhaler and the expected number of inhalations to be taken. The expected number of inhalations will be derived as the sum over the number of days on study drug (based on the subject's treatment start and stop date for that type of inhaler) of the expected number of inhalations per day (from each inhaler) .

The total number of inhalations taken will be based on the dose counter for each type of inhaler, all of which are re-supplied during the study. If there is no dose counter information at all then the compliance will be missing; however, as long as the information from one dose counter is present, the compliance will be calculated assuming that all doses were taken for the missing inhalers. If a dose counter start count is missing, then it will be assumed to be 30 for Ellipta and 60 for both Diskus and Turbuhaler.

In each calculation, all inhalers dispensed will be used, provided the dose counter stop counts are non-missing. The following formula will be used:

$$\frac{Total\_number\_of\_inhalations\_taken}{\sum_{i=1}^{n} Expected\_inhaltions\_for\_day_i} \times 100$$

Where:

- $n = Stop\_date - Start\_date + 1$. *Start_date* and *Stop_date* are the earliest treatment start date and latest treatment stop date respectively recorded for all inhalers used during the time period.
- *Total_number_of_inhalations_taken* is the sum of (dose counter start count – dose counter stop count) for all inhalers used during the time period
- *Expected_inhalations_for_day*$_i$ is equal to 1 for Ellipta and 2 for Diskus and 2 or 4 for Turbuhaler for any given day*, depending on the dose*

12.6.4. Safety

SAEs of Special Interest

SAE groups of special interest have been defined as SAEs which are included in specified areas of interest for one or more of the treatment groups (FF/VI, FF and/or VI). They are identified by groupings of preferred terms based on the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version used in each reporting effort. Groupings or subgroups may be defined, based on relevant combination of preferred terms, or on Standardised MedDRA queries (SMQs).
SAEs of special interest will be confirmed prior to final data, based on the MedDRA version in use at the time.

Special Interest SAE Group
Asthma/bronchospasm
Cardiovascular effects
Decreased bone mineral density and associated fractures
Hypersensitivity
Local steroid effects
LRTI excluding pneumonia
Pneumonia
Adrenal suppression
Ocular effects
Effects on glucose
Effects on potassium
Tremor

Laboratory Parameters

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

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

12.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion was defined in the protocol as a subject who has completed all study visits. The end of the study is defined as the last subject's last visit. • The definition of subject early withdrawal from the study will be any subject who is randomised and, for any reason, does not complete all study visits. • Withdrawn subjects will not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

12.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in subject listing displays (if applicable). Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
Exposure start and stop date	• If a subject's treatment start date is missing, then their Visit 2 date will be assumed to be the exposure start date. If a subject's treatment stop date is missing, this will be taken to be the date of Week 24 (Visit 6) (if the subject completes Visit 6) or the early withdrawal visit date.

12.7.2.1. Handling of Missing or Partial Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
SAEs and ADRs	• The eCRF does not allow the possibility of partial dates (i.e., only month and year) to be recorded for SAE and ADR start and end dates; • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.

Element	Reporting Detail
	• The recorded partial date will be displayed in listings.

12.7.2.2. Handling of Missing Data for Statistical Analysis

In general, missing data will not be imputed except for the sensitivity analyses defined in Section 8.1.2.

12.8. Appendix 8: Values of Potential Clinical Importance

12.8.1. Vital Signs

Not applicable

12.9. Appendix 9: Multicenter Studies

12.9.1. Methods for Handling Centres

In this multicentre study conducted in France and Germany, enrolment will be presented by investigative site.

12.10. Appendix 10: Examination of Covariates, Subgroups & Other Strata

12.10.1. Examination of Strata and Covariates

The following is a list of covariates that may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses.

Additional covariates of clinical interest may also be considered.

Category	Covariates and / or Subgroups
Strata	Separate randomisation schedules were utilised for France and Germany respectively thereby stratifying the randomisation by country. Country will be included in all analyses as a covariate. A sensitivity analysis will examine the randomized treatment-by-country interaction for the primary and key secondary endpoints.
Covariates	For the primary efficacy analysis, the following baseline variables will be adjusted for: • Randomised treatment (FF/VI, Usual ICS/LABA) • Baseline ACT total score • Age • Gender • Country Similar covariates will be considered for all other analyses; in each case the relevant baseline score (e.g. baseline AQLQ[S] score for the AQLQ[S] endpoints) will be included instead of baseline ACT total score.

12.10.2. Examination of subgroups

- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.
- For statistical analyses by subgroup, models will include subgroup and treatment by subgroup interaction as covariates.

Category	Subgroups
Country	• France • Germany
Number of severe asthma exacerbations in the previous year prior to randomisation	• 0 • ≥ 1
Smoking Status at Baseline	• Current smoker • Former smoker

Category	Subgroups
	• Never smoked
Age Group	• ≤ 50 years old • > 50 years old
Gender	• Male • Female

12.10.3. Examination of seasonal effect

A sensitivity analysis for the primary efficacy endpoint examining seasonal effect is defined in Section 8.1.2, specifying a season at randomisation covariate defined as follows:

Season at Randomisation	Calendar Month of Randomisation
Spring	• March • April • May
Summer	• June • July • August
Autumn	• September • October • November
Winter	• December • January • February

Furthermore, the summary of severe asthma exacerbations will be repeated by season using the same definition (according to calendar month) as specified above.

12.11. Appendix 11: Multiple Comparisons & Multiplicity

12.11.1. Handling of Multiple Comparisons & Multiplicity

Non inferiority of FF/VI to ICS/LABA will be first tested at the 0.05 two-sided nominal level of significance. If non-inferiority is statistically achieved, then superiority of FF/VI to ICS/LABA will be tested at the 0.05 two-sided nominal level of significance.

If and only if non-inferiority is achieved for the primary endpoint at Week 12 (Visit 4), then the key secondary endpoint, i.e. the change from baseline in the total ACT score assessed at Week 24 (Visit 6) will be tested. At Week 24 (Visit 6), non-inferiority of FF/VI to ICS/LABA will be first tested at the 0.05 two-sided nominal level of significance. If non-inferiority is achieved, then superiority of FF/VI to ICS/LABA will be tested at the 0.05 two-sided nominal level of significance.

Of note, this step-down testing procedure still strongly controls the overall type I error at the 0.05 two-sided level for the non-inferiority endpoints. The overall type I error is not controlled for the superiority tests at Week 12 (Visit 4) and Week 24 (Visit 6).

12.12. Appendix 12: Model Checking and Diagnostics for Statistical Analyses

12.12.1. Statistical Analysis Assumptions

Endpoint(s)	• Change from Baseline in the ACT Total Score at Week 12 (Visit 4) • Change from Baseline in the ACT Total Score at Week 24 (Visit 6)
Analysis	• MMRM (ANCOVA for LOCF and WOCF sensitivity analyses)
• Should computational issues be encountered when running the model with an unstructured variance-covariance matrix, other structures including autoregressive 1 and compound symmetry will be considered. • Distributional assumptions underlying the model will be checked with graphical methods (including quantile-quantile (Q-Q) plots of studentized residuals, plots of studentized residuals versus fitted values, etc.). To investigate the relationship between baseline ACT total score and the change from baseline in ACT total score, baseline ACT total will be categorized according to the distribution quartiles and the model will be fitted using this categorized variable in place of continuous baseline ACT total score. • If the distributional assumption of normality fails then the LS means, estimated LS mean treatment difference and associated 95% CI from the model will be presented, with the p-value for the difference between treatment groups from a model on the rank-transformed values. Should the distributional assumption of normality also fail for the ranked model, other methods of analysis will be investigated.	

Endpoint(s)	• Percentage of subjects with correct use of inhaler device at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4) • ACT total score of ≥ 20 or ≥ 3 point increase from baseline in ACT total score at Week 12 (Visit 4) and Week 24 (Visit 6) • Increase from baseline of ≥ 0.5 in AQLQ(S) total score at Week 24 (Visit 6) • Increase from baseline of ≥ 0.5 in AQLQ(S) environmental stimuli domain score at Week 24 (Visit 6) • Proportion of subjects with 'no problems' at Endpoint in the EQ-5D-5L questionnaire
Analysis	• Logistic regression model
• If the likelihood maximisation algorithm fails to converge due to complete or quasi-complete separation of the data then Firth's penalized likelihood (Firth, 1993) will be implemented by use of the FIRTH option on the MODEL statement in PROC LOGISTIC. • The fit of the logistic regression model will be assessed by examining the ROC curve and other diagnostic plots.	

Endpoint(s)	• Change from baseline in trough (pre-dose) FEV1 at Week 12 (Visit 4) • Change from baseline in EQ-5D Utility Score • Change from baseline in EQ-5D VAS Score
Analysis	• ANCOVA model
• Distributional assumptions underlying the model will be checked with graphical methods (including quantile-quantile (Q-Q) plots of studentized residuals, plots of studentized residuals versus fitted values, etc.). • If the distributional assumption of normality fails then the LS means, estimated LS mean treatment difference and associated 95% CI from the ANCOVA model will be presented, with the p-value for the	

difference between treatment groups from an ANCOVA model on the rank-transformed values. Should the distributional assumption of normality also fail for the ranked ANCOVA, an exact p-value from a two-sample Wilcoxon Rank Sum test will be presented for the difference between treatment groups.

Endpoint(s)	• Annual severe asthma exacerbation rate over the study period
Analysis	• GLM assuming the Negative Binomial distribution
• If a GLM assuming the Negative Binomial distribution cannot be fitted due to the lack of repeat events within a subject, a GLM assuming the Poisson distribution will be used. The underlying assumption for the Poisson distribution that the mean and variance of the response variable are equal will be examined. If the variance of the fitted model exceeds the mean (over-dispersion), the dispersion parameter will be estimated as a ratio of the Pearson Chi-Square to its associated degrees of freedom (using the PSCALE option in PROC GENMOD).	

Endpoint(s)	• Time to first severe asthma exacerbation
Analysis	• Cox proportional hazards model
• Proportional hazards assumptions will be checked by plotting the log of the negative log of the estimated survivor functions against log time, for each treatment group. If hazards are proportional, the lines should be approximately parallel. • If the assumption of proportionality is not met, the use of other models such as models including time-dependent covariates will be considered. • If there are computational issues in implementing the exact method for handling ties, then the Efron method (Efron, 1977) will be used instead.	

12.13. Appendix 13: Blinding Strategy

The Blinding Strategy is maintained separately in a document entitled HZA116492 - Blinding Strategy.

12.14. Appendix 14: Abbreviations & Trade Marks

12.14.1. Abbreviations

Abbreviation	Description
ACT	Asthma Control Test
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
AQLQ(S)	Standardised Asthma Quality of Life Questionnaire
ASE	All Subjects Enrolled
BMI	Body Mass Index
BUD	Budesonide
CI	Confidence Interval
CIL	Clinical Investigational Lead
CRF	Case Report Form
CRO	Contract Research Organisation
DBF	Database Freeze
DBP	Diastolic Blood Pressure
DBR	Database Release
DM	Data Management
DP	Decimal Place
DPI	Dry Powder Inhaler
DQL	Data Quality Lead
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol Questionnaire
F	Formoterol
FEV1	Forced Expiratory Volume in 1 Second
FF	Fluticasone Furoate
FP	Fluticasone Propionate
GINA	Global Initiative for Asthma
GLM	Generalised Linear Model
GSK	GlaxoSmithKline
HL	Hodges-Lehmann
HR	Heart Rate
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
IDSL	Integrated Data Standards Library
IP	Investigational Product
ITT	Intent-to-Treat
LABA	Long-acting Beta Agonist
LOCF	Last Observation Carried Forward
LRTI	Lower Respiratory Tract Infection
LS	Least Squares
MAR	Missing at Random
MARS-A	Medication Adherence Report Scale for Asthma
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Description
MI	Multiple Imputation
MID	Minimally Important Difference
MMRM	Mixed Model Repeated Measures
PASAP-Q	Patient Satisfaction and Preference Questionnaire
PD	Protocol Deviation
PDMP	Protocol Deviation Management Plan
PP	Per Protocol
Q-Q	Quantile-Quantile
RAP	Reporting and Analysis Plan
REML	Restricted Maximum Likelihood
S	Salmeterol
S&P	Statistics and Programming
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SMQ	Standardised MedDRA Query
VAS	Visual Analogue Scale
VI	Vilanterol
WOCF	Worst Observation Carried Forward

12.14.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
DISKUS
ELLIPTA
GSK
NUCALA
SERETIDE

Trademarks not owned by the GlaxoSmithKline Group of Companies
ACT
Asthma Quality of Life Questionnaire - AQLQ(S)
EQ-5D
MARS-A Questionnaire
PASAP Questionnaire
Symbicort Turbuhaler
TURBUHALER
XOLAIR

12.15. Appendix 15: List of Data Displays

12.15.1. 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	

12.15.2. Mock Example Shell Referencing

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

.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln

NOTES:

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

12.15.3. Deliverable [Priority]

Delivery [Priority] [1]	Description
Data Look [1]	Data Look Outputs (blinded review)
SAC [2]	Final Statistical Analysis Complete

NOTES:

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

12.15.4. Study Population Tables

Study Population: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Enrolled Subjects	Non-Standard POP_T1	Summary of Subject Populations	Randomised population line will provide the denominators for the ITT, PP and Safety percentages.	Data Look [1] SAC [2]
1.2.	All Enrolled Subjects	IE2	Summary of Inclusion/Exclusion Criteria Failures for Subjects Not Starting Treatment		Data Look [1] SAC [2]
1.3.	ITT	ES1	Summary of End of Study Record		Data Look [1] SAC [2]
1.4.	PP	ES1	Summary of End of Study Record Per Protocol Population		Data Look [1] SAC [2]
1.5.	ITT	Non-Standard POP_T2	Summary of Attendance at Each Clinic Visit and Phone Call Visit		Data Look [1] SAC [2]
1.6.	All Enrolled Subjects	NS1	Summary of Number of Subjects by Country and Centre		SAC [2]
1.7.	ITT	NS1	Summary of Number of Subjects by Country and Centre		Data Look [1] SAC [2]
1.8.	PP	NS1	Summary of Number of Subjects by Country and Centre Per Protocol Population		SAC [2]
Protocol Deviations					
1.9.	ITT	IE2	Summary of Deviations from the Inclusion/Exclusion Criteria		Data Look [1] SAC [2]
1.10.	ITT	Non-Standard POP_T3	Summary of Important Protocol Deviations		Data Look [1] SAC [2]

Study Population: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.11.	ITT	Non-Standard POP_T3	Summary of Important Protocol Deviations Resulting in Exclusion from the PP Population		Data Look [1] SAC [2]
Demographic and Baseline Characteristics					
1.12.	ITT	DM1	Summary of Demographic Characteristics		Data Look [1] SAC [2]
1.13.	PP	DM1	Summary of Demographic Characteristics Per Protocol Population		SAC [2]
1.14.	Safety	DM1	Summary of Demographic Characteristics Safety Population		SAC [2]
1.15.	All Enrolled Subjects	DM11	Summary of Age Ranges		Data Look [1] SAC [2]
1.16.	ITT	DM5	Summary of Race and Racial Combinations		Data Look [1] SAC [2]
1.17.	ITT	DM6	Summary of Race and Racial Combinations Details		Data Look [1] SAC [2]
1.18.	ITT	MH4	Summary of Current Medical Conditions		Data Look [1] SAC [2]
1.19.	ITT	MH4	Summary of Past Medical Conditions		SAC [2]
1.20.	ITT	Non-Standard POP_T4	Summary of Asthma Duration at Baseline		Data Look [1] SAC [2]
1.21.	PP	Non-Standard POP_T4	Summary of Asthma Duration at Baseline Per Protocol Population		Data Look [1] SAC [2]
1.22.	ITT	Non-Standard POP_T5	Summary of Asthma Exacerbation History at Baseline		Data Look [1] SAC [2]

Study Population: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.23.	PP	Non-Standard POP_T5	Summary of Asthma Exacerbation History at Baseline Per Protocol Population		Data Look [1] SAC [2]
1.24.	ITT	Non-Standard POP_T6	Summary of Smoking History at Baseline		Data Look [1] SAC [2]
1.25.	PP	Non-Standard POP_T6	Summary of Smoking History at Baseline Per Protocol Population		SAC [2]
Concomitant Medications					
1.26.	ITT	CM8	Summary of Pre-Treatment Concomitant Medications		SAC [2]
1.27.	ITT	CM8	Summary of On-Treatment Concomitant Medications		SAC [2]
1.28.	ITT	CM8	Summary of On-Treatment Asthma Concomitant Medications		Data Look [1] SAC [2]
Exposure					
1.29.	ITT	Non-Standard POP_T7	Summary of Study Medication Dosage Modification		Data Look [1] SAC [2]
1.30.	ITT	Non-Standard POP_T8	Summary of Extent of Exposure to Study Medication (Regardless of Modification to Study Medication Dosage)		Data Look [1] SAC [2]
1.31.	ITT	Non-Standard POP_T8	Summary of Extent of Exposure to Study Medication (up to First Modification to Study Medication Dosage)		SAC [2]

Study Population: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.32.	ITT	Non-Standard POP_T9	Summary of Extent of Exposure to Study Medication by Medication and Dosage	Repeat on subsequent pages for Medication/Dosage = FF/VI 184 mcg/22 mcg OD, FP/S 250 mcg/50 mcg BID, FP/S 500 mcg/50 mcg BID, BUD/F 200 mcg/6 mcg BID (1 inhalation per dose), BUD/F 200 mcg/6 mcg BID (2 inhalations per dose), BUD/F 400 mcg/12 mcg BID (1 inhalation per dose), BUD/F 400 mcg/12 mcg BID (2 inhalations per dose).	Data Look [1] SAC [2]
Number of Subjects by Subgroup					
1.33.	ITT	Non-Standard POP_T10	Summary of Number of Subjects by Subgroup		SAC [2]

12.15.5. Study Population Figures

Study Population: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
1.1.	ITT	Non-Standard POP_F1	Plot of Exposure to Study Medication (Regardless of Modification to Study Medication Dosage)	Display increments of 6 weeks on the x-axis, up to the maximum exposure (e.g. 0, 6, 12, 18, 24, 30).	Data Look [1] SAC [2]

12.15.6. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in ACT Total Score at Week 12 (Visit 4)					
2.1.	ITT	Non-Standard EFF_T1	Summary of Change from Baseline in ACT Total Score		Data Look [1] SAC [2]
2.2.	PP	Non-Standard EFF_T1	Summary of Change from Baseline in ACT Total Score Per Protocol Population		SAC [2]
2.3.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4)		Data Look [1] SAC [2]
2.4.	PP	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) Per Protocol Population		SAC [2]
2.5.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (ANCOVA with LOCF)	Footnotes as follows: “Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline ACT total score, gender, age and country. Note: Missing values at Week 12 (Visit 4) were replaced by last available post-randomization value based on the last observation carried forward (LOCF) method.”	Data Look [1] SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.6.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (Multiple Imputation – Missing at Random Approach)	Footnotes as follows: "Note: Missing values post-randomisation were imputed using multiple imputation methods based on pattern mixture models. Note: Each imputed data set was analysed using an ANCOVA model at Week 12 (Visit 4) adjusted for randomised treatment, baseline ACT total score, gender, age and country and the resulting treatment differences and their standard errors combined using Rubin's rules."	Data Look [1] SAC [2]
2.7.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (Multiple Imputation – Copy Differences from Reference Approach)	Footnotes as follows: "Note: Missing values post-randomisation were imputed using multiple imputation methods based on pattern mixture models. Note: Each imputed data set was analysed using an ANCOVA model at Week 12 (Visit 4) adjusted for randomised treatment, baseline ACT total score, gender, age and country and the resulting treatment differences and their standard errors combined using Rubin's rules."	Data Look [1] SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (Hodges-Lehmann Approach)	Present the "Difference" and "95% CI" lines of "FF/VI vs. Usual ICS/LABA" section only. Footnotes as follows: "Note: The difference between treatment groups at Week 12 (Visit 4) was calculated using the Hodges-Lehmann approach."	Data Look [1] SAC [2]
2.9.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (ANCOVA with WOCF)	Footnotes as follows: "Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline ACT total score, gender, age and country. Note: Missing values at Week 12 (Visit 4) due to treatment withdrawal prior to this time point were replaced by worst post-randomisation value based on the worst observation carried forward (WOCF) method."	Data Look [1] SAC [2]
2.10.	ITT	Non-Standard EFF_T3	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), Adjusting for Seasonal Effect	Repeat on subsequent pages for Season at randomisation = Summer, Autumn, Winter.	Data Look [1] SAC [2]
2.11.	PP	Non-Standard EFF_T3	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), Adjusting for Seasonal Effect Per Protocol Population	Repeat on subsequent pages for Season at randomisation = Summer, Autumn, Winter.	SAC [2]
2.12.	ITT	Non-Standard EFF_T1	Summary of Change from Baseline in ACT Total Score, FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed FP/S at Randomisation		Data Look [1] SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.13.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed FP/S at Randomisation	Output only to be produced if ≥25% of Usual ICS/LABA patients are prescribed FP/S at randomisation.	Data Look [1] SAC [2]
2.14.	ITT	Non-Standard EFF_T1	Summary of Change from Baseline in ACT Total Score, FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed BUD/F at Randomisation		SAC [2]
2.15.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed BUD/F at Randomisation	Output only to be produced if ≥25% of Usual ICS/LABA patients are prescribed BUD/F at randomisation.	SAC [2]
2.16.	ITT	Non-Standard EFF_T1S	Summary of Change from Baseline in ACT Total Score by Country		Data Look [1] SAC [2]
2.17.	ITT	Non-Standard EFF_T2S	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Country		Data Look [1] SAC [2]
2.18.	ITT	Non-Standard EFF_T1S	Summary of Change from Baseline in ACT Total Score by Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation		SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.19.	ITT	Non-Standard EFF_T2S	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, number of severe asthma exacerbations in the previous year prior to randomisation, two- and three- way interactions between randomised treatment, visit and number of severe asthma exacerbations in the previous year prior to randomisation, and patient fitted as a random factor."	SAC [2]
2.20.	ITT	Non-Standard EFF_T1S	Summary of Change from Baseline in ACT Total Score by Smoking Status at Baseline		SAC [2]
2.21.	ITT	Non-Standard EFF_T2S	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Smoking Status at Baseline	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, smoking status at baseline, two- and three- way interactions between randomised treatment, visit and smoking status at baseline, and patient fitted as a random factor."	SAC [2]
2.22.	ITT	Non-Standard EFF_T1S	Summary of Change from Baseline in ACT Total Score by Age Group		SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.23.	ITT	Non-Standard EFF_T2S	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Age Group	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, country, age group, two- and three- way interactions between randomised treatment, visit and age group, and patient fitted as a random factor."	SAC [2]
2.24.	ITT	Non-Standard EFF_T1S	Summary of Change from Baseline in ACT Total Score by Gender		SAC [2]
2.25.	ITT	Non-Standard EFF_T2S	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Gender	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, two- and three- way interactions between randomised treatment, visit and gender, and patient fitted as a random factor."	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in ACT Total Score at Week 24 (Visit 6)					
2.26.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6)	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient fitted as a random factor."	Data Look [1] SAC [2]
2.27.	PP	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) Per Protocol Population	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient fitted as a random factor."	SAC [2]
2.28.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (ANCOVA with LOCF)	Footnotes as follows: "Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline ACT total score, gender, age and country. Note: Missing values at Week 24 (Visit 6) were replaced by last available post-randomization value based on the last observation carried forward (LOCF) method."	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.29.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (Multiple Imputation – Missing at Random Approach)	Footnotes as follows: "Note: Missing values post-randomisation were imputed using multiple imputation methods based on pattern mixture models. Note: Each imputed data set was analysed using an ANCOVA model at Week 24 (Visit 6) adjusted for randomised treatment, baseline ACT total score, gender, age and country and the resulting treatment differences and their standard errors combined using Rubin's rules."	SAC [2]
2.30.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (Multiple Imputation – Copy Differences from Reference Approach)	Footnotes as follows: "Note: Missing values post-randomisation were imputed using multiple imputation methods based on pattern mixture models. Note: Each imputed data set was analysed using an ANCOVA model at Week 24 (Visit 6) adjusted for randomised treatment, baseline ACT total score, gender, age and country and the resulting treatment differences and their standard errors combined using Rubin's rules."	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.31.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (Hodges-Lehmann Approach)	Present the "Difference" and "95% CI" lines of "FF/VI vs. Usual ICS/LABA" section only. Footnotes as follows: "Note: The difference between treatment groups at Week 24 (Visit 6) was calculated using the Hodges-Lehmann approach."	SAC [2]
2.32.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (ANCOVA with WOCF)	Footnotes as follows: "Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline ACT total score, gender, age and country. Note: Missing values at Week 24 (Visit 6) due to treatment withdrawal prior to this time point were replaced by worst post-randomisation value based on the worst observation carried forward (WOCF) method."	SAC [2]
2.33.	ITT	Non-Standard EFF_T3	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6), Adjusting for Seasonal Effect	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, season at randomisation, two- and three- way interactions between randomised treatment, visit and season at randomisation, and patient fitted as a random factor."	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.34.	PP	Non-Standard EFF_T3	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6), Adjusting for Seasonal Effect Per Protocol Population	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, season at randomisation, two- and three- way interactions between randomised treatment, visit and season at randomisation, and patient fitted as a random factor."	SAC [2]
2.35.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6), FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed FP/S at Randomisation	Output only to be produced if ≥25% of Usual ICS/LABA patients are prescribed FP/S at randomisation. First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient fitted as a random factor."	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.36.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed BUD/F at Randomisation	Output only to be produced if ≥25% of Usual ICS/LABA patients are prescribed BUD/F at randomisation. First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient fitted as a random factor."	SAC [2]
2.37.	ITT	Non-Standard EFF_T2S	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) by Country	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, two- and three- way interactions between randomised treatment, visit and country, and patient fitted as a random factor."	SAC [2]
Correct Use of Inhaler Device					
2.38.	ITT	Non-Standard EFF_T4	Summary of Inhaler Device Use Errors	Repeat on subsequent pages for Visit = Week 12 and Week 24. "Number of patients using..." line will provide the denominators for each section's percentages.	Data Look [1] SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.39.	PP	Non-Standard EFF_T4	Summary of Inhaler Device Use Errors Per Protocol Population	Repeat on subsequent pages for Visit = Week 12 and Week 24. "Number of patients using..." line will provide the denominators for each section's percentages.	SAC [2]
2.40.	ITT	Non-Standard EFF_T5	Summary of Correct Use of Inhaler Device		Data Look [1] SAC [2]
2.41.	PP	Non-Standard EFF_T5	Summary of Correct Use of Inhaler Device Per Protocol Population		SAC [2]
2.42.	ITT	Non-Standard EFF_T6	Summary of the Statistical Analysis of Correct Use of Inhaler Device at Week 12 (Visit 4) and at Week 24 (Visit 6) Independently of the Use at Week 12 (Visit 4)		Data Look [1] SAC [2]
2.43.	PP	Non-Standard EFF_T6	Summary of the Statistical Analysis of Correct Use of Inhaler Device at Week 12 (Visit 4) and at Week 24 (Visit 6) Independently of the Use at Week 12 (Visit 4) Per Protocol Population		SAC [2]
Lung Function Tests					
2.44.	ITT	Non-Standard EFF_T1	Summary of Change from Baseline in Lung Function Tests	Present an additional column to the left of "Visit", labelled "Test" with values "Trough (Pre-dose) FEV1 (L)" and "Trough (Pre-dose) Percent Predicted FEV1 (%)" to allow presentation of results by Test. Present the following visits: Randomisation (Day 0), Week 12, Change from Baseline at Week 12, Early Withdrawal and Change from Baseline at Early Withdrawal.	Data Look [1] SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.45.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in Trough (Pre-dose) FEV1 at Week 12 (Visit 4)	Footnote as follows: "Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline trough (pre-dose) FEV1, gender, age and country."	Data Look [1] SAC [2]
Subjects Who Have Either an ACT Total Score >= 20 or >= 3 Point Increase from Baseline in ACT Total Score					
2.46.	ITT	Non-Standard EFF_T7	Summary of Percentage of Subjects Who Have Either an ACT Total Score >= 20 or >= 3 Point Increase from Baseline in ACT Total Score	Repeat for Visit = Week 18, Week 24, Early Withdrawal.	Data Look [1] SAC [2]
2.47.	ITT	Non-Standard EFF_T6	Summary of the Statistical Analysis of Percentage of Subjects Who Have Either an ACT Total Score >= 20 or >= 3 Point Increase from Baseline in ACT Total Score at Week 12 (Visit 4) and Week 24 (Visit 6)	Replace "With correct use [1]" with "Responder [1]" and "Without correct use" with "Non-Responder". Footnotes as follows: "[1] Responder is defined as an ACT total score >= 20 or >= 3 point increase from baseline in ACT total score at that visit. Note: The analysis method was logistic regression adjusted for randomised treatment, baseline ACT total score, baseline ACT total score squared, gender, age and country."	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual ACT Question Scores					
2.48.	ITT	Non-Standard EFF_T8	Summary of Individual ACT Question Scores	Repeat on subsequent pages for Question = 2. Shortness of breath, 3. Asthma symptoms woken up at night or earlier than usual, 4. Used rescue inhaler or nebuliser medication, 5. Asthma control.	Data Look [1] SAC [2]
Compliance with Study Medication					
2.49.	ITT	Non-Standard EFF_T9	Summary of Compliance with Study Medication		Data Look [1] SAC [2]
2.50.	PP	Non-Standard EFF_T9	Summary of Compliance with Study Medication Per Protocol Population		SAC [2]
MARS-A					
2.51.	ITT	Non-Standard EFF_T10	Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study	Repeat on subsequent pages for Visit = Week 12, Week 24 and Early Withdrawal.	Data Look [1] SAC [2]
2.52.	ITT	Non-Standard EFF_T10S	Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study by Status of Patient in Relation to the Reminder Sent to French Centres	Repeat on subsequent pages for Visit = Week 12, Week 24 and Early Withdrawal, and for Status = Patients in France, all MARS-A assessments completed pre-reminder, Patients in France, some MARS-A assessments completed pre-reminder, some post-reminder, Patients in France, all MARS-A assessments completed post-reminder, Patients in Germany	Data Look [1] SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Severe On-Treatment Asthma Exacerbations					
2.53.	ITT	Non-Standard EFF_T11	Summary of Severe On-Treatment Asthma Exacerbations		Data Look [1] SAC [2]
2.54.	ITT	Non-Standard EFF_T11S	Summary of Severe On-Treatment Asthma Exacerbations by Season	Repeat on subsequent pages for Season = Summer, Autumn, Winter.	Data Look [1] SAC [2]
2.55.	ITT	Non-Standard EFF_T12	Summary of the Statistical Analysis of Severe On-Treatment Asthma Exacerbations		Data Look [1] SAC [2]
2.56.	ITT	Non-Standard EFF_T13	Summary of the Statistical Analysis of Time to First Severe On-Treatment Asthma Exacerbation		Data Look [1] SAC [2]
AQLQ(S)					
2.57.	ITT	Non-Standard EFF_T1	Summary of Change from Baseline in AQLQ(S) Total Score and Domain Scores	Present an additional column to the left of "Visit", labelled "Domain" with values "Total Score", "Environmental Stimuli", "Symptoms", "Activity Limitations" and "Emotional Function" to allow presentation of results by Domain. Present the following visits: Randomisation (Day 0), Week 24, Change from Baseline at Week 24, Early Withdrawal and Change from Baseline at Early Withdrawal.	SAC [2]
2.58.	ITT	Non-Standard EFF_T14	Summary of Percentage of Subjects Who Have an Increase from Baseline of >=0.5 in AQLQ(S) Total Score and Domain Scores	Repeat on subsequent pages for Domain = Environmental Stimuli, Symptoms, Activity Limitations and Emotional Function.	Data Look [1] SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.59.	ITT	Non-Standard EFF_T6	Summary of the Statistical Analysis of Percentage of Subjects Who Have an Increase from Baseline of >=0.5 in AQLQ(S) Total Score and Environmental Stimuli Domain Score at Week 24 (Visit 6)	Replace "With correct use [1]" with "Responder [1]" and "Without correct use" with "Non-Responder". Do not display the "Visit" column. Footnotes as follows: "[1] Responder is defined as an increase from baseline of >= 0.5. Note: The analysis method was logistic regression adjusted for randomised treatment, baseline score, gender, age and country."	SAC [2]
EQ-5D-5L					
2.60.	ITT	Non-Standard EFF_T15	Summary of EQ-5D-5L Descriptive System Dimensions	Repeat on subsequent pages for Visit = Early Withdrawal and for Dimension = Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression.	Data Look [1] SAC [2]
2.61.	ITT	Non-Standard EFF_T6	Summary of the Statistical Analysis of Proportion of Responders According to EQ-5D-5L Descriptive System Dimensions at Week 24 (Visit 6)	Replace "With correct use [1]" with "Responder [1]" and "Without correct use" with "Non-Responder". Do not display the "Visit" column. Footnotes as follows: "[1] Responder is defined as a score of 1 ('no problems'). Note: The analysis method was logistic regression adjusted for randomised treatment, baseline EQ-5D-5L domain score, gender, age and country."	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.62.	ITT	Non-Standard EFF_T1	Summary of EQ-5D-5L Utility Score	Present the following visits: Randomisation (Day 0), Week 24, Change from Baseline at Week 24, Early Withdrawal and Change from Baseline at Early Withdrawal.	Data Look [1] SAC [2]
2.63.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in EQ-5D-5L Utility Score at Week 24 (Visit 6)	Footnote as follows: "Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline EQ-5D-5L utility score, gender, age and country."	SAC [2]
2.64.	ITT	Non-Standard EFF_T1	Summary of EQ-5D-5L Visual Analogue Scale (VAS) Score	Present the following visits: Randomisation (Day 0), Week 24, Change from Baseline at Week 24, Early Withdrawal and Change from Baseline at Early Withdrawal.	SAC [2]
2.65.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in EQ-5D-5L Visual Analogue Scale (VAS) Score at Week 24 (Visit 6)	Footnote as follows: "Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline EQ-5D-5L VAS score, gender, age and country."	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PASAP-Q					
2.66.	ITT	Non-Standard EFF_T1	Summary of PASAP-Q Scores	Present an additional column to the left of "Visit", labelled "Score" with values "Performance", "Convenience", "Overall Satisfaction", "Total Score" and "Willingness to Continue Using Inhaler" to allow presentation of results by Domain. Present the following visits: Week 12 and Early Withdrawal. Add the following footnotes: "Note: Performance, Convenience, Total Score, and Willingness to Continue Using Inhaler are expressed on a scale of 0 to 100. Note: Overall Satisfaction is expressed on a scale of 1 to 7."	SAC [2]

12.15.7. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in ACT Total Score at Week 12 (Visit 4)					
2.1.	ITT	Non-Standard EFF_F1	Summary of Change from Baseline in ACT Total Score	Present "ACT Total Score" on y-axis and "Visit" on x-axis (Randomisation (Day 0), Week 6, Week 12, Week 18, Week 24). Present mean ACT Total Score ± SD separately for treatment group (FF/VI, Usual ICS/LABA) at each visit, connecting the means with a solid line. Distinguish the treatment groups by different line types.	Data Look [1] SAC [2]
2.2.	PP	Non-Standard EFF_F1	Summary of Change from Baseline in ACT Total Score Per Protocol Population	Present "ACT Total Score" on y-axis and "Visit" on x-axis (Randomisation (Day 0), Week 6, Week 12, Week 18, Week 24). Present mean ACT Total Score ± SD separately for treatment group (FF/VI, Usual ICS/LABA) at each visit, connecting the means with a solid line. Distinguish the treatment groups by different line types.	SAC [2]
2.3.	ITT	Non-Standard EFF_F1	Summary of Change from Baseline in ACT Total Score by Country	Present "ACT Total Score" on y-axis and "Visit" on x-axis (Randomisation (Day 0), Week 6, Week 12, Week 18, Week 24). Present mean ACT Total Score ± SD separately for treatment group (FF/VI, Usual ICS/LABA) at each visit, connecting the means with a solid line. Distinguish the treatment groups by different line types.	SAC [2]

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.4.	ITT/PP	Non-Standard EFF_F2	Summary of Primary and Sensitivity Analyses for Change from Baseline in ACT Total Score at Week 12 (Visit 4)	Present “Treatment difference” on the x-axis, and reverse axis so treatment difference increases from left to right. Replace “Ratio (95% CI)” with “Treatment Difference (95% CI)”. Present lines for the following: Primary analysis (ITT), Primary analysis (PP), ANCOVA with LOCF (ITT), Multiple Imputation (Missing at Random) (ITT), Multiple Imputation (Copy Differences from Reference) (ITT), Hodges-Lehmann (ITT), ANCOVA with WOCF (ITT).	Data Look [1] SAC [2]
2.5.	ITT	Non-Standard EFF_F3	Summary of Interaction Tests for Change from Baseline in ACT Total Score at Week 12 (Visit 4)	Present “LS Mean Change” on the x-axis, and reverse axis so it increases from left to right. Replace “Ratio (95% CI)” with “LS Mean Change (95% CI)”. Present the following subgroups: Country (France, Germany); Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation (0, >= 1); Smoking Status at Baseline (Current smoker, Former smoker, Never smoked); Age Group (≤ 50 Years Old, > 50 Years Old); Gender (Male, Female).	Data Look [1] SAC [2]

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in ACT Total Score at Week 24 (Visit 6)					
2.6.	ITT/PP	Non-Standard EFF_F2	Summary of Key Secondary and Sensitivity Analyses for Change from Baseline in ACT Total Score at Week 24 (Visit 6)	Present "Treatment difference" on the x-axis, and reverse axis so treatment difference increases from left to right. Replace "Ratio (95% CI)" with "Treatment Difference (95% CI)". Present lines for the following: Primary analysis (ITT), Primary analysis (PP), ANCOVA with LOCF (ITT), Multiple Imputation (Missing at Random) (ITT), Multiple Imputation (Copy Differences from Reference) (ITT), Hodges-Lehmann (ITT), ANCOVA with WOCF (ITT).	SAC [2]
Subjects Who Have Either an ACT Total Score >= 20 or >= 3 Point Increase from Baseline in ACT Total Score					
2.7.	ITT	Non-Standard EFF_F4	Summary of Percentage of Subjects Who Have Either an ACT Total Score >= 20 or >= 3 Point Increase from Baseline in ACT Total Score	Present "Percent of Subjects (%)" on y-axis and "Visit" on x-axis (Week 6, Week 12, Week 18, Week 24, Early Withdrawal). For each visit, present 3 vertical bars distinguished by fill pattern (similar to non-standard EFF_F6). Each bar represents: "ACT Total Score >= 20 or >= 3 Point Increase from Baseline in ACT Total Score", "ACT Total Score >= 20" and ">= 3 Point Increase from Baseline in ACT Total Score" respectively and should be labelled as such on the legend.	Data Look [1] SAC [2]

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Compliance with Study Medication					
2.8.	ITT	Non-Standard EFF_F5	Box Plot of Compliance with Study Medication	Label y-axis title as “Compliance (%)”, maximum of y-axis may be > 100%.	Data Look [1] SAC [2]
MARS-A					
2.9.	ITT	Non-Standard EFF_F6	Histogram of the Questions and Answers of the MARS-A Questionnaire	Repeat on subsequent pages for Visit = Week 24, Week 52 and Early Withdrawal; and for Randomised Treatment = FF/VI.	Data Look [1] SAC [2]
2.10.	ITT	Non-Standard EFF_F6	Histogram of the Questions and Answers of the MARS-A Questionnaire by Status of Patient in Relation to the Reminder Sent to French Centres	Present bylines and footnotes per “Repeat for” programming note on shell.	SAC [2]
2.11.	ITT	Non-Standard EFF_F7	Histogram of the Distribution of MARS-A Scores During the Study	Repeat on subsequent pages for Visit = Week 52 and Early Withdrawal.	Data Look [1] SAC [2]
2.12.	ITT	Non-Standard EFF_F7	Histogram of the Distribution of MARS-A Scores During the Study by Status of Patient in Relation to the Reminder Sent to French Centres	Present bylines and footnotes per “Repeat for” programming note on shell.	SAC [2]
Severe On-Treatment Asthma Exacerbations					
2.13.	ITT	Non-Standard EFF_F8	Box Plot of Severe On-Treatment Asthma Exacerbation Rates Adjusted for Exposure to Treatment		Data Look [1] SAC [2]
2.14.	ITT	Non-Standard EFF_F9	Kaplan-Meier Plot of Time to First Severe On-Treatment Asthma Exacerbation	Display increments of 6 weeks on the x-axis, up to the maximum exposure (e.g. 0, 6, 12, 18, 24, 30).	Data Look [1] SAC [2]

12.15.8. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
SAEs and ADRs					
3.1.	Safety	Non-Standard SAFE_T1	On-Treatment Serious Adverse Events and Adverse Drug Reactions Overview	Based on IDSL standard template AE13.	Data Look [1] SAC [2]
3.2.	Safety	AE1	Summary of On-Treatment Non-Serious Adverse Drug Reactions		SAC [2]
3.3.	Safety	AE1	Summary of On-Treatment Serious Adverse Drug Reactions		SAC [2]
3.4.	Safety	AE1	Summary of On-Treatment Adverse Drug Reactions		Data Look [1] SAC [2]
3.5.	Safety	AE1	Summary of On-Treatment Serious Adverse Events		Data Look [1] SAC [2]
3.6.	Safety	AE1	Summary of On-Treatment or Post-Treatment Serious Adverse Events and Adverse Drug Reactions Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study		SAC [2]
3.7.	Safety	AE1	Summary of On-Treatment or Post-Treatment Serious Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study		SAC [2]
3.8.	Safety	AE1	Summary of On-Treatment or Post-Treatment Adverse Drug Reactions Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study		SAC [2]
3.9.	Safety	AE1	Summary of Most Frequent On-Treatment Non-Serious Adverse Drug Reactions, Reported by 1% or More of Subjects in Any Treatment Group		SAC [2]

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
SAEs and ADRs of Special Interest					
3.10.	Safety	Non-Standard SAFE_T2	Summary of On-Treatment Non-Serious Adverse Drug Reactions of Special Interest	Based on IDSL standard template AE1.	Data Look [1] SAC [2]
3.11.	Safety	Non-Standard SAFE_T2	Summary of On-Treatment Serious Adverse Drug Reactions of Special Interest	Based on IDSL standard template AE1.	SAC [2]
3.12.	Safety	Non-Standard SAFE_T2	Summary of On-Treatment Adverse Drug Reactions of Special Interest	Based on IDSL standard template AE1.	SAC [2]
3.13.	Safety	Non-Standard SAFE_T2	Summary of On-Treatment Serious Adverse Events of Special Interest	Based on IDSL standard template AE1.	SAC [2]
Fatal SAEs and ADRs					
3.14.	Safety	AE1	Summary of On-Treatment Fatal Serious Adverse Events		SAC [2]
3.15.	Safety	AE1	Summary of On-Treatment Fatal Serious Adverse Drug Reactions		SAC [2]
3.16.	Safety	Non-Standard SAFE_T2	Summary of On-Treatment Fatal Serious Adverse Events of Special Interest	Based on IDSL standard template AE1.	SAC [2]
Non-Fatal SAEs and ADRs					
3.17.	Safety	AE1	Summary of On-Treatment Non-Fatal Serious Adverse Events		SAC [2]
3.18.	Safety	Non-Standard SAFE_T2	Summary of On-Treatment Non-Fatal Serious Adverse Events of Special Interest	Based on IDSL standard template AE1.	SAC [2]
Top Ten Most Commonly Reported ADRs					
3.19.	Safety	Non-Standard SAFE_T3	Top Ten Most Commonly Reported On-Treatment Adverse Drug Reactions Per Treatment Group	Present the ten most frequent preferred terms in Usual ICS/LABA, and the ten most frequent in FF/VI (do not use percentages to determine “most frequent”)	Data Look [1] SAC [2]

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
3.20.	Safety	VS1	Summary of Vital Signs		SAC [2]
3.21.	Safety	VS1	Summary of Change from Baseline in Vital Signs		SAC [2]
3.22.	Safety	AE15	Summary of Common (>=3%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC [2]
3.23.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC [2]

12.15.9. Safety Figures

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Benefit:Risk					
3.1.	ITT/Safety	Non-Standard SAFE_F1	Summary of Benefit:Risk for FF/VI vs. Usual ICS/LABA		Data Look [1] SAC [2]

12.15.10. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
1.	ITT	ES2	Reasons for Study Withdrawal		SAC [2]
2.	ITT	TA1	Randomised and Actual Treatments		SAC [2]
3.	ITT	IE3	Subjects with Inclusion, Exclusion or Randomisation Criteria Deviations		SAC [2]
4.	ITT	DM2	Demographic Characteristics		SAC [2]
5.	ITT	DM9	Race		SAC [2]
Adverse Events					
6.	Safety	AE7	Subject Numbers for Individual Serious Adverse Events and Non-Serious Adverse Drug Reactions		SAC [2]
7.	Safety	AE8	All Serious Adverse Events and Non-Serious Adverse Drug Reactions		SAC [2]
8.	Safety	AE8	Fatal Serious Adverse Events		SAC [2]
9.	Safety	AE8	Serious Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study		SAC [2]
10.	Safety	AE8	Non-Serious Adverse Drug Reactions Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study		SAC [2]

12.15.11. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
11.	ASE	Non-Standard POP_L1	Subjects Screened but Not in the Intent-to-Treat Population		SAC [2]
12.	ITT	Non-Standard POP_L2	Reasons for Important Protocol Deviations		SAC [2]
13.	ITT	MH2	Medical Conditions		SAC [2]
14.	ITT	Non-Standard POP_L3	Asthma History		SAC [2]
15.	ITT	Non-Standard POP_L4	Smoking History		SAC [2]
16.	ITT	CM3	Concomitant Medications	Only include medications included in pre-treatment and on-treatment summary tables.	SAC [2]
17.	ITT	CM6	Relationship between Ingredient and Verbatim Text		SAC [2]
18.	ITT	Non-Standard POP_L5	Exposure to Study Medication	Repeat on subsequent pages for Treatment = FF/VI, and use GSK drug synonym as drug name.	SAC [2]
Efficacy					
19.	ITT	Non-Standard EFF_L1	ACT Scores	Repeat on subsequent pages for Treatment = FF/VI.	SAC [2]
20.	ITT	Non-Standard EFF_L2	Inhaler Device Use	Repeat on subsequent pages for Treatment = FF/VI.	SAC [2]
21.	ITT	Non-Standard EFF_L3	Lung Function Tests	Repeat on subsequent pages for Treatment = FF/VI.	SAC [2]

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
22.	ITT	Non-Standard EFF_L4	Medication Adherence Report Scale for Asthma (MARS-A) Scores	Repeat on subsequent pages for Treatment = FF/VI.	SAC [2]
23.	ITT	Non-Standard EFF_L5	Severe Asthma Exacerbations	Repeat on subsequent pages for Treatment = FF/VI.	SAC [2]
24.	ITT	Non-Standard EFF_L6	AQLQ(S) Scores	Repeat on subsequent pages for Treatment = FF/VI.	SAC [2]
25.	ITT	Non-Standard EFF_L7	EQ-5D-5L Descriptive System Dimension Scores	Repeat on subsequent pages for Treatment = FF/VI.	SAC [2]
26.	ITT	Non-Standard EFF_L8	PASAP-Q Scores	Repeat on subsequent pages for Treatment = FF/VI.	SAC [2]
Safety					
27.	Safety	Non-Standard SAFE_L1	AE Terms of Special Interest	The AE special interest dataset and the AE SMQ dataset will be set together in order to report this table and all the subgroups that come from the AE SMQ dataset will be flagged with a [1].	SAC [2]
28.	Safety	VS4	Vital Signs		SAC [2]
29.	Safety	Non-Standard SAFE_L2	Inhaler Device Malfunctions		SAC [2]
Liver Chemistry					
30.	Safety	LIVER5	Liver Event Results and Time of Event Relative to Treatment		SAC [2]
31.	Safety	LIVER6	Liver Event Information for RUCAM Score		SAC [2]
32.	Safety	LIVER7	Liver Biopsy Details		SAC [2]
33.	Safety	LIVER8	Liver Imaging Details		SAC [2]

12.16. Appendix 16: Example Mock Shells for Data Displays

12.16.1. Study Population Table Shells

Example : POP_T1
Protocol : HZA116492
Population : All Subjects Enrolled

Table 1.xx
Summary of Subject Populations

Population	Usual ICS/LABA	FF/VI	Total
All Subjects Enrolled (ASE)			xxx
Randomised	xxx	xxx	xxx
Intent-to-Treat (ITT)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Per Protocol (PP)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Safety	xxx (xx%)	xxx (xx%)	xxx (xx%)

ASE: All subjects screened and for whom a record exists on the study database.
ITT: All randomised subjects having received at least one dose of the prescription of study medication (FF/VI or Usual ICS/LABA).
PP: All ITT subjects who without any protocol deviations excluding them from this population.
Safety: All randomised subjects having received at least one dose of the prescription of study medication (FF/VI or Usual ICS/LABA).
Note: The randomised summary is not a defined population and consists of all subjects who were randomised and given a randomisation number.

Programming Note: randomised population line will provide the denominators for the ITT, PP and Safety percentages.

Example : POP_T2
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Attendance at Each Clinic Visit

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Screening	xxx (xx%)	xxx (xx%)	xxx (xx%)
Randomisation (Day 0)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Week 6	xxx (xx%)	xxx (xx%)	xxx (xx%)
Week 12	xxx (xx%)	xxx (xx%)	xxx (xx%)
Week 18	xxx (xx%)	xxx (xx%)	xxx (xx%)
Week 24	xxx (xx%)	xxx (xx%)	xxx (xx%)
Early Withdrawal	xxx (xx%)	xxx (xx%)	xxx (xx%)

Note: Weeks 6 and 18 are telephone contacts.

Example : POP_T3
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Important Protocol Deviations

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Any Important Protocol Deviation	xxx (xx%)	xxx (xx%)	xxx (xx%)
Reason 1	xxx (xx%)	xxx (xx%)	xxx (xx%)
Reason 2	xxx (xx%)	xxx (xx%)	xxx (xx%)
Reason 3	xxx (xx%)	xxx (xx%)	xxx (xx%)
...	xxx (xx%)	xxx (xx%)	xxx (xx%)

Note: A subject may have more than one protocol deviation.
Note: Includes any important deviation from the protocol.

Repeat for:
Summary of Important Protocol Deviations Resulting in Exclusion from the PP Population (ITT Population)

Example : POP_T4
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Asthma Duration at Baseline

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Duration of Asthma			
< 6 months	xxx (xx%)	xxx (xx%)	xxx (xx%)
>= 6 months to < 1 year	xxx (xx%)	xxx (xx%)	xxx (xx%)
>= 1 year to < 5 years	xxx (xx%)	xxx (xx%)	xxx (xx%)
>= 5 years to < 10 years	xxx (xx%)	xxx (xx%)	xxx (xx%)
>= 10 years	xxx (xx%)	xxx (xx%)	xxx (xx%)
Duration of Asthma (years):			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	x.xx	x.xx	x.xx
Median	xx.x	xx.x	xx.x
Min.	xx	xx	xx
Max.	xx	xx	Xx

Repeat for:
Summary of Asthma Duration at Baseline (PP Population)

Example : POP_T5
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Asthma Exacerbation History at Baseline

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Did not require oral/systemic corticosteroids (not involving hospitalisation)			
n	xx	xx	xx
0	xx (xx%)	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)	xx (xx%)
> 1	xx (xx%)	xx (xx%)	xx (xx%)
Required oral/systemic corticosteroids (not involving hospitalisation)			
n	xx	xx	xx
0	xx (xx%)	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)	xx (xx%)
> 1	xx (xx%)	xx (xx%)	xx (xx%)
Required hospitalisation			
n	xx	xx	xx
0	xx (xx%)	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)	xx (xx%)
> 1	xx (xx%)	xx (xx%)	xx (xx%)

Note: Number of severe asthma exacerbations reported in the 12 months prior to Randomisation (Day 0).

Example : POP_T5
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Asthma Exacerbation History at Baseline

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Total number of exacerbations during the 12 months prior to randomisation			
n	xx	xx	xx
0	xx (xx%)	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)	xx (xx%)
> 1	xx (xx%)	xx (xx%)	xx (xx%)
Number of exacerbations during the 12 months prior to randomisation			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	x.xx	x.xx	x.xx
Median	xx.x	xx.x	xx.x
Min.	xx	xx	xx
Max.	xx	xx	xx

Note: Number of severe asthma exacerbations reported in the 12 months prior to Randomisation (Day 0).

Repeat for:
Summary of Asthma Exacerbation History at Baseline (PP Population)

Example : POP_T6
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Smoking History at Baseline

		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
History of Smoking Use	Current smoker	xxx (xx%)	xxx (xx%)	xxx (xx%)
	Former smoker	xxx (xx%)	xxx (xx%)	xxx (xx%)
	Never smoked	xxx (xx%)	xxx (xx%)	xxx (xx%)
For Current and Former Smokers:				
Years Smoked	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Cigarettes/Day	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx

[1] Smoking Pack Years = (Number of cigarettes smoked per day/20) x number of years smoked.

Example : POP_T6
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Smoking History at Baseline

		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Smoking Pack Years[1]				
Overall	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Current Smokers	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Former Smokers	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx

[1] Smoking Pack Years = (Number of cigarettes smoked per day/20) x number of years smoked.
Repeat for: *Summary of Smoking History at Baseline (PP Population)*

Example : POP_T7
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Study Medication Dosage Modification

Dosage Modification / Prescription Treatment Path	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Did Not Modify Dose During the Study	xxx (xx%)	xxx (xx%)	xxx (xx%)
Modified Dose at Least Once During the Study	xxx (xx%)	xxx (xx%)	xxx (xx%)
Randomised to FF/VI		xxx	xxx
FF/VI 92 mcg/22 mcg OD		xxx (xx%)	xxx (xx%)
FF/VI 92 mcg/22 mcg OD -> FF/VI 184 mcg/22 mcg OD		xxx (xx%)	xxx (xx%)
Randomised to Usual ICS/LABA and Prescribed FP/S	xxx		xxx
FP/S 250 mcg/50 mcg BID	xxx (xx%)		xxx (xx%)
FP/S 250 mcg/50 mcg BID -> FP/S 500 mcg/50 mcg BID	xxx (xx%)		xxx (xx%)
Randomised to Usual ICS/LABA and Prescribed BUD/F	xxx		xxx
BUD/F 200 mcg/6 mcg BID (1 inh)	xxx (xx%)	xxx (xx%)	xxx (xx%)
BUD/F 200 mcg/6 mcg BID (1 inh) -> BUD/F 200 mcg/6 mcg BID (2 inh)	xxx (xx%)	xxx (xx%)	xxx (xx%)
BUD/F 200 mcg/6 mcg BID (1 inh) -> BUD/F 400 mcg/12 mcg BID (1 inh)	xxx (xx%)	xxx (xx%)	xxx (xx%)
BUD/F 200 mcg/6 mcg BID (2 inh)	xxx (xx%)	xxx (xx%)	xxx (xx%)
BUD/F 200 mcg/6 mcg BID (2 inh) -> BUD/F 400 mcg/12 mcg BID (1 inh)	xxx (xx%)	xxx (xx%)	xxx (xx%)
BUD/F 200 mcg/6 mcg BID (2 inh) -> BUD/F 400 mcg/12 mcg BID (2 inh)	xxx (xx%)	xxx (xx%)	xxx (xx%)

Note: 1 inh = 1 inhalation per dose, 2 inh = 2 inhalations per dose.
Note: Subjects randomised to FF/VI initiated treatment on 92 mcg/22 mcg OD and could increase to 184 mcg/22 mcg OD.
Note: Subjects randomised to Usual ICS/LABA and prescribed FP/S initiated treatment on 250 mcg/50 mcg BID and could increase to 500 mcg/50 mcg BID.

Note: Subjects randomised to Usual ICS/LABA and prescribed BUD/F could: initiate treatment on 200 mcg/6 mcg BID (1 inh) and increase to 200 mcg/6 mcg BID (2 inh) or 400 mcg/12 mcg BID (1 inh); or initiate on 200 mcg/6 mcg BID (2 inh) and modify to 400 mcg/12 mcg BID (1 inh) or increase to 400 mcg/12 mcg BID (2 inh).

Example : POP_T8
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Extent of Exposure to Study Medication (Regardless of Modification to Study Medication Dosage)

Overall		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Exposure (days) [1]	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Total Years Exposed (yrs)		xx	xx
Range of Exposure (days)	<= 6 weeks	xxx (xx%)	xxx (xx%)
	<= 12 weeks	xxx (xx%)	xxx (xx%)
	<= 18 weeks	xxx (xx%)	xxx (xx%)
	<= 24 weeks	xxx (xx%)	xxx (xx%)
	> 24 weeks	xxx (xx%)	xxx (xx%)
Subjects Exposed for six months (24 weeks ± 2 weeks)		xxx (xx%)	xxx (xx%)

[1] Exposure to study medication = treatment stop date – treatment start date + 1, regardless of dosage modification.

Repeat for:
Summary of Summary of Extent of Exposure to Study Medication (up to First Modification to Study Medication Dosage) (ITT Population)
Footnote: "[1] Exposure to study medication = treatment stop date - treatment start date + 1."

Example : POP_T9
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Extent of Exposure to Study Medication by Medication and Dosage

Medication/Dosage	Overall		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
FF/VI 92 mcg/22 mcg OD	Exposure (days) [1]	n	xx	xx
		Mean	xx.x	xx.x
		SD	x.xx	x.xx
		Median	xx.x	xx.x
		Min.	xx	xx
		Max.	xx	xx
	Total Years Exposed (yrs)		xx	xx
	Range of Exposure (days)	<= 6 weeks	xxx (xx%)	xxx (xx%)
		<= 12 weeks	xxx (xx%)	xxx (xx%)
		<= 18 weeks	xxx (xx%)	xxx (xx%)
		<= 24 weeks	xxx (xx%)	xxx (xx%)
		> 24 weeks	xxx (xx%)	xxx (xx%)
	Subjects Exposed for six months (24 weeks ± 2 weeks)		xxx (xx%)	xxx (xx%)

[1] Exposure to study medication = treatment stop date – treatment start date + 1.

Programming note: repeat on subsequent pages for Medication/Dosage = FF/VI 184 mcg/22 mcg OD, FP/S 250 mcg/50 mcg BID, FP/S 500 mcg/50 mcg BID, BUD/F 200 mcg/6 mcg BID (1 inhalation per dose), BUD/F 200 mcg/6 mcg BID (2 inhalations per dose), BUD/F 400 mcg/12 mcg BID (1 inhalation per dose), BUD/F 400 mcg/12 mcg BID (2 inhalations per dose).

Example : POP_T10
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Number of Subjects by Subgroup

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Country			
n	xxx	xxx	xxx
France	xxx (xx%)	xxx (xx%)	xxx (xx%)
Germany	xxx (xx%)	xxx (xx%)	xxx (xx%)
Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation			
n	xxx	xxx	xxx
0	xxx (xx%)	xxx (xx%)	xxx (xx%)
>= 1	xxx (xx%)	xxx (xx%)	xxx (xx%)
Smoking Status at Baseline			
n	xxx	xxx	xxx
Current smoker	xxx (xx%)	xxx (xx%)	xxx (xx%)
Former smoker	xxx (xx%)	xxx (xx%)	xxx (xx%)
Never smoked	xxx (xx%)	xxx (xx%)	xxx (xx%)
Age Group			
n	xxx	xxx	xxx
≤ 50 years old	xxx (xx%)	xxx (xx%)	xxx (xx%)
> 50 years old	xxx (xx%)	xxx (xx%)	xxx (xx%)

Note: Spring = March, April and May; Summer = June, July and August; Autumn = September, October and November; Winter = December, January and February.

Example : POP_T10
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Number of Subjects by Subgroup

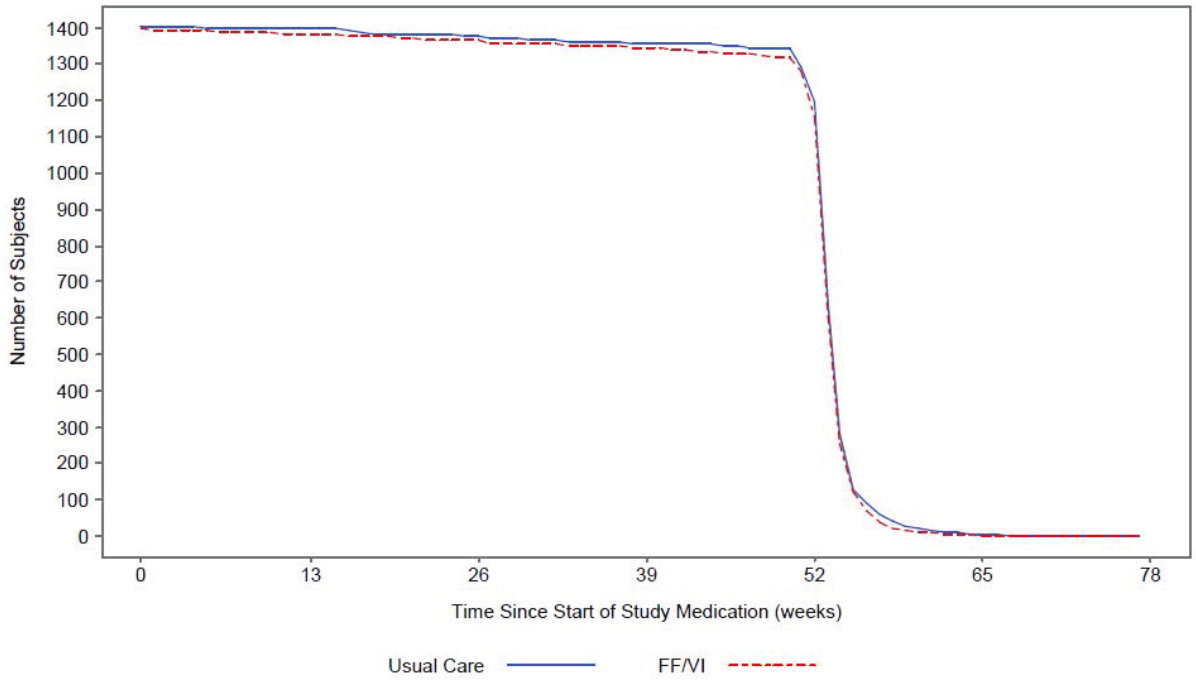
	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Gender			
n	xxx	xxx	xxx
Male	xxx (xx%)	xxx (xx%)	xxx (xx%)
Female	xxx (xx%)	xxx (xx%)	xxx (xx%)
Season at randomisation			
n	xxx	xxx	xxx
Spring	xxx (xx%)	xxx (xx%)	xxx (xx%)
Summer	xxx (xx%)	xxx (xx%)	xxx (xx%)
Autumn	xxx (xx%)	xxx (xx%)	xxx (xx%)
Winter	xxx (xx%)	xxx (xx%)	xxx (xx%)

Note: Spring = March, April and May; Summer = June, July and August; Autumn = September, October and November; Winter = December, January and February.

12.16.2. Study Population Figure Shells

Example : POP_F1
Protocol : HZA116492
Population : Intent-to-Treat

Figure 1.xx
Plot of Exposure to Study Medication (Regardless of Modification to Study Medication Dosage)



Programming note: display increments of 6 weeks on the x-axis, up to the maximum exposure (e.g. 0, 6, 12, 18, 24, 30).

12.16.3. Efficacy Table Shells

Example : EFF_T1
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Change from Baseline in ACT Total Score

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Randomisation (Day 0)	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Week 6	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Change from Baseline at Week 6	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x

Min.	xx	xx
Max.	xx	xx

Programming note: repeat for Week 12, Change from Baseline at Week 12, Week 18, Change from Baseline at Week 18, Week 24, Change from Baseline at Week 24, Early Withdrawal, Change from Baseline at Early Withdrawal

Repeat for:
Summary of Change from Baseline in ACT Total Score Per Protocol Population (PP Population)

Summary of Change from Baseline in Lung Function Tests (ITT Population)
Programming note: Present an additional column to the left of "Visit", labelled "Test" with values "Trough (Pre-dose) FEV1 (L)" and "Trough (Pre-dose) Percent Predicted FEV1 (%)" to allow presentation of results by Test. Present the following visits: Randomisation (Day 0), Week 12, Change from Baseline at Week 12, Early Withdrawal and Change from Baseline at Early Withdrawal.

Summary of Change from Baseline in AQLQ(S) Total Score and Domain Scores (ITT Population)
Programming note: Present an additional column to the left of "Visit", labelled "Domain" with values "Total Score", "Environmental Stimuli", "Symptoms", "Activity Limitations", "Emotional Function" to allow presentation of results by Domain. Present the following visits: Randomisation (Day 0), Week 24, Change from Baseline at Week 24, Early Withdrawal and Change from Baseline at Early Withdrawal.

Summary of PASAP-Q Scores (ITT Population)
Programming note: Present an additional column to the left of "Visit", labelled "Score" with values "Performance", "Convenience", "Total Score", "Overall Satisfaction", and "Willingness to Continue Using Inhaler" to allow presentation of results by Domain. Present the following visits: Week 12 and Early Withdrawal.
Add the following footnotes:
"Note: Performance, Convenience, Total Score, and Willingness to Continue Using Inhaler are expressed on a scale of 0 to 100.
Note: Overall Satisfaction is expressed on a scale of 1 to 7."

Summary of EQ-5D-5L Utility Score (ITT Population)
Summary of EQ-5D-5L Visual Analogue Scale (VAS) Score (ITT Population)
Programming note: Present the following visits: Randomisation (Day 0), Week 24, Change from Baseline at Week 24, Early Withdrawal, Change from Baseline at Early Withdrawal.

Example : EFF_T1S
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Change from Baseline in ACT Total Score by Country

Country: France

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Randomisation (Day 0)	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Week 6	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Change from Baseline at Week 6	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx

Example : EFF_T1S
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Change from Baseline in ACT Total Score by Country

Country: Germany

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Randomisation (Day 0)	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Week 6	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Change from Baseline at Week 6	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx

Repeat for:
Summary of Change from Baseline in ACT Total Score by Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation (ITT Population)
Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation: 0
Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation: >= 1

Summary of Change from Baseline in ACT Total Score by Smoking Status at Baseline (ITT Population)
Smoking Status at Baseline: Current smoker
Smoking Status at Baseline: Former smoker
Smoking Status at Baseline: Never smoked

Summary of Change from Baseline in ACT Total Score by Age Group (ITT Population)
Age Group: ≤ 50 Years Old
Age Group: > 50 Years Old

Summary of Change from Baseline in ACT Total Score by Gender (ITT Population)
Gender: Male
Gender: Female

Example : EFF_T2
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4)

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
n	xx	xx
LS Mean Change (SE)	xx.xx (x.xxx)	xx.xx (x.xxx)
FF/VI vs. Usual ICS/LABA		
Difference		xx.x
95% CI		(xx.x, xx.x)
p-value		x.xxx

Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient fitted as a random factor.
Note: The Restricted Maximum Likelihood (REML) estimation approach was used with a default covariance structure of unstructured.

Programming note: Should computational issues be encountered when using an unstructured covariance structure, other structures including AR1 and CS should be considered and the second footnote updated as appropriate. Should the distributional assumption of normality fail then the p-value from a model on the rank-transformed values should be presented and the following footnote added: "Note: the p-value presented was obtained from an MMRM on the rank-transformed values of change from baseline in ACT total score at Week 12 (Visit 4) with the same specification as the untransformed model."

Repeat for:
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) Per Protocol Population (PP Population)

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (ANCOVA with LOCF) (ITT Population)
Programming note: Should the distributional assumption of normality fail then the p-value from a model on the rank-transformed values should be presented and the following footnote added: "Note: the p-value presented was obtained from an ANCOVA on the rank-transformed values of change from baseline in ACT total score at Week 12 (Visit 4) with the same specification as the untransformed model."
Footnotes as follows:
"Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline ACT total score, gender, age and country.
Note: Missing values at Week 12 (Visit 4) were replaced by last available post-randomisation value based on the last observation carried forward (LOCF) method."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (Multiple Imputation – Missing at Random Approach) (ITT Population)
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (Multiple Imputation – Copy Differences from Reference Approach) (ITT Population)
Programming note: Present the "FF/VI vs. Usual ICS/LABA" section only. Footnotes as follows:
"Note: Missing values post-randomisation were imputed using multiple imputation methods based on pattern mixture models.
Note: Each imputed data set was analysed using an ANCOVA model at Week 12 (Visit 4) adjusted for randomised treatment, baseline ACT total score, gender, age and country and the resulting treatment differences and their standard errors combined using Rubin's rules."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (Hodges-Lehmann Approach) (ITT Population)
Programming note: Present the "Difference" and "95% CI" lines of "FF/VI vs. Usual ICS/LABA" section only. Footnotes as follows:
"Note: The difference between treatment groups at Week 12 (Visit 4) was calculated using the Hodges-Lehmann approach."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (ANCOVA with WOCF) (ITT Population)
Programming note: Should the distributional assumption of normality fail then the p-value from a model on the rank-transformed values should be presented and the following footnote added: "Note: the p-value presented was obtained from an ANCOVA on the rank-transformed values of change from baseline in ACT total score at Week 12 (Visit 4) with the same specification as the untransformed model."
Footnotes as follows:
"Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline ACT total score, gender, age and country.
Note: Missing values at Week 12 (Visit 4) due to treatment withdrawal prior to this time point were replaced by worst post-randomisation value based on the worst observation carried forward (WOCF) method."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed FP/S at Randomisation (ITT Population)
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed BUD/F at Randomisation (ITT Population)

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (ITT Population)
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) Per Protocol Population (PP Population)
Programming note: first footnote as follows:
"Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient fitted as a random factor."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (ANCOVA with LOCF) (ITT Population)
Programming note: Should the distributional assumption of normality fail then the p-value from a model on the rank-transformed values should be presented and the following footnote added: "Note: the p-value presented was obtained from an ANCOVA on the rank-transformed values of change from baseline in ACT total score at Week 24 (Visit 6) with the same specification as the untransformed model."
Footnotes as follows:
"Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline ACT total score, gender, age and country.
Note: Missing values at Week 24 (Visit 6) were replaced by last available post-randomisation value based on the last observation carried forward (LOCF) method."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (Multiple Imputation – Missing at Random Approach) (ITT Population)
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (Multiple Imputation – Copy Differences from Reference Approach) (ITT Population)
Programming note: Present the "FF/VI vs. Usual ICS/LABA" section only. Footnotes as follows:
"Note: Missing values post-randomisation were imputed using multiple imputation methods based on pattern mixture models.
Note: Each imputed data set was analysed using an ANCOVA model at Week 24 (Visit 6) adjusted for randomised treatment, baseline ACT total score, gender, age and country and the resulting treatment differences and their standard errors combined using Rubin's rules."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (Hodges-Lehmann Approach) (ITT Population)
Present the "Difference" and "95% CI" lines of "FF/VI vs. Usual ICS/LABA" section only. Footnotes as follows:
"Note: The difference between treatment groups at Week 24 (Visit 6) was calculated using the Hodges-Lehmann approach."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (ANCOVA with WOCF) (ITT Population)

Programming note: Should the distributional assumption of normality fail then the p-value from a model on the rank-transformed values should be presented and the following footnote added: “Note: the p-value presented was obtained from an ANCOVA on the rank-transformed values of change from baseline in ACT total score at Week 24 (Visit 6) with the same specification as the untransformed model.”
Footnotes as follows:
“Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline ACT total score, gender, age and country.
Note: Missing values at Week 24 (Visit 6) due to treatment withdrawal prior to this time point were replaced by worst post-randomisation value based on the worst observation carried forward (WOCF) method.”

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6), FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed FP/S at Randomisation (ITT Population)
Programming note: Output only to be produced if ≥25% of Usual ICS/LABA patients are prescribed FP/S at randomisation. First footnote as follows:
“Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient fitted as a random factor.”

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6), FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed BUD/F at Randomisation (ITT Population)
Programming note: Output only to be produced if ≥25% of Usual ICS/LABA patients are prescribed BUD/F at randomisation. First footnote as follows:
“Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient fitted as a random factor.”

Summary of the Statistical Analysis of Change from Baseline in Trough (Pre-dose) FEV1 at Week 12 (Visit 4) (ITT Population)
Programming note: Should the distributional assumption of normality fail then the p-value from a model on the rank-transformed values should be presented and the following footnote added: “Note: the p-value presented was obtained from an ANCOVA on the rank-transformed values of change from baseline in trough (pre-dose) FEV1 at Week 12 (Visit 4) with the same specification as the untransformed model.”
Footnote as follows:
“Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline trough (pre-dose) FEV1, gender, age and country.”

Summary of the Statistical Analysis of Change from Baseline in EQ-5D-5L Utility Score at Week 24 (Visit 6) (ITT Population)
Programming note: Should the distributional assumption of normality fail then the p-value from a model on the rank-transformed values should be presented and the following footnote added: “Note: the p-value presented was obtained from an ANCOVA on the rank-transformed values of change from baseline in EQ-5D-5L utility score at Week 24 (Visit 6) with the same specification as the untransformed model.”
Footnote as follows:
“Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline EQ-5D-5L utility score, gender, age and country.”

Summary of the Statistical Analysis of Change from Baseline in EQ-5D-5L Visual Analogue Scale (VAS) Score at Week 24 (Visit 6) (ITT Population)

Programming note: Should the distributional assumption of normality fail then the p-value from a model on the rank-transformed values should be presented and the following footnote added: “Note: the p-value presented was obtained from an ANCOVA on the rank-transformed values of change from baseline in EQ-5D-5L VAS score at Week 24 (Visit 6) with the same specification as the untransformed model.”

Footnote as follows:

“Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline EQ-5D-5L VAS score, gender, age and country.”

Example : EFF_T2S
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Country

Country: France

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
n	xx	xx
LS Mean Change (SE)	xx.xx (x.xxx)	xx.xx (x.xxx)
FF/VI vs. Usual ICS/LABA		
Difference		xx.x
95% CI		(xx.x, xx.x)

Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, two- and three- way interactions between randomised treatment, visit and country, and patient fitted as a random factor.
Note: The Restricted Maximum Likelihood (REML) estimation approach was used with a default covariance structure of unstructured.

Example : EFF_T2S
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Country

Country: Germany

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
n	xx	xx
LS Mean Change (SE)	xx.xx (x.xxx)	xx.xx (x.xxx)
FF/VI vs. Usual ICS/LABA		
Difference		xx.x
95% CI		(xx.x, xx.x)

Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country, randomised treatment-by-country interaction and patient fitted as a random factor.
Note: The Restricted Maximum Likelihood (REML) estimation approach was used with a default covariance structure of unstructured.

Programming note: Should computational issues be encountered when using an unstructured covariance structure, other structures including AR1 and CS should be considered and the second footnote updated as appropriate.

Repeat for:

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation (ITT Population)

Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation: 0

Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation: >= 1

Programming note: first footnote as follows:

"Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, number of severe asthma exacerbations in the previous year prior to randomisation, two- and three- way interactions between randomised treatment, visit and number of severe asthma exacerbations in the previous year prior to randomisation, and patient fitted as a random factor."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Smoking Status at Baseline (ITT Population)

Programming note: first footnote as follows:

"Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, smoking status at baseline, two- and three- way interactions between randomised treatment, visit and smoking status at baseline, and patient fitted as a random factor."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Age Group (ITT Population)

Programming note: first footnote as follows:

"Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, country, age group, two- and three- way interactions between randomised treatment, visit and age group, and patient fitted as a random factor."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Gender (ITT Population)

Programming note: first footnote as follows:

"Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, two- and three- way interactions between randomised treatment, visit and gender, and patient fitted as a random factor."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) by Country (ITT Population)

Programming note: first footnote as follows:

"Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, two- and three- way interactions between randomised treatment, visit and country, and patient fitted as a random factor."

Example : EFF_T3
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), Adjusting for Seasonal Effect

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Randomised treatment-by-season at randomisation interaction		
p-value		x.xxx
Season at randomisation: Spring		
n	xx	xx
LS Mean Change (SE)	xx.xx (x.xxx)	xx.xx (x.xxx)
FF/VI vs. Usual ICS/LABA		
Difference		xx.x
95% CI		(xx.x, xx.x)
....		

Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, season at randomisation, two- and three- way interactions between randomised treatment, visit and season at randomisation, and patient fitted as a random factor.
Note: The Restricted Maximum Likelihood (REML) estimation approach was used with a default covariance structure of unstructured.
Note: Spring = March, April and May; Summer = June, July and August; Autumn = September, October and November; Winter = December, January and February.

Programming note: repeat on subsequent pages for Season at randomisation = Summer, Autumn, Winter. Should computational issues be encountered when using an unstructured covariance structure, other structures including AR1 and CS should be considered and the second footnote updated as appropriate.

Repeat for:

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), Adjusting for Seasonal Effect Per Protocol Population (PP Population)

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6), Adjusting for Seasonal Effect (ITT Population)
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6), Adjusting for Seasonal Effect Per Protocol Population (PP Population)
First footnote as follows:
"Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, season at randomisation, two- and three- way interactions between randomised treatment, visit and season at randomisation, and patient fitted as a random factor."

Example : EFF_T4
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Inhaler Device Use Errors

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Randomisation (Day 0)	Number of patients using Ellipta		xxx
	Number of patients with correct use [1]		xxx (xx%)
	Number of patients without correct use		xxx (xx%)
	Number of patients with at least one critical error		xxx (xx%)
	Type of critical error:		
	Failed to open cover		xxx (xx%)
	Shook the device upside down after dose preparation		xxx (xx%)
	Exhaled directly into mouthpiece		xxx (xx%)
	No seal by the lips around the mouthpiece during the inhalation		xxx (xx%)
	Number of patients with at least one non-critical error		xxx (xx%)
	Type of non-critical error:		
	No exhalation before an inhalation		xxx (xx%)
	Inhalation manoeuvre was not: long, steady and deep		xxx (xx%)
	Blocked air inlet during inhalation manoeuvre		xxx (xx%)
	Did not hold breath		xxx (xx%)
	Did not close the device		xxx (xx%)

[1] Correct use is defined as not making any critical or non-critical errors at that visit.

Table 2.xx
Summary of Inhaler Device Use Errors

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Randomisation (Day 0)	Number of patients using Diskus	xxx	
	Number of patients with correct use [1]	xxx (xx%)	
	Number of patients without correct use	xxx (xx%)	
	Number of patients with at least one critical error	xxx (xx%)	
	Type of critical error:		
	Failed to open cover	xxx (xx%)	
	Lever is not pushed back	xxx (xx%)	
	Shook the device after dose preparation	xxx (xx%)	
	Exhaled directly into mouthpiece	xxx (xx%)	
	No seal by the lips around the mouthpiece during the inhalation	xxx (xx%)	
	Number of patients with at least one non-critical error	xxx (xx%)	
	Type of non-critical error:		
	No exhalation before an inhalation	xxx (xx%)	
	Inhalation manoeuvre was not: steady and deep	xxx (xx%)	
	Did not hold breath	xxx (xx%)	
	Did not close the device	xxx (xx%)	

[1] Correct use is defined as not making any critical or non-critical errors at that visit.

Table 2.xx
Summary of Inhaler Device Use Errors

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Randomisation (Day 0)	Number of patients using Turbuhaler	xxx	
	Number of patients with correct use [1]	xxx (xx%)	
	Number of patients without correct use	xxx (xx%)	
	Number of patients with at least one critical error	xxx (xx%)	
	Type of critical error:		
	Failed to remove cap	xxx (xx%)	
	Did not hold device upright during dose preparation	xxx (xx%)	
	Base not twisted fully backwards and forwards, no click heard	xxx (xx%)	
	Shook the device after dose preparation	xxx (xx%)	
	Exhaled directly into mouthpiece	xxx (xx%)	
	No seal by the lips around the mouthpiece during the inhalation	xxx (xx%)	
	Number of patients with at least one non-critical error	xxx (xx%)	
	Type of non-critical error:		
	Device tipped downwards after dose preparation	xxx (xx%)	
	No exhalation before an inhalation	xxx (xx%)	
	Inhalation manoeuvre was not: forceful and deep	xxx (xx%)	
	Blocked air inlet during inhalation manoeuvre	xxx (xx%)	
	Did not hold breath	xxx (xx%)	
	Did not close the device	xxx (xx%)	

[1] Correct use is defined as not making any critical or non-critical errors at that visit.
Programming note: repeat on subsequent pages for Visit = Week 12 and Week 24. "Number of patients using..." line will provide the denominators for each section's percentages.

Repeat for:
Summary of Inhaler Device Use Errors Per Protocol Population (PP Population)

Example : EFF_T5
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Correct Use of Inhaler Device

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Randomisation (Day 0)	n	xxx	xxx
	Number of patients with correct use [1]	xxx (xx%)	xxx (xx%)
	Number of patients without correct use	xxx (xx%)	xxx (xx%)
	Number of patients with at least one critical error	xxx (xx%)	xxx (xx%)
	Number of patients with at least one non-critical error	xxx (xx%)	xxx (xx%)
Week 12	n	xxx	xxx
	Number of patients with correct use [1]	xxx (xx%)	xxx (xx%)
	Number of patients without correct use	xxx (xx%)	xxx (xx%)
	Number of patients with at least one critical error	xxx (xx%)	xxx (xx%)
	Number of patients with at least one non-critical error	xxx (xx%)	xxx (xx%)
Week 24	n	xxx	xxx
	Number of patients with correct use [1]	xxx (xx%)	xxx (xx%)
	Number of patients without correct use	xxx (xx%)	xxx (xx%)
	Number of patients with at least one critical error	xxx (xx%)	xxx (xx%)
	Number of patients with at least one non-critical error	xxx (xx%)	xxx (xx%)

[1] Correct use is defined as not making any critical or non-critical errors at that visit.

Repeat for:
Summary of Correct Use of Inhaler Device Per Protocol Population (PP Population)

Example : EFF_T6
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Correct Use of Inhaler Device at Week 12 (Visit 4) and at Week 24 (Visit 6) Independently of the Use at Week 12 (Visit 4)

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Week 12	n	xxx	xxx
	With correct use [1]	xxx (xx%)	xxx (xx%)
	Without correct use	xxx (xx%)	xxx (xx%)
	FF/VI vs. Usual ICS/LABA		
	Adjusted Odds Ratio		x.xx
	95% CI		(x.xx, x.xx)
	p-value		x.xxx
Week 24	n	xxx	xxx
	With correct use [1]	xxx (xx%)	xxx (xx%)
	Without correct use	xxx (xx%)	xxx (xx%)
	FF/VI vs. Usual ICS/LABA		
	Adjusted Odds Ratio		x.xx
	95% CI		(x.xx, x.xx)
	p-value		x.xxx

[1] Correct use is defined as not making any critical or non-critical errors at that visit.

Note: The analysis method was logistic regression adjusted for randomised treatment, correct use of inhaler device at baseline, gender, age and country.

Programming note: If the likelihood maximisation algorithm fails to converge due to complete or quasi-complete separation of the data then implement Firth's penalized likelihood and add the following footnote: "Note: Firth's penalized likelihood was implemented due to [complete / quasi-complete] separation of data.", deleting "complete" or "quasi-complete" as appropriate.

Repeat for:

Summary of the Statistical Analysis of Correct Use of Inhaler Device at Week 12 (Visit 4) and at Week 24 (Visit 6) Independently of the Use at Week 12 (Visit 4) Per Protocol Population (PP Population)

Summary of the Statistical Analysis of Percentage of Subjects Who Have Either an ACT Total Score >= 20 or >= 3 Point Increase from Baseline in ACT Total Score at Week 12 (Visit 4) and Week 24 (Visit 6) (ITT Population)
Programming note: Replace "With correct use [1]" with "Responder [1]" and "Without correct use" with "Non-Responder".
Footnotes as follows:
"[1] Responder is defined as an ACT total score >= 20 or >= 3 point increase from baseline in ACT total score at that visit.
Note: The analysis method was logistic regression adjusted for randomised treatment, baseline ACT total score, baseline ACT total score squared, gender, age and country."

Summary of the Statistical Analysis of Percentage of Subjects Who Have an Increase from Baseline of >=0.5 in AQLQ(S) Total Score and Environmental Stimuli Domain Score at Week 24 (Visit 6) (ITT Population)
Domain: Total Score
Domain: Environmental Stimuli

Programming note: Replace "With correct use [1]" with "Responder [1]" and "Without correct use" with "Non-Responder". Do not display the "Visit" column.
Footnotes as follows:
"[1] Responder is defined as an increase from baseline of >= 0.5.
Note: The analysis method was logistic regression adjusted for randomised treatment, baseline score, gender, age and country."

Summary of the Statistical Analysis of Proportion of Responders According to EQ-5D-5L Descriptive System Dimensions at Week 24 (Visit 6) (ITT Population)
Dimension: Mobility
Dimension: Self-care
Dimension: Usual activities
Dimension: Pain/Discomfort

Dimension: Anxiety/Depression

Programming note: Replace “With correct use [1]” with “Responder [1]” and “Without correct use” with “Non-Responder”. Do not display the “Visit” column.
Footnotes as follows:
“[1] Responder is defined as a score of 1 (‘no problems’).
Note: The analysis method was logistic regression adjusted for randomised treatment, baseline EQ-5D-5L domain score, gender, age and country.”

Example : EFF_T7
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Percentage of Subjects Who Have Either an ACT Total Score of >= 20 or >= 3 Point Increase from Baseline in ACT Total Score

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Week 6	n	xxx	xxx
	ACT Total Score >= 20 or >= 3 Point Increase from Baseline	xxx (xx%)	xxx (xx%)
	ACT Total Score >= 20	xxx (xx%)	xxx (xx%)
	>= 3 Point Increase from Baseline	xxx (xx%)	xxx (xx%)
Week 12	n	xxx	xxx
	ACT Total Score >= 20 or >= 3 Point Increase from Baseline	xxx (xx%)	xxx (xx%)
	ACT Total Score >= 20	xxx (xx%)	xxx (xx%)
	>= 3 Point Increase from Baseline	xxx (xx%)	xxx (xx%)
...			

Programming note: repeat for Visit = Week 18, Week 24, Early Withdrawal.

Example : EFF_T8
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Individual ACT Question Scores

Question: 1. Getting as much done at work, school or home

Visit	Response	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Randomisation (Day 0)	n	xxx	xxx
	1. All of the time	xxx (xx%)	xxx (xx%)
	2. Most of the time	xxx (xx%)	xxx (xx%)
	3. Some of the time	xxx (xx%)	xxx (xx%)
	4. A little of the time	xxx (xx%)	xxx (xx%)
	5. None of the time.	xxx (xx%)	xxx (xx%)
Week 6	n	xxx	xxx
	1. All of the time	xxx (xx%)	xxx (xx%)
	2. Most of the time	xxx (xx%)	xxx (xx%)
	3. Some of the time	xxx (xx%)	xxx (xx%)
	4. A little of the time	xxx (xx%)	xxx (xx%)
	5. None of the time.	xxx (xx%)	xxx (xx%)
Week 12	n	xxx	xxx
	1. All of the time	xxx (xx%)	xxx (xx%)
	2. Most of the time	xxx (xx%)	xxx (xx%)
	3. Some of the time	xxx (xx%)	xxx (xx%)
	4. A little of the time	xxx (xx%)	xxx (xx%)
	5. None of the time.	xxx (xx%)	xxx (xx%)

Example : EFF_T8
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Individual ACT Question Scores

Question: 1. Getting as much done at work, school or home

Visit	Response	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Week 18	n	xxx	xxx
	1. All of the time	xxx (xx%)	xxx (xx%)
	2. Most of the time	xxx (xx%)	xxx (xx%)
	3. Some of the time	xxx (xx%)	xxx (xx%)
	4. A little of the time	xxx (xx%)	xxx (xx%)
	5. None of the time.	xxx (xx%)	xxx (xx%)
Week 24	n	xxx	xxx
	1. All of the time	xxx (xx%)	xxx (xx%)
	2. Most of the time	xxx (xx%)	xxx (xx%)
	3. Some of the time	xxx (xx%)	xxx (xx%)
	4. A little of the time	xxx (xx%)	xxx (xx%)
	5. None of the time.	xxx (xx%)	xxx (xx%)
Early Withdrawal	n	xxx	xxx
	1. All of the time	xxx (xx%)	xxx (xx%)
	2. Most of the time	xxx (xx%)	xxx (xx%)
	3. Some of the time	xxx (xx%)	xxx (xx%)
	4. A little of the time	xxx (xx%)	xxx (xx%)
	5. None of the time.	xxx (xx%)	xxx (xx%)

Programming note: repeat on subsequent pages for Question = 2. Shortness of breath, 3. Asthma symptoms woken up at night or earlier than usual, 4. Used rescue inhaler or nubuliser medication, 5. Asthma control.

Example : EFF_T9
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Compliance with Study Medication

Time period	Compliance (%)	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Randomisation (Day 0) to Week 24	n	xxx	xxx
	< 80%	xxx (xx%)	xxx (xx%)
	80% to 120% inclusive	xxx (xx%)	xxx (xx%)
	> 120%	xxx (xx%)	xxx (xx%)
	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx

Note:
Compliance = {[Total no. of inhalations taken]/[Dose frequency x (Stop date – Start date)]} x 100.
Note: Total number of inhalations taken is the sum of (dose counter start count – dose counter stop count) for all inhalers used during the time period, Dose frequency is equal to 1 for Ellipta, 2 for Diskus and 2 or 4 for Turbuhaler, and Start date and Stop date are the earliest treatment start date and latest treatment stop date respectively recorded for all inhalers used during the time period.

Programming note: repeat on subsequent pages for Time period = Randomisation (Day 0) to Week 12, Week 12 to Week 24.

Repeat for:
Summary of Compliance with Study Medication Per Protocol Population (PP Population)

Example : EFF_T10
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study

Visit: Randomisation (Day 0)

MARS-A Questions		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
I only use it when I need it	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
Only use it when I feel breathless	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
I decide to miss out a dose	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)

Note: MARS-A: Medication Adherence Report Scale for Asthma.
[1] MARS-A 10-Score is based on the mean score across all ten questions.

Example : EFF_T10
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study

Visit: Randomisation (Day 0)

MARS-A Questions		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
I try to avoid using it	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
I forget to take it	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
I alter the dose	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)

Note: MARS-A: Medication Adherence Report Scale for Asthma.
[1] MARS-A 10-Score is based on the mean score across all ten questions.

Example : EFF_T10
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study

Visit: Randomisation (Day 0)

MARS-A Questions		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
I stop taking it for a while	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
Reserve if treatment doesn't work	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
Before doing something	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)

Note: MARS-A: Medication Adherence Report Scale for Asthma.
[1] MARS-A 10-Score is based on the mean score across all ten questions.

Example : EFF_T10
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study

Visit: Randomisation (Day 0)

MARS-A Questions		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
I take less than instructed	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
MARS-A 10-Score [1]	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx

Note: MARS-A: Medication Adherence Report Scale for Asthma.
[1] MARS-A 10-Score is based on the mean score across all ten questions.

Programming note: Repeat on subsequent pages for Visit = Week 12, Week 24 and Early Withdrawal.

Example : EFF_T10S
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study by Status of Patient in Relation to the Reminder Sent to French Centres

Status: Patients in France who had completed all MARS-A assessments prior to the reminder being implemented
Visit: Randomisation (Day 0)

MARS-A Questions		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
I only use it when I need it	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
Only use it when I feel breathless	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
I decide to miss out a dose	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)

Note: MARS-A: Medication Adherence Report Scale for Asthma.

Note: Due to an issue identified with the French translation of the MARS-A, a reminder was sent to centres in France instructing that the questionnaire refers to the patient's preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study).
[1] MARS-A 10-Score is based on the mean score across all ten questions.

Table 2.xx
Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study by Status of Patient in Relation to the Reminder Sent to French Centres

Status: Patients in France who had completed all MARS-A assessments prior to the reminder being implemented
Visit: Randomisation (Day 0)

MARS-A Questions		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
I try to avoid using it	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
I forget to take it	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
I alter the dose	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)

Note: MARS-A: Medication Adherence Report Scale for Asthma.

Note: Due to an issue identified with the French translation of the MARS-A, a reminder was sent to centres in France instructing that the questionnaire refers to the patient's preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study).
[1] MARS-A 10-Score is based on the mean score across all ten questions.

Table 2.xx
Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study by Status of Patient in Relation to the Reminder Sent to French Centres

Status: Patients in France who had completed all MARS-A assessments prior to the reminder being implemented
Visit: Randomisation (Day 0)

MARS-A Questions		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
I stop taking it for a while	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
Reserve if treatment doesn't work	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
Before doing something	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)

Note: MARS-A: Medication Adherence Report Scale for Asthma.

Note: Due to an issue identified with the French translation of the MARS-A, a reminder was sent to centres in France instructing that the questionnaire refers to the patient's preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study).
[1] MARS-A 10-Score is based on the mean score across all ten questions.

Table 2.xx
Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study by Status of Patient in Relation to the Reminder Sent to French Centres

Status: Patients in France, all MARS-A assessments completed pre-reminder
Visit: Randomisation (Day 0)

MARS-A Questions		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
I take less than instructed	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
MARS-A 10-Score [1]	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx

Note: MARS-A: Medication Adherence Report Scale for Asthma.
Note: Due to an issue identified with the French translation of the MARS-A, a reminder was sent to centres in France instructing that the questionnaire refers to the patient's preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study).
[1] MARS-A 10-Score is based on the mean score across all ten questions.

Programming note: Repeat on subsequent pages for Visit = Week 12, Week 24 and Early Withdrawal, and for Status = "Patients in France, some MARS-A assessments completed pre-reminder, some post-reminder", "Patients in France, all MARS-A assessments completed post-reminder", "Patients in Germany"

Example : EFF_T11
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Severe On-Treatment Asthma Exacerbations

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
No. of subjects with one or more severe asthma exacerbation	xx (xx%)	xx (xx%)
Total no. of severe asthma exacerbations	xx	xx
Number of severe asthma exacerbations per subject		
0	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)
> 1	xx (xx%)	xx (xx%)
Duration of severe asthma exacerbation (days) [1]		
n	xx	xx
Mean	xx.x	xx.x
SD	x.xx	x.xx
Median	xx.x	xx.x
Min.	xx	xx
Max.	xx	xx

[1] Summary only includes exacerbations for which a date of resolution or death is provided.

Example : EFF_T11
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Severe On-Treatment Asthma Exacerbations

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Outcome		
Resolved	xx (xx%)	xx (xx%)
Fatal	xx (xx%)	xx (xx%)
Not resolved	xx (xx%)	xx (xx%)
No. of exacerbations:		
Requiring use of systemic/oral corticosteroids	xx (xx%)	xx (xx%)
Leading to hospitalisation	xx (xx%)	xx (xx%)
Requiring emergency room visit	xx (xx%)	xx (xx%)
No. of exacerbations requiring intubation	xx (xx%)	xx (xx%)
No. of exacerbations leading to withdrawal from study	xx (xx%)	xx (xx%)

[1] Summary only includes exacerbations for which a date of resolution or death is provided.

Example : EFF_T11S
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Severe On-Treatment Asthma Exacerbations by Season

Season: Spring

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
No. of subjects with one or more severe asthma exacerbation	xx (xx%)	xx (xx%)
Total no. of severe asthma exacerbations	xx	xx
Number of severe asthma exacerbations per subject		
0	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)
> 1	xx (xx%)	xx (xx%)
Duration of severe asthma exacerbation (days) [1]		
n	xx	xx
Mean	xx.x	xx.x
SD	x.xx	x.xx
Median	xx.x	xx.x
Min.	xx	xx
Max.	xx	xx

Note: Spring = March, April and May; Summer = June, July and August; Autumn = September, October and November; Winter = December, January and February.
[1] Summary only includes exacerbations for which a date of resolution or death is provided.

Example : EFF_T11
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Severe On-Treatment Asthma Exacerbations by Season

Season: Spring

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Outcome		
Resolved	xx (xx%)	xx (xx%)
Fatal	xx (xx%)	xx (xx%)
Not resolved	xx (xx%)	xx (xx%)
No. of exacerbations:		
Requiring use of systemic/oral corticosteroids	xx (xx%)	xx (xx%)
Leading to hospitalisation	xx (xx%)	xx (xx%)
Requiring emergency room visit	xx (xx%)	xx (xx%)
No. of exacerbations requiring intubation	xx (xx%)	xx (xx%)
No. of exacerbations leading to withdrawal from study	xx (xx%)	xx (xx%)

Note: Spring = March, April and May; Summer = June, July and August; Autumn = September, October and November; Winter = December, January and February.
[1] Summary only includes exacerbations for which a date of resolution or death is provided.

Programming note: repeat on subsequent pages for Season = Summer, Autumn, Winter.

Example : EFF_T12
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Severe On-Treatment Asthma Exacerbations

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
n	xxx	xxx
LS Mean Annual Rate	x.xx	x.xx
FF/VI vs. Usual ICS/LABA		
Ratio		x.xx
95% CI		(x.xx, x.xx)
p-value		x.xxx
Percent Reduction		x.xx
95% CI		(x.xx, x.xx)

Note: The analysis method was Generalised Linear Model assuming an underlying negative binomial distribution with a log-link function and logarithm of time on treatment as an offset variable and adjusted for randomised treatment, number of severe asthma exacerbations in the previous year prior to randomisation, gender, age and country.

Example : EFF_T13
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Time to First Severe On-Treatment Asthma Exacerbation

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Number of subjects with event	xx (xx%)	xx (xx%)
Number of subjects censored	xx (xx%)	xx (xx%)
Probability of having event (%) [1]	xx.x	xx.x
95% CI	(xx.x, xx.x)	(xx.x, xx.x)
FF/VI vs. Usual ICS/LABA		
Hazard Ratio [2]		x.xx
95% CI		(xx.x, xx.x)
p-value		x.xxx

[1] Kaplan-Meier estimates.
[2] Overall hazard ratios, CIs and p-values are from a Cox proportional hazards model with randomised treatment, gender, age and country as covariates. A hazard ratio <1 indicates a lower risk with FF/VI compared with Usual ICS/LABA.
Note: At Day 168 all subjects who have not experienced a severe asthma exacerbation are considered censored, regardless of whether their on-treatment phase continues beyond Day 168.

Example : EFF_T14
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Percentage of Subjects Who Have an Increase from Baseline of >=0.5 in AQLQ(S) Total Score and Domain Scores

Domain: Total Score

Visit	Response	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Week 24	n	xxx	xxx
	Responder [1]	xxx (xx%)	xxx (xx%)
	Non-Responder	xxx (xx%)	xxx (xx%)
Early Withdrawal	n	xxx	xxx
	Responder [1]	xxx (xx%)	xxx (xx%)
	Non-Responder	xxx (xx%)	xxx (xx%)

[1] Responder is defined as an increase from baseline of >= 0.5.

Programming note: repeat on subsequent pages for Domain = Environmental Stimuli, Symptoms, Activity Limitations, Emotional Function.

Example : EFF_T15
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of EQ-5D-5L Descriptive System Dimensions

Dimension: Mobility

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Randomisation (Day 0)	n	xxx	xxx
	I am not anxious or depressed	xxx (xx%)	xxx (xx%)
	I am slightly anxious or depressed	xxx (xx%)	xxx (xx%)
	I am moderately anxious or depressed	xxx (xx%)	xxx (xx%)
	I am severely anxious or depressed	xxx (xx%)	xxx (xx%)
	I am extremely anxious or depressed	xxx (xx%)	xxx (xx%)
	Missing	xxx (xx%)	xxx (xx%)
Week 24	n	xxx	xxx
	I am not anxious or depressed	xxx (xx%)	xxx (xx%)
	I am slightly anxious or depressed	xxx (xx%)	xxx (xx%)
	I am moderately anxious or depressed	xxx (xx%)	xxx (xx%)
	I am severely anxious or depressed	xxx (xx%)	xxx (xx%)
	I am extremely anxious or depressed	xxx (xx%)	xxx (xx%)
	Missing	xxx (xx%)	xxx (xx%)

Programming note: repeat on subsequent pages for Visit = Early Withdrawal and for Dimension = Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression.

12.16.4. Efficacy Figure Shells

Example : EFF_F1
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Summary of ACT Total Score

Programming note: present "ACT Total Score" on y-axis and "Visit" on x-axis (Randomisation (Day 0), Week 6, Week 12, Week 18, Week 24). Present mean ACT Total Score ± SD separately for treatment group (FF/VI, Usual ICS/LABA) at each visit, connecting the means with a solid line. Distinguish the treatment groups by different line types and colours.

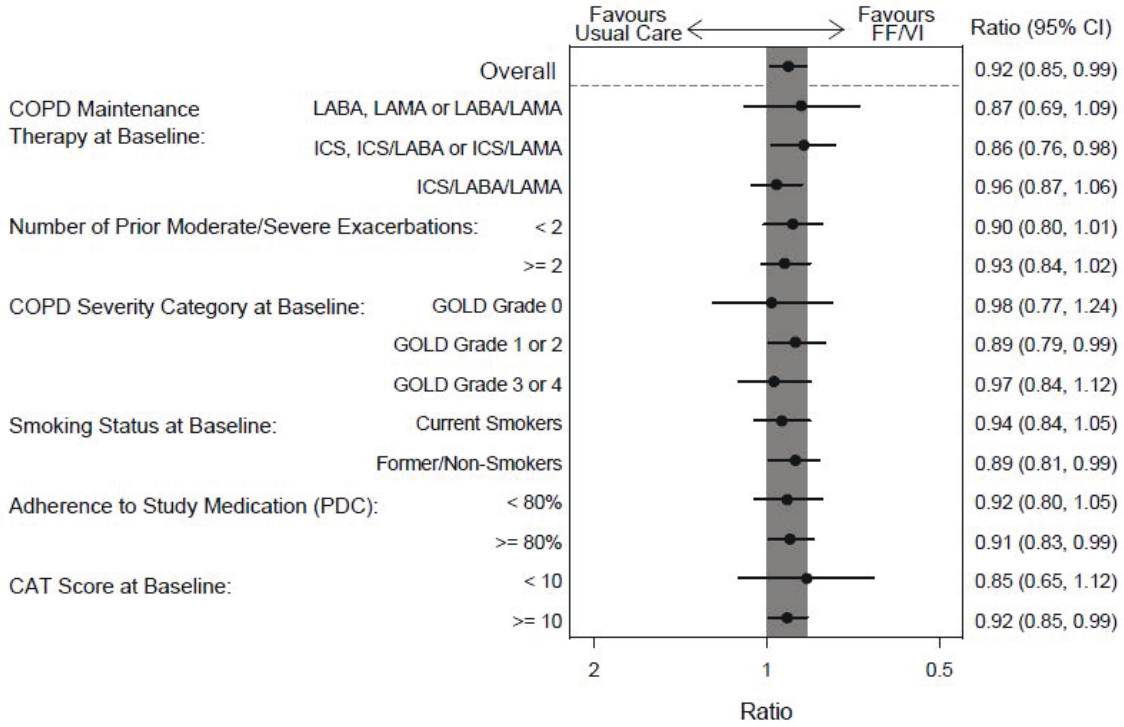
Repeat for:

Summary of Change from Baseline in ACT Total Score Per Protocol Population (PP Population)

Summary of Change from Baseline in ACT Total Score by Country (ITT Population)
Country: France
Country: Germany

Example : EFF_F2
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Summary of Primary and Sensitivity Analyses for Change from Baseline in ACT Total Score at Week 12 (Visit 4)

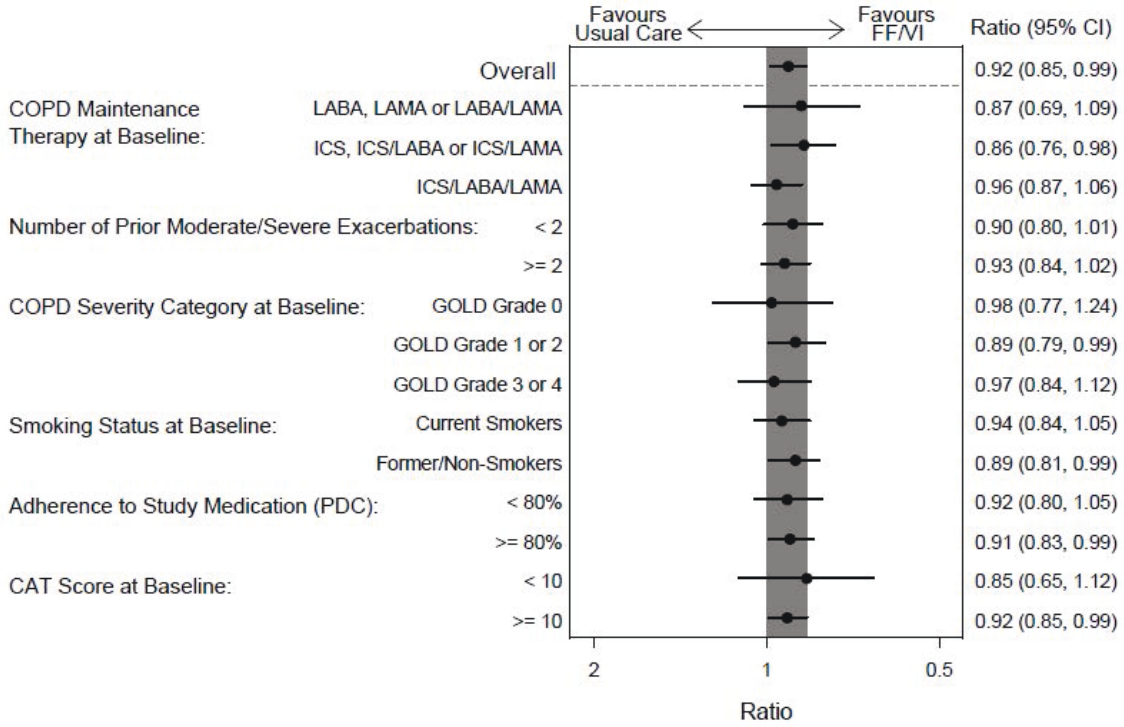


Programming note: present "Treatment difference" on the x-axis, and reverse axis so treatment difference increases from left to right. Replace "Ratio (95% CI)" with "Treatment Difference (95% CI)". Present lines for the following: Primary analysis (ITT), Primary analysis (PP), ANCOVA with LOCF (ITT), Multiple Imputation (Missing at Random) (ITT), Multiple Imputation (Copy Differences from Reference) (ITT), Hodges-Lehmann (ITT), ANCOVA with WOCF (ITT).

Repeat for:

Summary of Key Secondary and Sensitivity Analyses for Change from Baseline in ACT Total Score at Week 24 (Visit 6)
Example : EFF_F3
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Summary of Interaction Tests for Change from Baseline in ACT Total Score at Week 12 (Visit 4)



Programming note: present "LS Mean Change" on the x-axis, and reverse axis so it increases from left to right. Replace "Ratio (95% CI)" with "LS Mean Change (95% CI)". Present the following subgroups: Country (France, Germany); Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation (0, >= 1); Smoking Status at Baseline (Current smoker, Former smoker, Never smoked); Age Group (≤ 50 Years Old, > 50 Years Old); Gender (Male, Female).

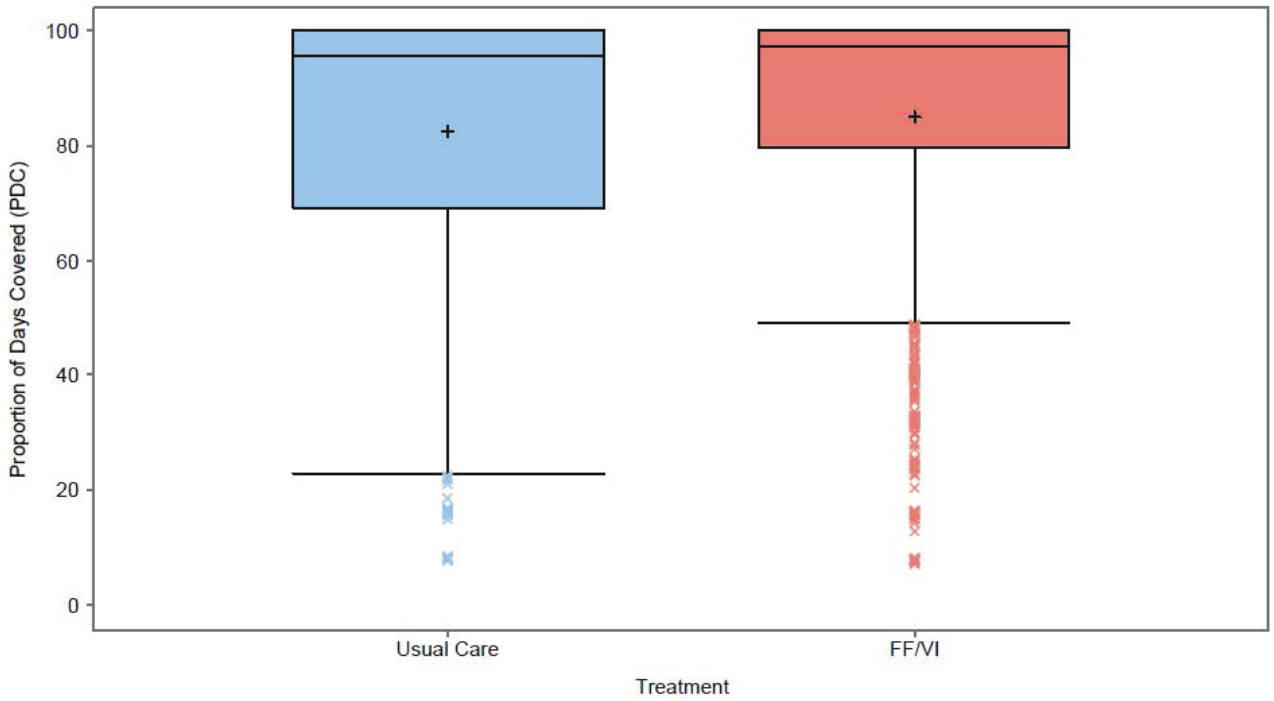
Example : EFF_F4
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Histogram of Percentage of Subjects Who Have Either an ACT Total Score of >= 20 or >= 3 Point Increase from Baseline in ACT Total Score

Programming note: present "Percent of Subjects (%)" on y-axis and "Visit" on x-axis (Week 6, Week 12, Week 18, Week 24, Early Withdrawal). For each visit, present 3 vertical bars distinguished by fill pattern (similar to non-standard EFF_F6). Each bar represents: "ACT Total Score >= 20 or >= 3 Point Increase from Baseline in ACT Total Score", "ACT Total Score >= 20" and ">= 3 Point Increase from Baseline in ACT Total Score" respectively and should be labelled as such on the legend.

Example : EFF_F5
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Box Plot of Compliance with Study Medication

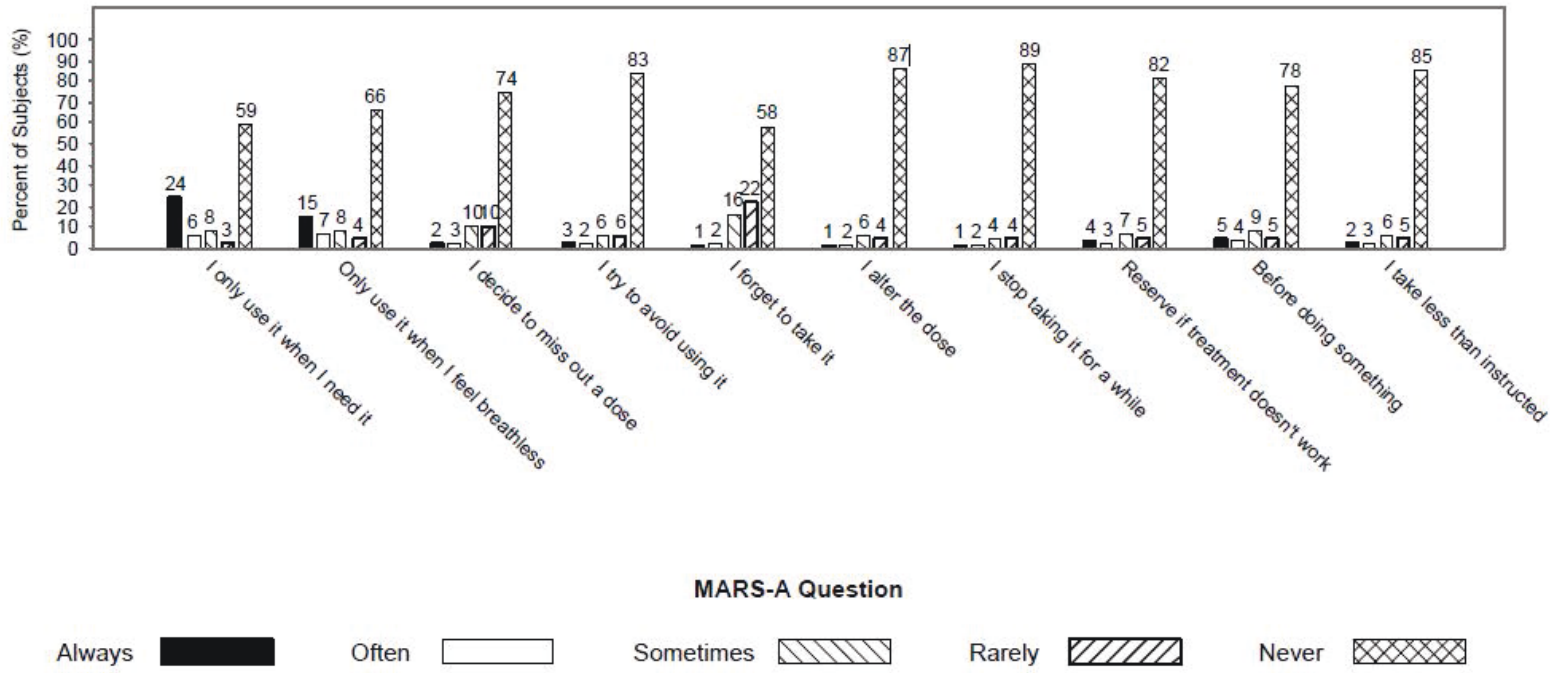


Programming Note: label y-axis title as "Compliance (%)", maximum of y-axis may be > 100%.

Example : EFF_F6
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Histogram of the Questions and Answers of the MARS-A Questionnaire

Randomised Treatment: Usual ICS/LABA
Visit: Randomisation (Day 0)



Note: MARS-A = Medication Adherence Report Scale for Asthma.

Programming note: repeat on subsequent pages for Visit = Day 0 and repeated for Week 12, Week 24, and Early Withdrawal; and for Randomised Treatment = FF/VI.

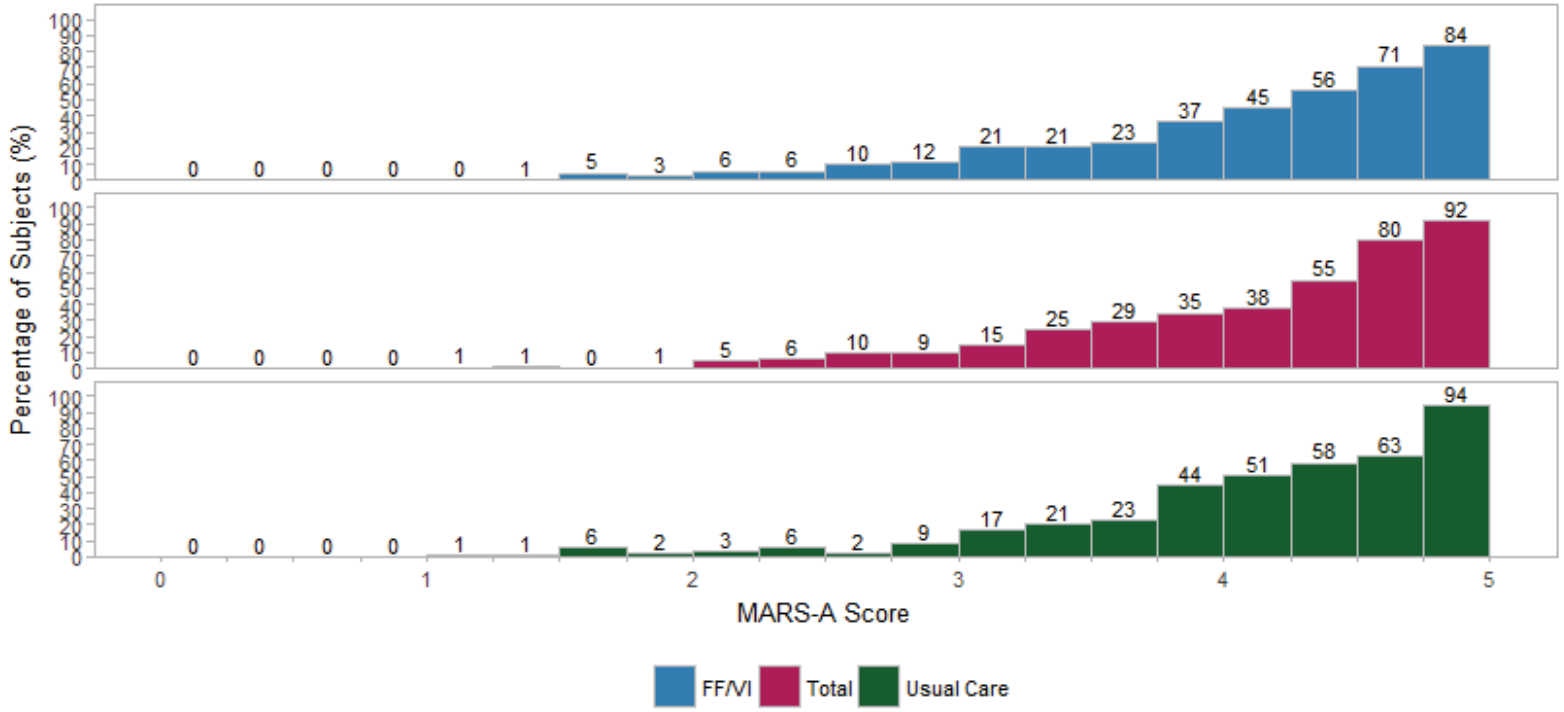
Repeat for:

Histogram of the Questions and Answers of the MARS-A Questionnaire by Status of Patient in Relation to the Reminder Sent to French Centres (ITT Population)
Status: Patients in France, all MARS-A assessments completed pre-reminder
Status: Patients in France, some MARS-A assessments completed pre-reminder, some post-reminder
Status: Patients in France, all MARS-A assessments completed post-reminder
Status: Patients in Germany
Add the following footnote: “Note: Due to an issue identified with the French translation of the MARS-A, a reminder was sent to centres in France instructing that the questionnaire refers to the patient’s preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study).”

Example : EFF_F7
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Histogram of the Distribution of MARS-A Scores During the Study

Visit: Randomisation (Day 0)



Note: MARS-A = Medication Adherence Report Scale for Asthma.
Note: MARS-A 10-Score is based on the mean score across all ten questions.

Programming note: repeat on subsequent pages for Visit = Week 52 and Early Withdrawal.

Repeat for:

Histogram of the Distribution of MARS-A Scores During the Study by Status of Patient in Relation to the Reminder Sent to French Centres (ITT Population)

Status: Patients in France, all MARS-A assessments completed pre-reminder

Status: Patients in France, some MARS-A assessments completed pre-reminder, some post-reminder

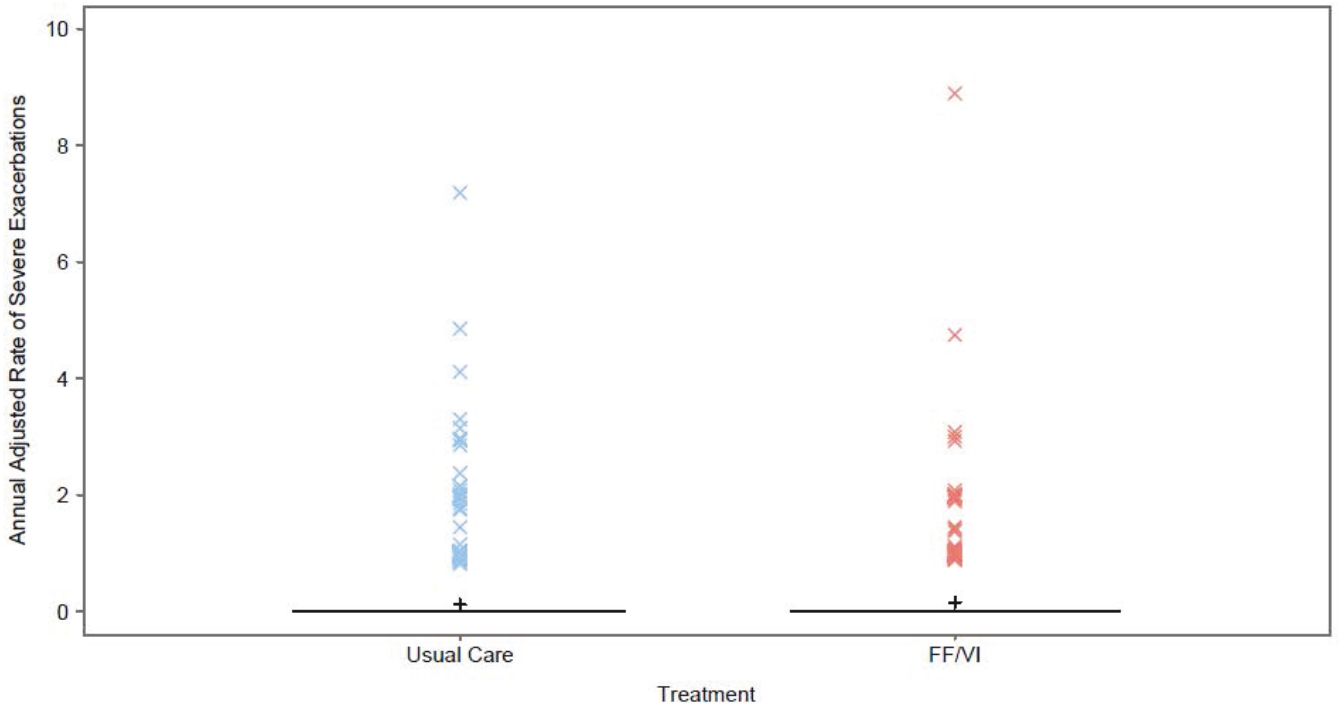
Status: Patients in France, all MARS-A assessments completed post-reminder

Status: Patients in Germany

Add the following footnote: “Note: Due to an issue identified with the French translation of the MARS-A, a reminder was sent to centres in France instructing that the questionnaire refers to the patient’s preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study).”

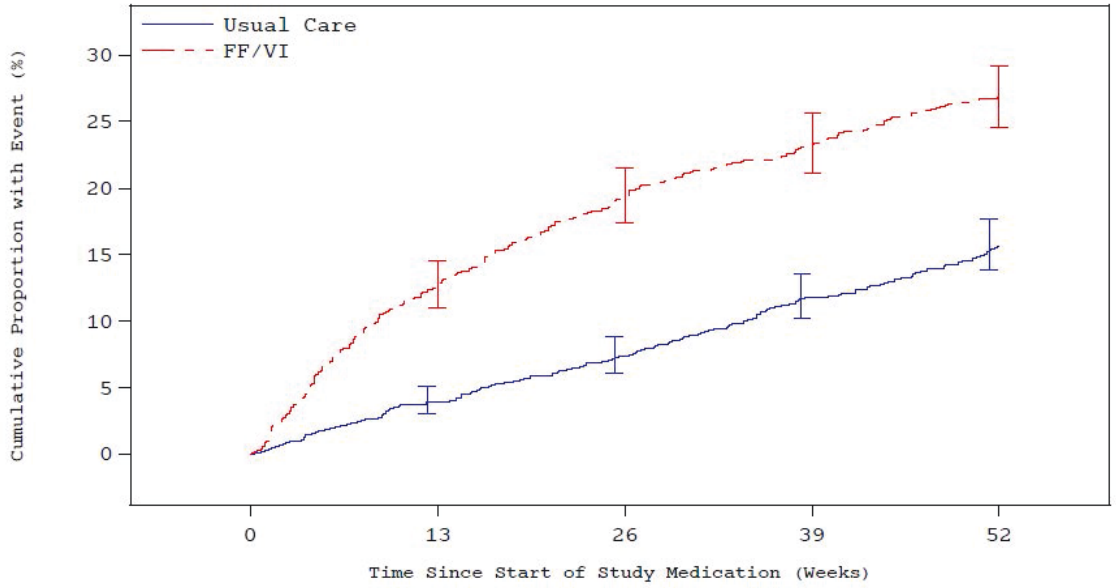
Example : EFF_F8
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Box Plot of Severe On-Treatment Asthma Exacerbation Rates Adjusted for Exposure to Treatment



Example : EFF_F9
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Kaplan-Meier Plot of Time to First Severe On-Treatment Asthma Exacerbation



Programming note: display increments of 6 weeks on the x-axis, up to the maximum exposure (e.g. 0, 6, 12, 18, 24).

12.16.5. Safety Table Shells

Example : SAFE_T1
Protocol : HZA116492
Population : Safety

Table 3.xx
On-Treatment Serious Adverse Events and Adverse Drug Reactions Overview

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Any on-treatment ADRs	xxx (xx%)	xxx (xx%)
Any on-treatment non serious ADRs	xxx (xx%)	xxx (xx%)
Any on-treatment serious ADRs	xxx (xx%)	xxx (xx%)
Any post-treatment serious ADRs	xxx (xx%)	xxx (xx%)
Any on-treatment SAEs	xxx (xx%)	xxx (xx%)
Any post-treatment SAEs	xxx (xx%)	xxx (xx%)
Any SAEs or ADRs leading to permanent discontinuation of study drug or withdrawal from study [1]	xxx (xx%)	xxx (xx%)
Any on-treatment fatal serious ADRs	xxx (xx%)	xxx (xx%)
Any on-treatment fatal SAEs	xxx (xx%)	xxx (xx%)
Any post-treatment fatal SAEs	xxx (xx%)	xxx (xx%)

[1] Includes both on-treatment and post-treatment SAEs and ADRs.

Programming note: Based on IDSL standard template AE13.

Example : SAFE_T2
Protocol : HZA116492
Population : Safety

Table 3.xx
Summary of On-Treatment Non-Serious Adverse Drug Reactions of Special Interest

Special Interest Group/ Subgroup Preferred Term	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Adrenal suppression		
Any event	xxx (xx%)	xxx (xx%)
Blood cortisol decreased	xxx (xx%)	xxx (xx%)
Cardiovascular effects		
Any event	xxx (xx%)	xxx (xx%)
Cardiac Arrhytmia [1]	xxx (xx%)	xxx (xx%)
Any event	xxx (xx%)	xxx (xx%)
Palpitations	xxx (xx%)	xxx (xx%)
Extrasystoles	xxx (xx%)	xxx (xx%)
Cardiac Ischaemia [1]	xxx (xx%)	xxx (xx%)
Any event	xxx (xx%)	xxx (xx%)
Angina pectoris	xxx (xx%)	xxx (xx%)
Chest pain	xxx (xx%)	xxx (xx%)
Effects on potassium		
Any event	xxx (xx%)	xxx (xx%)
XXXXXXX	xxx (xx%)	xxx (xx%)
XXXXXXX	xxx (xx%)	xxx (xx%)

[1] This special interest group/subgroup was defined using Special MedDRA Queries.

Programming note: Based on IDSL standard template AE1.

Repeat for:

Summary of On-Treatment Serious Adverse Drug Reactions of Special Interest (ITT Population)
Summary of On-Treatment Adverse Drug Reactions of Special Interest (ITT Population)
Summary of On-Treatment Serious Adverse Events of Special Interest (ITT Population)
Summary of On-Treatment Fatal Serious Adverse Events of Special Interest (ITT Population)
Summary of On-Treatment Non-Fatal Serious Adverse Events of Special Interest (ITT Population)

Example : SAFE_T3
Protocol : HZA116492
Population : Safety

Table 3.xx
Top Ten Most Commonly Reported On-Treatment Adverse Drug Reactions Per Treatment Group

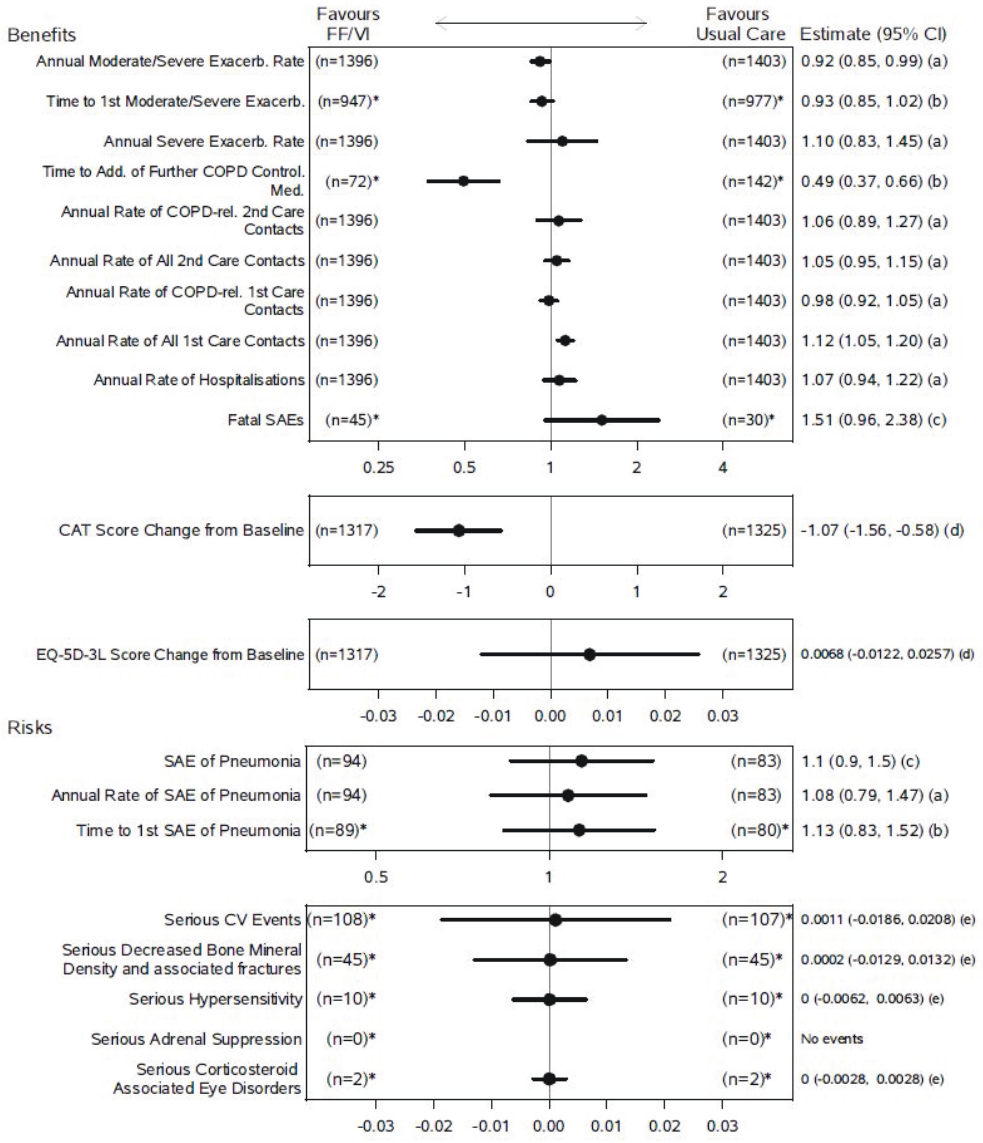
Preferred Term	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
.....		

Programming note: Present the ten most frequent preferred terms in Usual ICS/LABA, and the ten most frequent in FF/VI (do not use percentages to determine "most frequent").

12.16.6. Safety Figure Shells

Example : SAFE_F1
Protocol : HZA116492 Page 1
of 1
Population : Intent-to-Treat/Safety

Figure 2.xx
Summary of Benefit:Risk for FF/VI vs. Usual ICS/LABA



* = Number of subjects with event
(a) Difference in LS mean change from baseline from an MMRM
(b) Difference in LS mean change from baseline from an ANCOVA model
(c) Adjusted odds ratio obtained from a logistic regression model
(d) Risk difference

Programming note: present the following endpoints:

- *Benefits:*
- *First panel, x-axis decreasing from left to right:*
    - *Difference in LS mean change from baseline and 95% CI for: change from baseline in ACT total score at Week 12 (Visit 4) and at Week 24 (Visit 6) (labeled (a))*
    - *Difference in LS mean change from baseline and 95% CI for change from baseline in trough (pre-dose) FEV1 at Week 12 (Visit 4) (labeled (b))*
- *Second panel, x-axis increasing from left to right:*
    - *Adjusted odds ratio and 95% CI for: percentage of subjects with correct use of inhaler device at Week 12 (Visit 4) and at Week 24 (Visit 6) (labeled (c))*
- *Risks:*
- *Third panel, x-axis increasing from left to right:*
    - *Risk difference and 95% CI of the following SAEs of special interest: asthma/bronchospasm, cardiovascular effects, decreased bone mineral density and associated fractures, hypersensitivity, local steroid effects, lower respiratory tract infection (LRTI) excluding pneumonia, pneumonia, adrenal suppression, ocular effects, effects on glucose, effects on potassium, tremor (labeled (d))*

12.16.7. Non-ICH Listing Shells

Example : POP_L1
Protocol : HZA116492
Population : All Subjects Enrolled

Listing x
Subjects Screened but Not in the Intent-to-Treat Population

Randomised Treatment	Site Id./ Unique Subject Id.	Disposition Status	Reason for Screen Failure/Withdrawal
Screen Failure	xxxxxx	Screen Failure	Xxxxxxxxxxxx
FF/VI	xxxxxx	Early Withdrawal	Xxxxxxxxxxxx
...			

Example : POP_L2
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Reasons for Important Protocol Deviations

Randomised Treatment	Site Id./ Unique Subject Id.	Important Protocol Deviation	Excluded from PP?	Date of Deviation	Study Day of Deviation
FF/VI	xxxxx	xxxxxxxxxxxx	No	DDMMMYYYY	xx
	xxxxx	xxxxxxxxxxxx	No	DDMMMYYYY	xx
Usual ICS/LABA	xxxxx	xxxxxxxxxxxx	No	DDMMMYYYY	xx
	xxxxx	xxxxxxxxxxxx	Yes	DDMMMYYYY	xx
	xxxxx	xxxxxxxxxxxx	No	DDMMMYYYY	xx
	xxxxx	xxxxxxxxxxxx	No	DDMMMYYYY	xx

....

Example : POP_L3
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Asthma History

Treatment	Site Id./ Unique Subject Id.	Asthma Duration	Number of asthma exacerbations in the last 12 months that: Did not require oral/systemic corticosteroids (not involving hospitalisation)	Required oral/systemic corticosteroids (not involving hospitalisation)	Required hospitalisation
xxxxxx	xxxxxx	xxxxxxxxxxxx	xx	xx	xx
	xxxxxx	xxxxxxxxxxxx	xx	xx	xx
	xxxxxx	xxxxxxxxxxxx	xx	xx	xx
	xxxxxx	xxxxxxxxxxxx	xx	xx	xx

Example : POP_L4
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Smoking History

Treatment	Site Id./ Unique Subject Id.	Smoking Status	Years Smoked/ Cigarettes per day	Smoking Pack Years
xxxxxx	Xxxxxx/ xxxxxx	Current	xx/ xx	xx
	Xxxxxx/ xxxxxx	Former	xx/ xx	xx
	Xxxxxx/ xxxxxx	Never		

Example : POP_L5
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Exposure to Study Medication

Treatment: Usual ICS/LABA

Site Id./ Unique Subject Id.	Treatment Start Date/ Treatment End date	Start date of dose/ End date of dose/ Duration of dose (days)	Drug	Dose/ Dose Units/ Dose Frequency	Inhalers Dispensed/ Inhalers Returns	Dose counter start/ Dose counter stop	Compliance (%) During the study
XXXX	DDMMMYYY/ DDMMMYYY						XX.XX
		DDMMMYYYY/ DDMMMYYYY/ xx	XXXXXXX	XX/ XX/XXXX	X/X	XXX/XX	
		DDMMMYYYY/ DDMMMYYYY xx	XXXXXXX	XX/ XX/XXXX	X/X	XXX/XX	
XXXX	DDMMMYYY						XX.XX
		DDMMMYYYY/ DDMMMYYYY/ xx	XXXXXXX	XX/ XX/XXXX	X/X	XXX/XX	

Programming note: Repeat on subsequent pages for Treatment = FF/VI, and use GSK drug synonym as drug name.

Example : EFF_L1
Protocol : HZA116492

Population : Intent-to-Treat

Listing x
ACT Scores

Treatment: Usual ICS/LABA

Site Id./ Unique Subject Id.	Visit/ Study Date/ Study Day	Impact at home or work [1]	Frequency of shortness of breath [1]	Frequency of sleep trouble [1]	Frequency of rescue medication [1]	Asthma control rating [1]	ACT Total Score [2] / Change from Baseline
xxxxxx/ xxxxx	Randomisation (Day 0)/ DDMMMYYYY/ xx	x	x	x	x	x	xx
	Week 6/ DDMMMYYYY/ xx	x	x	x	x	x	xx / -x
	Week 12/ DDMMMYYYY/ xx	x	x	x	x	x	xx / x
...							

[1] Responses range between 1 (worst response) and 5 (best response).
[2] ACT Total Score ranges between 5 (worst asthma control state) and 25 (best asthma control state).

Programming note: Repeat on subsequent pages for Treatment = FF/VI.

Example : EFF_L2
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Inhaler Device Use

Treatment: Usual ICS/LABA

Site Id./ Unique Subject Id.	Visit/ Study Date/ Study Day	Inhaler	Critical errors: Any?	Critical errors: If yes, errors:	Non-critical errors: Any?	Non-critical errors: If yes, errors:
xxxxxx/ xxxxx	Randomisation (Day 0)/ DDMMMYYYY/ xx	Turbuhaler	No		No	
	Week 12/ DDMMMYYYY/ xx	Turbuhaler	No		Yes	Did not hold breath
	Week 24/ DDMMMYYYY/ xx	Turbuhaler	Yes	Exhaled directly into mouthpiece	No	
xxxxxx/ xxxxx	Randomisation (Day 0)/ DDMMMYYYY/ xx	Diskus	Yes	Did not hold device upright during dose preparation Shook the device after dose preparation	Yes	No exhalation before an inhalation
	Week 12/ DDMMMYYYY/ xx	Diskus	Yes	Shook the device after dose preparation	No	

Programming note: Repeat on subsequent pages for Treatment = FF/VI.

Example : EFF_L3
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Lung Function Tests

Treatment: Usual ICS/LABA

Site Id./ Unique Subject Id.	Visit	Study Date/ Time	Study Day	Trough (Pre-dose) FEV1 (L)			Trough (Pre-dose) Percent Predicted FEV1 (%)		Bronchodilator taken in last 4 hours?
				Absolute	Change from Baseline	Predicted normal FEV1 (L)	Absolute	Change from Baseline	
xxxxxx/ xxxxx	Randomisation (Day 0)	DDMMMYYYY/ HH:MM	xx	x.xxx		x.xxx	xx.x		No
	Week 6	DDMMMYYYY/ HH:MM	xx	x.xxx	x.xxx	x.xxx	xx.x	xx.x	No
xxxxxx/ xxxxx	Randomisation (Day 0)	DDMMMYYYY/ HH:MM	xx	x.xxx	x.xxx	x.xxx	xx.x	xx.x	No

Programming note: Repeat on subsequent pages for Treatment = FF/VI.

Example : EFF_L4
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Medication Adherence Report Scale for Asthma (MARS-A) Scores

Treatment: Usual ICS/LABA

Site Id./ Unique Subject Id.	Status [1]	Visit/ Study Date/ Study Day	Assessor Code	MARS-A Questions	Score [2]
xxxxxx/ xxxxx	During	Randomisation (Day 0)/ DDMMMYYYY/ xx	Subject/Other	I only use it when I need it	x
				Only use it when I feel breathless	x
				I decide to miss out a dose	x
				I try to avoid using it	x
				I forget to take it	x
				I alter the dose	x
				I stop taking it for a while	x
				Reserve if treatment doesn't work	x
				Before doing something	x
				I take less than instructed	x
				MARS-A 10-Score [3]	x.xx
		Week 12/ DDMMMYYYY/ xx	Subject/Other	I only use it when I need it	x
				Only use it when I feel breathless *.....etc*	x

[1] Due to an issue identified with the French translation of the MARS-A, a reminder was sent to centres in France instructing that the questionnaire refers to the patient's preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study. Status = Prior (patient in France who had

completed all MARS-A assessments prior to the reminder), During (patient in France who had completed at least one MARS-A assessment prior to the reminder but also completed at least one MARS-A assessment after the reminder), After (patient in France who had not completed any MARS-A assessments prior to the reminder), Germany (patient in Germany).
[2] Question scores range between 1 (always) and 5 (never).
[3] MARS-A 10-Score is based on the mean score across all ten questions.

Programming note: Repeat on subsequent pages for Treatment = FF/VI.

Example : EFF_L5
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Severe Asthma Exacerbations

Treatment: Usual ICS/LABA

Site Id./ Unique Subject Id.	Date of Onset/ Study day/ Date of Resolution/ Study day	Resolution/ Withdrawn from Study?	Required use of systemic/oral corticosteroids?	Led to hospitalisation?	Required emergency room visit?	Required intubation?
Xxxxxx/ xxxxx	DDMMMYYYY/ xx/ DDMMMYYYY/ xx	Resolved/ N	Y	N	N	N
	DDMMMYYYY/ xx/ DDMMMYYYY/ xx	Resolved/ N	N	N	Y	N
	DDMMMYYYY/ xx/ DDMMMYYYY/ xx	Fatal/ Y	Y	Y	N	Y

Programming note: Repeat on subsequent pages for Treatment = FF/VI.

Example : EFF_L6
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
AQLQ(S) Scores

Treatment: Usual ICS/LABA

Site Id./ Unique Subject Id.	Visit/ Study Date/ Study Day	Symptoms [1]	Activity Limitations [1]	Emotional Function [1]	Environmental Stimuli [1]	AQLQ(S) Total Score [1] / Change from Baseline
xxxxxx/ xxxxx	Randomisation (Day 0)/ DDMMMYYYY/ xx	x.x	x.x	x.x	x.x	x.x
	Week 24/ DDMMMYYYY/ xx	x.x	x.x	x.x	x.x	x.x / x.x
...						

[1] Scores range between 1 (lower quality of life) and 7 (higher quality of life) for AQLQ(S) total and domains.

Programming note: Repeat on subsequent pages for Treatment = FF/VI.

Example : EFF_L7
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
EQ-5D-5L Descriptive System Dimension Scores

Treatment: Usual ICS/LABA

Site Id./ Unique Subject Id.	Visit/ Study Date/ Study Day	Assessor Code	Subscale/ Item	Level of Problem	Score [1]
xxxxxx/ xxxxx	Randomisation (Day 0) DDMMMYYYY/ xx	Subject/Other	EQ-5D-5L Utility Score		xx.xx
			Mobility	1	
			Self-Care	1	
			Usual Activities	1	
			Pain/Discomfort	1	
			Anxiety/Depression	1	
			EQ-5D-5L VAS		xx.xx
	Week 12 DDMMMYYYY/ xx	Subject/Other	EQ-5D-5L Utility Score		xx.xx
			Mobility .....etc	1	

[1] Scores range between 0 (worst imaginable health state) and 1 (best imaginable health state) for EQ-5D-5L Utility Score and range between 0 (worst imaginable health state) and 100 (best imaginable health state) for EQ-5D-5L Visual Analogue Scale (VAS).

Example : EFF_L8
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
PASAP-Q Scores

Treatment: Usual ICS/LABA

Site Id./ Unique Subject Id.	Visit/ Study Date/ Study Day	Domain / Question	Response	Score [1]
xxxxxx/ xxxxx	Randomisation (Day 0) DDMMMYYYY/ xx	Performance		xx.x
		Overall feeling of inhaling	x	
		Inhaled dose goes to lungs	x	
		Medication left	x	
		Works reliably	x	
		Ease of inhaling a dose	x	
		Using the inhaler	x	
		Speed medicine comes out	x	
		Convenience		xx.x
		Instructions for use	x	
		Size of inhaler	x	
		Durability of inhaler	x	
		Ease of cleaning inhaler	x	
		Ease of holding during use	x	
		Convenience of carrying	x	
		Total Score		xx.x
		Overall Satisfaction		x
		Willingness to Continue Using Inhaler		xx.x

[1] Performance, Convenience, Total Score, and Willingness to Continue Using Inhaler are expressed on a scale of 0 to 100. Overall Satisfaction is expressed on a scale of 1 to 7.

Programming note: Repeat on subsequent pages for Treatment = FF/VI.

Example : SAFE_L1
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
AE Terms of Special Interest

Special Interest Group	Subgroup	Preferred Term
xxxxx xxxxx xxxxxx	Xxxxxxx	xxxxxxx
		xxxxxxx xxxxxxx
		xxxx
		xxxxxxx xxx
xxxxxxx xxxxxxxxxx	xxxxxxxxxxxxxxx [1]	xxxxxxx xxxxxx
		xxxxxxx xxxx xxxxx xxxxx
		xxxx
xxxxxxxxxxx	xxxxxxx [1]	xxxxxxx
		xxxx xxxxxx xxxxxxx
xxxxxx xxxxxxx		xxxxxxxxx
		xxxxx xxxxxx xxxxxxx xxxxxx

[1] This special interest group/subgroup was defined using Special MedDRA Queries.Note: All of the pre-specified preferred terms that were assigned to special interest terms are shown, regardless of whether they actually occurred in the study.

Programming Note: The AE special interest dataset and the AE SMQ dataset will be set together in order to report this table and all the subgroups that come from the AE SMQ dataset will be flagged with a [1].

Example : SAFE_L2
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Inhaler Device Malfunctions

Treatment	Site Id./ Unique Subject Id.	Inhaler Device	Comment / Reason for Malfunction
Usual ICS/LABA	xxxxxx/ xxxxx	Turbuhaler	XXXXXXXXXXX
Usual ICS/LABA	xxxxxx/ xxxxx	Diskus	XXXXXXXXXXX
FF/VI	xxxxxx/ xxxxx	Ellipta	Powder fell out prior to use Other: XXXXXXXX

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

Title	:	Reporting and Analysis Plan for A 6-month, open label, randomised, efficacy study to evaluate fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) Inhalation Powder delivered once daily via the Dry Powder Inhaler Ellipta™ compared with usual ICS/LABA maintenance therapy delivered by Dry Powder Inhaler in subjects with Persistent Asthma
Compound Number	:	GW685698+GW642444
Effective Date	:	05-DEC-2016

Description :

The purpose of this document is to describe the final planned analyses and output to be included in the Clinical Study Report for Protocol HZA116492.

This RAP is intended to describe the planned efficacy and safety analyses required for the study.

This RAP will be provided to the study team members to convey the content of the final Statistical Analysis Complete (SAC) deliverable.

Author's Name and Functional Area:

PPD Principal Statistician (Clinical Statistics)	05-DEC-2016

Approved by:

PPD Director, Statistics & Programming (Clinical Statistics)	05-DEC-2016

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REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the RAP
Purpose	This RAP details all planned analyses and output required for the final Clinical Study Report of study HZA116492.
Protocol	This RAP is based on the protocol amendment 02 (Dated: 28-APR-2016) of study HZA116492 (GSK Document No.: 2014N190259_02).
Primary Objective	To compare the efficacy of fluticasone furoate (FF)/vilanterol(VI) 92 mcg/22 mcg or FF 184 mcg/22 mcg with usual fixed combinations inhaled corticosteroid / long-acting beta agonist (ICS/LABA) for asthma maintenance therapy at Week 12 (Visit 4).
Primary Endpoint	Change from baseline in the Asthma Control Test (ACT) total score at Week 12 (Visit 4).
Study Design	This is a Phase IIIb multi-center randomised open label, parallel group study performed in subjects in primary and in respiratory specialist care / research sites who have a diagnosis of asthma and a regular treatment for asthma. Subjects with unsatisfactorily controlled asthma (defined as an ACT < 20) and intended to be treated by usual ICS/LABA maintenance therapy to seek a better control of their asthma will be randomised to receive either FF/VI (FF/VI 92 mcg/22 mcg or FF/VI 184 mcg/22 mcg) once daily or another usual ICS/LABA combination therapy in inhalation powder twice daily (fluticasone propionate[FP]/salmeterol [S] or budesonide[BUD]/formoterol [F]) decided by the physician. Physicians will be allowed during the treatment period to adapt prescription to different doses if necessary as well as to adapt doses of any comparative treatment according to products label.
Planned Analyses	No interim analysis is planned for this study. All decisions regarding final analysis for the reporting effort, as defined in this RAP document, will be made prior to Database Freeze (DBF) (unblinding) of the study data. All planned analyses will be carried out once DBF has taken place. Once this has been achieved, unblinding will occur and the analyses will be performed. The open-label study design and the method of recording study medication data in the datasets means that extra steps must be taken to ensure that Statistics and Programming (S&P) remain blinded to study investigator prescribing of study medication until the formal unblinding takes place at DBF. See Section 10.13 for more details.

Overview	Key Elements of the RAP
Analysis Populations	**All Subjects Enrolled (ASE) population:** All subjects screened (provided consent) and for whom a record exists on the study database. Note, this population is not identified in the protocol, but is needed for displays that include subjects screened but not in the intent-to-treat (ITT) population (e.g. tabulation of reasons for withdrawal before randomisation). **Intent-to-treat (ITT) population:** All randomized subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy). The ITT population will be used to analyze the primary efficacy endpoint analysis, the secondary efficacy endpoint and other efficacy endpoints. Subjects will be assigned to the treatment group as randomized for the ITT population. **Per protocol (PP) population**: all ITT subjects without any protocol deviations specifically defined in this RAP. Protocol deviations will be reviewed and will be classified as important or not important during data review meetings that will be held before DBF. Deviations classified as important will be further defined according to whether they require the patient to be excluded from the PP population. Deviations that exclude a patient from the PP population are defined in this RAP (see Section 10.1.2). Subjects will be assigned to the treatment group as treated for the PP population. **Safety population:** All enrolled subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy) and considered as-treated. The Safety population will be the basis for safety analyses. Subjects will be assigned to the treatment group as treated for the Safety population.
Hypothesis	The primary analysis is designed to determine whether the fixed combination FF/VI is non-inferior to any other ICS/LABA combinations in inhalation powder assuming a non-inferiority margin of 1.5. Non-inferiority will be claimed if the 95% two-sided confidence interval (CI) on the difference in mean primary efficacy endpoints (FF/VI versus ICS/LABA comparator) precludes the non-inferiority margin of -1.5. If (and only if) non-inferiority is significantly achieved at Week 12 (Visit 4) with regard to the primary endpoint, then non-inferiority of the fixed combination FF/VI to any other ICS/LABA combinations will be tested at Week 24 (Visit 6) considering the same non-inferiority margin of 1.5. Non-inferiority will be claimed if the 95% two-sided CI on the difference in mean primary efficacy endpoints (FF/VI versus ICS/LABA comparator) at Week 24 (Visit 6) precludes the non-inferiority margin of -1.5. This step-down testing procedure strongly controls the overall type I error of the non-inferiority endpoints at the 0.05 two-sided level.
Primary Analyses	The primary endpoint will be analysed using a mixed model repeated measures (MMRM) approach. The model will include factors and covariates as follows: randomised treatment, scheduled visit time point (Week 6 and Week 12), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient will be fitted as a random factor. The Restricted Maximum Likelihood (REML) estimation approach will be used, and the default covariance structure will be unstructured. Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point will be performed. The adjusted means for each treatment and the estimated treatment differences for the treatment comparisons will be presented together with the 95% CIs for the differences (FF/VI versus ICS/LABA comparator) and p-values at Week 12 (Visit 4). If non-inferiority is statistically achieved at Week 12 (Visit 4), then superiority of FF/VI to any other comparator will be tested at the usual 0.05 two-sided nominal level of significance.

Overview	Key Elements of the RAP
	The same models and analyses mentioned above will be used to assess the superiority hypothesis.
Secondary Analyses	**Key secondary analysis** The key secondary endpoint assessed at Week 24 (Visit 6) will also be analyzed using a MMRM approach where data up to and including Week 24 (Visit 6) will be used in the model. The model will include factors and covariates as follows: randomised treatment, scheduled visit time point (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient will be fitted as a random factor. The REML estimation approach will be used, and the default covariance structure will be unstructured. Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point will be performed. The adjusted means for each treatment and the estimated treatment difference for the treatment comparison will be presented together with the 95% CI for the difference (FF/VI versus ICS/LABA comparator) and p-value at Week 24 (Visit 6). If non-inferiority is statistically achieved at Week 24 (Visit 6), then superiority of FF/VI versus any other comparator will be tested at the usual 0.05 two-sided nominal level of significance. The same models and analyses mentioned above will be used to assess the superiority hypothesis. **Other secondary analyses** The other key secondary endpoint will be the correct use of the inhaler device assessed at randomisation (Visit 2), at Week 12 (Visit 4) and at Week 24 (Visit 6). The device will be considered as correctly used if the patient didn't make any critical or non-critical errors at the corresponding visits (randomisation [Visit 2], Week 12 [Visit 4] and Week 24 [Visit 6]). Percentages of subjects correctly using the device will be calculated within each group. A corresponding 95% CI of the difference in percentages will also be provided. An exploratory analysis of the categorised data will be performed using logistic regression models with covariates as follows: randomised treatment, correct use of inhaler device at baseline, randomised treatment-by-visit interaction, gender, age and country. The estimated treatment differences will be displayed as odds ratios together with 95% CIs and p-values.

1. SUMMARY OF KEY PROTOCOL INFORMATION

1.1. Changes to the Protocol Defined Statistical Analysis Plan

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

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• N/A	• The open-label study design and the method of recording study medication data in the datasets means that extra steps must be taken to ensure that S&P remain blinded to study investigator prescribing of study medication until the formal unblinding takes place at DBF. See Section 10.13 for more details.	• To preserve the integrity of the analyses, S&P will remain blinded prior to formal unblinding at DBF. All planned analyses will be carried out after this point.
• N/A	• **All Subjects Enrolled (ASE) Population:** All subjects screened (provided consent) and for whom a record exists on the study database. Note, this population is not identified in the protocol, but is needed for displays that include subjects screened but not in the ITT Population (e.g. tabulation of reasons for withdrawal before randomisation).	• Population needed for displays that include subjects screened but not in the ITT population.
• Continuous variables will be summarized using descriptive statistics (number of observed and missing data, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum). • Categorical variables will be summarized as numbers of observed and missing data, counts and percentage for each category (reported to the number of non-missing values). For binary variables, 95% confidence	• See Appendix 16: Example Mock Shells for Data Displays for example mock shells for data displays	• Continuous and categorical variables will be summarized in line with GSK Integrated Data Standards Library (IDSL) data standards

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
intervals for proportions will be estimated based on the Clopper-Pearson method.		
• If treatment is withdrawn, then the missing ACT score at the nearest visit after treatment withdrawal will be replaced by the ACT score assessed at withdrawal time. If no ACT score is assess at withdrawal time, then the ACT missing score at the nearest visit after treatment withdrawal will not be replaced.	• Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point will be performed.	• The protocol inconsistently describes whether or not missing scores will be imputed. Consistent with MMRM models and the MAR assumption they are based upon, no missing data will be imputed for the primary efficacy analysis. Sensitivity analyses for the primary endpoint are proposed in Section 6.1.2 and will consider imputation of missing data.
• The primary endpoint will be analysed using a mixed model repeated measures (MMRM) approach. The model will include factors and covariates as follows: treatment, scheduled visit time point (Week 6 and Week 12), baseline ACT, treatment by visit interaction, baseline ACT by visit interaction, gender, age and patient will be fitted as a random factor.	• The primary endpoint will be analysed using a MMRM approach. The model will include factors and covariates as follows: randomised treatment, scheduled visit time point (Week 6 and Week 12), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient will be fitted as a random factor.	• Clarified that *randomised* treatment and baseline ACT *total score* will be included. Additionally country will be included in the model due to the addition of Germany, and separate randomisation schedules for France and Germany achieving stratification by country • Same changes for secondary and other analyses
• Sensitivity analyses (for the primary endpoint)	• Text changed and clarified	• The text from the protocol regarding sensitivity analyses has been updated and clarified where necessary. Description of the multiple imputation (MI) process has been brought in line with GSK standard text.
• Usual ICS/LABA maintenance therapy	• Usual ICS/LABA	• The comparator arm is described as “Usual ICS/LABA” for consistency with reporting of the HZA115150 study (GSK Document No.: 2011N129785_02).
• EQ-5D	• EQ-5D-5L	• Clarity as to which version

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
		of the EuroQol questionnaire is being used
• Binary response defined as an ACT score ≥ 20 at a given visit OR a 3 point increase from baseline in ACT change. • The responder analyses will be conducted using a logistic regression model at a given Visit or Phone Call adjusting for treatment and stratification factors (baseline ACT score categorized into two classes, baseline asthma therapy, and potentially season at randomization). Treatment by stratification factors interaction effects will be further investigated in additional logistic models adjusting for these specific effects.	• This endpoint will be analysed using a logistic regression model adjusting for randomised treatment, gender, country, baseline ACT total score, baseline ACT total score squared and age	• Clarified that *randomised* treatment will be included. • Country will be included in the model due to the addition of Germany, and separate randomisation schedules for France and Germany achieving stratification by country • Due to this being a composite endpoint, a quadratic relationship is expected between baseline score and probability of response. Baseline ACT total score and baseline ACT total score squared will be included (instead of "baseline ACT score categorised into two classes") to account for this • All patients are on the same baseline asthma therapy class (ICS), therefore this will not be included as a covariate • Season at randomisation will not be included; this is only considered as sensitivity analysis for the primary efficacy endpoint
• N/A	• ≥ 3 point increase from baseline in ACT total score at Week 12 (Visit 4) and Week 24 (Visit 6) • Time to first severe asthma exacerbation	• These endpoints have been added for consistency with the HZA115150 study (GSK Document No.: 2011N129785_02).

1.2. Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
• To compare the efficacy of FF/VI 92 mcg/ 22 mcg or FF 184 mcg/22 mcg with usual fixed combinations ICS/LABA for asthma maintenance therapy at Week 12 (Visit 4).	• Change from baseline in the ACT total score at Week 12 (Visit 4).
Secondary Objectives	**Secondary Endpoints**
• To assess effect of FF/VI on asthma control compared with usual ICS/LABA fixed combination at Week 24 (Visit 6).	• Change from baseline in ACT score at Week 24 (Visit 6).
• To assess Ellipta™ inhaler correct use compared with other dry powder inhaler (DPI) (Diskus™ and Turbuhaler) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).	• Percentage of subjects with correct use of device (defined as not making any critical error or non-critical error) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).
Other Objectives	**Other Endpoints**
• To assess effect of FF/VI on trough (pre-dose) forced expiratory volume in 1 second (FEV1) compared with usual ICS/LABA fixed combination at Week 12 (Visit 4)	• Change from baseline in trough (pre-dose) FEV1 at Week 12 (Visit 4).
• To assess the effect of FF/VI on response to treatment at Week 12 (Visit 4) and Week 24 (Visit 6)	• ACT score ≥ 20 or ≥ 3 point increase from baseline in ACT at Week 12 (Visit 4) and Week 24 (Visit 6). Note: A 3 point increase in ACT total score was suggested as the Minimal Clinically Important Difference (MCID) in the literature (Schatz, 2009). • ACT score ≥ 20 at Week 12 (Visit 4) and Week 24 (Visit 6). • ≥ 3 Point Increase from Baseline in ACT Total Score at Week 12 (Visit 4) and Week 24 (Visit 6) • Change from baseline in individual question scores for ACT at Weeks 12, 24
• To assess the compliance with study medication and self-reported adherence to study medication at Week 12 (Visit 4) and Week 24 (Visit 6)	• Compliance with study medication from randomisation (Day 0) to Week 12 (Visit 4), from Week 12 (Visit 4) to Week 24 (Visit 6) and from randomisation (Day 0) to Week 24 (Visit 6). • Score of the Medication Adherence Report Scale for Asthma (MARS-A) questionnaire at randomisation (Day 0), Week 12 (Visit 4) and Week 24 (Visit 6).
• To assess the effect of FF/VI on severe asthma exacerbation over the study period	• Number of subject with at least 1 severe asthma exacerbation*, number of severe asthma exacerbation and annual severe exacerbation rate over the study period.

Objectives	Endpoints
	• Time to first severe asthma exacerbation
• To assess the effect of FF/VI on Health Related Quality of Life at Week 24 (Visit 6)	• Change from baseline in total score and domain scores of standardised Asthma Quality of Life Questionnaire (AQLQ[S]) at Week 24 (Visit 6). • An increase from baseline of ≥ 0.5 in AQLQ(s) total score at Week 24 (Visit 6). • An increase from baseline of ≥ 0.5 in AQLQ(s) environmental stimuli domain score at Week 24 (Visit 6). • Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) individual domain scores at Week 24 (Visit 6). • Change from baseline in total score and domain scores of AQLQ(S) at Week 24 (Visit 6). • Health status using the EuroQol Questionnaire (EQ-5D-5L) at Week 24 (Visit 6).
• To assess Patient Satisfaction and Preference assessment with different inhalers at Week 12 (Visit 4)	• Score of Patient Satisfaction and Preference Questionnaire (PASAP-Q) at Week 12 (Visit 4).
• To evaluate the Safety of FF/VI compared with usual ICS/LABA (FP/S and BUD/F).	• Serious Adverse Events (SAE) and non-serious Adverse Drug Reactions (ADR): ○ Frequency and type of SAEs, ○ Frequency and type of non-serious ADRs related to treatment.

* A severe asthma exacerbation will be defined as deterioration of asthma requiring the use of systemic corticosteroids[2] (tablets, suspension, or injection) for at least 3 days or an inpatient hospitalisation, or emergency department visit due to asthma that required systemic corticosteroids [1,2,3].

Notes defining endpoints:

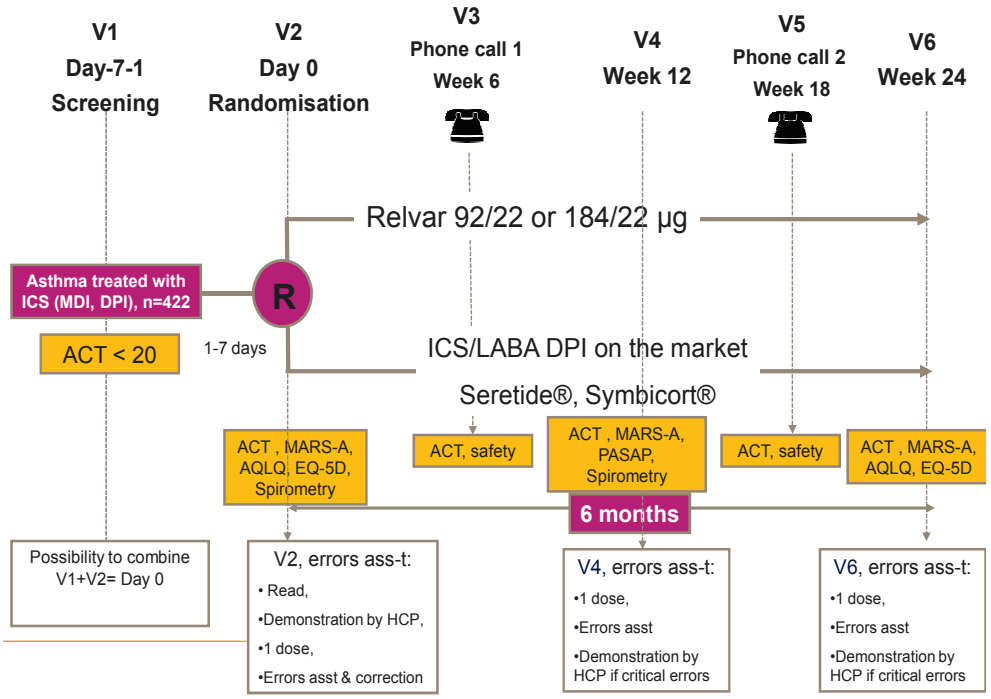
1. Contacts with a doctor or hospitalisation are defined as exacerbation-related contacts if these contacts were a direct result of an acute worsening of asthma symptoms.

2. A prescription of systemic corticosteroid is defined as exacerbation-related if the reason the drug was given, in whole or in part, was to treat an acute worsening of asthma symptoms.

3. Exacerbation-related hospitalisation includes hospitalisation that is prolonged as a result of an asthma exacerbation.

Overview of Study Design and Key Features	

HZA 116492: study design



- A phone call is provided at Week 6 and Week 18 in order to check whether the subject has experienced any AEs and then the Investigator calling the patient must determine whether the event is related to study medication (either arm) and whether the event is serious. At these telephone calls subjects will also be asked to complete the ACT questionnaire and to send it back to the Investigator.

- Week 12 (Visit 4) should be scheduled at the same time of day as the randomisation visit (Visit 2).

Design Features	• This is a Phase IIIb multi-center randomised open label, parallel group study performed in subjects in primary and respiratory specialist care / research sites who have a diagnosis of asthma and a regular treatment for asthma. • Subjects with unsatisfactorily controlled asthma (defined as ACT total score < 20) and intended to be treated by usual ICS/LABA maintenance therapy to seek a better control of their asthma will be randomised to receive either FF/VI once daily or another usual ICS/LABA combination therapy in inhalation powder twice daily (FP/S or BUD/F)

Overview of Study Design and Key Features

decided by the physician.

Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomisation schedule.

Subjects will be randomised in a 1:1 ratio to one of the 2 following treatment groups:

FF/VI (as per dose guidance below)

Initiate on usual inhaled dry powder ICS/LABA fixed combination for asthma maintenance therapy (i.e. Seretide Diskus™ or Symbicort Turbuhaler) according to usual physician's prescription.

Dose Guidance:

For subjects randomised to FF/VI, Investigator can make dosing decision based on the guidance below:

- FF/VI 92 mcg/22mcg dose once a day is approximately equivalent to FP/S medium dose (250 mcg/50mcg) and BUD/F medium dose (200 mcg/6 mcg) twice a day. See Table 2 for further guidance for doses conversion for other corticosteroids.
- FF/VI 184 mcg/22 mcg dose once a day is approximately equivalent to FP/S high dose (500 mcg/50 mcg) and to BUD/F high dose (400 mcg/12 mcg) twice a day. See Table 2 for guidance for dose conversion for other corticosteroids.
- Starting doses are: 92 mcg/22 mcg once daily for FF/VI; 250 mcg/50 mcg twice daily for FP/S and 200 mcg/6 mcg twice daily for BUD/F.

Table 2 ICS/LABA Daily Dose (SmPC Seretide Diskus™; Symbicort Turbuhaler)

Formulation	Inhaler Devices	Doses Available (mcg) ICS/LABA and Inhalations/day
Fluticasone propionate/salmeterol	DPI (Diskus)	1 inhalation x 2 Medium-dose 250/50 High-dose 500/50
Budesonide/formoterol	DPI (Turbuhaler)	1-2 inhalations x 2 Medium-dose 200/6 High-dose 400/12

Information extracted from Global Initiative for Asthma (GINA, 2012).

For patients with moderate to severe hepatic impairment, the 92/22 micrograms dose of FF/VI should be used and patients should be monitored for systemic corticosteroid-related

Overview of Study Design and Key Features	
	adverse reactions. **Planned Dose Adjustments** Subjects randomised to the usual ICS/LABA asthma maintenance therapy arm can have their treatment adjusted as would be normal clinical practice at the Investigator's discretion. This will not require the subject to be withdrawn from the study. These subjects should not receive FF/VI, if the medication is marketed during the study period. Subjects randomized to the FF/VI arm and for whom it is considered appropriate/ necessary to adjust treatment, can have their regimen changed as required as per normal clinical practice at any point in the study and the subject could remain in the study. Subjects on FF/VI arm can also change between the two FF/VI doses as appropriate and at the Investigator's discretion.
Interim Analysis	No interim analysis is planned for this study.

From this point onwards in the RAP, usual ICS/LABA maintenance therapy will be referred to as usual ICS/LABA.

1.3. Statistical Hypotheses

The primary endpoint is defined as the change from baseline in the ACT total score assessed at Week 12 (Visit 4). The primary analysis will assess the non-inferiority of fixed combination FF/VI to usual ICS/LABA in inhalation powder assuming a non-inferiority margin of 1.5. Non-inferiority will be claimed if the 95% two-sided confidence interval on the difference in mean primary efficacy endpoints (FF/VI versus usual ICS/LABA) precludes the non-inferiority margin of -1.5.

If (and only if) non-inferiority is significantly achieved at Week 12 (Visit 4) with regard to the primary endpoint, then non-inferiority of the fixed combination FF/VI to usual ICS/LABA will be tested at Week 24 (Visit 6) considering the same non-inferiority margin of 1.5. Non-inferiority will be claimed if the 95% two-sided confidence interval on the difference in mean primary efficacy endpoints (FF/VI versus usual ICS/LABA) at Week 24 (Visit 6) precludes the non-inferiority margin of -1.5.

Of note, as the two tests for non-inferiority are sequentially performed, the closure principle holds and there is no need to adjust the two-sided nominal level of significance (i.e. 0.05) for each test.

1.4. Sample Size Assumptions

Results based on the HZA106829 study have shown that the estimated SD of the change in ACT score was 3.7. Unpublished data have shown that the standard deviation of change of ACT ranged from 3.8 to 4.8. Therefore, a somewhat conservative choice of SD of 4.5 point is retained.

Based on the literature (Schatz, 2009), the Minimally Important Difference (MID) of the ACT could be considered as 3 points. Half this MID (i.e. 1.5) could therefore be used to define the non-inferiority margin.

Assuming a 4.5 point standard deviation for the change in ACT total score at Week 12 (Visit 4), a 1.5 point non-inferiority margin, and a two-sided nominal significance level of 0.05, the sample size needed per group to achieve at least a 90% power is 191 (i.e. a total of 382 subjects). Assuming a 10% dropout rate, around 422 subjects must be randomized either to FF/VI or to usual ICS/LABA in 1:1 ratio to achieve at least a 90% power.

2. PLANNED ANALYSES

2.1. Interim Analyses

Not applicable.

2.2. Data Look

At a date agreed by the study team and the contract research organisation (CRO) (selected to execute the statistical analyses specified in this RAP), a data look will be performed using blinded treatment codes on a subset of the data. The aim of the data look is solely to ensure that all of the required tables, figures and listings are being produced and formatted correctly, such that the output produced on unblinded data at the end of the study is correct and complete. This data look will be performed when sufficient data are available, but early enough to leave time for changes to be made to the planned outputs and methods prior to database release (DBR). Any changes will be documented before DBR.

2.3. Final Analyses

All planned analyses will be performed after the completion of the following sequential steps:

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

3. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	• Comprise of all subjects screened (provided consent) and for whom a record exists on the study database. • Note, this population is not identified in the protocol, but is needed for displays that include subjects screened but not in the ITT Population (e.g. tabulation of reasons for withdrawal before randomisation)	• Subject disposition tables
Intent-To-Treat (ITT)	• Comprise of all randomized subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA) • Subjects will be assigned to the treatment group as randomized for the ITT population	• Study Population • Efficacy
Per Protocol (PP)	• Comprise of all ITT subjects without any major violations of study procedures. • Major protocol violations will be identified prior to database lock. • Protocol deviations will be reviewed and classified as minor or major during a data review meeting that will be held before database lock. • Exclusion of subjects from the PP population are defined in Section 3.1 (Protocol Deviations) and Appendix 1: Protocol Deviation Management and Definitions for PP Population • Subjects will be assigned to the treatment group as treated for the PP population	• This population will be used for summaries and analyses of the primary efficacy secondary efficacy endpoints.
Safety	• Comprise of all enrolled subjects having received at least one dose of study medication (either FF/VI or usual ICS/LABA) and considered as-treated. • Subjects will be assigned to the treatment group as treated for the Safety population	• Safety

NOTES :

- Please refer to Appendix 15: List of Data Displays which details the population to be used for each displays being generated.

3.1. Protocol Deviations

All PDs (any deviation from the protocol) are tracked and monitored during the study. Important PDs are those deviations that may compromise subject rights, safety, or well-being, and/or data integrity, and/or study end-points, and are defined in the protocol deviation management plan (PDMP). Apart from any incorrect treatment deviations, all full and partial protocol deviations will be agreed upon prior the unblinding and the freezing of the database. All deviations from the inclusion/exclusion criteria, and important PDs will be summarised. A listing of treatment misallocations will be produced.

4. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 3 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 3 Overview of Appendices

Section	Component
10.1	Appendix 1: Protocol Deviation Management and Definitions for PP Population
10.2	Appendix 2: Time & Events
10.3	Appendix 3: Assessment Windows
10.4	Appendix 4: Treatment States and Phases
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
10.8	Appendix 8: Values of Potential Clinical Importance
10.9	Appendix 9: Multicenter Studies
10.10	Appendix 10: Examination of Covariates, Subgroups & Other Strata
10.11	Appendix 11: Multiple Comparisons & Multiplicity
10.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses
10.13	Appendix 13: Blinding Strategy
10.14	Appendix 14: Abbreviations & Trade Marks
10.15	Appendix 15: List of Data Displays
10.16	Appendix 16: Example Mock Shells for Data Displays

5. STUDY POPULATION ANALYSES

5.1. Overview of Planned Analyses

The study population analyses will be based on the ITT population, unless otherwise specified.

Table 4 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 15: List of Data Displays.

Table 4 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Populations	Y[1]		Y
Inclusion/exclusion Criteria Failures for Subjects Not Starting Treatment	Y[1]		
End of Study Record	Y[2]		Y
Attendance at Each Clinic Visit and Phone Call Visit	Y		
Number of Subjects by Country and Centre	Y[2,3]		
Randomised and Actual Treatments			Y
Protocol Deviations			
Deviations from the Inclusion/Exclusion Criteria	Y		Y
Important Protocol Deviations	Y		Y
Important Protocol Deviations Resulting in Exclusion from the PP Population	Y		Y
Treatment Misallocations			Y
Demographic and Baseline Characteristics			
Demographic Characteristics	Y[2,4]		Y
Race and Racial Combinations	Y		Y
Race and Racial Combinations Details	Y		
Current and Past Medical Conditions	Y		
Asthma Duration at Baseline	Y[2]		Y
Asthma Exacerbation History at Baseline	Y[2]		Y
Lung Function at Baseline	Y		
Smoking History at Baseline	Y[2]		Y
Concomitant Medications			
Pre-Treatment Concomitant Medications	Y		Y
On-Treatment Concomitant Medications	Y		Y
On-Treatment Asthma Concomitant Medications	Y		
Relationship between Ingredient and Verbatim Text			Y
Exposure and Medication Modifications			
Study Medication Dosage Modification	Y		
Extent of Exposure to Study Medication (Regardless of Modification to Study Medication Dosage)	Y	Y	Y
Extent of Exposure to Study Medication (up to First Modification of Study Medication Dosage)	Y		
Extent of Exposure to Study Medication by Medication and Dosage	Y		
Number of Subjects by Subgroup	Y		

NOTES :

- Y = Yes display generated.
- [1]: Display will be based on ASE population
- [2]: Display will be repeated for the PP population
- [3]: Display will be repeated for the ASE population
- [4]: Display will be repeated for the Safety population

6. PRIMARY STATISTICAL ANALYSES

6.1. Efficacy Analyses

6.1.1. Overview of Planned Efficacy Analyses

The primary efficacy analyses will be based on the ITT population and repeated for the PP population, unless otherwise specified.

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

Table 5 Overview of Planned Efficacy Analyses

Endpoint	Data displays generated						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
ACT Total Score							
Change from Baseline in the ACT Total Score at Week 12 (Visit 4)	Y[1,2,3,4,5,6,7]			Y[1,2,3,4,5,7]	Y[1]		Y[8]

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- Display will be repeated for the following subgroups (ITT only) (see Section 10.10 for more details):
  - [1]: Country
  - [2]: Number of severe asthma exacerbations in the previous year prior to randomisation
  - [3]: Smoking status at baseline
  - [4]: Age group
  - [5]: Gender
- [6]: Sensitivity analyses will be produced for the following approaches:
  - Last observation carried forward (LOCF) (ITT only)
  - MI analyses utilizing covariates (ITT only)
  - Semi-parametric Hodges-Lehmann (HL) approach (ITT only)
  - Worst observation carried forward (WOCF) for treatment withdrawals (ITT only)
  - Adjusting for seasonal effect
- [7]: Display will be repeated for:
  - FF/VI versus the subset of Usual ICS/LABA subjects prescribed FP/S at randomisation (only if ≥25% of Usual ICS/LABA patients are prescribed FP/S at randomisation)
  - FF/VI versus the subset of Usual ICS/LABA subjects prescribed BUD/F at randomisation (only if ≥25% of Usual ICS/LABA patients are prescribed BUD/F at randomisation)
- [8]: Display will be produced for the ITT population only.

6.1.2. Planned Efficacy Statistical Analyses

Primary Statistical Analyses

Endpoint(s)

- Change from Baseline in the ACT Total Score at Week 12 (Visit 4)

Model Specification

- The primary endpoint will be performed on both the ITT and the PP populations, and analysed using an MMRM model utilizing the REML estimation approach and a default covariance structure of unstructured
- Terms fitted in the model will include:

Response	: Change from Baseline in ACT Total Score
Fixed Categorical	: Randomised treatment, visit (Week 6 and Week 12), gender, country
Fixed Continuous	: Baseline ACT total score, age
Interaction terms	: Randomised treatment-by-visit, baseline ACT total score-by-visit
Random effect	: Subject

SAS Code to Perform Analysis

```
proc mixed data=input_data;
        class trtcd gender country visit subjid ;
        model ACT = trtcd gender country age baseline
                        visit visit*baseline visit*trtcd / ddfm=kr ;
        repeated visit / subject=subjid type=un ;
        random intercept / subject=subjid ;
        lsmeans visit*trtcd / cl diff e om=OMdset at (baseline age)=(&blm. &agem.) ;
run ;
```

where OMdset is a dataset with a row for every visit-subject combination that contains all of the covariates and blm and agem are macro variables containing the means for baseline and age for the subjects used in the analysis. These are used to derive the adjusted means using coefficients which are based on the subjects used in the analysis.

Model Checking & Diagnostics

- Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- For Week 12 (Visit 4), the adjusted (least squares [LS]) mean change from baseline for each treatment and the estimated treatment difference for FF/VI versus Usual ICS/LABA (i.e. the difference in LS mean change from baseline) will be presented together with the associated 95% CI and p-value.
- Summary statistics will be produced for absolute value of and change from baseline in ACT total score at each post-baseline visit (Week 6 [Visit 3], Week 12 [Visit 4], Week 18 [Visit 5] and Week 24 [Visit 6]).
- A listing of ACT total and change from baseline scores will be provided.
- Mean ACT total score ± SD will be plotted by visit.

Subgroup Analyses

- For the analyses by country (France, Germany) and gender (male, female), the model will additionally include the randomised treatment-by-subgroup and randomised treatment-by-subgroup-by-visit interactions as a covariate.
- For the analyses by number of severe asthma exacerbations in the previous year prior to randomisation (0, >1) and smoking status at baseline (non-smoker, former smoker, current smoker), the model will additionally include the subgroup, randomised treatment-by-subgroup interaction and randomised treatment-by-subgroup-by-visit interaction as covariates.
- For the analysis by age group (<50 years, ≥50 years), the continuous covariate age will be replaced by age group, randomised treatment-by-age group interaction and randomised treatment-by-age group-by-visit interaction.

Sensitivity and Supportive Statistical Analyses
Justification for Sensitivity Analyses Handling Missing Data
• While subjects missing Week 12 (Visit 4) data but having earlier data will be included in the MMRM primary analysis, the interpretability of the results from the primary model will depend on the missing data satisfying the Missing at Random (MAR) assumption. To support the validity of the conclusions drawn from this analysis, several sensitivity analyses will be performed to explore the dropout pattern and its possible impact on treatment comparisons. These sensitivity analyses will be performed on the ITT population only as subjects with missing ACT total score at Week 12 (Visit 4) are excluded from the PP population.
Last Observation Carried Forward
• Missing values at Week 12 (Visit 4) will be replaced by the last available post-randomization value (either the Week 6 (Visit 2) ACT score or the ACT score at treatment withdrawal time, if applicable), i.e. based on the LOCF method. The change from baseline in ACT at Week 12 (Visit 4) will be analyzed using an analysis of covariance (ANCOVA) model adjusting for randomised treatment, baseline ACT score, gender, country and age. For Week 12 (Visit 4), the LS mean change from baseline for each treatment and estimated LS mean change from baseline difference for FF/VI versus Usual ICS/LABA will be presented together with the associated 95% CI and p-value.
Multiple Imputation
• Sensitivity analyses will be performed using MI methods based on pattern mixture models. First, a repeated measures Normal model will be fitted to the data using a Bayesian approach, with non-informative priors for the mean and variance-covariance matrix to provide a joint posterior for the parameters in this model. The repeated measures Normal model will include separate mean profiles for each treatment group and the same covariates as those in the primary efficacy analysis. • Independent samples will then be drawn from the posterior distributions for the mean and variance-covariance matrix to provide inputs into an imputation model. For each subject with missing data, these sampled values of the parameters for mean vectors and the variance-covariance matrices specify a joint distribution for their observed and unobserved outcome data. • The post-withdrawal part of each pattern-specific distribution will be modelled using the approach discussed below. This imputation model will have the same covariates as those in the primary efficacy analysis. • Based on this imputation model, a single set of data will be sampled for the missing data based on the distribution for the subject's missing data conditional upon their observed data. Each imputed data set will then be analysed using simple ANCOVA at Week 12 (Visit 4) and the resulting treatment differences and their standard errors combined using Rubin's rules. • The post-withdrawal part of each pattern-specific distribution will be modelled using these two approaches: o MAR Approach. The means and variance-covariances following withdrawal are chosen to reflect the subject's own treatment group. This approach will provide similar results to using a mixed effects model where the unstructured covariance matrix is estimated separately for each arm, and all covariates are crossed with treatment. As such it is not truly a sensitivity analysis as we expect to get very similar results. Like the MMRM this answers an on-treatment question. o Copy Differences from Reference Approach. This approach addresses a potential pattern of informative missingness, in which subjects withdrawn from the test groups would have followed the same trend over time (difference in mean value between time-points) as those in the reference group, had they continued in the study. Therefore, this approach may be considered conservative because it will assume that following withdrawal from a test treatment arm, imputation for their missingness will be derived from observed reference data. The intention is to represent an ITT-like approach. • For each method, the LS mean change from baseline at Week 12 (Visit 4) for each treatment and

Sensitivity and Supportive Statistical Analyses
estimated LS mean change from baseline difference for FF/VI versus Usual ICS/LABA will be presented together with the associated 95% CI and p-value.
Hodges-Lehmann Approach
• A sensitivity analysis based on the semi parametric HL approach will be proposed to assess the robustness of the MMRM Model-based non-inferiority results. The HL difference between groups at Week 12 (Visit 4) and corresponding 95% CI will be provided.
Worst Observation Carried Forward
• When treatment withdrawal occurs, an alternative method for imputing the missing value at the nearest visit after withdrawal time will be proposed: the primary endpoint missing value will be estimated by the worst ACT score observed between baseline visit and withdrawal time, inclusive – i.e. using the WOCF method. An ANCOVA model adjusting for randomised treatment, baseline ACT score, gender, country and age will be used to analyse this imputed data, with the LS mean change from baseline for each treatment presented at Week 12 (Visit 4) together with the estimated LS mean change from baseline difference and associated 95% CI and p-value
Summary of Sensitivity Statistical Analyses
• A plot will be produced displaying the treatment differences and 95% CIs for the primary analysis and each of the sensitivity analyses described above.
Seasonal effect
• A sensitivity analysis adjusting for seasonal effect will be performed by repeating the primary efficacy analysis with the addition of season at randomisation, randomised treatment-by-season at randomisation interaction and randomised treatment-by-season at randomisation-by-visit interaction. See Section 10.10.3 for the definition of season at randomisation. The LS mean change from baseline at Week 12 (Visit 4) for each treatment and estimated LS mean change from baseline difference will be displayed for each season at randomisation together with the associated 95% CI and p-value, and the interaction p-value.

7. SECONDARY STATISTICAL ANALYSES

7.1. Efficacy Analyses

7.1.1. Overview of Planned Efficacy Analyses

The secondary efficacy analyses will be based on the ITT population, unless specified otherwise.

Table 6 provides an overview of the planned efficacy analyses, with further details of data displays being presented in Appendix 15: List of Data Displays.

Table 6 Overview of Planned Efficacy Analyses

Endpoint	Data displays generated						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
ACT Total Score							
Change from Baseline in the ACT Total Score at Week 24 (Visit 4)	Y[1,2,3,4]	Y		Y[1,2,4,5,6,7,8]	Y[1,2]		
Correct Use of Device							
Percentage of Subjects with Correct Use of Inhaler Device at Week 12 (Visit 4) and at Week 24 (Visit 6) Independently of the Use at Week 12 (Visit 4)	Y[1]			Y[1]			Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1]: Display will be repeated for the PP population
- [2]: Display will be repeated by Country (ITT only)
- [3]: Sensitivity analyses will be produced for the following approaches:
  - LOCF (ITT only)
  - MI analyses utilizing covariates (ITT only)
  - Semi-parametric HL approach (ITT only)
  - WOCF for treatment withdrawals (ITT only)
  - Adjusting for seasonal effect
- [4]: Display will be repeated for:
  - FF/VI versus the subset of Usual ICS/LABA subjects prescribed FP/S at randomisation (only if ≥25% of Usual ICS/LABA patients are prescribed FP/S at randomisation)
  - FF/VI versus the subset of Usual ICS/LABA subjects prescribed BUD/F at randomisation (only if ≥25% of Usual ICS/LABA patients are prescribed BUD/F at randomisation)
- Display will be repeated for the following subgroups (ITT only) (see Section 10.10 for more details):
  - [5]: Number of severe asthma exacerbations in the previous year prior to randomisation
  - [6]: Smoking status at baseline
  - [7]: Age group
  - [8]: Gender

7.1.2. Planned Efficacy Statistical Analyses

Secondary Statistical Analyses
Endpoint(s)
• Change from Baseline in the ACT Total Score at Week 24 (Visit 6)
Model Specification
• This endpoint will be performed on both the ITT and the PP populations, and analysed using an MMRM model utilizing the REML estimation approach and a default variance-covariance structure of unstructured • Terms fitted in the model will include: Response : Change from Baseline in ACT Total Score Fixed Categorical : Randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), gender, country Fixed Continuous : Baseline ACT total score, age Interaction terms : Randomised treatment-by-visit, baseline ACT total score-by-visit Random effect : Subject
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• For Week 24 (Visit 6), the LS mean change from baseline for each treatment and the estimated difference in LS mean change from baseline for FF/VI versus Usual ICS/LABA will be presented together with the associated 95% CI and p-value. • Summary statistics, a listing and plots of mean ACT total score ± SD will be produced as part of the primary efficacy endpoint analysis (see Section 6.1.2).
Subgroup Analysis
• For the analysis by country (France, Germany), the model will additionally include the randomised treatment-by-country and randomised treatment-by-country-by-visit interactions as a covariate.

Sensitivity and Supportive Statistical Analyses
• The same sensitivity analyses as those described for the primary endpoint will be performed for the key secondary endpoint of change from baseline in the ACT total score at Week 24 (Visit 6) .

Secondary Statistical Analyses
Endpoint(s)
• Percentage of subjects with correct use of inhaler device at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4)
Model Specification
• These endpoints will be analysed for both the ITT and the PP populations using logistic regression models • Terms fitted in the model will include: Response : Endpoint Fixed Categorical : Randomised treatment, correct use of inhaler device at baseline, gender, country Fixed Continuous : Age
SAS Code to Perform Analysis

proc logistic data=input_data plots=(all);
class trtcd country baseline gender / ref=first param=ref;
model corr_use (event="Y") = trtcd baseline age gender country;
contrast "Trt_effect" trtcd 1 / estimate=exp;
run;

Secondary Statistical Analyses
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• The number and percentage of subjects with correct use within each randomised treatment group will be presented by visit, together with the adjusted odds ratio comparing FF/VI with Usual ICS/LABA, associated p-value and 95% CI. • A summary and listing of correct use / errors of inhaler use will be produced.

7.2. Safety Analyses

7.2.1. Overview of Planned Analyses

The safety analyses will be based on the Safety population.

Table 7 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 15: List of Data Displays.

Table 7 Overview of Planned Safety Analyses

Endpoint	Data displays generated					
	Stats Analysis		Summary		Individual	
	T	F	T	F	F	L
Adverse Events						
SAEs and ADRs Overview			Y			
Non-Serious ADRs			Y			Y
Serious ADRs			Y			
All ADRs			Y			
SAEs			Y			Y
SAEs and ADRs Leading to Permanent Discontinuation of Study Medication or Withdrawal from Study			Y			Y
SAEs Leading to Permanent Discontinuation of Study Medication or Withdrawal from Study			Y			
ADRs Leading to Permanent Discontinuation of Study Medication or Withdrawal from Study			Y			
Non-Serious ADRs Leading to Permanent Discontinuation of Study Medication or Withdrawal from Study						Y
Most Frequent Non-Serious ADRs, Reported by ≥1% or More of Subjects in Any Treatment Group			Y			
Non-Serious ADRs of Special Interest			Y			
Serious ADRs of Special Interest			Y			
All ADRs of Special Interest			Y			
SAEs of Special Interest			Y			
Fatal SAEs			Y			Y
Fatal Serious ADRs			Y			
Fatal SAEs of Special Interest			Y			
Non-Fatal SAEs			Y			Y
Non-Fatal SAEs of Special Interest			Y			
AE terms of Special Interest						Y
Top Ten Most Commonly Reported On-treatment ADRs per Treatment Group			Y			
Vital Signs						
Vital Signs			Y			Y

Endpoint	Data displays generated					
	Stats Analysis		Summary		Individual	
	T	F	T	F	F	L
Inhaler Device Malfunctions						
Inhaler Device Malfunctions						Y
Liver chemistry						
Liver event						Y
Liver biopsy						Y
Liver imaging						Y
Other						
Pregnancy						Y

NOTES :

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

7.2.2. Benefit:Risk analyses

Benefit:Risk analyses will be based on the ITT population for Benefit, and Safety population for Risk.

Table 8 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 15: List of Data Displays.

Table 8 Overview of Planned Benefit:Risk Analyses

Endpoint	Data displays generated				
	Stats Analysis		Summary		Individual
	T	F	T	F	L
Summary of Benefit:Risk		Y			

NOTES :

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

Benefit Risk Statistical Safety Analyses
Endpoint(s)
• Summary of Benefit:Risk: various endpoints analyses in the context of safety and effectiveness analyses
Model Specification
• Estimates and their 95% CIs obtained from selected safety and effectiveness analyses will be presented for the ITT population on a multiple panel forest plot which will display effectiveness and safety data. • For certain endpoints, the x-axis may be reversed to ensure benefit/risk to either FF/VI or Usual ICS/LABA is shown accurately. • Due to endpoints being presented using different scales, the forest plot will be split into additional panels to allow better visibility of the results.

Benefit Risk Statistical Safety Analyses
Model Checking & Diagnostics
• Model checking and diagnostics are described in each endpoint analysis section.
Model Results Presentation
• The top panel ("Benefits") of the forest plot will display: o difference in LS mean change from baseline from the MMRM analysis of the primary efficacy endpoint, defined as the change from baseline in ACT total score at Week 12 (Visit 4), as described in Section 6.1.2 o difference in LS mean change from baseline from the MMRM analysis of the change from baseline in ACT total score at Week 24 (Visit 6), as described in Section 7.1.2 o adjusted odds ratio from the logistic regression analysis of percentage of subjects with correct use of inhaler device at Week 12 (Visit 4), as described in Section 7.1.2 o adjusted odds ratio from the logistic regression analysis of percentage of subjects with correct use of inhaler device at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4), as described in Section 7.1.2 • The bottom panel ("Risks") of the forest plot will display the risk difference for FF/VI vs. usual ICS/LABA of the incidence of the following SAEs of special interest: o Asthma/bronchospasm, cardiovascular effects, decreased bone mineral density and associated fractures, hypersensitivity, local steroid effects, lower respiratory tract infection (LRTI) excluding pneumonia, pneumonia, adrenal suppression, ocular effects, effects on glucose, effects on potassium, tremor

8. OTHER STATISTICAL ANALYSES

8.1. Other Analyses

8.1.1. Overview of Planned Other Analyses

The other statistical analyses will be based on the ITT population, unless otherwise specified.

Table 9 provides an overview of the planned other analyses, with full details of data displays being presented in Appendix 15: List of Data Displays.

Table 9 Overview of Planned Other Analyses

Endpoint	Absolute						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Trough (Pre-dose) FEV1							
Change from Baseline in Trough (Pre-dose) FEV1 at Week 12 (Visit 4)	Y			Y			Y
ACT							
ACT Total Score ≥ 20 or ≥ 3 Point Increase from Baseline in ACT Total Score at Week 12 (Visit 4) and Week 24 (Visit 6)	Y			Y	Y		
ACT Total Score ≥ 20 at Week 12 (Visit 4) and Week 24 (Visit 6)				Y	Y		
≥ 3 Point Increase from Baseline in ACT Total Score at Week 12 (Visit 4) and Week 24 (Visit 6)				Y	Y		
Change from Baseline in Individual ACT Questions at Week 12 (Visit 4) and Week 24 (Visit 6)				Y			
Compliance with Study Medication							
Compliance with Study Medication from Randomisation (Day 0) to Week 12 (Visit 4), from Week 12 (Visit 4) to Week 24 (Visit 6) and from Randomisation (Day 0) to Week 24 (Visit 6)				Y[1]	Y		Y

Endpoint	Absolute						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
MARS-A Score at Randomisation (Day 0), Week 12 (Visit 4) and Week 24 (Visit 6).				Y[2]	Y[2]		Y
Severe asthma exacerbations							
Number of Subjects With at Least 1 Severe Asthma Exacerbation and Number of Severe Asthma Exacerbations				Y[3]			Y
Annual Severe Asthma Exacerbation Rate over the Study Period	Y	Y					
Time to First Severe Asthma Exacerbation	Y	Y					
Asthma Quality of Life Questionnaire (AQLQ[S])							
Change from Baseline in Total Score and Domain Scores of AQLQ(S) at Week 24 (Visit 6)				Y			Y
An Increase from Baseline of ≥ 0.5 in AQLQ(s) Total Score at Week 24 (Visit 6)	Y			Y			
An Increase from Baseline of ≥ 0.5 in AQLQ(s) Environmental Stimuli Domain Score at Week 24 (Visit 6)	Y			Y			
An Increase from Baseline of ≥ 0.5 in AQLQ(S) Individual Domain Scores (Symptoms, Activity limitations and Emotional Function) at Week 24 (Visit 6)				Y			
EQ-5D-5L							
EQ-5D-5L Descriptive System Dimensions at Week 24 (Visit 6)	Y			Y			Y
EQ-5D-5L Utility Score at Week 24 (Visit 6)	Y			Y			Y
EQ-5D-5L Visual Analogue Scale (VAS) Score at Week 24 (Visit 6)	Y			Y			Y

Endpoint	Absolute						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
PASAP-Q							
PASAP-Q Scores at Week 12 (Visit 4)				Y			Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1]: Display will be repeated for the PP population
- [2]: A reminder was sent to centres in France instructing that the MARS-A questionnaire refers to the patient's preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study). See Section 10.6.3 for further details. Display will be repeated split by:
  - Patients in France who had completed all MARS-A assessments prior to the reminder being implemented
  - Patients in France who had completed at least one MARS-A assessment prior to the reminder being implemented but also completed at least one MARS-A assessment after the reminder being implemented
  - Patients in France who had not completed any MARS-A assessments prior to the reminder being implemented
  - Patients in Germany
- [3]: Display will be repeated by season.

8.1.2. Planned Other Statistical Analyses

Other Statistical Analyses

Endpoint(s)

- Change from baseline in trough (pre-dose) FEV1 at Week 12 (Visit 4)
- Change from baseline in EQ-5D-5L Utility Score at Week 24 (Visit 6)
- Change from baseline in EQ-5D-5L VAS Score at Week 24 (Visit 6)

Model Specification

- These endpoints will be analysed for the ITT population using ANCOVA models
- Terms fitted in the model will include:

Response	: Endpoint
Fixed Categorical	: Randomised treatment, gender, country
Fixed Continuous	FEV1 endpoint: Baseline trough (pre-dose) FEV1 and age EQ-5D-5L Utility Score endpoint: Baseline EQ-5D-5L Utility Score and age EQ-5D-5L VAS Score endpoint: Baseline EQ-5D-5L VAS Score and age

Model Checking & Diagnostics

- Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.

SAS Code to Perform Analysis

```
proc mixed data=input_data;
        class trtcd gender country;
        model FEV1 = trtcd gender country age baseline  / ddfm=kr ;
        lsmeans trtcd / cl diff e;
run ;
```

Model Results Presentation

- The LS mean change from baseline for each treatment and the difference in estimated LS mean change from baseline for FF/VI versus Usual ICS/LABA will be presented together with the associated 95% CI and p-value.

Other Statistical Analyses
• Summary statistics. • Listings will be provided.

Other Statistical Analyses	
Endpoint(s)	
• Percentage of subjects who had either an ACT total score ≥ 20 or ≥ 3 point increase from baseline in ACT total score at Week 12 (Visit 4) and Week 24 (Visit 6) • Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) total score at Week 24 (Visit 6) • Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) environmental stimuli domain score at Week 24 (Visit 6) • Percentage of subjects with 'no problems' in each dimension of the EQ-5D-5L questionnaire at Week 24 (Visit 6)	
Model Specification	
• These endpoints will be analysed for the ITT population using logistic regression models • Terms fitted in the model will include:	
Response	: Endpoint
Fixed Categorical	: Randomised treatment, gender, country
Fixed Continuous	ACT endpoints: Baseline ACT total score, baseline ACT total score squared and age AQLQ(S) endpoints: Baseline AQLQ(S) score and age EQ-5D-5L endpoints: Baseline EQ-5D-5L dimension score and age
Model Checking & Diagnostics	
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.	
Model Results Presentation	
• The number and percentage of subjects with a response within each randomised treatment group will be presented by visit, together with the adjusted odds ratio comparing FF/VI with Usual ICS/LABA, associated 95% CIs and p-values. • The number and percentage of subjects with ACT total score ≥20 or ≥3 point increase from baseline in ACT total score will be summarized by visit to include the tabulations of frequencies together and separately. • The number and percentage of subjects with an increase from baseline of ≥ 0.5 in AQLQ(S) total and individual domain scores at Week 24 (Visit 6) will be summarized. • The responses to each EQ-5D-5L dimension will be descriptively summarised	

Other Statistical Analyses	
Endpoint(s)	
• Annual severe asthma exacerbation rate over the study period	
Model Specification	
• This endpoint will be analysed for the ITT population using a generalised linear model (GLM), assuming the Negative Binomial distribution • Terms fitted in the model will include:	
Response	: Annual severe asthma exacerbation rate over the study period
Fixed Categorical	: Randomised treatment, gender, country, number of severe asthma exacerbations in the previous year prior to randomisation (0, ≥1)
Fixed Continuous	: Age

Other Statistical Analyses	
Offset variable	: Logarithm of time on treatment

Model Checking & Diagnostics

- Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.

SAS Code to Perform Analysis

```
proc genmod data=input_data;
  class trtcd gender country;
  model no_exac = trtcd exacbl gender country age / dist=negbin link=log offset=log_tm type3;
  lsmeans trtcd /cl diff=control("0") om exp;
run;
```

Model Results Presentation

- The LS mean number / annual rate, adjusted treatment ratio and associated 95% CI and p-value will be presented.
- Percentage reduction in mean number / annual rate and associated 95% CI will also be presented.
- The severe asthma exacerbation data will be summarized to include the tabulations of exacerbation frequencies, exacerbation duration (days) and the outcome, the prescription of oral corticosteroids and/or antibiotics to treat exacerbations, hospitalisations and emergency department visits due to an exacerbation, intubations due to an exacerbation and withdrawal of IP or withdrawal from the study as a result of an exacerbation.
- A listing of severe exacerbations will be provided.
- Box plots will be provided for the severe annual exacerbation rates.

Other Statistical Analyses

Endpoint(s)

- Time to first severe asthma exacerbation

Model Specification

- The cumulative distribution of this endpoint will be illustrated for the ITT population using Kaplan-Meier estimates and evaluated using the Wald Chi-Square test based on a Cox proportional hazards model.
- The analyses and summaries will include on-treatment exacerbations, from start date of exposure to min(stop date of exposure + 1 day, date of study discontinuation).
- The exact method for handling ties in times will be used.
- Terms fitted in the model will include:

Response	: Time to first severe asthma exacerbation
Fixed Categorical	: Randomised treatment, gender, country
Fixed Continuous	: Age

Model Checking & Diagnostics

- Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- The hazard ratio for FF/VI versus Usual ICS/LABA with associated 95% CI and p-value will be presented.
- Cumulative incidence curves of time to first severe asthma exacerbation will be presented.
- Summary statistics will also be presented.

9. REFERENCES

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10. APPENDICES

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

10.1.1. Protocol Deviations

All PDs (any deviation from the protocol) are tracked and monitored during the study. Important PDs are those deviations that may compromise subject rights, safety, or well-being, and/or data integrity, and/or study end-points, and are defined in the PDMP. Apart from any incorrect treatment deviations, all full and partial protocol deviations will be agreed upon prior the unblinding and the freezing of the database. All deviations from the inclusion/exclusion criteria, and important PDs will be summarised. A listing of treatment misallocations will be produced.

10.1.2. Exclusions from PP Population

Important PDs that will result in exclusion from the PP population are specified in Table 10, and will be summarised in a data display.

Table 10 PDs resulting in exclusion from the PP population

Deviation Category	Deviation Subcategory
Informed consent	• Signed informed consent/assent not available on site • Wrong informed consent/assent version signed[1] • Informed consent/assent not signed and/or dated by subject (parent/Legally Acceptable representative, if applicable) • Informed consent/assent not signed and/or dated by appropriate site staff. [1] • Informed consent/assent not signed prior to any study procedure[1] • Other informed consent/assent deviations[1]
Eligibility criteria not met – inclusion criteria	• Informed consent • Gender and Age[2] • Type of subject • Current Asthma Therapy • Inability of subject to complete questionnaires
Eligibility criteria not met – exclusion criteria	• History of Life-threatening asthma • Subjects having a severe and unstable asthma • COPD Respiratory Disease • Other diseases/abnormalities[1] • Subjects with a history of adverse reaction to any intranasal, inhaled, or systemic corticosteroid and LABA therapy and to components of the inhalation powder[1] • Investigational Medications used within 30 days or five half-lives of prior study[1] • Chronic user of systemic corticosteroids • Subjects treated by the monoclonal antibody omalizumab (Xolair) or mepolizumab (Nucala™) • Subjects involved in other clinical trials[1]
Not withdrawn after developing	• Not withdrawn from study[1]

Deviation Category	Deviation Subcategory
withdrawal criteria	• Not discontinued from study treatment[1] • Other deviation of not being withdrawn after developing withdrawal criteria[1]
Excluded medication, vaccine or device	• Medication, excluded by the protocol, was administered[3] • Other excluded medication, vaccine or device deviation[3]
Visit completion	• Missed visit/phone contact[4] • Out of window visit/phone contact[4] • Other visit window deviation[4]
Wrong study treatment / administration / dose	• Study treatment not administered per protocol[1] • Wrong study treatment or assignment administered • Expired study treatment administered[1] • Use of study treatment impacted by a temperature excursion which was not reported or approved or which was disapproved for further use.[1] • Study treatment not available at site for administration[1] • Other deviations related to wrong study treatment/administration/dose[1]
Study procedures	• Non study treatment supply procedures[1] • Equipment procedures[1] • Other deviations from study procedures[1]

[1]: To be reviewed on a case-by-case basis
[2]: Patients < 18 years will be excluded from PP population, others will be reviewed on a case-by-case basis
[3]: To be judged by the medical monitor
[4]: Missed or out of window Visit 4 will lead to exclusion from the PP population, missed or out of window other visits will not

10.2. Appendix 2: Time & Events

10.2.1. Protocol Defined Time & Events

Study Visits	Visit 1* Screening	Visit 2* Randomisation	Visit 3 Phone call 1	Visit 4**	Visit 5 Phone call 2	Visit 6	Early Withdrawal
Study Week (± specified no. of days)	Day -7 to -1	Day 0	Week 6 (±3 days)	Week 12 (±7 days)	Week 18 (±3 days)	Week 24 (±14 days)	**Early Withdrawal**
Visit	x	x		x		x	x
Phone interview			x		x		
Assessments							
Informed Consent	x						
Eligibility criteria	x	x					
Demography	x						
Smoking status	x						
Medical/Family history of consented subjects including CV Risk factors and exacerbation history	x						
PGx (saliva sample)***		x					
Physical examination	x	x		x		x	x
Safety Assessments							
Urine Pregnancy Test¥		x		x		x	x
Exacerbation Assessment		x	x	x	x	x	x
Vital signs	x	x		x		x	x
Serious Adverse Event and Adverse Drug Reaction Assessment[1]		x	x	x	x	x	x
Efficacy Assessments							
Spirometry Testing (Pre-dose trough FEV1)		x		x			x ****
Subject Questionnaires							
Asthma Control Test	x	x	x	x	x	x	x
EQ-5D		x				x	x
Asthma Quality of Life Questionnaire		x				x	x
MARS-A questionnaire		x		x		x	x
Patient Satisfaction and Preference (PASAP-Q)				x			x
Inhaler correct use assessment							
Type A/overall errors record		x		x		x	
Medication							

Study Visits	**Visit 1* Screening**	**Visit 2* Randomisation**	**Visit 3 Phone call 1**	**Visit 4****	**Visit 5 Phone call 2**	**Visit 6**	**Early Withdrawal**
Study Week (± specified no. of days)	Day -7 to -1	Day 0	Week 6 (±3 days)	Week 12 (±7 days)	Week 18 (±3 days)	Week 24 (±14 days)	**Early Withdrawal**
Visit	**x**	**x**		**x**		**x**	**x**
Phone interview			**x**		**x**		
Assessments							
Concomitant Medication Assessment	**x**	**x**		**x**		**x**	**x**
Dispense Study Medication[2]		**x**		**x**			
Collect Study Medication[2]				**x**		**x**	**x**
RAMOS/eCRF							
RAMOS NG		**x**		**x**			
eCRF	**x**	**x**	**x**	**x**	**x**	**x**	**x**

1. SAE and ADR monitoring will occur from Day 1. SAE related to study participation should begin from signing of informed consent form (ICF). An additional safety and ACT check is provided by phone at Week 6 and 18.
2. Throughout the study the study medication will be dispensed and collected by the investigator site.

* Visit 1 and Visit 2 can be combined if the subject did not take his usual asthma medication before coming on site. Then this visit will be Day 0 and all baseline characteristics will be collected at this visit. Written Informed Consent must be obtained prior to initiation of study procedures or initiating changes in medications.

** Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation visit).

***PGx saliva sample collected at Visit 2 (Randomisation) or any scheduled clinic visit thereafter.

**** Only if early withdrawal occurs before Week 12.

¥ Only for childbearing women.

10.3. Appendix 3: Assessment Windows

Clinic visits/phone calls are scheduled to take place as specified in the protocol. For the ACT and MARS-A questionnaires, measurements that are not within ±7 days of the visit target day for Week 6 (Visit 3) and Week 18 (Visit 5), or ±14 days for Week 12 (Visit 4) and Week 24 (Visit 6) will be excluded from the analyses. For EQ-5D-5L and AQLQ(S), measurements that are not within ±14 days of the visit target day of Week 24 (Visit 6) will be excluded from the summaries. For PASAP-Q, measurements that are not within ±14 days of the visit target day of Week 12 (Visit 4) will be excluded from the summaries.

Table 11 Visit slotting rules for ACT and MARS-A

Days relative to randomisation *	Target Study Day	Visit Slot
35 – 49	42	Week 6 (Visit 3)
70 – 98	84	Week 12 (Visit 4)
119 – 133	126	Week 18 (Visit 5)
154 – 182	168	Week 24 (Visit 6)
* Date of assessment – Randomisation date + 1		

Table 12 Visit slotting rules for EQ-5D-5L and AQLQ(S)

Days relative to randomisation *	Target Study Day	Visit Slot
154 – 182	168	Week 24 (Visit 6)
* Date of assessment – Randomisation date + 1		

Table 13 Visit slotting rules for PASAP-Q

Days relative to randomisation *	Target Study Day	Visit Slot
70 – 98	84	Week 12 (Visit 4)
* Date of assessment – Randomisation date + 1		

For all other endpoints, individual measurements collected outside of the assessment window for scheduled visits will be included in the ITT and PP analyses without adjustment.

If multiple measurements are collected within the same assessment window, the last valid value prior to randomisation will be used as the baseline value and the value closest to the target day for that window will be used for all post-randomisation visits.

10.4. Appendix 4: Treatment States and Phases

10.4.1. Treatment Phases

In general, assessments and events will be classified according to the time of occurrence relative to study treatment, unless otherwise specified. Endpoint/measurement specific definitions are defined in Section 10.4.2.

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

NOTES:

- If it is not possible to determine the treatment phase of an assessment or event it will be considered as On-Treatment.

10.4.2. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of the study treatment. The earliest and latest exposure treatment start and stop dates will be used to determine whether an assessment or event was pre-treatment, on-treatment or post-treatment. If it is not possible to tell whether an assessment or event was on-treatment or not it will be considered as on-treatment.

10.4.2.1. Treatment States for Concomitant Medications

Treatment State	Definition
Pre-Treatment	(Start Date of Medication < Study Treatment Start Date) and (End Date of Medication < Study Treatment Start Date)
On-Treatment	[(Start Date of Medication < Study Treatment Start Date) and (End Date of Medication ≥ Study Treatment Start Date)] or (Study Treatment Start Date ≤ Start Date of Medication ≤ Study Treatment Stop Date + 1)
Post-Treatment	Start Date of Medication > Study Treatment Stop Date +1

10.4.2.2. Treatment States for Efficacy Measurements

Treatment State	Definition
Pre-Treatment	Date of Measurement ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date of Measurement ≤ Study Treatment Stop Date + 1
Post-Treatment	Date of Measurement > Study Treatment Stop Date +1

10.4.2.3. Treatment States for Exacerbation Data

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

NOTES:

- If the study treatment stop date is missing then the exacerbation will be considered to be On-Treatment
- See Section 10.6.3 for details on missing onset and/or resolution dates.

10.4.2.4. Treatment States for AE Data

Treatment states for adverse events are described below. Severe asthma exacerbations will be treated in the same way, with the exacerbation start date used in place of the AE start date.

Treatment State	Definition
Pre-Treatment	AE Onset Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ AE Onset Date ≤ Study Treatment Stop Date + 1
Post-Treatment	AE Onset Date > Study Treatment Stop Date + 1
Onset Time Since 1st Dose (Days)	If Study Treatment Start Date > AE Onset Date = AE Onset Date - Study Treatment Start Date If Study Treatment Start Date ≤ AE Onset Date = AE Onset Date - Study Treatment Start Date +1 Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' or is missing on the AE case report form (CRF) page.

NOTES:

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

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	Fluticasone furoate /vilanterol inhalation Powder delivered once daily	FF/VI	2
B	Usual ICS/LABA maintenance therapy delivered by Dry Powder Inhaler	Usual ICS/LABA	1

NOTES:

1. Order represents treatments being presented in data displays, as appropriate.

10.5.2. Baseline Definition & Derivations

10.5.2.1. Baseline Definitions

For all endpoints the baseline value will be the last assessment prior to randomisation.

10.5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]
Maximum Change from Baseline	= Calculate the change from baseline at each given timepoint and determine the maximum change

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.5.2.1 will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

10.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area	: /arenv/arprod/gw685698_gw642444/hza116492/final
QC Spreadsheet	: /arenv/arwork/gw685698_gw642444/hza116492/final/qc
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards.	

Reporting Process
• For creation of ADaM datasets (e.g. ADCM, ADAE) the same version of dictionary datasets will be implemented for conversion from SI to SDTM.
Generation of RTF Files
• RTF files will be generated for all tables in the final reporting effort.

Reporting Standards	
General	
• The current GSK IDSL will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics	
Formats	
• All data will be reported according to the treatment the subject was randomised to unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DPs) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the electronic case report form (eCRF) or recorded in the raw dataset if from non eCRF sources. • 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 Times	
• Reporting for tables, figures and formal statistical analyses : • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). • Unscheduled or unplanned readings will be presented within the subject's listings. • For visits outside the time-windows, please see Section 10.3.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables or figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Multiple Measurements at One Time Point
• If there are multiples values within a time window the last valid value prior to randomisation will be used as the baseline value and the value closest to the target day for that window will be used for all post-randomisation visits. If values are the same distance from the target then the mean will be taken. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

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

Time Since First Dose

• Calculated as the number of days from the date of first dose :
  • Ref Date = Missing → Time Since First Dose = Missing
  • Ref Date < First Dose Date → Time Since First Dose = Ref Date – First Dose Date
  • Ref Date ≥ First Dose Date → Time Since First Dose = Ref Date – (First Dose Date) + 1

Study Treatment Discontinuation
• In this study, subjects who are intentionally and permanently withdrawn from study medication may not continue in the study attending the remaining visits (excluding the Follow-up contact) and completing the scheduled assessments.

10.6.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ Any subject with a missing day will have this imputed as day '15'.
  ○ Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.
• Completely missing dates of birth will remain as missing, with no imputation applied. Consequently, the age of the subject will not be calculated and will remain missing.
• Age, in whole years, will be calculated with respect to the date of screening (Visit 1).

Body Mass Index
• Calculated as Weight (kg) / [Height (m)]^2
Race
• In the demographic summary table race will be summarised as follows; White is defined as those subjects who chose only the White (Arabic/North African Heritage) and/or White

Demographics
(White/Caucasian/European Heritage) categories on the CRF, Black is defined as those subjects who chose only the African American/African Heritage category on the CRF, and Other is defined as those subjects who chose any of the other races on the CRF.

Extent of Exposure
Subjects randomised to FF/VI or to Usual ICS/LABA can have their treatment dosage adjusted at the investigators discretion, and will be recorded in the eCRF. Treatment sequence identifier will be incremented by 1 each time the study medication is modified, and recorded on eCRF. Extent of exposure will be presented in three different ways: • The extent of exposure to study medication, regardless of study medication dosage modifications during the study, will be defined as the number of days on study medication and will be calculated for each subject as follows: Exposure = (study medication stop date – study medication start date) + 1 If medication start date is missing then the randomisation date (i.e. date of Visit 2) of the subject will be used for medication start date. If the medication stop date is missing, the Visit 6 date or early withdrawal visit date will be used instead. If all these dates are missing, then the extent of exposure will be set to missing. • The extent of exposure to study medication, up to first study medication dosage modification • The extent of exposure to each dose of study medication, presented separately for FF/VI 92 mcg/22 mcg, FF/VI 184 mcg/22mcg, FP/S 250 mcg/50 mcg, FP/S 500 mcg/50 mcg, BUD/F 200 mcg/6 mcg, BUD/F 400 mcg/12 mcg

10.6.3. Efficacy

Primary Endpoint
ACT
The ACT is a validated self-administered questionnaire utilising 5 questions to assess asthma control during the past 4 Weeks on a 5-point categorical scale (1 to 5). By answering all 5 questions, a subject with asthma can obtain a score that may range between 5 and 25, with higher scores indicating better control. An ACT score of 5 to 19 suggests that the subject's asthma is unlikely to be well controlled. A score of 20 to 25 suggests that the subject's asthma is likely to be well controlled. The MID for ACT is 3 (Schatz, 2009). The total score is calculated as the sum of the scores from all 5 questions, provided all scores are non-missing; if any individual scores are missing then the overall score will be set to missing.

Secondary Endpoint
Correct Use of Device
Inhaler use will be assessed at Randomisation (Visit 2), Week 12 (Visit 4) and Week 24 (Visit 6). Correct use of device is defined as making no critical or non-critical errors.
Critical and Non-Critical Errors for Ellipta
Critical errors: • Failed to open cover • Shook the device upside down after dose preparation • Exhaled directly into mouthpiece • No seal by the lips around the mouthpiece during the inhalation Non-critical errors: • No exhalation before an inhalation • Inhalation manoeuvre was not: – long – steady – deep • Blocked air inlet during inhalation manoeuvre • Did not hold breath • Did not close the device (Note: this is an error but one which does not affect the medication that is inhaled)
Critical and Non-Critical Errors for Diskus
Critical errors: • Failed to open cover • Lever is not pushed back • Shook the device after dose preparation • Exhaled directly into mouthpiece • No seal by the lips round the mouthpiece during the inhalation Non-critical errors: • No exhalation before an inhalation • Inhalation manoeuvre was not: – steady – deep • Did not hold breath • Did not close the device (Note: this is an error but one which does not affect the medication that is inhaled)
Critical and Non-Critical Errors for Turbuhaler
Critical errors: • Failed to remove cap • Did not hold device upright (±45° OK) during dose preparation • Base not twisted fully backwards and forwards, no click heard • Shook the device after dose preparation • Exhaled directly into mouthpiece • No seal by the lips round the mouthpiece during the inhalation

Primary Endpoint
Non-critical errors: • Device tipped downwards after dose preparation • No exhalation before an inhalation • Inhalation manoeuvre was not: – forceful – deep • Blocked air inlet during inhalation manoeuvre • Did not hold breath • Did not close the device (Note: this is an error but one which does not affect the medication that is inhaled)

Other Endpoints
FEV1
FEV1 will be measured to assess lung function at Randomisation (Visit 2) and Week 12 (Visit 4). Visit 4 should be scheduled at the same time of day as Visit 2, FEV1 measurements should be taken pre-dose and subjects should be instructed not to take their asthma medication/study drug prior to coming into the clinic at these visits. Subjects should also withhold from using their rescue medication for at least 4 hours prior to Visit 2 and Visit 4. All sites will use standardised spirometry equipment provided by GSK. For each observation, at least 3 (with no more than 8) efforts will be obtained. At least two of the spirometry efforts should be acceptable and repeatable. The best FEV1 value will be recorded in the eCRF.
MARS-A
The MARS-A questionnaire is a 10-item questionnaire. The response to all ten questions will be presented and included in the calculation of the MARS-A 10-score. The responses to the MARS-A questions will be scored as follows: Always=1, Often=2, Sometimes=3, Rarely=4, Never=5. The MARS-A 10-Score will be calculated for each subject as the sum of scores for each of the ten questions divided by the number of non-missing responses to the ten questions. If some responses are missing the MARS-A 10-score is calculated as follows for each subject: • If eight or more of the questions have been answered, the missing responses for that subject will be imputed to the average score • If less than eight of the questions have been answered, the overall MARS-A 10-score for that subject will be set to missing The French translation of the MARS-A questionnaire did not go through cognitive debriefing; therefore while the study was ongoing it was determined that there is no word for “preventer” in French. “Preventer inhaler” was translated as “dispositif d’inhalation” (i.e., “inhalation device”). A reminder was sent to centres in France instructing that the MARS-A questionnaire refers to the patient’s preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study) as opposed to their reliever inhaler. The German translation went through cognitive debriefing and was correctly translated. The MARS-A data displays will therefore be repeated split by: • Patients in France who had completed all MARS-A assessments prior to the reminder being implemented

Other Endpoints

- Patients in France who had completed at least one MARS-A assessment prior to the reminder being implemented but also completed at least one MARS-A assessment after the reminder being implemented
- Patients in France who had not completed any MARS-A assessments prior to the reminder being implemented
- Patients in Germany

The reminder was sent on 17OCT2016, and it was assumed that the centres started implementing the instructions two days after this, i.e. on 19OCT2016.

Severe Asthma Exacerbations

Missing onset or resolution dates will be handled as follows:

- Single event with missing onset and/or resolution dates:
  - (a) Missing onset date: set onset date = study treatment start date
  - (b) Missing resolution date: set resolution date = study treatment stop date
  - (c) Both missing: imputed per both (a) and (b)
- Multiple events, one event with some missing onset/resolution dates; on the assumption any partial date information does not occur during the other events:
  - (a) Missing onset date: set onset date = max[(resolution date of the nearest previous event) + 1 day, study treatment start date]
  - (b) Missing resolution date: set resolution date = min[(onset date of the nearest subsequent event) - 1 day, study treatment stop date]
  - (c) Both missing: determine the largest gap between study treatment start date and first event onset date, between first event resolution date and next event(s) onset dates (if any), between last event resolution date and study treatment stop date. If there is more than one gap which is the largest, then take the first occurrence. Then impute as follows:
    onset date = (onset date of largest gap) + 1 day
    resolution date = (resolution date of largest gap) + 1 day

Time to First Severe Asthma Exacerbation

The date of a severe asthma exacerbation is defined as the exacerbation onset date. Subjects who complete the study without a severe asthma exacerbation will be censored. Time to first severe asthma exacerbation is measured from the date of randomisation (i.e., study treatment start date) to the onset date of first severe asthma exacerbation, as recorded on eCRF, or study treatment stop date (Visit 6 or early withdrawal visit) for subject who complete the study without any severe asthma exacerbations (censored). Analyses of time to first severe asthma exacerbation will be censored at Day 168.

AQLQ(S) Domain and Total Scores

The AQLQ(S) contains 32 items in four domains: activity limitation (11 items), symptoms (12 items), emotional function (5 items) and environmental stimuli (4 items). The following items are included in each of the 4 domains:

- Symptoms: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
- Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
- Emotional Function: 7, 13, 15, 21, 27
- Environmental Stimuli: 9, 17, 23, 26

The response format consists of a seven-point scale where a value of 1 indicates “total impairment” and a value of 7 indicates “no impairment”. The total AQLQ(S) score is the mean of all 32 items in the questionnaire and each individual domain score is calculated as the mean of the items within that domain. Hence, the total and domain scores are also each defined on a range from 1 to 7 with higher scores

Other Endpoints

indicating a higher quality of life. The MID for AQLQ(S) is 0.5 (Juniper, 1993).

For the total AQLQ(S) score, the score for a subject at any time point will only be calculated if at least 90% of the questions were answered (calculated as the mean of those non-missing questions). If fewer than 90% of the questions were answered then the mean score for that subject at that time point will be considered missing.

For each individual domain of the AQLQ(S) score, the score for a subject at any time point will only be calculated if at least 90% of the questions for that domain were answered (calculated as the mean of those non-missing questions). If fewer than 90% of the questions were answered for that domain then the mean score for that subject and domain at that time point will be considered missing.

EQ-5D-5L Utility and VAS Scores

The EQ-5D-5L is administered at randomisation (Visit 2), Week 24 (Visit 6) and Early Withdrawal. The EQ-5D-5L consists of 2 parts: the EQ-5D-5L descriptive system and the EQ VAS.

The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels, where Level 1 (coded as '1') = 'No problems', Level 2 (coded as '2') = 'Slight problems', Level 3 (coded as '3') = 'Moderate problems', Level 4 (coded as '4') = 'Severe problems' and Level 5 (coded as '5') = 'Extreme problems'. Subjects indicate their health state for each dimension by ticking (or placing a cross) in the box of the most appropriate level for that dimension. Ambiguous values (e.g. 2 boxes are ticked for a single dimension) will be considered missing. Missing values will be coded as '9'. The responses (1, 2, 3, 4 or 5) to the five questions will be converted into a single utility score using the developer's instructions (EuroQol, 2013): the responses (1, 2, 3, 4 or 5) to the five questions in the descriptive system can be represented as one of 5^5=3125 possible health states (11111, 11112, ... , 55555). These will be converted into a single summary index (y) that attaches value to each of the levels in each dimension by applying the formula below, which is based on the EQ-5D-5L value set for England (Devlin, 2016).

$$\begin{aligned} y = 1 - 0.9675 \times (&0.051M_2 + 0.063M_3 + 0.212M_4 + 0.275M_5 + 0.057S_2 + 0.076S_3 \\ &+ 0.181S_4 + 0.217S_5 + 0.051U_2 + 0.067U_3 + 0.174U_4 + 0.190U_5 + 0.060P_2 \\ &+ 0.075P_3 + 0.276P_4 + 0.341P_5 + 0.079A_2 + 0.104A_3 + 0.296A_4 \\ &+ 0.301A_5) \end{aligned}$$

where variables with subscript n are indicator variables equal to 1 when the corresponding level for the dimension is 'n' and equal to 0 otherwise, M_n variables represent responses for the mobility domain, S_n variables represent responses for the self-care domain, U_n variables represent responses for the usual activities domain, P_n variables represent responses for the pain / discomfort domain, and A_n variables represent responses for the anxiety / depression domain.
For example, health state where domains MSUPA = 11223 would be equal to:

$$1 - 0.9675 \times (0.051 + 0.060 + 0.104) \approx 0.7920$$

The EQ VAS records the subject's self-rated health state on a vertical, VAS where 0='worst imaginable health state' and 100='best imaginable health state'. Subjects indicate their own health state by drawing a line from the box on the left of the scale to whichever point on the scale indicates how good or bad their own health state is that day. Ambiguous values (e.g. the line crosses the VAS twice) will be considered missing. Missing values will be coded as '999'.

Only validated EuroQoLs completed in the same language as that completed at Baseline (Visit 2) will be

Other Endpoints

summarised.

PASAP-Q Domain and Total Scores

The PASAP-Q is a self-administered 16-item questionnaire measuring satisfaction and preference with inhaler devices (Kozma, 2005). Two domains (performance and convenience) are calculated from 13 satisfaction items, measured on a Likert-type scale where a value of 1 indicates "very dissatisfied" and 7 indicates "very satisfied". The performance and convenience domains together form the total score. The other items include an overall satisfaction question (again measured from 1 to 7), a preference question (not applicable and so not asked for this study) and a question on willingness to continue using the device in the future, measured on a scale of 0 (not willing) to 100 (definitely willing).

The performance and convenience domains include t he following items:

- Performance: 1, 2, 3, 4, 5, 10, 11
- Convenience: 6, 7, 8, 9, 12, 13

If the patient completes at least half of the items in a domain, values for missing items are imputed using the mean of the completed items in that domain. The domain score is then transformed to a scale from 0 (least) to 100 (most) as follows:

$$\text{Domain Score} = [\text{Mean}(\text{responses for items in domain}) - 1] \times \frac{100}{6}$$

If the patient completes less than half of the items in a domain, then the missing items are not imputed and the domain score is set to missing. The total score can be calculated only when both domain scores are computable and substitution for missing items at the domain level has taken place, and is calculated on the same scale as:

$$\text{Total Score} = [\text{Mean}(\text{responses for all 13 items}) - 1] \times \frac{100}{6}$$

The overall satisfaction and willingness questions are summarised on their original scales of 1 to 7 and 0 to 100 respectively.

Other Endpoints
Treatment Compliance
Overall percentage treatment compliance for every subject will be calculated for each type of inhaler (Diskus, Turbuhaler and Ellipta) separately. Compliance for Diskus, Turbuhaler and Ellipta will be based on the total number of inhalations taken from each type of inhaler and the expected number of inhalations to be taken. The expected number of inhalations will be derived as the expected number of inhalations per day (from each inhaler) multiplied by the number of days on study drug based on the subjects treatment start and stop date for that type of inhaler. The total number of inhalations taken will be based on the dose counter for each type of inhaler, all of which are re-supplied during the study. If there is no dose counter information at all then the compliance will be missing; however, as long as the information from one dose counter is present, the compliance will be calculated. If a dose counter start count is missing then it will be assumed to be 30 for Ellipta and 60 for both Diskus and Turbuhaler. In each calculation, all inhalers dispensed will be used, provided the dose counter stop counts are non-missing. The following formula will be used: $$\text{Compliance} = \frac{\text{Total number of inhalations taken}}{\text{Dose frequency} \times (\text{Stop date} - \text{Start date})} \times 100$$ where Total number of inhalations taken is the sum of (dose counter start count – dose counter stop count) for all inhalers used during the time period, Dose frequency is equal to 1 for Ellipta and 2 for Diskus and Turbuhaler, and Start date and Stop date are the earliest treatment start date and latest treatment stop date respectively recorded for all inhalers used during the time period.

10.6.4. Safety

SAEs of Special Interest
SAE groups of special interest have been defined as SAEs which are included in specified areas of interest for one or more of the treatment groups (FF/VI, FF and/or VI). They are identified by groupings of preferred terms based on the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version used in each reporting effort. Groupings or subgroups may be defined, based on relevant combination of preferred terms, or on Standardised MedDRA queries (SMQs). SAEs of special interest will be confirmed prior to final data, based on the MedDRA version in use at the time.

Special Interest SAE Group
Asthma/bronchospasm
Cardiovascular effects
Decreased bone mineral density and associated fractures
Hypersensitivity
Local steroid effects
LRTI excluding pneumonia
Pneumonia
Adrenal suppression
Ocular effects
Effects on glucose
Effects on potassium
Tremor

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

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

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion was defined in the protocol as a subject who has completed all study visits. The end of the study is defined as the last subject's last visit. • The definition of subject early withdrawal from the study will be any subject who is randomised and, for any reason, does not complete all study visits. • Withdrawn subjects will not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument : ○ These data will be indicated by the use of a "blank" in subject listing displays (if applicable). Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
Exposure start and stop date	• If a subject's treatment start date is missing then their Visit 2 date will be assumed to be the exposure start date. If a subject's treatment stop date is missing, this will be taken to be the date of Week 24 (Visit 6) (if the subject completes Visit 6) or the early withdrawal visit date.

10.7.2.1. Handling of Missing or Partial Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
SAEs and ADRs	• The eCRF does not allow the possibility of partial dates (i.e., only month and year) to be recorded for SAE and ADR start and end dates; • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.

Element	Reporting Detail
	• The recorded partial date will be displayed in listings.

10.7.2.2. Handling of Missing Data for Statistical Analysis

In general, missing data will not be imputed except for the sensitivity analyses defined in Section 6.1.2.

10.8. Appendix 8: Values of Potential Clinical Importance

10.8.1. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure (SBP)	mmHg	< 85	> 160
Diastolic Blood Pressure (DBP)	mmHg	< 45	> 100
Heart Rate (HR)	bpm	< 40	> 110

Vital Sign Parameter (Change from Baseline)	Units	Clinical Concern Range			
		Decrease		Increase	
		Lower	Upper	Lower	Upper
SBP	mmHg	≥ 20	≥ 40	≥ 20	≥ 40
DBP	mmHg	≥ 10	≥ 20	≥ 10	≥ 20
HR	bpm	≥ 15	≥ 30	≥ 15	≥ 30

10.9. Appendix 9: Multicenter Studies

10.9.1. Methods for Handling Centres

In this multicentre study conducted in France and Germany, enrolment will be presented by investigative site.

10.10. Appendix 10: Examination of Covariates, Subgroups & Other Strata

10.10.1. Examination of Strata and Covariates

The following is a list of covariates that may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses.

Additional covariates of clinical interest may also be considered.

Category	Covariates and / or Subgroups
Strata	Separate randomisation schedules were utilised for France and Germany respectively thereby stratifying the randomisation by country. Country will be included in all analyses as a covariate. A sensitivity analysis will examine the randomized treatment-by-country interaction for the primary and key secondary endpoints.
Covariates	For the primary efficacy analysis, the following baseline variables will be adjusted for: • Randomised treatment (FF/VI, Usual ICS/LABA) • Baseline ACT total score • Age • Gender • Country Similar covariates will be considered for all other analyses; in each case the relevant baseline score (e.g. baseline AQLQ[S] score for the AQLQ[S] endpoints) will be included instead of baseline ACT total score.

10.10.2. Examination of subgroups

- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.
- For statistical analyses by subgroup, models will include subgroup and treatment by subgroup interaction as covariates.

Category	Subgroups
Country	• France • Germany
Number of severe asthma exacerbations in the previous year prior to randomisation	• 0 • ≥ 1
Smoking Status at Baseline	• Current smokers

Category	Subgroups
	• Former smokers • Non-smokers
Age Group	• 18 – 50 years old • > 50 years old
Gender	• Male • Female

10.10.3. Examination of seasonal effect

A sensitivity analysis for the primary efficacy endpoint examining seasonal effect is defined in Section 6.1.2, specifying a season at randomisation covariate defined as follows:

Season at Randomisation	Calendar Month of Randomisation
Spring	• March • April • May
Summer	• June • July • August
Autumn	• September • October • November
Winter	• December • January • February

Furthermore, the summary of severe asthma exacerbations will be repeated by season using the same definition (according to calendar month) as specified above.

10.11. Appendix 11: Multiple Comparisons & Multiplicity

10.11.1. Handling of Multiple Comparisons & Multiplicity

Non inferiority of FF/VI to ICS/LABA will be first tested at the 0.05 two-sided nominal level of significance. If non-inferiority is statistically achieved, then superiority of FF/VI to ICS/LABA will be tested at the 0.05 two-sided nominal level of significance.

If and only if non-inferiority is achieved for the primary endpoint at Week 12 (Visit 4), then the key secondary endpoint, i.e. the change from baseline in the total ACT score assessed at Week 24 (Visit 6) will be tested. At Week 24 (Visit 6), non inferiority of FF/VI to ICS/LABA will be first tested at the 0.05 two-sided nominal level of significance. If non-inferiority is achieved, then superiority of FF/VI to ICS/LABA will be tested at the 0.05 two-sided nominal level of significance.

Of note, this step-down testing procedure still strongly controls the overall type I error at the 0.05 two-sided level for the non-inferiority endpoints. The overall type I error is not controlled for the superiority tests at Week 12 (Visit 4) and Week 24 (Visit 6).

10.12. Appendix 12: Model Checking and Diagnostics for Statistical Analyses

10.12.1. Statistical Analysis Assumptions

Endpoint(s)	• Change from Baseline in the ACT Total Score at Week 12 (Visit 4) • Change from Baseline in the ACT Total Score at Week 24 (Visit 6)
Analysis	• MMRM (ANCOVA for LOCF and WOCF sensitivity analyses)
• Should computational issues be encountered when running the model with an unstructured variance-covariance matrix, other structures including autoregressive 1 and compound symmetry will be considered. • Distributional assumptions underlying the model will be checked with graphical methods (including quantile-quantile (Q-Q) plots of studentized residuals, plots of studentized residuals versus fitted values, etc.). To investigate the relationship between baseline ACT total score and the change from baseline in ACT total score, baseline ACT total will be categorized according to the distribution quartiles and the model will be fitted using this categorized variable in place of continuous baseline ACT total score. • If the distributional assumption of normality fails then the LS means, estimated LS mean treatment difference and associated 95% CI from the model will be presented, with the p-value for the difference between treatment groups from a model on the rank-transformed values. Should the distributional assumption of normality also fail for the ranked model, other methods of analysis will be investigated.	

Endpoint(s)	• Percentage of subjects with correct use of inhaler device at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4) • ACT total score of ≥ 20 or ≥ 3 point increase from baseline in ACT total score at Week 12 (Visit 4) and Week 24 (Visit 6) • Increase from baseline of ≥ 0.5 in AQLQ(S) total score at Week 24 (Visit 6) • Increase from baseline of ≥ 0.5 in AQLQ(S) environmental stimuli domain score at Week 24 (Visit 6) • Proportion of subjects with 'no problems' at Endpoint in the EQ-5D-5L questionnaire
Analysis	• Logistic regression model
• If the likelihood maximisation algorithm fails to converge due to complete or quasi-complete separation of the data then Firth's penalized likelihood (Firth, 1993) will be implemented by use of the FIRTH option on the MODEL statement in PROC LOGISTIC. • The fit of the logistic regression model will be assessed by examining the ROC curve and other diagnostic plots.	

Endpoint(s)	• Change from baseline in trough (pre-dose) FEV1 at Week 12 (Visit 4) • Change from baseline in EQ-5D Utility Score • Change from baseline in EQ-5D VAS Score
Analysis	• ANCOVA model
• Distributional assumptions underlying the model will be checked with graphical methods (including quantile-quantile (Q-Q) plots of studentized residuals, plots of studentized residuals versus fitted values, etc.). • If the distributional assumption of normality fails then the LS means, estimated LS mean treatment difference and associated 95% CI from the ANCOVA model will be presented, with the p-value for the	

difference between treatment groups from an ANCOVA model on the rank-transformed values. Should the distributional assumption of normality also fail for the ranked ANCOVA, an exact p-value from a two-sample Wilcoxon Rank Sum test will be presented for the difference between treatment groups.

Endpoint(s)	• Annual severe asthma exacerbation rate over the study period
Analysis	• GLM assuming the Negative Binomial distribution
• If a GLM assuming the Negative Binomial distribution cannot be fitted due to the lack of repeat events within a subject, a GLM assuming the Poisson distribution will be used. The underlying assumption for the Poisson distribution that the mean and variance of the response variable are equal will be examined. If the variance of the fitted model exceeds the mean (over-dispersion), the dispersion parameter will be estimated as a ratio of the Pearson Chi-Square to its associated degrees of freedom (using the PSCALE option in PROC GENMOD).	

Endpoint(s)	• Time to first severe asthma exacerbation
Analysis	• Cox proportional hazards model
• Proportional hazards assumptions will be checked by plotting the log of the negative log of the estimated survivor functions against log time, for each treatment group. If hazards are proportional, the lines should be approximately parallel. • If the assumption of proportionality is not met, the use of other models such as models including time-dependent covariates will be considered. • If there are computational issues in implementing the exact method for handling ties, then the Efron method (Efron, 1977) will be used instead.	

10.13. Appendix 13: Blinding Strategy

Purpose

- The trial design (open label) and the ways the study medication data are recorded in the datasets means that extra steps must be taken to ensure that S&P remain blinded to investigational product (IP) data until the formal unblinding takes place at DBF. Maintaining the blind prior to DBF is a requirement for the French Ethics Committee.
- S&P also need to be able to have sufficient data to pre-program up to the point of DBF. This needs to done on sufficient 'real' data to ensure the programs can handle all possibilities of data, particularly regarding treatment modifications during the study.
- Datasets containing IP data that need to be considered: EXPOSURE and INVPCOMP
- Other datasets that contain data that could unblind S&P and therefore also need to be considered: DS, DV1, FADTH, INDEVERR, and IPDEVMAL
- Note: assigning subjects to dummy (blinded) randomised treatment group (FF/VI or Other ICS/LABA) prior to DBF will be done in the usual way using standard GSK procedures.
- To ensure unblinding does not occur through other sources, access to INFORM, E-Track, Study Explorer, DMENV (\\uk1salx00175.corpnet2.com\dmenv\dmwork\gw685698_gw642444\hza116492) and SPECTRE is prohibited for S&P.

Proposal for the EXPOSURE dataset

Prior to DBF:

Data Management (DM) to provide two datasets to S&P based on the source EXPOSURE dataset.

(1) Dataset EXPOSURE – same as the source EXPOSURE dataset but with EXINVPCD (study treatment code) and EXINVP (study treatment) blanked out as '999' and 'CENSORED' respectively. This will allow S&P to use the subjects' real exposure start dates and times and stop dates in order to assign other data items to pre, during and post treatment, derive study day, overall exposure duration etc
(2) Dataset named DUM_EXP_SP, which will be a scrambled sample of the EXPOSURE dataset. Each time S&P are provided a new update of data from DM a different scrambled sample of data will be used.

The method to be used by DM to sample and scramble the data is as follows:

- Select a sample of subjects, in the EXPOSURE dataset using a random sampling method which uses a seed (so that the same ones could be chosen again if it needs to be re-run). The exact size of this sample will change according to the number of subjects in the EXPOSURE dataset at that time, ensuring that no more than ≈50% of the total sample size (N=422) is used at any point and defined per the following table:

No. of subjects in EXPOSURE dataset	Percentage of subjects used for sampling
≤ 199	94%
200 to 299 inclusive	70%
≥ 300	40%

- Store which subjects have been chosen so it can be checked over time that all subjects get seen by programmers before DBR
- Make a random adjustment to the dates and times in the sample, such that e.g. the first subject has 10 days added to all their dates and 34 minutes added to their start times, the second subject has 17 days subtracted from all their dates and 95 minutes added to their start times – this means they do not match with any real dates or times in the EXPOSURE dataset above, but it means the within-subject integrity of dates remains. The range of the date adjustment is set at the range ± 60 days, and the range of the time adjustment is set at the range ± 120 minutes.
- Rename subjid to orig_subj – this enables DM to be able to trace the subject in the event of data queries from S&P
- Randomly map this sampled data onto the SUBJIDs in the EXPOSURE dataset, so that every true SUBJID in the EXPOSURE dataset has scrambled subject data assigned to it
- Data management keep a copy of this with the orig_subj number in it
- Data management remove orig_subj and pass this data to S&P

At DBF:

DM will provide to S&P the one unmodified version of EXPOSURE dataset, with all variables uncensored.

Proposal for the INVPCOMP, INDEVERR and IPDEVMAL datasets

Prior to DBF:

DM to provide a single version of each dataset to S&P based on the source datasets.

(1) Dataset named DUM_INVP_SP, DUM_IERR_SP and DUM_IMAL_SP which will be a scrambled (subjid) sample of the INVPCOMP, INDEVERR and IPDEVMAL datasets respectively. Each time S&P are provided a new update of data from DM a different scrambled sample of data will be used.

These datasets must be produced in conjunction with DUM_EXP so that the same subjects get selected, the same date adjustment per subject is made and the same merging onto real subject data gets done.

At DBF:

DM will provide the single unmodified versions of INVPCOMP, INDEVERR and IPDEVMAL datasets, with all variables uncensored
Other datasets and variables to be censored before being sent to S&P up until DBF

Dataset	Variables to be censored before being sent to S&P up until DBF
DS	DSRSSP, DSSBRSSP
DV1	DVTERM
FADTH	DDORRSTX, DDORRSSP

Documentation
Once this blinding strategy has been agreed between S&P and DM, and approved by the study Clinical Investigation Lead (CIL), the Data Quality Lead (DQL) will send an email to S&P stating that the blinding strategy is in place and is being followed.

10.14. Appendix 14: Abbreviations & Trade Marks

10.14.1. Abbreviations

Abbreviation	Description
ACT	Asthma Control Test
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
AQLQ(S)	Standardised Asthma Quality of Life Questionnaire
ASE	All Subjects Enrolled
BMI	Body Mass Index
BUD	Budesonide
CI	Confidence Interval
CIL	Clinical Investigational Lead
CRF	Case Report Form
CRO	Contract Research Organisation
DBF	Database Freeze
DBP	Diastolic Blood Pressure
DBR	Database Release
DM	Data Management
DP	Decimal Place
DPI	Dry Powder Inhaler
DQL	Data Quality Lead
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol Questionnaire
F	Formoterol
FEV1	Forced Expiratory Volume in 1 Second
FF	Fluticasone Furoate
FP	Fluticasone Propionate
GINA	Global Initiative for Asthma
GLM	Generalised Linear Model
GSK	GlaxoSmithKline
HL	Hodges-Lehmann
HR	Heart Rate
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
IDSL	Integrated Data Standards Library
IP	Investigational Product
ITT	Intent-to-Treat
LABA	Long-acting Beta Agonist
LOCF	Last Observation Carried Forward
LRTI	Lower Respiratory Tract Infection
LS	Least Squares
MAR	Missing at Random
MARS-A	Medication Adherence Report Scale for Asthma
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Description
MI	Multiple Imputation
MID	Minimally Important Difference
MMRM	Mixed Model Repeated Measures
PASAP-Q	Patient Satisfaction and Preference Questionnaire
PD	Protocol Deviation
PDMP	Protocol Deviation Management Plan
PP	Per Protocol
Q-Q	Quantile-Quantile
RAP	Reporting and Analysis Plan
REML	Restricted Maximum Likelihood
S	Salmeterol
S&P	Statistics and Programming
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SMQ	Standardised MedDRA Query
VAS	Visual Analogue Scale
VI	Vilanterol
WOCF	Worst Observation Carried Forward

10.14.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
DISKUS
ELLIPTA
GSK
NUCALA
SERETIDE

Trademarks not owned by the GlaxoSmithKline Group of Companies
ACT
Asthma Quality of Life Questionnaire - AQLQ(S)
EQ-5D
MARS-A Questionnaire
PASAP Questionnaire
Symbicort Turbuhaler
TURBUHALER
XOLAIR

10.15. Appendix 15: List of Data Displays

10.15.1. 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	

10.15.2. Mock Example Shell Referencing

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

.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln

NOTES:

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

10.15.3. Deliverable [Priority]

Delivery [Priority] [1]	Description
Data Look [1]	Data Look Outputs (blinded review)
SAC [2]	Final Statistical Analysis Complete

NOTES:

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

10.15.4. Study Population Tables

Study Population: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Enrolled Subjects	Non-Standard POP_T1	Summary of Subject Populations	Randomised population line will provide the denominators for the ITT, PP and Safety percentages.	Data Look [1] SAC [2]
1.2.	All Enrolled Subjects	IE2	Summary of Inclusion/Exclusion Criteria Failures for Subjects Not Starting Treatment		Data Look [1] SAC [2]
1.3.	ITT	ES1	Summary of End of Study Record		Data Look [1] SAC [2]
1.4.	PP	ES1	Summary of End of Study Record Per Protocol Population		Data Look [1] SAC [2]
1.5.	ITT	Non-Standard POP_T2	Summary of Attendance at Each Clinic Visit and Phone Call Visit		Data Look [1] SAC [2]
1.6.	All Enrolled Subjects	NS3	Summary of Number of Subjects by Country and Centre		SAC [2]
1.7.	ITT	NS3	Summary of Number of Subjects by Country and Centre		Data Look [1] SAC [2]
1.8.	PP	NS3	Summary of Number of Subjects by Country and Centre Per Protocol Population		SAC [2]
Protocol Deviations					
1.9.	ITT	IE2	Summary of Deviations from the Inclusion/Exclusion Criteria		Data Look [1] SAC [2]
1.10.	ITT	Non-Standard POP_T3	Summary of Important Protocol Deviations		Data Look [1] SAC [2]

Study Population: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.11.	ITT	Non-Standard POP_T3	Summary of Important Protocol Deviations Resulting in Exclusion from the PP Population		Data Look [1] SAC [2]
Demographic and Baseline Characteristics					
1.12.	ITT	DM1	Summary of Demographic Characteristics		Data Look [1] SAC [2]
1.13.	PP	DM1	Summary of Demographic Characteristics Per Protocol Population		SAC [2]
1.14.	Safety	DM1	Summary of Demographic Characteristics Safety Population		SAC [2]
1.15.	All Enrolled Subjects	DM11	Summary of Age Ranges		Data Look [1] SAC [2]
1.16.	ITT	DM5	Summary of Race and Racial Combinations		Data Look [1] SAC [2]
1.17.	ITT	DM6	Summary of Race and Racial Combinations Details		Data Look [1] SAC [2]
1.18.	ITT	MH4	Summary of Current Medical Conditions		Data Look [1] SAC [2]
1.19.	ITT	MH4	Summary of Past Medical Conditions		SAC [2]
1.20.	ITT	Non-Standard POP_T4	Summary of Asthma Duration at Baseline		Data Look [1] SAC [2]
1.21.	PP	Non-Standard POP_T4	Summary of Asthma Duration at Baseline Per Protocol Population		Data Look [1] SAC [2]
1.22.	ITT	Non-Standard POP_T5	Summary of Asthma Exacerbation History at Baseline		Data Look [1] SAC [2]

Study Population: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.23.	PP	Non-Standard POP_T5	Summary of Asthma Exacerbation History at Baseline Per Protocol Population		Data Look [1] SAC [2]
1.24.	ITT	Non-Standard POP_T6	Summary of Smoking History at Baseline		Data Look [1] SAC [2]
1.25.	PP	Non-Standard POP_T6	Summary of Smoking History at Baseline Per Protocol Population		SAC [2]
Concomitant Medications					
1.26.	ITT	CM8	Summary of Pre-Treatment Concomitant Medications		SAC [2]
1.27.	ITT	CM8	Summary of On-Treatment Concomitant Medications		SAC [2]
1.28.	ITT	CM8	Summary of On-Treatment Asthma Concomitant Medications		Data Look [1] SAC [2]
Exposure					
1.29.	ITT	Non-Standard POP_T7	Summary of Study Medication Dosage Modification		Data Look [1] SAC [2]
1.30.	ITT	Non-Standard POP_T8	Summary of Extent of Exposure to Study Medication (Regardless of Modification to Study Medication Dosage)		Data Look [1] SAC [2]
1.31.	ITT	Non-Standard POP_T8	Summary of Extent of Exposure to Study Medication (up to First Modification to Study Medication Dosage)		SAC [2]

Study Population: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.32.	ITT	Non-Standard POP_T9	Summary of Extent of Exposure to Study Medication by Medication and Dosage	Repeat on subsequent pages for Medication/Dosage = FF/VI 184 mcg/22 mcg OD, FP/S 250 mcg/50 mcg BID, FP/S 500 mcg/50 mcg BID, BUD/F 200 mcg/6 mcg BID (1 inhalation per dose), BUD/F 200 mcg/6 mcg BID (2 inhalations per dose), BUD/F 400 mcg/12 mcg BID (1 inhalation per dose), BUD/F 400 mcg/12 mcg BID (2 inhalations per dose).	Data Look [1] SAC [2]
Number of Subjects by Subgroup					
1.33.	ITT	Non-Standard POP_T10	Summary of Number of Subjects by Subgroup		SAC [2]

10.15.5. Study Population Figures

Study Population: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
1.1.	ITT	Non-Standard POP_F1	Plot of Exposure to Study Medication (Regardless of Modification to Study Medication Dosage)	Display increments of 6 weeks on the x-axis, up to the maximum exposure (e.g. 0, 6, 12, 18, 24, 30).	Data Look [1] SAC [2]

10.15.6. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in ACT Total Score at Week 12 (Visit 4)					
2.1.	ITT	Non-Standard EFF_T1	Summary of Change from Baseline in ACT Total Score		Data Look [1] SAC [2]
2.2.	PP	Non-Standard EFF_T1	Summary of Change from Baseline in ACT Total Score Per Protocol Population		SAC [2]
2.3.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4)		Data Look [1] SAC [2]
2.4.	PP	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) Per Protocol Population		SAC [2]
2.5.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (ANCOVA with LOCF)	Footnotes as follows: "Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline ACT total score, gender, age and country. Note: Missing values at Week 12 (Visit 4) were replaced by last available post-randomization value based on the last observation carried forward (LOCF) method."	Data Look [1] SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.6.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (Multiple Imputation – Missing at Random Approach)	Footnotes as follows: "Note: Missing values post-randomisation were imputed using multiple imputation methods based on pattern mixture models. Note: Each imputed data set was analysed using an ANCOVA model at Week 12 (Visit 4) adjusted for randomised treatment, baseline ACT total score, gender, age and country and the resulting treatment differences and their standard errors combined using Rubin's rules."	Data Look [1] SAC [2]
2.7.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (Multiple Imputation – Copy Differences from Reference Approach)	Footnotes as follows: "Note: Missing values post-randomisation were imputed using multiple imputation methods based on pattern mixture models. Note: Each imputed data set was analysed using an ANCOVA model at Week 12 (Visit 4) adjusted for randomised treatment, baseline ACT total score, gender, age and country and the resulting treatment differences and their standard errors combined using Rubin's rules."	Data Look [1] SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (Hodges-Lehmann Approach)	Present the "Difference" and "95% CI" lines of "FF/VI vs. Usual ICS/LABA" section only. Footnotes as follows: "Note: The difference between treatment groups at Week 12 (Visit 4) was calculated using the Hodges-Lehmann approach."	Data Look [1] SAC [2]
2.9.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (ANCOVA with WOCF)	Footnotes as follows: "Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline ACT total score, gender, age and country. Note: Missing values at Week 12 (Visit 4) due to treatment withdrawal prior to this time point were replaced by worst post-randomisation value based on the worst observation carried forward (WOCF) method."	Data Look [1] SAC [2]
2.10.	ITT	Non-Standard EFF_T3	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), Adjusting for Seasonal Effect	Repeat on subsequent pages for Season at randomisation = Summer, Autumn, Winter.	Data Look [1] SAC [2]
2.11.	PP	Non-Standard EFF_T3	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), Adjusting for Seasonal Effect Per Protocol Population	Repeat on subsequent pages for Season at randomisation = Summer, Autumn, Winter.	SAC [2]
2.12.	ITT	Non-Standard EFF_T1	Summary of Change from Baseline in ACT Total Score, FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed FP/S at Randomisation		Data Look [1] SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.13.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed FP/S at Randomisation	Output only to be produced if ≥25% of Usual ICS/LABA patients are prescribed FP/S at randomisation.	Data Look [1] SAC [2]
2.14.	ITT	Non-Standard EFF_T1	Summary of Change from Baseline in ACT Total Score, FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed BUD/F at Randomisation		SAC [2]
2.15.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed BUD/F at Randomisation	Output only to be produced if ≥75% of Usual ICS/LABA patients are prescribed BUD/F at randomisation.	SAC [2]
2.16.	ITT	Non-Standard EFF_T1S	Summary of Change from Baseline in ACT Total Score by Country		Data Look [1] SAC [2]
2.17.	ITT	Non-Standard EFF_T2S	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Country		Data Look [1] SAC [2]
2.18.	ITT	Non-Standard EFF_T1S	Summary of Change from Baseline in ACT Total Score by Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation		SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.19.	ITT	Non-Standard EFF_T2S	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, number of severe asthma exacerbations in the previous year prior to randomisation, two- and three- way interactions between randomised treatment, visit and number of severe asthma exacerbations in the previous year prior to randomisation, and patient fitted as a random factor."	SAC [2]
2.20.	ITT	Non-Standard EFF_T1S	Summary of Change from Baseline in ACT Total Score by Smoking Status at Baseline		SAC [2]
2.21.	ITT	Non-Standard EFF_T2S	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Smoking Status at Baseline	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, smoking status at baseline, two- and three- way interactions between randomised treatment, visit and smoking status at baseline, and patient fitted as a random factor."	SAC [2]
2.22.	ITT	Non-Standard EFF_T1S	Summary of Change from Baseline in ACT Total Score by Age Group		SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.23.	ITT	Non-Standard EFF_T2S	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Age Group	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, country, age group, two- and three- way interactions between randomised treatment, visit and age group, and patient fitted as a random factor."	SAC [2]
2.24.	ITT	Non-Standard EFF_T1S	Summary of Change from Baseline in ACT Total Score by Gender		SAC [2]
2.25.	ITT	Non-Standard EFF_T2S	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Gender	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, two- and three- way interactions between randomised treatment, visit and gender, and patient fitted as a random factor."	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in ACT Total Score at Week 24 (Visit 6)					
2.26.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6)	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient fitted as a random factor."	Data Look [1] SAC [2]
2.27.	PP	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) Per Protocol Population	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient fitted as a random factor."	SAC [2]
2.28.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (ANCOVA with LOCF)	Footnotes as follows: "Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline ACT total score, gender, age and country. Note: Missing values at Week 24 (Visit 6) were replaced by last available post-randomization value based on the last observation carried forward (LOCF) method."	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.29.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (Multiple Imputation – Missing at Random Approach)	Footnotes as follows: "Note: Missing values post-randomisation were imputed using multiple imputation methods based on pattern mixture models. Note: Each imputed data set was analysed using an ANCOVA model at Week 24 (Visit 6) adjusted for randomised treatment, baseline ACT total score, gender, age and country and the resulting treatment differences and their standard errors combined using Rubin's rules."	SAC [2]
2.30.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (Multiple Imputation – Copy Differences from Reference Approach)	Footnotes as follows: "Note: Missing values post-randomisation were imputed using multiple imputation methods based on pattern mixture models. Note: Each imputed data set was analysed using an ANCOVA model at Week 24 (Visit 6) adjusted for randomised treatment, baseline ACT total score, gender, age and country and the resulting treatment differences and their standard errors combined using Rubin's rules."	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.31.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (Hodges-Lehmann Approach)	Present the "Difference" and "95% CI" lines of "FF/VI vs. Usual ICS/LABA" section only. Footnotes as follows: "Note: The difference between treatment groups at Week 24 (Visit 6) was calculated using the Hodges-Lehmann approach."	SAC [2]
2.32.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (ANCOVA with WOCF)	Footnotes as follows: "Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline ACT total score, gender, age and country. Note: Missing values at Week 24 (Visit 6) due to treatment withdrawal prior to this time point were replaced by worst post-randomisation value based on the worst observation carried forward (WOCF) method."	SAC [2]
2.33.	ITT	Non-Standard EFF_T3	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6), Adjusting for Seasonal Effect	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, season at randomisation, two- and three- way interactions between randomised treatment, visit and season at randomisation, and patient fitted as a random factor."	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.34.	PP	Non-Standard EFF_T3	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6), Adjusting for Seasonal Effect Per Protocol Population	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, season at randomisation, two- and three- way interactions between randomised treatment, visit and season at randomisation, and patient fitted as a random factor."	SAC [2]
2.35.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6), FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed FP/S at Randomisation	Output only to be produced if ≥25% of Usual ICS/LABA patients are prescribed FP/S at randomisation. First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient fitted as a random factor."	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.36.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed BUD/F at Randomisation	Output only to be produced if ≥25% of Usual ICS/LABA patients are prescribed BUD/F at randomisation. First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient fitted as a random factor."	SAC [2]
2.37.	ITT	Non-Standard EFF_T2S	Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) by Country	First footnote as follows: "Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, two- and three- way interactions between randomised treatment, visit and country, and patient fitted as a random factor."	SAC [2]
Correct Use of Inhaler Device					
2.38.	ITT	Non-Standard EFF_T4	Summary of Inhaler Device Use Errors	Repeat on subsequent pages for Visit = Week 12 and Week 24. "Number of patients using..." line will provide the denominators for each section's percentages.	Data Look [1] SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.39.	PP	Non-Standard EFF_T4	Summary of Inhaler Device Use Errors Per Protocol Population	Repeat on subsequent pages for Visit = Week 12 and Week 24. "Number of patients using..." line will provide the denominators for each section's percentages.	SAC [2]
2.40.	ITT	Non-Standard EFF_T5	Summary of Correct Use of Inhaler Device		Data Look [1] SAC [2]
2.41.	PP	Non-Standard EFF_T5	Summary of Correct Use of Inhaler Device Per Protocol Population		SAC [2]
2.42.	ITT	Non-Standard EFF_T6	Summary of the Statistical Analysis of Correct Use of Inhaler Device at Week 12 (Visit 4) and at Week 24 (Visit 6) Independently of the Use at Week 12 (Visit 4)		Data Look [1] SAC [2]
2.43.	PP	Non-Standard EFF_T6	Summary of the Statistical Analysis of Correct Use of Inhaler Device at Week 12 (Visit 4) and at Week 24 (Visit 6) Independently of the Use at Week 12 (Visit 4) Per Protocol Population		SAC [2]
Lung Function Tests					
2.44.	ITT	Non-Standard EFF_T1	Summary of Change from Baseline in Lung Function Tests	Present an additional column to the left of "Visit", labelled "Test" with values "Trough (Pre-dose) FEV1" and "Trough (Pre-dose) Percent Predicted FEV1" to allow presentation of results by Test. Present the following visits: Day 0, Week 12, Change from Baseline at Week 12, Early Withdrawal and Change from Baseline at Early Withdrawal.	Data Look [1] SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.45.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in Trough (Pre-dose) FEV1 at Week 12 (Visit 4)	Footnote as follows: "Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline trough (pre-dose) FEV1, gender, age and country."	Data Look [1] SAC [2]
Subjects Who Have Either an ACT Total Score >= 20 or >= 3 Point Increase from Baseline in ACT Total Score					
2.46.	ITT	Non-Standard EFF_T7	Summary of Percentage of Subjects Who Have Either an ACT Total Score >= 20 or >= 3 Point Increase from Baseline in ACT Total Score	Repeat for Visit = Week 18, Week 24, Early Withdrawal.	Data Look [1] SAC [2]
2.47.	ITT	Non-Standard EFF_T6	Summary of the Statistical Analysis of Percentage of Subjects Who Have Either an ACT Total Score >= 20 or >= 3 Point Increase from Baseline in ACT Total Score at Week 12 (Visit 4) and Week 24 (Visit 6)	Replace "With correct use [1]" with "Responder [1]" and "Without correct use" with "Non-Responder". Footnotes as follows: "[1] Responder is defined as an ACT total score >= 20 or >= 3 point increase from baseline in ACT total score at that visit. Note: The analysis method was logistic regression adjusted for randomised treatment, baseline ACT total score, baseline ACT total score squared, gender, age and country."	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual ACT Question Scores					
2.48.	ITT	Non-Standard EFF_T8	Summary of Individual ACT Question Scores	Repeat on subsequent pages for Question = 2. Shortness of breath, 3. Asthma symptoms woken up at night or earlier than usual, 4. Used rescue inhaler or nubuliser medication, 5. Asthma control.	Data Look [1] SAC [2]
Compliance with Study Medication					
2.49.	ITT	Non-Standard EFF_T9	Summary of Compliance with Study Medication		Data Look [1] SAC [2]
2.50.	PP	Non-Standard EFF_T9	Summary of Compliance with Study Medication Per Protocol Population		SAC [2]
MARS-A					
2.51.	ITT	Non-Standard EFF_T10	Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study	Repeat on subsequent pages for Visit = Week 12, Week 24 and Early Withdrawal.	Data Look [1] SAC [2]
2.52.	ITT	Non-Standard EFF_T10S	Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study by Status of Patient in Relation to the Reminder Sent to French Centres	Repeat on subsequent pages for Visit = Week 12, Week 24 and Early Withdrawal, and for Status = Patients in France who had completed at least one MARS-A assessment prior to the reminder being implemented but also completed at least one MARS-A assessment after the reminder being implemented, Patients in France who had not completed any MARS-A assessments prior to the reminder being implemented, Patients in Germany.	Data Look [1] SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Severe On-Treatment Asthma Exacerbations					
2.53.	ITT	Non-Standard EFF_T11	Summary of Severe On-Treatment Asthma Exacerbations		Data Look [1] SAC [2]
2.54.	ITT	Non-Standard EFF_T11S	Summary of Severe On-Treatment Asthma Exacerbations by Season	Repeat on subsequent pages for Season = Summer, Autumn, Winter.	Data Look [1] SAC [2]
2.55.	ITT	Non-Standard EFF_T12	Summary of the Statistical Analysis of Severe On-Treatment Asthma Exacerbations		Data Look [1] SAC [2]
2.56.	ITT	Non-Standard EFF_T13	Summary of the Statistical Analysis of Time to First Severe On-Treatment Asthma Exacerbation		Data Look [1] SAC [2]
AQLQ(S)					
2.57.	ITT	Non-Standard EFF_T1	Summary of Change from Baseline in AQLQ(S) Total Score and Domain Scores	Present an additional column to the left of "Visit", labelled "Domain" with values "Total Score", "Environmental Stimuli", "Symptoms", "Activity Limitations" and "Emotional Function" to allow presentation of results by Domain. Present the following visits: Day 0, Week 24, Change from Baseline at Week 24, Early Withdrawal and Change from Baseline at Early Withdrawal.	SAC [2]
2.58.	ITT	Non-Standard EFF_T14	Summary of Percentage of Subjects Who Have an Increase from Baseline of >=0.5 in AQLQ(S) Total Score and Domain Scores	Repeat on subsequent pages for Domain = Environmental Stimuli, Symptoms, Activity Limitations and Emotional Function.	Data Look [1] SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.59.	ITT	Non-Standard EFF_T6	Summary of the Statistical Analysis of Percentage of Subjects Who Have an Increase from Baseline of >=0.5 in AQLQ(S) Total Score and Environmental Stimuli Domain Score at Week 24 (Visit 6)	Replace "With correct use [1]" with "Responder [1]" and "Without correct use" with "Non-Responder". Do not display the "Visit" column. Footnotes as follows: "[1] Responder is defined as an increase from baseline of >= 0.5. Note: The analysis method was logistic regression adjusted for randomised treatment, baseline score, gender, age and country."	SAC [2]
EQ-5D-5L					
2.60.	ITT	Non-Standard EFF_T15	Summary of EQ-5D-5L Descriptive System Dimensions	Repeat on subsequent pages for Visit = Early Withdrawal and for Dimension = Mobility, Pain/Discomfort, Self-care, Usual activities.	Data Look [1] SAC [2]
2.61.	ITT	Non-Standard EFF_T6	Summary of the Statistical Analysis of Proportion of Responders According to EQ-5D-5L Descriptive System Dimensions at Week 24 (Visit 6)	Replace "With correct use [1]" with "Responder [1]" and "Without correct use" with "Non-Responder". Do not display the "Visit" column. Footnotes as follows: "[1] Responder is defined as a score of 1 ('no problems'). Note: The analysis method was logistic regression adjusted for randomised treatment, baseline EQ-5D-5L domain score, gender, age and country."	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.62.	ITT	Non-Standard EFF_T1	Summary of EQ-5D-5L Utility Score	Present the following visits: Day 0, Week 24, Change from Baseline at Week 24, Early Withdrawal and Change from Baseline at Early Withdrawal.	Data Look [1] SAC [2]
2.63.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in EQ-5D-5L Utility Score at Week 24 (Visit 6)	Footnote as follows: "Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline EQ-5D-5L utility score, gender, age and country."	SAC [2]
2.64.	ITT	Non-Standard EFF_T1	Summary of EQ-5D-5L Visual Analogue Scale (VAS) Score	Present the following visits: Day 0, Week 24, Change from Baseline at Week 24, Early Withdrawal and Change from Baseline at Early Withdrawal.	SAC [2]
2.65.	ITT	Non-Standard EFF_T2	Summary of the Statistical Analysis of Change from Baseline in EQ-5D-5L Visual Analogue Scale (VAS) Score at Week 24 (Visit 6)	Footnote as follows: "Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline EQ-5D-5L VAS score, gender, age and country."	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PASAP-Q					
2.66.	ITT	Non-Standard EFF_T1	Summary of PASAP-Q Scores	Present an additional column to the left of "Visit", labelled "Score" with values "Performance", "Convenience", "Overall Satisfaction", "Total Score" and "Willingness to Continue Using Inhaler" to allow presentation of results by Domain. Present the following visits: Week 12 and Early Withdrawal. Add the following footnotes: "Note: Performance, Convenience, Total Score, and Willingness to Continue Using Inhaler are expressed on a scale of 0 to 100. Note: Overall Satisfaction is expressed on a scale of 1 to 7."	SAC [2]

10.15.7. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in ACT Total Score at Week 12 (Visit 4)					
2.1.	ITT	Non-Standard EFF_F1	Summary of Change from Baseline in ACT Total Score	Present "ACT Total Score" on y-axis and "Visit" on x-axis (Day 0, Week 6, Week 12, Week 18, Week 24). Present mean ACT Total Score ± SD separately for treatment group (FF/VI, Usual ICS/LABA) at each visit, connecting the means with a solid line. Distinguish the treatment groups by different line types.	Data Look [1] SAC [2]
2.2.	PP	Non-Standard EFF_F1	Summary of Change from Baseline in ACT Total Score Per Protocol Population	Present "ACT Total Score" on y-axis and "Visit" on x-axis (Day 0, Week 6, Week 12, Week 18, Week 24). Present mean ACT Total Score ± SD separately for treatment group (FF/VI, Usual ICS/LABA) at each visit, connecting the means with a solid line. Distinguish the treatment groups by different line types.	SAC [2]
2.3.	ITT	Non-Standard EFF_F1	Summary of Change from Baseline in ACT Total Score by Country	Present "ACT Total Score" on y-axis and "Visit" on x-axis (Day 0, Week 6, Week 12, Week 18, Week 24). Present mean ACT Total Score ± SD separately for treatment group (FF/VI, Usual ICS/LABA) at each visit, connecting the means with a solid line. Distinguish the treatment groups by different line types.	SAC [2]

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.4.	ITT/PP	Non-Standard EFF_F2	Summary of Primary and Sensitivity Analyses for Change from Baseline in ACT Total Score at Week 12 (Visit 4)	Present "Treatment difference" on the x-axis, and reverse axis so treatment difference increases from left to right. Replace "Ratio (95% CI)" with "Treatment Difference (95% CI)". Present lines for the following: Primary analysis (ITT), Primary analysis (PP), ANCOVA with LOCF (ITT), Multiple Imputation (Missing at Random) (ITT), Multiple Imputation (Copy Differences from Reference) (ITT), Hodges-Lehmann (ITT), ANCOVA with WOCF (ITT).	Data Look [1] SAC [2]
2.5.	ITT	Non-Standard EFF_F3	Summary of Interaction Tests for Change from Baseline in ACT Total Score at Week 12 (Visit 4)	Present "LS Mean Change" on the x-axis, and reverse axis so it increases from left to right. Replace "Ratio (95% CI)" with "LS Mean Change (95% CI)". Present the following subgroups: Country (France, Germany); Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation (0, >= 1); Smoking Status at Baseline (Current Smokers, Former Smokers, Never Smoked); Age Group (18 – 50 Years Old, > 50 Years Old); Gender (Male, Female).	Data Look [1] SAC [2]

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in ACT Total Score at Week 24 (Visit 6)					
2.6.	ITT/PP	Non-Standard EFF_F2	Summary of Key Secondary and Sensitivity Analyses for Change from Baseline in ACT Total Score at Week 24 (Visit 6)	Present "Treatment difference" on the x-axis, and reverse axis so treatment difference increases from left to right. Replace "Ratio (95% CI)" with "Treatment Difference (95% CI)". Present lines for the following: Primary analysis (ITT), Primary analysis (PP), ANCOVA with LOCF (ITT), Multiple Imputation (Missing at Random) (ITT), Multiple Imputation (Copy Differences from Reference) (ITT), Hodges-Lehmann (ITT), ANCOVA with WOCF (ITT).	SAC [2]
Subjects Who Have Either an ACT Total Score >= 20 or >= 3 Point Increase from Baseline in ACT Total Score					
2.7.	ITT	Non-Standard EFF_F4	Summary of Percentage of Subjects Who Have Either an ACT Total Score >= 20 or >= 3 Point Increase from Baseline in ACT Total Score	Present "Percent of Subjects (%)" on y-axis and "Visit" on x-axis (Week 6, Week 12, Week 18, Week 24, Early Withdrawal). For each visit, present 3 vertical bars distinguished by fill pattern (similar to non-standard EFF_F6). Each bar represents: "ACT Total Score >= 20 or >= 3 Point Increase from Baseline in ACT Total Score", "ACT Total Score >= 20" and ">= 3 Point Increase from Baseline in ACT Total Score" respectively and should be labelled as such on the legend.	Data Look [1] SAC [2]

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Compliance with Study Medication					
2.8.	ITT	Non-Standard EFF_F5	Box Plot of Compliance with Study Medication	Label y-axis title as “Compliance (%)”, maximum of y-axis may be > 100%.	Data Look [1] SAC [2]
MARS-A					
2.9.	ITT	Non-Standard EFF_F6	Histogram of the Questions and Answers of the MARS-A Questionnaire	Repeat on subsequent pages for Visit = Week 24, Week 52 and Early Withdrawal; and for Randomised Treatment = FF/VI.	Data Look [1] SAC [2]
2.10.	ITT	Non-Standard EFF_F6	Histogram of the Questions and Answers of the MARS-A Questionnaire by Status of Patient in Relation to the Reminder Sent to French Centres	Present bylines and footnotes per “Repeat for” programming note on shell.	SAC [2]
2.11.	ITT	Non-Standard EFF_F7	Histogram of the Distribution of MARS-A Scores During the Study	Repeat on subsequent pages for Visit = Week 52 and Early Withdrawal.	Data Look [1] SAC [2]
2.12.	ITT	Non-Standard EFF_F7	Histogram of the Distribution of MARS-A Scores During the Study by Status of Patient in Relation to the Reminder Sent to French Centres	Present bylines and footnotes per “Repeat for” programming note on shell.	SAC [2]
Severe On-Treatment Asthma Exacerbations					
2.13.	ITT	Non-Standard EFF_F8	Box Plot of Severe On-Treatment Asthma Exacerbation Rates Adjusted for Exposure to Treatment		Data Look [1] SAC [2]
2.14.	ITT	Non-Standard EFF_F9	Kaplan-Meier Plot of Time to First Severe On-Treatment Asthma Exacerbation	Display increments of 6 weeks on the x-axis, up to the maximum exposure (e.g. 0, 6, 12, 18, 24, 30).	Data Look [1] SAC [2]

10.15.8. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
SAEs and ADRs					
3.1.	Safety	Non-Standard SAFE_T1	On-Treatment Serious Adverse Events and Adverse Drug Reactions Overview	Based on IDSL standard template AE13.	Data Look [1] SAC [2]
3.2.	Safety	AE1	Summary of On-Treatment Non-Serious Adverse Drug Reactions		SAC [2]
3.3.	Safety	AE1	Summary of On-Treatment Serious Adverse Drug Reactions		SAC [2]
3.4.	Safety	AE1	Summary of On-Treatment Adverse Drug Reactions		Data Look [1] SAC [2]
3.5.	Safety	AE1	Summary of On-Treatment Serious Adverse Events		Data Look [1] SAC [2]
3.6.	Safety	AE1	Summary of On-Treatment or Post-Treatment Serious Adverse Events and Adverse Drug Reactions Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study		SAC [2]
3.7.	Safety	AE1	Summary of On-Treatment or Post-Treatment Serious Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study		SAC [2]
3.8.	Safety	AE1	Summary of On-Treatment or Post-Treatment Adverse Drug Reactions Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study		SAC [2]
3.9.	Safety	AE1	Summary of Most Frequent On-Treatment Non-Serious Adverse Drug Reactions, Reported by 1% or More of Subjects in Any Treatment Group		SAC [2]

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
SAEs and ADRs of Special Interest					
3.10.	Safety	Non-Standard SAFE_T2	Summary of On-Treatment Non-Serious Adverse Drug Reactions of Special Interest	Based on IDSL standard template AE1.	Data Look [1] SAC [2]
3.11.	Safety	Non-Standard SAFE_T2	Summary of On-Treatment Serious Adverse Drug Reactions of Special Interest	Based on IDSL standard template AE1.	SAC [2]
3.12.	Safety	Non-Standard SAFE_T2	Summary of On-Treatment Adverse Drug Reactions of Special Interest	Based on IDSL standard template AE1.	SAC [2]
3.13.	Safety	Non-Standard SAFE_T2	Summary of On-Treatment Serious Adverse Events of Special Interest	Based on IDSL standard template AE1.	SAC [2]
Fatal SAEs and ADRs					
3.14.	Safety	AE1	Summary of On-Treatment Fatal Serious Adverse Events		SAC [2]
3.15.	Safety	AE1	Summary of On-Treatment Fatal Serious Adverse Drug Reactions		SAC [2]
3.16.	Safety	Non-Standard SAFE_T2	Summary of On-Treatment Fatal Serious Adverse Events of Special Interest	Based on IDSL standard template AE1.	SAC [2]
Non-Fatal SAEs and ADRs					
3.17.	Safety	AE1	Summary of On-Treatment Non-Fatal Serious Adverse Events		SAC [2]
3.18.	Safety	Non-Standard SAFE_T2	Summary of On-Treatment Non-Fatal Serious Adverse Events of Special Interest	Based on IDSL standard template AE1.	SAC [2]
Top Ten Most Commonly Reported ADRs					
3.19.	Safety	Non-Standard SAFE_T3	Top Ten Most Commonly Reported On-Treatment Adverse Drug Reactions Per Treatment Group	Present the ten most frequent preferred terms in Usual ICS/LABA, and the ten most frequent in FF/VI (do not use percentages to determine “most frequent”)	Data Look [1] SAC [2]

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
3.20.	Safety	VS1	Summary of Vital Signs		SAC [2]
3.21.	Safety	VS2	Summary of Vital Sign Data Outside Clinical Concern Range		SAC [2]

10.15.9. Safety Figures

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Benefit:Risk					
3.1.	ITT/Safety	Non-Standard SAFE_F1	Summary of Benefit:Risk for FF/VI vs. Usual ICS/LABA		Data Look [1] SAC [2]

10.15.10. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
1.	ITT	ES2	Reasons for Study Withdrawal		SAC [2]
2.	ITT	TA1	Randomised and Actual Treatments	For subjects with multiple 'actual' treatments, present in the order the treatments were received.	SAC [2]
3.	ITT	IE3	Subjects with Inclusion, Exclusion or Randomisation Criteria Deviations		SAC [2]
4.	ITT	DM2	Demographic Characteristics		SAC [2]
5.	ITT	DM9	Race		SAC [2]
Adverse Events					
6.	Safety	AE7	Subject Numbers for Individual Serious Adverse Events and Non-Serious Adverse Drug Reactions		SAC [2]
7.	Safety	AE8	All Serious Adverse Events and Non-Serious Adverse Drug Reactions		SAC [2]
8.	Safety	AE8	Fatal Serious Adverse Events		SAC [2]
9.	Safety	AE8	Serious Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study		SAC [2]
10.	Safety	AE8	Non-Serious Adverse Drug Reactions Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study		SAC [2]
11.	Safety	AE7	Subject Numbers for Individual Serious Adverse Events and Non-Serious Adverse Drug Reactions		SAC [2]

10.15.11. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
12.	ASE	Non-Standard POP_L1	Subjects Screened but Not in the Intent-to-Treat Population		SAC [2]
13.	ITT	Non-Standard POP_L2	Reasons for Important Protocol Deviations		SAC [2]
14.	ITT	MH3	Medical Conditions		SAC [2]
15.	ITT	Non-Standard POP_L3	Asthma History		SAC [2]
16.	ITT	Non-Standard POP_L4	Smoking History		SAC [2]
17.	ITT	CM3	Concomitant Medications	Only include medications included in pre-treatment and on-treatment summary tables.	SAC [2]
18.	ITT	CM6	Relationship between Ingredient and Verbatim Text		SAC [2]
19.	ITT	Non-Standard POP_L5	Exposure to Study Medication	Repeat on subsequent pages for Treatment = FF/VI, and use GSK drug synonym as drug name.	SAC [2]
Efficacy					
20.	ITT	Non-Standard EFF_L1	ACT Scores	Repeat on subsequent pages for Treatment = FF/VI.	SAC [2]
21.	ITT	Non-Standard EFF_L2	Inhaler Device Use	Repeat on subsequent pages for Treatment = FF/VI.	SAC [2]
22.	ITT	Non-Standard EFF_L3	Lung Function Tests	Repeat on subsequent pages for Treatment = FF/VI.	SAC [2]

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
23.	ITT	Non-Standard EFF_L4	Medication Adherence Report Scale for Asthma (MARS-A) Scores	Repeat on subsequent pages for Treatment = FF/VI.	SAC [2]
24.	ITT	Non-Standard EFF_L5	Severe Asthma Exacerbations	Repeat on subsequent pages for Treatment = FF/VI.	SAC [2]
25.	ITT	Non-Standard EFF_L6	AQLQ(S) Scores	Repeat on subsequent pages for Treatment = FF/VI.	SAC [2]
26.	ITT	Non-Standard EFF_L7	EQ-5D-5L Descriptive System Dimension Scores	Repeat on subsequent pages for Treatment = FF/VI.	SAC [2]
27.	ITT	Non-Standard EFF_L8	PASAP-Q Scores	Repeat on subsequent pages for Treatment = FF/VI.	SAC [2]
Safety					
28.	Safety	Non-Standard SAFE_L1	AE Terms of Special Interest	The AE special interest dataset and the AE SMQ dataset will be set together in order to report this table and all the subgroups that come from the AE SMQ dataset will be flagged with a [1].	SAC [2]
29.	Safety	VS4	Vital Signs		SAC [2]
30.	Safety	Non-Standard SAFE_L2	Inhaler Device Malfunctions		SAC [2]
Liver Chemistry					
31.	Safety	LIVER5	Liver Event Results and Time of Event Relative to Treatment		SAC [2]
32.	Safety	LIVER6	Liver Event Information for RUCAM Score		SAC [2]
33.	Safety	LIVER7	Liver Biopsy Details		SAC [2]
34.	Safety	LIVER8	Liver Imaging Details		SAC [2]

10.16. Appendix 16: Example Mock Shells for Data Displays

10.16.1. Study Population Table Shells

Example : POP_T1
Protocol : HZA116492
Population : All Subjects Enrolled

Table 1.xx
Summary of Subject Populations

Population	Usual ICS/LABA	FF/VI	Total
All Subjects Enrolled (ASE)			xxx
Randomised	xxx	xxx	xxx
Intent-to-Treat (ITT)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Per Protocol (PP)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Safety	xxx (xx%)	xxx (xx%)	xxx (xx%)

ASE: All subjects screened and for whom a record exists on the study database.
ITT: All randomised subjects having received at least one dose of the prescription of study medication (FF/VI or Usual ICS/LABA).
PP: All ITT subjects who without any protocol deviations excluding them from this population.
Safety: All randomised subjects having received at least one dose of the prescription of study medication (FF/VI or Usual ICS/LABA).
Note: The randomised summary is not a defined population and consists of all subjects who were randomised and given a randomisation number.

Programming Note: randomised population line will provide the denominators for the ITT, PP and Safety percentages.

Example : POP_T2
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Attendance at Each Clinic Visit

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Visit 1: Screening	xxx (xx%)	xxx (xx%)	xxx (xx%)
Visit 2: Randomisation (Day 0)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Visit 3: Week 6	xxx (xx%)	xxx (xx%)	xxx (xx%)
Visit 4: Week 12	xxx (xx%)	xxx (xx%)	xxx (xx%)
Visit 5: Week 18	xxx (xx%)	xxx (xx%)	xxx (xx%)
Visit 6: Week 24	xxx (xx%)	xxx (xx%)	xxx (xx%)
Early Withdrawal	xxx (xx%)	xxx (xx%)	xxx (xx%)

Note: Weeks 6 and 18 are telephone contacts.

Example : POP_T3
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Important Protocol Deviations

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Any Important Protocol Deviation	xxx (xx%)	xxx (xx%)	xxx (xx%)
Reason 1	xxx (xx%)	xxx (xx%)	xxx (xx%)
Reason 2	xxx (xx%)	xxx (xx%)	xxx (xx%)
Reason 3	xxx (xx%)	xxx (xx%)	xxx (xx%)
...	xxx (xx%)	xxx (xx%)	xxx (xx%)

Note: A subject may have more than one protocol deviation.
Note: Includes any important deviation from the protocol.

Repeat for:
Summary of Important Protocol Deviations Resulting in Exclusion from the PP Population (ITT Population)

Example : POP_T4
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Asthma Duration at Baseline

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Duration of Asthma			
< 6 months	xxx (xx%)	xxx (xx%)	xxx (xx%)
>= 6 months to < 1 year	xxx (xx%)	xxx (xx%)	xxx (xx%)
>= 1 year to < 5 years	xxx (xx%)	xxx (xx%)	xxx (xx%)
>= 5 years to < 10 years	xxx (xx%)	xxx (xx%)	xxx (xx%)
>= 10 years	xxx (xx%)	xxx (xx%)	xxx (xx%)
Duration of Asthma (years):			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	x.xx	x.xx	x.xx
Median	xx.x	xx.x	xx.x
Min.	xx	xx	xx
Max.	xx	xx	Xx

Repeat for:
Summary of Asthma Duration at Baseline (PP Population)

Example : POP_T5
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Asthma Exacerbation History at Baseline

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Did not require oral/systemic corticosteroids (not involving hospitalisation)			
n	xx	xx	xx
0	xx (xx%)	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)	xx (xx%)
> 1	xx (xx%)	xx (xx%)	xx (xx%)
Required oral/systemic corticosteroids (not involving hospitalisation)			
n	xx	xx	xx
0	xx (xx%)	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)	xx (xx%)
> 1	xx (xx%)	xx (xx%)	xx (xx%)
Required hospitalisation			
n	xx	xx	xx
0	xx (xx%)	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)	xx (xx%)
> 1	xx (xx%)	xx (xx%)	xx (xx%)

Note: Number of severe asthma exacerbations reported in the 12 months prior to Day 0.

Example : POP_T5
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Asthma Exacerbation History at Baseline

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Total number of exacerbations during the 12 months prior to randomisation			
n	xx	xx	xx
0	xx (xx%)	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)	xx (xx%)
> 1	xx (xx%)	xx (xx%)	xx (xx%)
Number of exacerbations during the 12 months prior to randomisation			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	x.xx	x.xx	x.xx
Median	xx.x	xx.x	xx.x
Min.	xx	xx	xx
Max.	xx	xx	xx

Note: Number of severe asthma exacerbations reported in the 12 months prior to Visit 2 (Day 0).

Repeat for:
Summary of Asthma Exacerbation History at Baseline (PP Population)

Example : POP_T6
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Smoking History at Baseline

		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
History of Smoking Use	Current Smokers	xxx (xx%)	xxx (xx%)	xxx (xx%)
	Former Smokers	xxx (xx%)	xxx (xx%)	xxx (xx%)
	Never Smoked	xxx (xx%)	xxx (xx%)	xxx (xx%)
For Current and Former Smokers:				
Years Smoked	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Cigarettes/Day	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx

[1] Smoking Pack Years = (Number of cigarettes smoked per day/20) x number of years smoked.

Example : POP_T6
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Smoking History at Baseline

		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Smoking Pack Years[1]				
Overall	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Current Smokers	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx
Former Smokers	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min.	xx	xx	xx
	Max.	xx	xx	xx

[1] Smoking Pack Years = (Number of cigarettes smoked per day/20) x number of years smoked.
Repeat for:

Summary of Smoking History at Baseline (PP Population)

Example : POP_T7
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Study Medication Dosage Modification

Dosage Modification / Prescription Treatment Path	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Did Not Modify Dose During the Study	xxx (xx%)	xxx (xx%)	xxx (xx%)
Modified Dose at Least Once During the Study	xxx (xx%)	xxx (xx%)	xxx (xx%)
Randomised to FF/VI		xxx	xxx
FF/VI 92 mcg/22 mcg OD		xxx (xx%)	xxx (xx%)
FF/VI 92 mcg/22 mcg OD -> FF/VI 184 mcg/22 mcg OD		xxx (xx%)	xxx (xx%)
Randomised to Usual ICS/LABA and Prescribed FP/S	xxx		xxx
FP/S 250 mcg/50 mcg BID	xxx (xx%)		xxx (xx%)
FP/S 250 mcg/50 mcg BID -> FP/S 500 mcg/50 mcg BID	xxx (xx%)		xxx (xx%)
Randomised to Usual ICS/LABA and Prescribed BUD/F	xxx		xxx
BUD/F 200 mcg/6 mcg BID (1 inh)	xxx (xx%)	xxx (xx%)	xxx (xx%)
BUD/F 200 mcg/6 mcg BID (1 inh) -> BUD/F 200 mcg/6 mcg BID (2 inh)	xxx (xx%)	xxx (xx%)	xxx (xx%)
BUD/F 200 mcg/6 mcg BID (1 inh) -> BUD/F 400 mcg/12 mcg BID (1 inh)	xxx (xx%)	xxx (xx%)	xxx (xx%)
BUD/F 200 mcg/6 mcg BID (2 inh)	xxx (xx%)	xxx (xx%)	xxx (xx%)
BUD/F 200 mcg/6 mcg BID (2 inh) -> BUD/F 400 mcg/12 mcg BID (1 inh)	xxx (xx%)	xxx (xx%)	xxx (xx%)
BUD/F 200 mcg/6 mcg BID (2 inh) -> BUD/F 400 mcg/12 mcg BID (2 inh)	xxx (xx%)	xxx (xx%)	xxx (xx%)

Note: 1 inh = 1 inhalation per dose, 2 inh = 2 inhalations per dose.
Note: Subjects randomised to FF/VI initiated treatment on 92 mcg/22 mcg OD and could increase to 184 mcg/22 mcg OD.
Note: Subjects randomised to Usual ICS/LABA and prescribed FP/S initiated treatment on 250 mcg/50 mcg BID and could increase to 500 mcg/50 mcg BID.

Note: Subjects randomised to Usual ICS/LABA and prescribed BUD/F could: initiate treatment on 200 mcg/6 mcg BID (1 inh) and increase to 200 mcg/6 mcg BID (2 inh) or 400 mcg/12 mcg BID (1 inh); or initiate on 200 mcg/6 mcg BID (2 inh) and modify to 400 mcg/12 mcg BID (1 inh) or increase to 400 mcg/12 mcg BID (2 inh).

Example : POP_T8
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Extent of Exposure to Study Medication (Regardless of Modification to Study Medication Dosage)

Overall		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Exposure (days) [1]	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Total Years Exposed (yrs)		xx	xx
Range of Exposure (days)	<= 6 weeks	xxx (xx%)	xxx (xx%)
	<= 12 weeks	xxx (xx%)	xxx (xx%)
	<= 18 weeks	xxx (xx%)	xxx (xx%)
	<= 24 weeks	xxx (xx%)	xxx (xx%)
	> 24 weeks	xxx (xx%)	xxx (xx%)
Subjects Exposed for six months (24 weeks ± 2 weeks)		xxx (xx%)	xxx (xx%)

[1] Exposure to study medication = treatment stop date – treatment start date + 1, regardless of dosage modification.

Repeat for:
Summary of Summary of Extent of Exposure to Study Medication (up to First Modification to Study Medication Dosage) (ITT Population)
Footnote: "[1] Exposure to study medication = treatment stop date - treatment start date + 1."

Example : POP_T9
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Extent of Exposure to Study Medication by Medication and Dosage

Medication/Dosage	Overall		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
FF/VI 92 mcg/22 mcg OD	Exposure (days) [1]	n	xx	xx
		Mean	xx.x	xx.x
		SD	x.xx	x.xx
		Median	xx.x	xx.x
		Min.	xx	xx
		Max.	xx	xx
	Total Years Exposed (yrs)		xx	xx
	Range of Exposure (days)	<= 6 weeks	xxx (xx%)	xxx (xx%)
		<= 12 weeks	xxx (xx%)	xxx (xx%)
		<= 18 weeks	xxx (xx%)	xxx (xx%)
		<= 24 weeks	xxx (xx%)	xxx (xx%)
		> 24 weeks	xxx (xx%)	xxx (xx%)
	Subjects Exposed for six months (24 weeks ± 2 weeks)		xxx (xx%)	xxx (xx%)

[1] Exposure to study medication = treatment stop date – treatment start date + 1.

Programming note: repeat on subsequent pages for Medication/Dosage = FF/VI 184 mcg/22 mcg OD, FP/S 250 mcg/50 mcg BID, FP/S 500 mcg/50 mcg BID, BUD/F 200 mcg/6 mcg BID (1 inhalation per dose), BUD/F 200 mcg/6 mcg BID (2 inhalations per dose), BUD/F 400 mcg/12 mcg BID (1 inhalation per dose), BUD/F 400 mcg/12 mcg BID (2 inhalations per dose).

Example : POP_T10
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Number of Subjects by Subgroup

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Country			
n	xxx	xxx	xxx
France	xxx (xx%)	xxx (xx%)	xxx (xx%)
Germany	xxx (xx%)	xxx (xx%)	xxx (xx%)
Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation			
n	xxx	xxx	xxx
0	xxx (xx%)	xxx (xx%)	xxx (xx%)
>= 1	xxx (xx%)	xxx (xx%)	xxx (xx%)
Smoking Status at Baseline			
n	xxx	xxx	xxx
Current smokers	xxx (xx%)	xxx (xx%)	xxx (xx%)
Former smokers	xxx (xx%)	xxx (xx%)	xxx (xx%)
Never smoked	xxx (xx%)	xxx (xx%)	xxx (xx%)
Age Group			
n	xxx	xxx	xxx
18 – 50 years old	xxx (xx%)	xxx (xx%)	xxx (xx%)
> 50 years old	xxx (xx%)	xxx (xx%)	xxx (xx%)

Note: Spring = March, April and May; Summer = June, July and August; Autumn = September, October and November; Winter = December, January and February.

Example : POP_T10
Protocol : HZA116492
Population : Intent-to-Treat

Table 1.xx
Summary of Number of Subjects by Subgroup

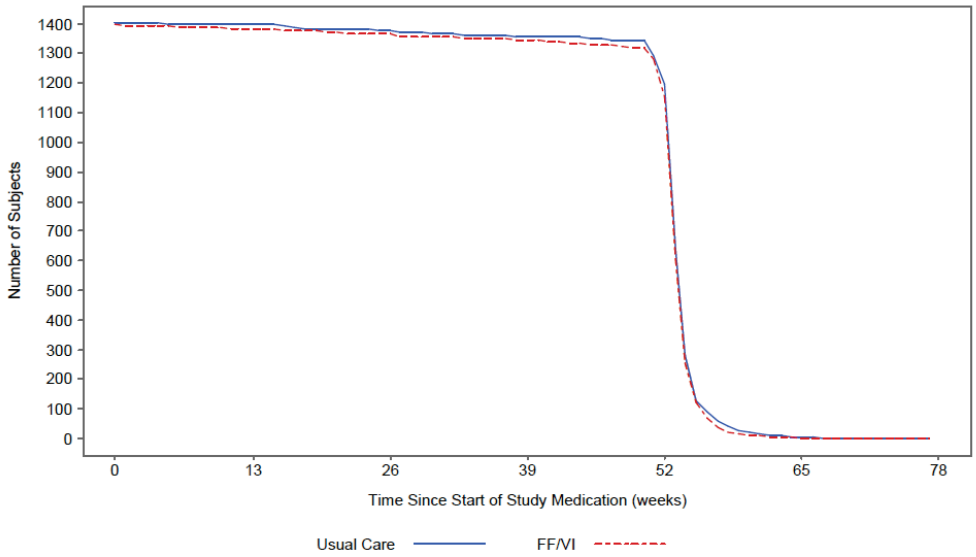
	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)	Total (N=xxx)
Gender			
n	xxx	xxx	xxx
Male	xxx (xx%)	xxx (xx%)	xxx (xx%)
Female	xxx (xx%)	xxx (xx%)	xxx (xx%)
Season at randomisation			
n	xxx	xxx	xxx
Spring	xxx (xx%)	xxx (xx%)	xxx (xx%)
Summer	xxx (xx%)	xxx (xx%)	xxx (xx%)
Autumn	xxx (xx%)	xxx (xx%)	xxx (xx%)
Winter	xxx (xx%)	xxx (xx%)	xxx (xx%)

Note: Spring = March, April and May; Summer = June, July and August; Autumn = September, October and November; Winter = December, January and February.

10.16.2. Study Population Figure Shells

Example : POP_F1
Protocol : HZA116492
Population : Intent-to-Treat

Figure 1.xx
Plot of Exposure to Study Medication (Regardless of Modification to Study Medication Dosage)



Programming note: display increments of 6 weeks on the x-axis, up to the maximum exposure (e.g. 0, 6, 12, 18, 24, 30).

10.16.3. Efficacy Table Shells

Example : EFF_T1
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Change from Baseline in ACT Total Score

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Day 0	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Week 6	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Change from Baseline at Week 6	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x

Min.	xx	xx
Max.	xx	xx

Programming note: repeat for Week 12, Change from Baseline at Week 12, Week 18, Change from Baseline at Week 18, Week 24, Change from Baseline at Week 24, Early Withdrawal, Change from Baseline at Early Withdrawal

Repeat for:
Summary of Change from Baseline in ACT Total Score Per Protocol Population (PP Population)

Summary of Change from Baseline in Lung Function Tests (ITT Population)
Programming note: Present an additional column to the left of "Visit", labelled "Test" with values "Trough (Pre-dose) FEV1" and "Trough (Pre-dose) Percent Predicted FEV1" to allow presentation of results by Test. Present the following visits: Day 0, Week 12, Change from Baseline at Week 12, Early Withdrawal and Change from Baseline at Early Withdrawal.

Summary of Change from Baseline in AQLQ(S) Total Score and Domain Scores (ITT Population)
Programming note: Present an additional column to the left of "Visit", labelled "Domain" with values "Total Score", "Environmental Stimuli", "Symptoms", "Activity Limitations" and "Emotional Function" to allow presentation of results by Domain. Present the following visits: Day 0, Week 24, Change from Baseline at Week 24, Early Withdrawal and Change from Baseline at Early Withdrawal.

Summary of PASAP-Q Scores (ITT Population)
Programming note: Present an additional column to the left of "Visit", labelled "Score" with values "Performance", "Convenience", "Overall Satisfaction", "Total Score" and "Willingness to Continue Using Inhaler" to allow presentation of results by Domain. Present the following visits: Week 12 and Early Withdrawal.
Add the following footnotes:
"Note: Performance, Convenience, Total Score, and Willingness to Continue Using Inhaler are expressed on a scale of 0 to 100.
Note: Overall Satisfaction is expressed on a scale of 1 to 7."

Summary of EQ-5D-5L Utility Score (ITT Population)
Summary of EQ-5D-5L Visual Analogue Scale (VAS) Score (ITT Population)
Programming note: Present the following visits: Day 0, Week 24, Change from Baseline at Week 24, Early Withdrawal, Change from Baseline at Early Withdrawal.

Example : EFF_T1S
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Change from Baseline in ACT Total Score by Country

Country: France

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Day 0	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Week 6	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Change from Baseline at Week 6	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx

Example : EFF_T1S
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Change from Baseline in ACT Total Score by Country

Country: Germany

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Day 0	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Week 6	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx
Change from Baseline at Week 6	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx

Repeat for:
Summary of Change from Baseline in ACT Total Score by Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation (ITT Population)
Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation: 0
Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation: >= 1

Summary of Change from Baseline in ACT Total Score by Smoking Status at Baseline (ITT Population)
Smoking Status at Baseline: Current Smokers
Smoking Status at Baseline: Former Smokers
Smoking Status at Baseline: Never Smoked

Summary of Change from Baseline in ACT Total Score by Age Group (ITT Population)
Age Group: 18 – 50 Years Old
Age Group: > 50 Years Old

Summary of Change from Baseline in ACT Total Score by Gender (ITT Population)
Gender: Male
Gender: Female

Example : EFF_T2
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4)

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
n	xx	xx
LS Mean Change (SE)	xx.xx (x.xxx)	xx.xx (x.xxx)
FF/VI vs. Usual ICS/LABA		
Difference		xx.x
95% CI		(xx.x, xx.x)
p-value		x.xxx

Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient fitted as a random factor.
Note: The Restricted Maximum Likelihood (REML) estimation approach was used with a default covariance structure of unstructured.

Programming note: Should computational issues be encountered when using an unstructured covariance structure, other structures including AR1 and CS should be considered and the second footnote updated as appropriate. Should the distributional assumption of normality fail then the p-value from a model on the rank-transformed values should be presented and the following footnote added: "Note: the p-value presented was obtained from an MMRM on the rank-transformed values of change from baseline in ACT total score at Week 12 (Visit 4) with the same specification as the untransformed model."

Repeat for:
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) Per Protocol Population (PP Population)

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (ANCOVA with LOCF) (ITT Population)
Programming note: Should the distributional assumption of normality fail then the p-value from a model on the rank-transformed values should be presented and the following footnote added: "Note: the p-value presented was obtained from an ANCOVA on the rank-transformed values of change from baseline in ACT total score at Week 12 (Visit 4) with the same specification as the untransformed model."
Footnotes as follows:
"Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline ACT total score, gender, age and country.
Note: Missing values at Week 12 (Visit 4) were replaced by last available post-randomisation value based on the last observation carried forward (LOCF) method."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (Multiple Imputation – Missing at Random Approach) (ITT Population)
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (Multiple Imputation – Copy Differences from Reference Approach) (ITT Population)
Programming note: Present the "FF/VI vs. Usual ICS/LABA" section only. Footnotes as follows:
"Note: Missing values post-randomisation were imputed using multiple imputation methods based on pattern mixture models.
Note: Each imputed data set was analysed using an ANCOVA model at Week 12 (Visit 4) adjusted for randomised treatment, baseline ACT total score, gender, age and country and the resulting treatment differences and their standard errors combined using Rubin's rules."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (Hodges-Lehmann Approach) (ITT Population)
Programming note: Present the "Difference" and "95% CI" lines of "FF/VI vs. Usual ICS/LABA" section only. Footnotes as follows:
"Note: The difference between treatment groups at Week 12 (Visit 4) was calculated using the Hodges-Lehmann approach."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) (ANCOVA with WOCF) (ITT Population)
Programming note: Should the distributional assumption of normality fail then the p-value from a model on the rank-transformed values should be presented and the following footnote added: "Note: the p-value presented was obtained from an ANCOVA on the rank-transformed values of change from baseline in ACT total score at Week 12 (Visit 4) with the same specification as the untransformed model."
Footnotes as follows:
"Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline ACT total score, gender, age and country.
Note: Missing values at Week 12 (Visit 4) due to treatment withdrawal prior to this time point were replaced by worst post-randomisation value based on the worst observation carried forward (WOCF) method."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed FP/S at Randomisation (ITT Population)
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed BUD/F at Randomisation (ITT Population)

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (ITT Population)
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) Per Protocol Population (PP Population)
Programming note: first footnote as follows:
"Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient fitted as a random factor."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (ANCOVA with LOCF) (ITT Population)
Programming note: Should the distributional assumption of normality fail then the p-value from a model on the rank-transformed values should be presented and the following footnote added: "Note: the p-value presented was obtained from an ANCOVA on the rank-transformed values of change from baseline in ACT total score at Week 24 (Visit 6) with the same specification as the untransformed model."
Footnotes as follows:
"Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline ACT total score, gender, age and country.
Note: Missing values at Week 24 (Visit 6) were replaced by last available post-randomisation value based on the last observation carried forward (LOCF) method."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (Multiple Imputation – Missing at Random Approach) (ITT Population)
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (Multiple Imputation – Copy Differences from Reference Approach) (ITT Population)
Programming note: Present the "FF/VI vs. Usual ICS/LABA" section only. Footnotes as follows:
"Note: Missing values post-randomisation were imputed using multiple imputation methods based on pattern mixture models.
Note: Each imputed data set was analysed using an ANCOVA model at Week 24 (Visit 6) adjusted for randomised treatment, baseline ACT total score, gender, age and country and the resulting treatment differences and their standard errors combined using Rubin's rules."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (Hodges-Lehmann Approach) (ITT Population)
Present the "Difference" and "95% CI" lines of "FF/VI vs. Usual ICS/LABA" section only. Footnotes as follows:
"Note: The difference between treatment groups at Week 24 (Visit 6) was calculated using the Hodges-Lehmann approach."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) (ANCOVA with WOCF) (ITT Population)

Programming note: Should the distributional assumption of normality fail then the p-value from a model on the rank-transformed values should be presented and the following footnote added: “Note: the p-value presented was obtained from an ANCOVA on the rank-transformed values of change from baseline in ACT total score at Week 24 (Visit 6) with the same specification as the untransformed model.”
Footnotes as follows:
“Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline ACT total score, gender, age and country.
Note: Missing values at Week 24 (Visit 6) due to treatment withdrawal prior to this time point were replaced by worst post-randomisation value based on the worst observation carried forward (WOCF) method.”

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6), FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed FP/S at Randomisation (ITT Population)
Programming note: Output only to be produced if ≥25% of Usual ICS/LABA patients are prescribed FP/S at randomisation. First footnote as follows:
“Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient fitted as a random factor.”

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6), FF/VI Versus the Subset of Usual ICS/LABA Subjects Prescribed BUD/F at Randomisation (ITT Population)
Programming note: Output only to be produced if ≥25% of Usual ICS/LABA patients are prescribed BUD/F at randomisation. First footnote as follows:
“Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country and patient fitted as a random factor.”

Summary of the Statistical Analysis of Change from Baseline in Trough (Pre-dose) FEV1 at Week 12 (Visit 4) (ITT Population)
Programming note: Should the distributional assumption of normality fail then the p-value from a model on the rank-transformed values should be presented and the following footnote added: “Note: the p-value presented was obtained from an ANCOVA on the rank-transformed values of change from baseline in trough (pre-dose) FEV1 at Week 12 (Visit 4) with the same specification as the untransformed model.”
Footnote as follows:
“Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline trough (pre-dose) FEV1, gender, age and country.”

Summary of the Statistical Analysis of Change from Baseline in EQ-5D-5L Utility Score at Week 24 (Visit 6) (ITT Population)
Programming note: Should the distributional assumption of normality fail then the p-value from a model on the rank-transformed values should be presented and the following footnote added: “Note: the p-value presented was obtained from an ANCOVA on the rank-transformed values of change from baseline in EQ-5D-5L utility score at Week 24 (Visit 6) with the same specification as the untransformed model.”
Footnote as follows:
“Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline EQ-5D-5L utility score, gender, age and country.”

Summary of the Statistical Analysis of Change from Baseline in EQ-5D-5L Visual Analogue Scale (VAS) Score at Week 24 (Visit 6) (ITT Population)
Programming note: Should the distributional assumption of normality fail then the p-value from a model on the rank-transformed values should be presented and the following footnote added: “Note: the p-value presented was obtained from an ANCOVA on the rank-transformed values of change from baseline in EQ-5D-5L VAS score at Week 24 (Visit 6) with the same specification as the untransformed model.”
Footnote as follows:
“Note: The analysis method was an ANCOVA model adjusted for randomised treatment, baseline EQ-5D-5L VAS score, gender, age and country.”

Example : EFF_T2S
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Country

Country: France

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
n	xx	xx
LS Mean Change (SE)	xx.xx (x.xxx)	xx.xx (x.xxx)
FF/VI vs. Usual ICS/LABA		
Difference		xx.x
95% CI		(xx.x, xx.x)

Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, two- and three- way interactions between randomised treatment, visit and country, and patient fitted as a random factor.
Note: The Restricted Maximum Likelihood (REML) estimation approach was used with a default covariance structure of unstructured.

Example : EFF_T2S
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Country

Country: Germany

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
n	xx	xx
LS Mean Change (SE)	xx.xx (x.xxx)	xx.xx (x.xxx)
FF/VI vs. Usual ICS/LABA		
Difference		xx.x
95% CI		(xx.x, xx.x)

Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, randomised treatment-by-visit interaction, baseline ACT total score-by-visit interaction, gender, age, country, randomised treatment-by-country interaction and patient fitted as a random factor.
Note: The Restricted Maximum Likelihood (REML) estimation approach was used with a default covariance structure of unstructured.

Programming note: Should computational issues be encountered when using an unstructured covariance structure, other structures including AR1 and CS should be considered and the second footnote updated as appropriate.

Repeat for:

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation (ITT Population)

Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation: 0

Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation: >= 1

Programming note: first footnote as follows:

"Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, number of severe asthma exacerbations in the previous year prior to randomisation, two- and three- way interactions between randomised treatment, visit and number of severe asthma exacerbations in the previous year prior to randomisation, and patient fitted as a random factor."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Smoking Status at Baseline (ITT Population)

Programming note: first footnote as follows:

"Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, smoking status at baseline, two- and three- way interactions between randomised treatment, visit and smoking status at baseline, and patient fitted as a random factor."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Age Group (ITT Population)

Programming note: first footnote as follows:

"Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, country, age group, two- and three- way interactions between randomised treatment, visit and age group, and patient fitted as a random factor."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4) by Gender (ITT Population)

Programming note: first footnote as follows:

"Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, two- and three- way interactions between randomised treatment, visit and gender, and patient fitted as a random factor."

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6) by Country (ITT Population)

Programming note: first footnote as follows:

"Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, two- and three- way interactions between randomised treatment, visit and country, and patient fitted as a random factor."

Example : EFF_T3
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), Adjusting for Seasonal Effect

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Randomised treatment-by-season at randomisation interaction		
p-value		x.xxx
Season at randomisation: Spring		
n	xx	xx
LS Mean Change (SE)	xx.xx (x.xxx)	xx.xx (x.xxx)
FF/VI vs. Usual ICS/LABA		
Difference		xx.x
95% CI		(xx.x, xx.x)
....		

Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6 and Week 12), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, season at randomisation, two- and three- way interactions between randomised treatment, visit and season at randomisation, and patient fitted as a random factor.
Note: The Restricted Maximum Likelihood (REML) estimation approach was used with a default covariance structure of unstructured.
Note: Spring = March, April and May; Summer = June, July and August; Autumn = September, October and November; Winter = December, January and February.

Programming note: repeat on subsequent pages for Season at randomisation = Summer, Autumn, Winter. Should computational issues be encountered when using an unstructured covariance structure, other structures including AR1 and CS should be considered and the second footnote updated as appropriate.

Repeat for:

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 12 (Visit 4), Adjusting for Seasonal Effect Per Protocol Population (PP Population)

Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6), Adjusting for Seasonal Effect (ITT Population)
Summary of the Statistical Analysis of Change from Baseline in ACT Total Score at Week 24 (Visit 6), Adjusting for Seasonal Effect Per Protocol Population (PP Population)
First footnote as follows:
"Note: The analysis method was an MMRM adjusted for randomised treatment, visit (Week 6, Week 12, Week 18 and Week 24), baseline ACT total score, baseline ACT total score-by-visit interaction, gender, age, country, season at randomisation, two- and three- way interactions between randomised treatment, visit and season at randomisation, and patient fitted as a random factor."

Table 2.xx
Summary of Inhaler Device Use Errors

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Day 0	Number of patients using Ellipta		xxx
	Number of patients with correct use [1]		xxx (xx%)
	Number of patients without correct use		xxx (xx%)
	Number of patients with at least one critical error		xxx (xx%)
	Type of critical error:		
	Failed to open cover		xxx (xx%)
	Shook the device upside down after dose preparation		xxx (xx%)
	Exhaled directly into mouthpiece		xxx (xx%)
	No seal by the lips around the mouthpiece during the inhalation		xxx (xx%)
	Number of patients with at least one non-critical error		xxx (xx%)
	Type of non-critical error:		
	No exhalation before an inhalation		xxx (xx%)
	Inhalation manoeuvre was not: long, steady and deep		xxx (xx%)
	Blocked air inlet during inhalation manoeuvre		xxx (xx%)
	Did not hold breath		xxx (xx%)
	Did not close the device		xxx (xx%)

[1] Correct use is defined as not making any critical or non-critical errors at that visit.

Table 2.xx
Summary of Inhaler Device Use Errors

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Day 0	Number of patients using Diskus	xxx	
	Number of patients with correct use [1]	xxx (xx%)	
	Number of patients without correct use	xxx (xx%)	
	Number of patients with at least one critical error	xxx (xx%)	
	Type of critical error:		
	Failed to open cover	xxx (xx%)	
	Lever is not pushed back	xxx (xx%)	
	Shook the device after dose preparation	xxx (xx%)	
	Exhaled directly into mouthpiece	xxx (xx%)	
	No seal by the lips around the mouthpiece during the inhalation	xxx (xx%)	
	Number of patients with at least one non-critical error	xxx (xx%)	
	Type of non-critical error:		
	No exhalation before an inhalation	xxx (xx%)	
	Inhalation manoeuvre was not: steady and deep	xxx (xx%)	
	Did not hold breath	xxx (xx%)	
	Did not close the device	xxx (xx%)	

[1] Correct use is defined as not making any critical or non-critical errors at that visit.

Table 2.xx
Summary of Inhaler Device Use Errors

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Day 0	Number of patients using Turbuhaler	xxx	
	Number of patients with correct use [1]	xxx (xx%)	
	Number of patients without correct use	xxx (xx%)	
	Number of patients with at least one critical error	xxx (xx%)	
	Type of critical error:		
	Failed to remove cap	xxx (xx%)	
	Did not hold device upright during dose preparation	xxx (xx%)	
	Base not twisted fully backwards and forwards, no click heard	xxx (xx%)	
	Shook the device after dose preparation	xxx (xx%)	
	Exhaled directly into mouthpiece	xxx (xx%)	
	No seal by the lips around the mouthpiece during the inhalation	xxx (xx%)	
	Number of patients with at least one non-critical error	xxx (xx%)	
	Type of non-critical error:		
	Device tipped downwards after dose preparation	xxx (xx%)	
	No exhalation before an inhalation	xxx (xx%)	
	Inhalation manoeuvre was not: forceful and deep	xxx (xx%)	
	Blocked air inlet during inhalation manoeuvre	xxx (xx%)	
	Did not hold breath	xxx (xx%)	
	Did not close the device	xxx (xx%)	

[1] Correct use is defined as not making any critical or non-critical errors at that visit.
Programming note: repeat on subsequent pages for Visit = Week 12 and Week 24. "Number of patients using..." line will provide the denominators for each section's percentages.

Repeat for:
Summary of Inhaler Device Use Errors Per Protocol Population (PP Population)

Example : EFF_T5
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Correct Use of Inhaler Device

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Day 0	n	xxx	xxx
	Number of patients with correct use [1]	xxx (xx%)	xxx (xx%)
	Number of patients without correct use	xxx (xx%)	xxx (xx%)
	Number of patients with at least one critical error	xxx (xx%)	xxx (xx%)
	Number of patients with at least one non-critical error	xxx (xx%)	xxx (xx%)
Week 12	n	xxx	xxx
	Number of patients with correct use [1]	xxx (xx%)	xxx (xx%)
	Number of patients without correct use	xxx (xx%)	xxx (xx%)
	Number of patients with at least one critical error	xxx (xx%)	xxx (xx%)
	Number of patients with at least one non-critical error	xxx (xx%)	xxx (xx%)
Week 24	n	xxx	xxx
	Number of patients with correct use [1]	xxx (xx%)	xxx (xx%)
	Number of patients without correct use	xxx (xx%)	xxx (xx%)
	Number of patients with at least one critical error	xxx (xx%)	xxx (xx%)
	Number of patients with at least one non-critical error	xxx (xx%)	xxx (xx%)

[1] Correct use is defined as not making any critical or non-critical errors at that visit.

Repeat for:
Summary of Correct Use of Inhaler Device Per Protocol Population (PP Population)

Example : EFF_T6
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Correct Use of Inhaler Device at Week 12 (Visit 4) and at Week 24 (Visit 6) Independently of the Use at Week 12 (Visit 4)

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Week 12	n	xxx	xxx
	With correct use [1]	xxx (xx%)	xxx (xx%)
	Without correct use	xxx (xx%)	xxx (xx%)
	FF/VI vs. Usual ICS/LABA		
	Adjusted Odds Ratio		x.xx
	95% CI		(x.xx, x.xx)
	p-value		x.xxx
Week 24	n	xxx	xxx
	With correct use [1]	xxx (xx%)	xxx (xx%)
	Without correct use	xxx (xx%)	xxx (xx%)
	FF/VI vs. Usual ICS/LABA		
	Adjusted Odds Ratio		x.xx
	95% CI		(x.xx, x.xx)
	p-value		x.xxx

[1] Correct use is defined as not making any critical or non-critical errors at that visit.

Note: The analysis method was logistic regression adjusted for randomised treatment, correct use of inhaler device at baseline, gender, age and country.

Programming note: If the likelihood maximisation algorithm fails to converge due to complete or quasi-complete separation of the data then implement Firth's penalized likelihood and add the following footnote: "Note: Firth's penalized likelihood was implemented due to [complete / quasi-complete] separation of data.", deleting "complete" or "quasi-complete" as appropriate.

Repeat for:

Summary of the Statistical Analysis of Correct Use of Inhaler Device at Week 12 (Visit 4) and at Week 24 (Visit 6) Independently of the Use at Week 12 (Visit 4) Per Protocol Population (PP Population)

Summary of the Statistical Analysis of Percentage of Subjects Who Have Either an ACT Total Score >= 20 or >= 3 Point Increase from Baseline in ACT Total Score at Week 12 (Visit 4) and Week 24 (Visit 6) (ITT Population)
Programming note: Replace "With correct use [1]" with "Responder [1]" and "Without correct use" with "Non-Responder".
Footnotes as follows:
"[1] Responder is defined as an ACT total score >= 20 or >= 3 point increase from baseline in ACT total score at that visit.
Note: The analysis method was logistic regression adjusted for randomised treatment, baseline ACT total score, baseline ACT total score squared, gender, age and country."

Summary of the Statistical Analysis of Percentage of Subjects Who Have an Increase from Baseline of >=0.5 in AQLQ(S) Total Score and Environmental Stimuli Domain Score at Week 24 (Visit 6) (ITT Population)
Domain: Total Score
Domain: Environmental Stimuli

Programming note: Replace "With correct use [1]" with "Responder [1]" and "Without correct use" with "Non-Responder". Do not display the "Visit" column.
Footnotes as follows:
"[1] Responder is defined as an increase from baseline of >= 0.5.
Note: The analysis method was logistic regression adjusted for randomised treatment, baseline score, gender, age and country."

Summary of the Statistical Analysis of Proportion of Responders According to EQ-5D-5L Descriptive System Dimensions at Week 24 (Visit 6) (ITT Population)
Dimension: Anxiety/Depression
Dimension: Mobility
Dimension: Pain/Discomfort
Dimension: Self-care

Dimension: Usual activities

Programming note: Replace “With correct use [1]” with “Responder [1]” and “Without correct use” with “Non-Responder”. Do not display the “Visit” column.
Footnotes as follows:
“[1] Responder is defined as a score of 1 (‘no problems’).
Note: The analysis method was logistic regression adjusted for randomised treatment, baseline EQ-5D-5L domain score, gender, age and country.”

Example : EFF_T7
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Percentage of Subjects Who Have Either an ACT Total Score of >= 20 or >= 3 Point Increase from Baseline in ACT Total Score

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Week 6	n	xxx	xxx
	ACT Total Score >= 20 or >= 3 Point Increase from Baseline	xxx (xx%)	xxx (xx%)
	ACT Total Score >= 20	xxx (xx%)	xxx (xx%)
	>= 3 Point Increase from Baseline	xxx (xx%)	xxx (xx%)
Week 12	n	xxx	xxx
	ACT Total Score >= 20 or >= 3 Point Increase from Baseline	xxx (xx%)	xxx (xx%)
	ACT Total Score >= 20	xxx (xx%)	xxx (xx%)
	>= 3 Point Increase from Baseline	xxx (xx%)	xxx (xx%)

...

Programming note: repeat for Visit = Week 18, Week 24, Early Withdrawal.

Example : EFF_T8
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Individual ACT Question Scores

Question: 1. Getting as much done at work, school or home

Visit	Response	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Day 0	n	xxx	xxx
	1. All of the time	xxx (xx%)	xxx (xx%)
	2. Most of the time	xxx (xx%)	xxx (xx%)
	3. Some of the time	xxx (xx%)	xxx (xx%)
	4. A little of the time	xxx (xx%)	xxx (xx%)
	5. None of the time.	xxx (xx%)	xxx (xx%)
Week 6	n	xxx	xxx
	1. All of the time	xxx (xx%)	xxx (xx%)
	2. Most of the time	xxx (xx%)	xxx (xx%)
	3. Some of the time	xxx (xx%)	xxx (xx%)
	4. A little of the time	xxx (xx%)	xxx (xx%)
	5. None of the time.	xxx (xx%)	xxx (xx%)
Week 12	n	xxx	xxx
	1. All of the time	xxx (xx%)	xxx (xx%)
	2. Most of the time	xxx (xx%)	xxx (xx%)
	3. Some of the time	xxx (xx%)	xxx (xx%)
	4. A little of the time	xxx (xx%)	xxx (xx%)
	5. None of the time.	xxx (xx%)	xxx (xx%)

Example : EFF_T8
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Individual ACT Question Scores

Question: 1. Getting as much done at work, school or home

Visit	Response	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Week 18	n	xxx	xxx
	1. All of the time	xxx (xx%)	xxx (xx%)
	2. Most of the time	xxx (xx%)	xxx (xx%)
	3. Some of the time	xxx (xx%)	xxx (xx%)
	4. A little of the time	xxx (xx%)	xxx (xx%)
	5. None of the time.	xxx (xx%)	xxx (xx%)
Week 24	n	xxx	xxx
	1. All of the time	xxx (xx%)	xxx (xx%)
	2. Most of the time	xxx (xx%)	xxx (xx%)
	3. Some of the time	xxx (xx%)	xxx (xx%)
	4. A little of the time	xxx (xx%)	xxx (xx%)
	5. None of the time.	xxx (xx%)	xxx (xx%)
Early Withdrawal	n	xxx	xxx
	1. All of the time	xxx (xx%)	xxx (xx%)
	2. Most of the time	xxx (xx%)	xxx (xx%)
	3. Some of the time	xxx (xx%)	xxx (xx%)
	4. A little of the time	xxx (xx%)	xxx (xx%)
	5. None of the time.	xxx (xx%)	xxx (xx%)

Programming note: repeat on subsequent pages for Question = 2. Shortness of breath, 3. Asthma symptoms woken up at night or earlier than usual, 4. Used rescue inhaler or nubuliser medication, 5. Asthma control.

Example : EFF_T9
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Compliance with Study Medication

Time period	Compliance (%)	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Day 0 to Week 24	n	xxx	xxx
	< 80%	xxx (xx%)	xxx (xx%)
	80% to 120% inclusive	xxx (xx%)	xxx (xx%)
	> 120%	xxx (xx%)	xxx (xx%)
	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx

Note: Compliance = {[Total no. of inhalations taken]/[Dose frequency x (Stop date – Start date)]} x 100.
Note: Total number of inhalations taken is the sum of (dose counter start count – dose counter stop count) for all inhalers used during the time period, Dose frequency is equal to 1 for Ellipta, 2 for Diskus and 2 or 4 for Turbuhaler, and Start date and Stop date are the earliest treatment start date and latest treatment stop date respectively recorded for all inhalers used during the time period.

Programming note: repeat on subsequent pages for Time period = Day 0 to Week 12, Week 12 to Week 24.

Repeat for:
Summary of Compliance with Study Medication Per Protocol Population (PP Population)

Example : EFF_T10
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study

Visit: Day 0

MARS-A Questions		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
I only use it when I need it	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
Only use it when I feel breathless	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
I decide to miss out a dose	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)

Note: MARS-A: Medication Adherence Report Scale for Asthma.
[1]: MARS-A 10-Score is based on the mean score across all ten questions.

Example : EFF_T10
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study

Visit: Day 0

MARS-A Questions		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
I try to avoid using it	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
I forget to take it	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
I alter the dose	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)

Note: MARS-A: Medication Adherence Report Scale for Asthma.
[1]: MARS-A 10-Score is based on the mean score across all ten questions.

Table 2.xx
Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study

Visit: Day 0

MARS-A Questions		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
I stop taking it for a while	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
Reserve if treatment doesn't work	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
Before doing something	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)

Note: MARS-A: Medication Adherence Report Scale for Asthma.
[1]: MARS-A 10-Score is based on the mean score across all ten questions.

Example : EFF_T10
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study

Visit: Day 0

MARS-A Questions		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
I take less than instructed	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
MARS-A 10-Score [1]	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx

Note: MARS-A: Medication Adherence Report Scale for Asthma.
[1]: MARS-A 10-Score is based on the mean score across all ten questions.

Programming note: Repeat on subsequent pages for Visit = Week 12, Week 24 and Early Withdrawal.

Table 2.xx
Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study by Status of Patient in Relation to the Reminder Sent to French Centres

Status: Patients in France who had completed all MARS-A assessments prior to the reminder being implemented
Visit: Day 0

MARS-A Questions		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
I only use it when I need it	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
Only use it when I feel breathless	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
I decide to miss out a dose	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)

Note: MARS-A: Medication Adherence Report Scale for Asthma.

Note: Due to an issue identified with the French translation of the MARS-A, a reminder was sent to centres in France instructing that the questionnaire refers to the patient's preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study).
[1]: MARS-A 10-Score is based on the mean score across all ten questions.

Table 2.xx
Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study by Status of Patient in Relation to the Reminder Sent to French Centres

Status: Patients in France who had completed all MARS-A assessments prior to the reminder being implemented
Visit: Day 0

MARS-A Questions		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
I try to avoid using it	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
I forget to take it	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
I alter the dose	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)

Note: MARS-A: Medication Adherence Report Scale for Asthma.

Note: Due to an issue identified with the French translation of the MARS-A, a reminder was sent to centres in France instructing that the questionnaire refers to the patient's preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study).
[1]: MARS-A 10-Score is based on the mean score across all ten questions.

Table 2.xx
Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study by Status of Patient in Relation to the Reminder Sent to French Centres

Status: Patients in France who had completed all MARS-A assessments prior to the reminder being implemented
Visit: Day 0

MARS-A Questions		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
I stop taking it for a while	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
Reserve if treatment doesn't work	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
Before doing something	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)

Note: MARS-A: Medication Adherence Report Scale for Asthma.

Note: Due to an issue identified with the French translation of the MARS-A, a reminder was sent to centres in France instructing that the questionnaire refers to the patient's preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study).
[1]: MARS-A 10-Score is based on the mean score across all ten questions.

Table 2.xx
Summary of Use of Medication Adherence Report Scale for Asthma (MARS-A) During the Study by Status of Patient in Relation to the Reminder Sent to French Centres

Status: Patients in France who had completed all MARS-A assessments prior to the reminder being implemented
Visit: Day 0

MARS-A Questions		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
I take less than instructed	n	xxx	xxx
	Always	xxx (xx%)	xxx (xx%)
	Often	xxx (xx%)	xxx (xx%)
	Sometimes	xxx (xx%)	xxx (xx%)
	Rarely	xxx (xx%)	xxx (xx%)
	Never	xxx (xx%)	xxx (xx%)
MARS-A 10-Score [1]	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min.	xx	xx
	Max.	xx	xx

Note: MARS-A: Medication Adherence Report Scale for Asthma.
Note: Due to an issue identified with the French translation of the MARS-A, a reminder was sent to centres in France instructing that the questionnaire refers to the patient's preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study).
[1]: MARS-A 10-Score is based on the mean score across all ten questions.

Programming note: Repeat on subsequent pages for Visit = Week 12, Week 24 and Early Withdrawal, and for Status = Patients in France who had completed at least one MARS-A assessment prior to the reminder being implemented but also completed at least one MARS-A assessment after the reminder being implemented, Patients in France who had not completed any MARS-A assessments prior to the reminder being implemented, Patients in Germany.

Example : EFF_T11
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Severe On-Treatment Asthma Exacerbations

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
No. of subjects with one or more severe asthma exacerbation	xx (xx%)	xx (xx%)
Total no. of severe asthma exacerbations	xx	xx
Number of severe asthma exacerbations per subject		
0	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)
> 1	xx (xx%)	xx (xx%)
Duration of severe asthma exacerbation (days) [1]		
n	xx	xx
Mean	xx.x	xx.x
SD	x.xx	x.xx
Median	xx.x	xx.x
Min.	xx	xx
Max.	xx	xx

[1] Summary only includes exacerbations for which a date of resolution or death is provided.

Example : EFF_T11
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Severe On-Treatment Asthma Exacerbations

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Outcome		
Resolved	xx (xx%)	xx (xx%)
Fatal	xx (xx%)	xx (xx%)
Not resolved	xx (xx%)	xx (xx%)
Total no. of severe asthma exacerbations	xx	xx
No. of exacerbations:		
Requiring use of systemic/oral corticosteroids	xx (xx%)	xx (xx%)
Leading to hospitalisation	xx (xx%)	xx (xx%)
Requiring emergency room visit	xx (xx%)	xx (xx%)
No. of exacerbations requiring intubation	xx (xx%)	xx (xx%)
No. of exacerbations leading to withdrawal from study	xx (xx%)	xx (xx%)

[1] Summary only includes exacerbations for which a date of resolution or death is provided.

Example : EFF_T11S
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Severe On-Treatment Asthma Exacerbations by Season

Season: Spring

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
No. of subjects with one or more severe asthma exacerbation	xx (xx%)	xx (xx%)
Total no. of severe asthma exacerbations	xx	xx
Number of severe asthma exacerbations per subject		
0	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)
> 1	xx (xx%)	xx (xx%)
Duration of severe asthma exacerbation (days) [1]		
n	xx	xx
Mean	xx.x	xx.x
SD	x.xx	x.xx
Median	xx.x	xx.x
Min.	xx	xx
Max.	xx	xx

Note: Spring = March, April and May; Summer = June, July and August; Autumn = September, October and November; Winter = December, January and February.
[1] Summary only includes exacerbations for which a date of resolution or death is provided.

Example : EFF_T11
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Severe On-Treatment Asthma Exacerbations by Season

Season: Spring

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Outcome		
Resolved	xx (xx%)	xx (xx%)
Fatal	xx (xx%)	xx (xx%)
Not resolved	xx (xx%)	xx (xx%)
Total no. of severe asthma exacerbations	xx	xx
No. of exacerbations:		
Requiring use of systemic/oral corticosteroids	xx (xx%)	xx (xx%)
Leading to hospitalisation	xx (xx%)	xx (xx%)
Requiring emergency room visit	xx (xx%)	xx (xx%)
No. of exacerbations requiring intubation	xx (xx%)	xx (xx%)
No. of exacerbations leading to withdrawal from study	xx (xx%)	xx (xx%)

Note: Spring = March, April and May; Summer = June, July and August; Autumn = September, October and November; Winter = December, January and February.
[1] Summary only includes exacerbations for which a date of resolution or death is provided.

Programming note: repeat on subsequent pages for Season = Summer, Autumn, Winter.

Example : EFF_T12
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Severe On-Treatment Asthma Exacerbations

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
n	xxx	xxx
LS Mean Annual Rate	x.xx	x.xx
FF/VI vs. Usual ICS/LABA		
Ratio		x.xx
95% CI		(x.xx, x.xx)
p-value		x.xxx
Percent Reduction		x.xx
95% CI		(x.xx, x.xx)

Note: The analysis method was Generalised Linear Model assuming an underlying negative binomial distribution with a log-link function and logarithm of time on treatment as an offset variable and adjusted for randomised treatment, number of severe asthma exacerbations in the previous year prior to randomisation, gender, age and country.

Example : EFF_T13
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of the Statistical Analysis of Time to First Severe On-Treatment Asthma Exacerbation

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Number of subjects with event	xx (xx%)	xx (xx%)
Number of subjects censored	xx (xx%)	xx (xx%)
Probability of having event (%) [1]	xx.x	xx.x
95% CI	(xx.x, xx.x)	(xx.x, xx.x)
FF/VI vs. Usual ICS/LABA		
Hazard Ratio [2]		x.xx
95% CI		(xx.x, xx.x)
p-value		x.xxx

[1] Kaplan-Meier estimates.
[2] Overall hazard ratios, CIs and p-values are from a Cox proportional hazards model with randomised treatment, gender, age and country as covariates. A hazard ratio <1 indicates a lower risk with FF/VI compared with Usual ICS/LABA.
Note: At Day 168 all subjects who have not experienced a severe asthma exacerbation are considered censored, regardless of whether their on-treatment phase continues beyond Day 168.

Example : EFF_T14
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of Percentage of Subjects Who Have an Increase from Baseline of >=0.5 in AQLQ(S) Total Score and Domain Scores

Domain: Total Score

Visit	Response	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Week 24	n	xxx	xxx
	Responder [1]	xxx (xx%)	xxx (xx%)
	Non-Responder	xxx (xx%)	xxx (xx%)
Early Withdrawal	n	xxx	xxx
	Responder [1]	xxx (xx%)	xxx (xx%)
	Non-Responder	xxx (xx%)	xxx (xx%)

[1] Responder is defined as an increase from baseline of >= 0.5.

Programming note: repeat on subsequent pages for Domain = Environmental Stimuli, Symptoms, Activity Limitations and Emotional Function.

Example : EFF_T15
Protocol : HZA116492
Population : Intent-to-Treat

Table 2.xx
Summary of EQ-5D-5L Descriptive System Dimensions

Dimension: Anxiety/Depression

Visit		Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Day 0	n	xxx	xxx
	I am not anxious or depressed	xxx (xx%)	xxx (xx%)
	I am slightly anxious or depressed	xxx (xx%)	xxx (xx%)
	I am moderately anxious or depressed	xxx (xx%)	xxx (xx%)
	I am severely anxious or depressed	xxx (xx%)	xxx (xx%)
	I am extremely anxious or depressed	xxx (xx%)	xxx (xx%)
	Missing	xxx (xx%)	xxx (xx%)
Week 24	n	xxx	xxx
	I am not anxious or depressed	xxx (xx%)	xxx (xx%)
	I am slightly anxious or depressed	xxx (xx%)	xxx (xx%)
	I am moderately anxious or depressed	xxx (xx%)	xxx (xx%)
	I am severely anxious or depressed	xxx (xx%)	xxx (xx%)
	I am extremely anxious or depressed	xxx (xx%)	xxx (xx%)
	Missing	xxx (xx%)	xxx (xx%)

Programming note: repeat on subsequent pages for Visit = Early Withdrawal and for Dimension = Mobility, Pain/Discomfort, Self-care, Usual activities.

10.16.4. Efficacy Figure Shells

Example : EFF_F1
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Summary of ACT Total Score

Programming note: present "ACT Total Score" on y-axis and "Visit" on x-axis (Day 0, Week 6, Week 12, Week 18, Week 24). Present mean ACT Total Score ± SD separately for treatment group (FF/VI, Usual ICS/LABA) at each visit, connecting the means with a solid line. Distinguish the treatment groups by different line types and colours.

Repeat for:

Summary of Change from Baseline in ACT Total Score Per Protocol Population (PP Population)

Summary of Change from Baseline in ACT Total Score by Country (ITT Population)
Country: France
Country: Germany

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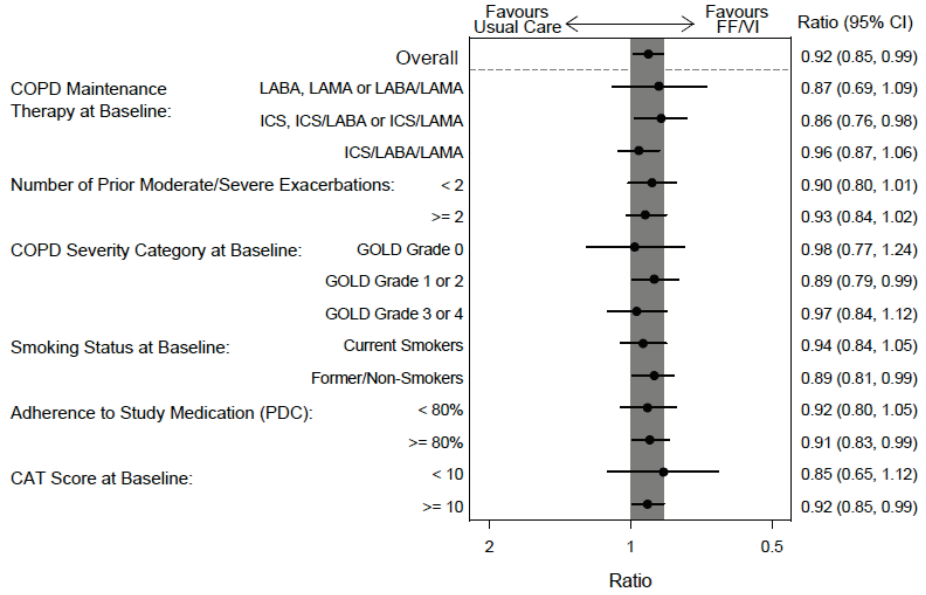
Example : EFF_F2
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Summary of Primary and Sensitivity Analyses for Change from Baseline in ACT Total Score at Week 12 (Visit 4)

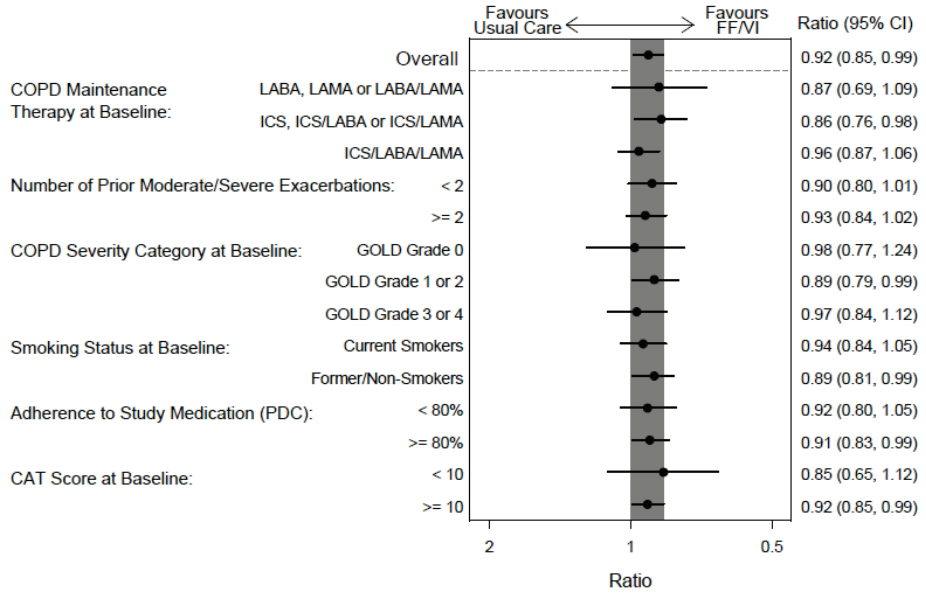


Programming note: present "Treatment difference" on the x-axis, and reverse axis so treatment difference increases from left to right. Replace "Ratio (95% CI)" with "Treatment Difference (95% CI)". Present lines for the following: Primary analysis (ITT), Primary analysis (PP), ANCOVA with LOCF (ITT), Multiple Imputation (Missing at Random) (ITT), Multiple Imputation (Copy Differences from Reference) (ITT), Hodges-Lehmann (ITT), ANCOVA with WOCF (ITT).

Repeat for:

Summary of Key Secondary and Sensitivity Analyses for Change from Baseline in ACT Total Score at Week 24 (Visit 6)
Example : EFF_F3
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Summary of Interaction Tests for Change from Baseline in ACT Total Score at Week 12 (Visit 4)



Programming note: present "LS Mean Change" on the x-axis, and reverse axis so it increases from left to right. Replace "Ratio (95% CI)" with "LS Mean Change (95% CI)". Present the following subgroups: Country (France, Germany); Number of Severe Asthma Exacerbations in the Previous Year Prior to Randomisation (0, >= 1); Smoking Status at Baseline (Current Smokers, Former Smokers, Never Smoked); Age Group (18 – 50 Years Old, > 50 Years Old); Gender (Male, Female).

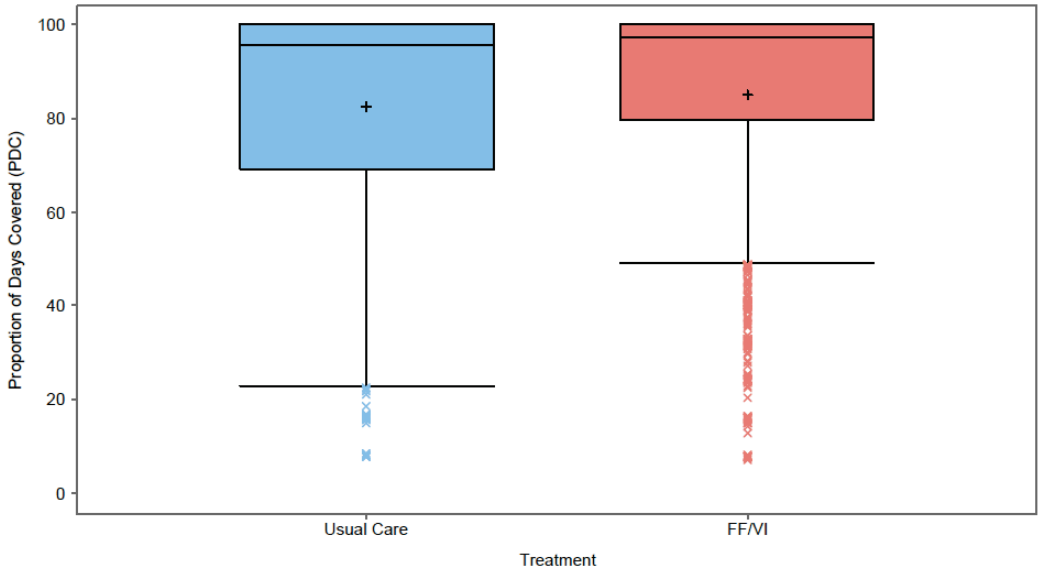
Example : EFF_F4
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Histogram of Percentage of Subjects Who Have Either an ACT Total Score of >= 20 or >= 3 Point Increase from Baseline in ACT Total Score

Programming note: present "Percent of Subjects (%)" on y-axis and "Visit" on x-axis (Week 6, Week 12, Week 18, Week 24, Early Withdrawal). For each visit, present 3 vertical bars distinguished by fill pattern (similar to non-standard EFF_F6). Each bar represents: "ACT Total Score >= 20 or >= 3 Point Increase from Baseline in ACT Total Score", "ACT Total Score >= 20" and ">= 3 Point Increase from Baseline in ACT Total Score" respectively and should be labelled as such on the legend.

Example : EFF_F5
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Box Plot of Compliance with Study Medication

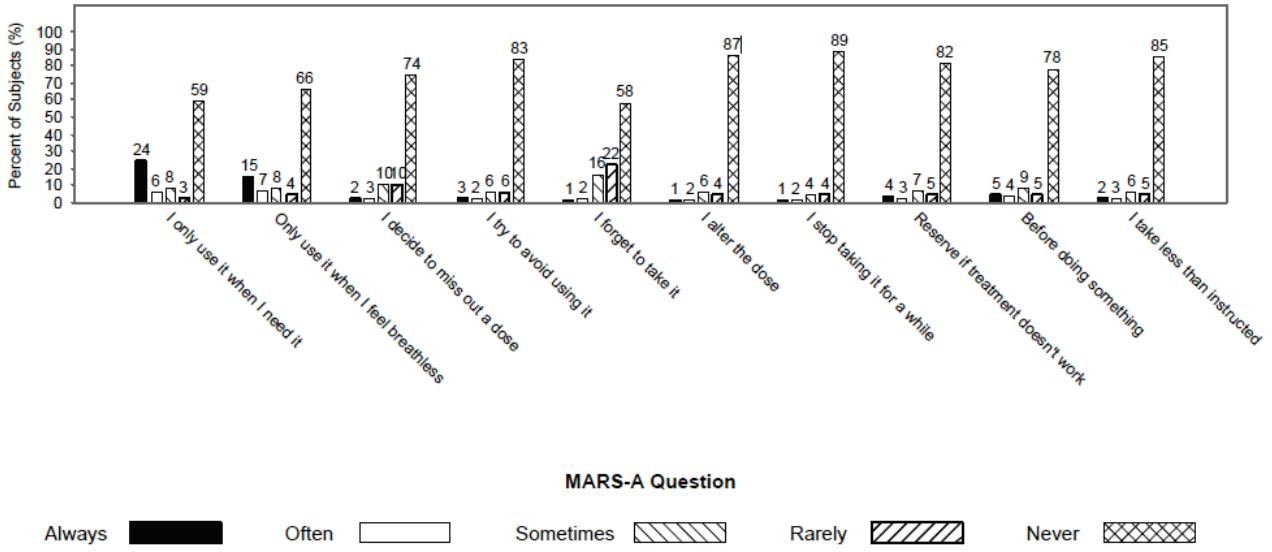


Programming Note: label y-axis title as "Compliance (%)", maximum of y-axis may be > 100%.

Example : EFF_F6
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Histogram of the Questions and Answers of the MARS-A Questionnaire

Randomised Treatment: Usual ICS/LABA
Visit: Day 0



Note: MARS-A = Medication Adherence Report Scale for Asthma.

Programming note: repeat on subsequent pages for Visit = Week 24, Week 52 and Early Withdrawal; and for Randomised Treatment = FF/VI.

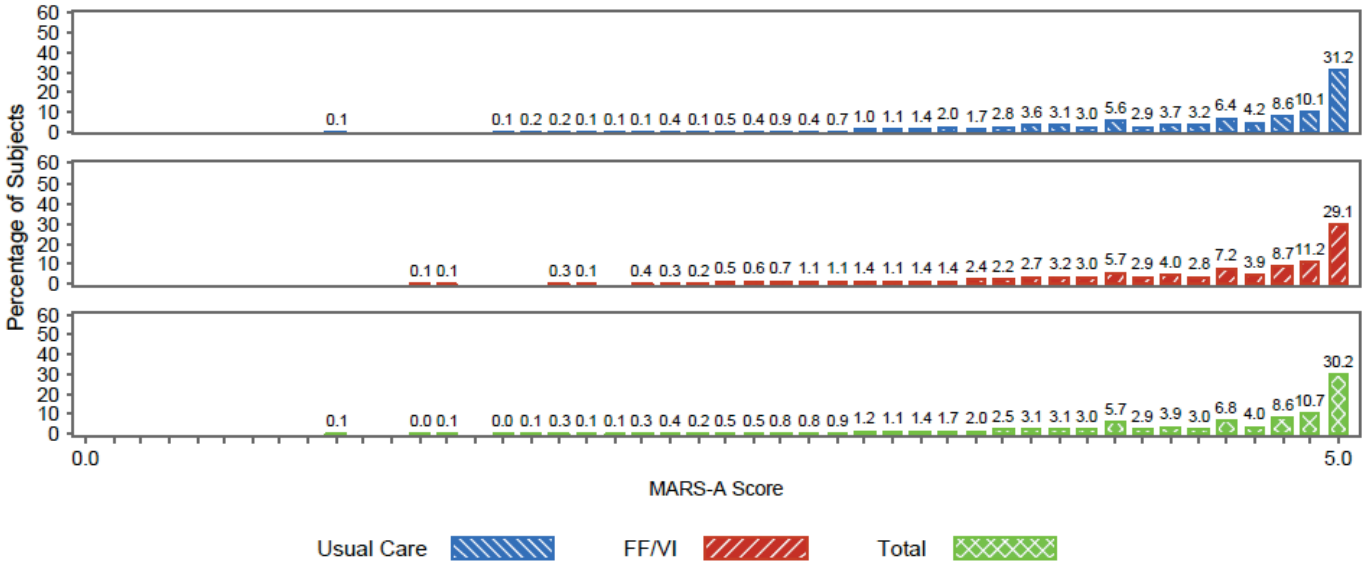
Repeat for:
Histogram of the Questions and Answers of the MARS-A Questionnaire by Status of Patient in Relation to the Reminder Sent to French Centres (ITT Population)
Status: Patients in France who had completed all MARS-A assessments prior to the reminder being implemented
Status: Patients in France who had completed at least one MARS-A assessment prior to the reminder being implemented but also completed at least one MARS-A assessment after the reminder being implemented
Status: Patients in France who had not completed any MARS-A assessments prior to the reminder being implemented
Status: Patients in Germany

Add the following footnote: “Note: Due to an issue identified with the French translation of the MARS-A, a reminder was sent to centres in France instructing that the questionnaire refers to the patient’s preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study).”

Example : EFF_F7
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Histogram of the Distribution of MARS-A Scores During the Study

Visit: Day 0



Note: MARS-A = Medication Adherence Report Scale for Asthma.
Note: MARS-A 10-Score is based on the mean score across all ten questions.

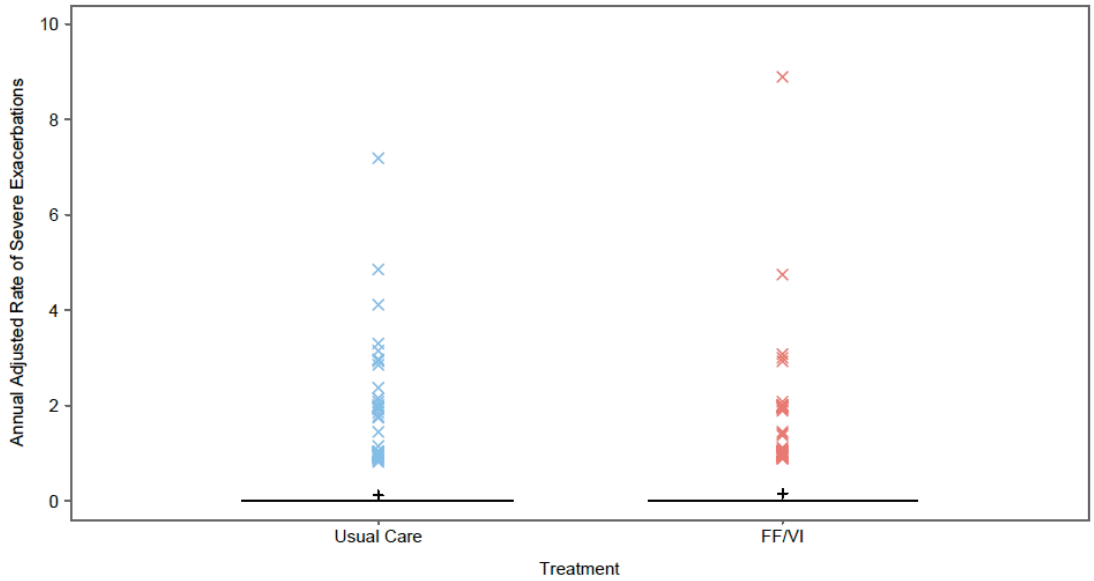
Programming note: repeat on subsequent pages for Visit = Week 52 and Early Withdrawal.

Repeat for:
Histogram of the Distribution of MARS-A Scores During the Study by Status of Patient in Relation to the Reminder Sent to French Centres (ITT Population)
Status: Patients in France who had completed all MARS-A assessments prior to the reminder being implemented
Status: Patients in France who had completed at least one MARS-A assessment prior to the reminder being implemented but also completed at least one MARS-A assessment after the reminder being implemented
Status: Patients in France who had not completed any MARS-A assessments prior to the reminder being implemented
Status: Patients in Germany

Add the following footnote: “Note: Due to an issue identified with the French translation of the MARS-A, a reminder was sent to centres in France instructing that the questionnaire refers to the patient’s preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study).”

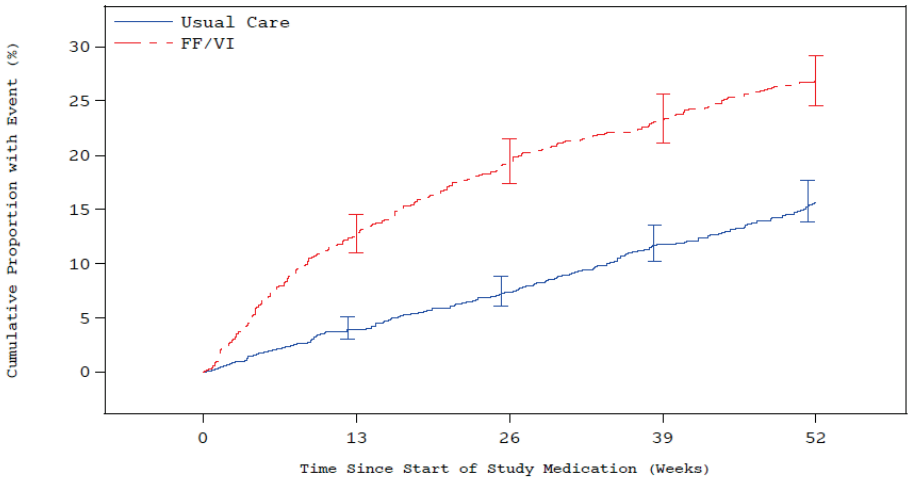
Example : EFF_F8
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Box Plot of Severe On-Treatment Asthma Exacerbation Rates Adjusted for Exposure to Treatment



Example : EFF_F9
Protocol : HZA116492
Population : Intent-to-Treat

Figure 2.xx
Kaplan-Meier Plot of Time to First Severe On-Treatment Asthma Exacerbation



Subjects at Risk

Usual Care	1403	1348	1300	1238	1081
FF/VI	1396	1221	1127	1072	918

Programming note: display increments of 6 weeks on the x-axis, up to the maximum exposure (e.g. 0, 6, 12, 18, 24, 30).

10.16.5. Safety Table Shells

Example : SAFE_T1
Protocol : HZA116492
Population : Safety

Table 3.xx
On-Treatment Serious Adverse Events and Adverse Drug Reactions Overview

	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Any on-treatment ADRs	xxx (xx%)	xxx (xx%)
Any on-treatment non serious ADRs	xxx (xx%)	xxx (xx%)
Any on-treatment serious ADRs	xxx (xx%)	xxx (xx%)
Any post-treatment serious ADRs	xxx (xx%)	xxx (xx%)
Any on-treatment SAEs	xxx (xx%)	xxx (xx%)
Any post-treatment SAEs	xxx (xx%)	xxx (xx%)
Any SAEs or ADRs leading to permanent discontinuation of study drug or withdrawal from study [1]	xxx (xx%)	xxx (xx%)
Any on-treatment fatal serious ADRs	xxx (xx%)	xxx (xx%)
Any on-treatment fatal SAEs	xxx (xx%)	xxx (xx%)
Any post-treatment fatal SAEs	xxx (xx%)	xxx (xx%)

[1] Includes both on-treatment and post-treatment SAEs and ADRs.

Programming note: Based on IDSL standard template AE13.

Example : SAFE_T2
Protocol : HZA116492
Population : Safety

Table 3.xx
Summary of On-Treatment Non-Serious Adverse Drug Reactions of Special Interest

Special Interest Group/ Subgroup Preferred Term	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
Adrenal suppression		
Any event	xxx (xx%)	xxx (xx%)
Blood cortisol decreased	xxx (xx%)	xxx (xx%)
Cardiovascular effects		
Any event	xxx (xx%)	xxx (xx%)
Cardiac Arrhytmia [1]	xxx (xx%)	xxx (xx%)
Any event	xxx (xx%)	xxx (xx%)
Palpitations	xxx (xx%)	xxx (xx%)
Extrasystoles	xxx (xx%)	xxx (xx%)
Cardiac Ischaemia [1]	xxx (xx%)	xxx (xx%)
Any event	xxx (xx%)	xxx (xx%)
Angina pectoris	xxx (xx%)	xxx (xx%)
Chest pain	xxx (xx%)	xxx (xx%)
Effects on potassium		
Any event	xxx (xx%)	xxx (xx%)
XXXXXXX	xxx (xx%)	xxx (xx%)
XXXXXXX	xxx (xx%)	xxx (xx%)

[1]: This subgroup was defined using Special MedDRA queries.

Programming note: Based on IDSL standard template AE1.

Repeat for:

Summary of On-Treatment Serious Adverse Drug Reactions of Special Interest (ITT Population)
Summary of On-Treatment Adverse Drug Reactions of Special Interest (ITT Population)
Summary of On-Treatment Serious Adverse Events of Special Interest (ITT Population)
Summary of On-Treatment Fatal Serious Adverse Events of Special Interest (ITT Population)
Summary of On-Treatment Non-Fatal Serious Adverse Events of Special Interest (ITT Population)

Example : SAFE_T3
Protocol : HZA116492
Population : Safety

Table 3.xx
Top Ten Most Commonly Reported On-Treatment Adverse Drug Reactions Per Treatment Group

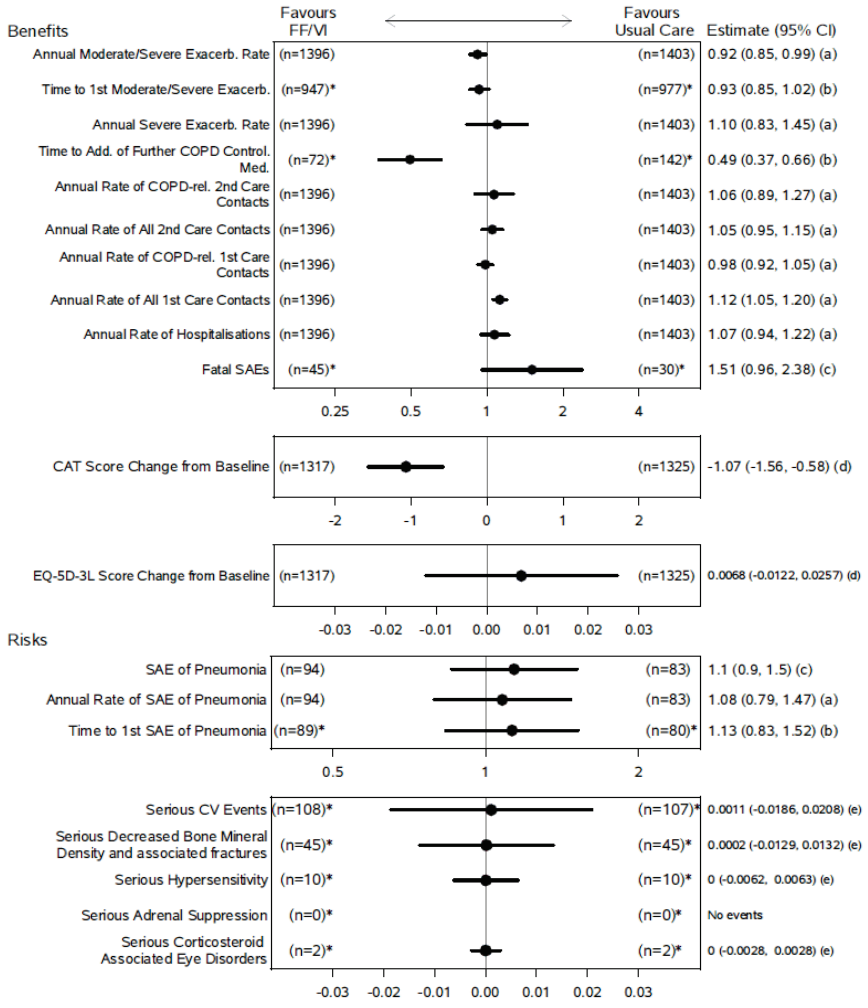
Preferred Term	Usual ICS/LABA (N=xxx)	FF/VI (N=xxx)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
xxxxxxx	xxx (xx%)	xxx (xx%)
.....		

Programming note: Present the ten most frequent preferred terms in Usual ICS/LABA, and the ten most frequent in FF/VI (do not use percentages to determine "most frequent").

10.16.6. Safety Figure Shells

Example : SAFE_F1
Protocol : HZA116492 Page 1
of 1
Population : Intent-to-Treat/Safety

Figure 2.xx
Summary of Benefit:Risk for FF/VI vs. Usual ICS/LABA



* = Number of subjects with event
(a) Difference in LS mean change from baseline from an MMRM
(b) Difference in LS mean change from baseline from an ANCOVA model
(c) Adjusted odds ratio obtained from a logistic regression model
(d) Risk difference

Programming note: present the following endpoints:

- *Benefits:*
- *First panel, x-axis decreasing from left to right:*
    - *Difference in LS mean change from baseline and 95% CI for: change from baseline in ACT total score at Week 12 (Visit 4) and at Week 24 (Visit 6) (labeled (a))*
    - *Difference in LS mean change from baseline and 95% CI for change from baseline in trough (pre-dose) FEV1 at Week 12 (Visit 4) (labeled (b))*
- *Second panel, x-axis increasing from left to right:*
    - *Adjusted odds ratio and 95% CI for: percentage of subjects with correct use of inhaler device at Week 12 (Visit 4) and at Week 24 (Visit 6) (labeled (c))*
- *Risks:*
- *Third panel, x-axis increasing from left to right:*
    - *Risk difference and 95% CI of the following SAEs of special interest: asthma/bronchospasm, cardiovascular effects, decreased bone mineral density and associated fractures, hypersensitivity, local steroid effects, lower respiratory tract infection (LRTI) excluding pneumonia, pneumonia, adrenal suppression, ocular effects, effects on glucose, effects on potassium, tremor (labeled (d))*

10.16.7. Non-ICH Listing Shells

Example : POP_L1
Protocol : HZA116492
Population : All Subjects Enrolled

Listing x
Subjects Screened but Not in the Intent-to-Treat Population

Randomised Treatment	Inv.	Subj.	Disposition Status	Reason for Screen Failure/Withdrawal
Screen Failure	xxxxxx	xxxxxx	Screen Failure	Xxxxxxxxxxxx
FF/VI	xxxxxx	xxxxxx	Early Withdrawal	Xxxxxxxxxxxx
...				

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Example : POP_L2
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Reasons for Important Protocol Deviations

Randomised Treatment	Inv.	Subj.	Important Protocol Deviation	Excluded from PP?	Date of Deviation	Study Day of Deviation
FF/VI	xxxxx	xxxxx	xxxxxxxxxxx	No	DDMMMYYYY	xx
	xxxxx	xxxxx	xxxxxxxxxxx	No	DDMMMYYYY	xx
Usual ICS/LABA	xxxxx	xxxxx	xxxxxxxxxxx	No	DDMMMYYYY	xx
	xxxxx	xxxxx	xxxxxxxxxxx	Yes	DDMMMYYYY	xx
	xxxxx	xxxxx	xxxxxxxxxxx	No	DDMMMYYYY	xx
	xxxxx	xxxxx	xxxxxxxxxxx	No	DDMMMYYYY	xx

....

Example : POP_L3
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Asthma History

				Number of asthma exacerbations in the last 12 months that:		
Treatment	Inv.	Subj.	Asthma Duration	Did not require oral/systemic corticosteroids (not involving hospitalisation)	Required oral/systemic corticosteroids (not involving hospitalisation)	Required hospitalisation
xxxxxx	xxxxxx	xxxxxx	xxxxxxxxxxxx	xx	xx	xx
	xxxxxx	xxxxxx	xxxxxxxxxxxx	xx	xx	xx
	xxxxxx	xxxxxx	xxxxxxxxxxxx	xx	xx	xx
	xxxxxx	xxxxxx	xxxxxxxxxxxx	xx	xx	xx

Example : POP_L4
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Smoking History

Treatment	Inv./ Subj.	Smoking Status	Years Smoked/ Cigarettes per day	Smoking Pack Years
xxxxxx	Xxxxxx/ xxxxxx	Current	xx/ xx	xx
	Xxxxxx/ xxxxxx	Former	xx/ xx	xx
	Xxxxxx/ xxxxxx	Never		

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Example : POP_L5
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Exposure to Study Medication

Treatment: Usual ICS/LABA

Inv./ Subj.	Treatment Start Date/ Treatment End date	Start date of dose/ End date of dose/ Duration of dose (days)	Drug	Dose/ Dose Units/ Dose Frequency	Inhalers Dispensed/ Inhalers Returns	Dose counter start/ Dose counter stop	Compliance (%) During the study
XXXX	DDMMMYYY/ DDMMMYYY						XX.XX
		DDMMMYYYY/ DDMMMYYYY/ xx	XXXXXXX	XX/ XX/XXXX	X/X	XXX/XX	
		DDMMMYYYY/ DDMMMYYYY xx	XXXXXXX	XX/ XX/XXXX	X/X	XXX/XX	
XXXX	DDMMMYYY						XX.XX
		DDMMMYYYY/ DDMMMYYYY/ xx	XXXXXXX	XX/ XX/XXXX	X/X	XXX/XX	

Programming note: Repeat on subsequent pages for Treatment = FF/VI, and use GSK drug synonym as drug name.

Example : EFF_L1
Protocol : HZA116492

Population : Intent-to-Treat

Listing x
ACT Scores

Treatment: Usual ICS/LABA

Inv./ Subj.	Visit/ Study Date/ Study Day	Impact at home or work [1]	Frequency of shortness of breath [1]	Frequency of sleep trouble [1]	Frequency of rescue medication [1]	Asthma control rating [1]	ACT Total Score [2] / Change from Baseline
xxxxxx/ xxxxx	Day 0/ DDMMMYYYY/ xx	x	x	x	x	x	xx
	Week 6/ DDMMMYYYY/ xx	x	x	x	x	x	xx / -x
	Week 12/ DDMMMYYYY/ xx	x	x	x	x	x	xx / x
...							

[1] Responses range between 1 (worst response) and 5 (best response).
[2] ACT Total Score ranges between 5 (worst asthma control state) and 25 (best asthma control state).

Programming note: Repeat on subsequent pages for Treatment = FF/VI.

Example : EFF_L2
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Inhaler Device Use

Treatment: Usual ICS/LABA

Inv./ Subj.	Visit/ Study Date/ Study Day	Inhaler	Critical errors: Any?	Critical errors: If yes, errors:	Non-critical errors: Any?	Non-critical errors: If yes, errors:
xxxxxx/ xxxxx	Day 0/ DDMMMYYYY/ xx	Turbuhaler	No		No	
	Week 12/ DDMMMYYYY/ xx	Turbuhaler	No		Yes	Did not hold breath
	Week 24/ DDMMMYYYY/ xx	Turbuhaler	Yes	Exhaled directly into mouthpiece	No	
xxxxxx/ xxxxx	Day 0/ DDMMMYYYY/ xx	Diskus	Yes	Did not hold device upright during dose preparation Shook the device after dose preparation	Yes	No exhalation before an inhalation
	Week 12/ DDMMMYYYY/ xx	Diskus	Yes	Shook the device after dose preparation	No	

Programming note: Repeat on subsequent pages for Treatment = FF/VI.

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Example : EFF_L3
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Lung Function Tests

Treatment: Usual ICS/LABA

				Trough (pre-dose) FEV1 (L)			Trough (pre-dose) percent predicted normal FEV1 (%)		
Inv./ Subj.	Visit	Study Date/ Time	Study Day	Absolute	Change from Baseline	Predicted normal FEV1 (L)	Absolute	Change from Baseline	Bronchodilator taken in last 4 hours?
xxxxxx/ xxxxx	Day 0	DDMMMYYYY/ HH:MM	xx	x.xxx		x.xxx	xx.x		No
	Week 6	DDMMMYYYY/ HH:MM	xx	x.xxx	x.xxx	x.xxx	xx.x	xx.x	No
xxxxxx/ xxxxx	Day 0	DDMMMYYYY/ HH:MM	xx	x.xxx	x.xxx	x.xxx	xx.x	xx.x	No

Programming note: Repeat on subsequent pages for Treatment = FF/VI.

Example : EFF_L4
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Medication Adherence Report Scale for Asthma (MARS-A) Scores

Treatment: Usual ICS/LABA

Inv./ Subj.	Status [1]	Visit/ Study Date/ Study Day	Assessor Code	MARS-A Questions	Score [2]
xxxxxx/ xxxxx	During	Day 0/ DDMMMYYYY/ xx	Subject/Other	I only use it when I need it	x
				Only use it when I feel breathless	x
				I decide to miss out a dose	x
				I try to avoid using it	x
				I forget to take it	x
				I alter the dose	x
				I stop taking it for a while	x
				Reserve if treatment doesn't work	x
				Before doing something	x
				I take less than instructed	x
				MARS-A 10-Score [3]	x.xx
		Week 12/ DDMMMYYYY/ xx	Subject/Other	I only use it when I need it	x
				Only use it when I feel breathless *.....etc*	x

[1] Due to an issue identified with the French translation of the MARS-A, a reminder was sent to centres in France instructing that the questionnaire refers to the patient's preventer inhaler (i.e. their maintenance therapy prior to entering the study, and study medication while on-study. Status = Prior (patient in France who had completed all MARS-A assessments prior to the reminder), During (patient in France who had completed at least one MARS-A assessment prior to the reminder but

also completed at least one MARS-A assessment after the reminder), After (patient in France who had not completed any MARS-A assessments prior to the reminder), Germany (patient in Germany).
[2] Question scores range between 1 (always) and 5 (never).
[3] MARS-A 10-Score is based on the mean score across all ten questions.

Programming note: Repeat on subsequent pages for Treatment = FF/VI.

Example : EFF_L5
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Severe Asthma Exacerbations

Treatment: Usual ICS/LABA

Inv./ Subj.	Date of Onset/ Study day/ Date of Resolution/ Study day	Resolution/ Withdrawn from Study?	Required use of systemic/oral corticosteroids?	Led to hospitalisation?	Required emergency room visit?	Required intubation?
Xxxxxx/ xxxxx	DDMMMYYYY/ xx/ DDMMMYYYY/ xx	Resolved/ N	Y	N	N	N
	DDMMMYYYY/ xx/ DDMMMYYYY/ xx	Resolved/ N	N	N	Y	N
	DDMMMYYYY/ xx/ DDMMMYYYY/ xx	Fatal/ Y	Y	Y	N	Y

Programming note: Repeat on subsequent pages for Treatment = FF/VI.

Example : EFF_L6
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
AQLQ(S) Scores

Treatment: Usual ICS/LABA

Inv./ Subj.	Visit/ Study Date/ Study Day	Symptoms [1]	Activity Limitations [1]	Emotional Function [1]	Environmental Stimuli [1]	AQLQ(S) Total Score [1] / Change from Baseline
xxxxxx/ xxxxx	Day 0/ DDMMMYYYY/ xx	x.x	x.x	x.x	x.x	x.x
	Week 24/ DDMMMYYYY/ xx	x.x	x.x	x.x	x.x	x.x / x.x
...						

[1] Scores range between 1 (lower quality of life) and 7 (higher quality of life) for AQLQ(S) total and domains.

Programming note: Repeat on subsequent pages for Treatment = FF/VI.

Example : EFF_L7
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
EQ-5D-5L Descriptive System Dimension Scores

Treatment: Usual ICS/LABA

Inv./ Subj.	Visit/ Study Date/ Study Day	Assessor Code	Subscale/ Item	Level of Problem	Score [1]
xxxxxx/ xxxxx	Day 0 DDMMMYYYY/ xx	Subject/Other	EQ-5D-5L Utility Score		xx.xx
			Mobility	1	
			Self-Care	1	
			Usual Activities	1	
			Pain/Discomfort	1	
			Anxiety/Depression	1	
			EQ-5D-5L VAS		xx.xx
	Week 12 DDMMMYYYY/ xx	Subject/Other	EQ-5D-5L Utility Score		xx.xx
			Mobility .....etc	1	

[1] Scores range between 0 (worst imaginable health state) and 1 (best imaginable health state) for EQ-5D-5L Utility Score and range between 0 (worst imaginable health state) and 100 (best imaginable health state) for EQ-5D-5L Visual Analogue Scale (VAS).

Example : EFF_L8
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
PASAP-Q Scores

Treatment: Usual ICS/LABA

Inv./ Subj.	Visit/ Study Date/ Study Day	Domain / Question	Response	Score [1]
xxxxxx/ xxxxx	Day 0 DDMMMYYYY/ xx	Performance		xx.x
		Overall feeling of inhaling	x	
		Inhaled dose goes to lungs	x	
		Medication left	x	
		Works reliably	x	
		Ease of inhaling a dose	x	
		Using the inhaler	x	
		Speed medicine comes out	x	
		Convenience		xx.x
		Instructions for use	x	
		Size of inhaler	x	
		Durability of inhaler	x	
		Ease of cleaning inhaler	x	
		Ease of holding during use	x	
		Convenience of carrying	x	
		Total Score		xx.x
		Overall Satisfaction		x
		Willingness to Continue Using Inhaler		xx.x

[1] Performance, Convenience, Total Score, and Willingness to Continue Using Inhaler are expressed on a scale of 0 to 100. Overall Satisfaction is expressed on a scale of 1 to 7.

Programming note: Repeat on subsequent pages for Treatment = FF/VI.

Example : SAFE_L1
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
AE Terms of Special Interest

Special Interest Term	Subgroup	Preferred Term
xxxxx xxxxx xxxxxx	Xxxxxxx	xxxxxxx
		xxxxxxx xxxxxxx
		xxxx
		xxxxxxx xxx
xxxxxxx xxxxxxxxxx	xxxxxxxxxxxxxx [1]	xxxxxxx xxxxxx
		xxxxxxx xxxx xxxxx xxxxx
		xxxx
xxxxxxxxxxx	xxxxxxx [1]	xxxxxxx
		xxxx xxxxxx xxxxxxx
xxxxxx xxxxxxx		xxxxxxxxx
		xxxxx xxxxxx xxxxxxx xxxxxx

[1]: This special interest term was defined using Special MedDRA Queries.
Note: All of the pre-specified preferred terms that were assigned to special interest terms are shown, regardless of whether they actually occurred in the study.

Programming Note: The AE special interest dataset and the AE SMQ dataset will be set together in order to report this table and all the subgroups that come from the AE SMQ dataset will be flagged with a [1].

Example : SAFE_L2
Protocol : HZA116492
Population : Intent-to-Treat

Listing x
Inhaler Device Malfunctions

Treatment	Inv./ Subj.	Inhaler Device	Comment / Reason for Malfunction
Usual ICS/LABA	xxxxxx/ xxxxx	Turbuhaler	XXXXXXXXXXX
Usual ICS/LABA	xxxxxx/ xxxxx	Diskus	XXXXXXXXXXX
FF/VI	xxxxxx/ xxxxx	Ellipta	Powder fell out prior to use Other: XXXXXXXX