

Statistical Analysis Plan Amendment 3

Study ID: 219912

Official Title: A Phase 4, 52-week (Primary Analysis at 24-weeks), Randomized, Stratified, Open-label, Active-controlled, Parallel-group, Effectiveness Study, Comparing FF/UMEC/VI With Non-ellipta Usual Care (ICS/LABA) in Adult Participants With Uncontrolled Asthma

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Statistical Analysis Plan for Real World Research Studies

Sponsor Name: GSK Research & Development Limited
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Protocol Number: 219912

Protocol Title: A Phase 4, 52-Week (primary analysis at 24-weeks), randomized, stratified, open-label, active-controlled, parallel-group, effectiveness study, comparing FF/UMEC/VI with non-ellipta usual care (ICS/LABA) in adult participants with uncontrolled asthma

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Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
0.1	05-Mar-2024	PPD	Initial Release Version
0.2	02-Apr-2024		Updated per sponsor team comments on v0.1
1.0	12-Apr-2024		Final stable version updated per sponsor team comments on v0.2
2.0	28-Aug-2024		eCOA section 8.3.5 and appendix III are added.
3.0	25-Jul-2025		Update per PA#3 Final dated Mar 20, 2025: - Objectives table and text updated to replace budesonide/formoterol with ICS/LABA throughout the document. - Add additional analysis for added additional exploratory objectives to evaluate the effects of FF/UMEC/VI on a composite endpoint (stabilized) compared with ICS/LABA after 24 and 52 weeks of treatment. - Replace “composite endpoint” with “composite endpoint (optimized)”, add composite endpoint (stabilized). - Update statistical hypotheses (section 6) to be aligned with protocol. - Section 4.1 and 4.2, update target population by using FAS – modified 1. - Section 4.3, add description of estimands for supportive analyses, FAS and FAS-modified 2. - Section 7, add additional analysis populations: FAS/SAF - modified 1 to exclude site(s) with falsified participants; FAS/SAF - modified 2 to exclude site(s) with GCP non-compliance/significant data integrity concerns or falsified participants; - Section 7, FAS and SAF population definitions are updated. - Section 8.1.1 statistical methods – update analysis populations for primary efficacy and safety analysis. - Section 8.1.5, Update to define baseline FEV1 as the last acceptable/borderline acceptable pre dose FEV1 obtained at the Randomization Visit (Visit 2). If trough FEV1 is missing at the randomization visit, baseline is defined as the last acceptable/borderline acceptable FEV1 either from the screening visit or from an unscheduled visit between screening and randomization (whichever is latest).

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Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
3.0	07-Aug-2025	PPD	11. Section 8.2.1, the number of subjects will be summarized by Region, Country and Site ID. This summary is based on the "Full Analysis Set" instead of "Enrolled Analysis Set". Region definition is added. 12. Section 8.2.3, remove "height (cm), weight (kg), body mass index (BMI) (kg/m2)" as they are not collected. 13. Section 8.3.2.1, add details of deriving the ACQ-7 score by using FEV1 % predicted values applying the cutoff values, the cut off values are included. 14. Section 8.3.3.7, addition of secondary analysis composite endpoint for 'no treatment'. 15. section 8.3.5.1 add endpoint "Achieving ACT Total Score $\geq$ 20 at Visit Week 52Section 8.3.5 add other exploratory analysis which are not included in PA3 but requested for country specific analysis. 16. Section 9.3 add unplanned analysis from PA3. 17. Section 15.2, If the concomitant medication stop date is completely missing, it is updated to "will not be imputed". 18. Add text mentioning Japan & China references for separate SAP documents 19. Update the cut-off for the ACQ-5 across the text which sponsor stats team identified as incorrect in the protocol, instead of ≤ 1.5 it should be < 1.5.

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I confirm that I have reviewed this document and agree with the content.

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1. Glossary of Abbreviations

Abbreviation	Definition
ACQ-5	Asthma Control Questionnaire-5
ACQ-6	Asthma Control Questionnaire-6
ACQ-7	Asthma Control Questionnaire-7
ACT	Asthma Control Test
AE	Adverse event
ANCOVA	Analysis of covariance
AQLQ	Asthma Quality of Life Questionnaire
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
CI	Confidence interval
CRF/eCRF	Case report form/electronic case report form
CSR	Clinical study report
CTMS	Clinical Trial Management System
CV	Cardiovascular
DBL	database lock
DBR	database release (DBR)
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
FAS	Full analysis set
FEV ₁	Forced expiratory volume in 1 second
FF	Fluticasone furoate
FP	Fluticasone propionate
FVC	Forced vital capacity
ICF	Informed consent form
ICH	International Council on Harmonisation
ICS	Inhaled corticosteroid
IVCS	Intravenous corticosteroid
IVRS/IWRS	Interactive voice/web response system
LABA	Long-acting beta-2 agonist
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
OCS	Oral corticosteroid
PD	Protocol deviation
PT	Preferred Term
S&P	Statistics & Programming
SABA	Short-acting beta-2 agonist
SAE	Serious adverse event
SAMA	Short-acting muscarinic antagonist
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SoA	Schedule of activities
SOC	System Organ Class

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Abbreviation	Definition
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TFL	Table, Figure, and Listing
UMEC	Umeclidinium bromide
VI	Vilanterol
WOCBP	Woman of childbearing potential
WPAI:Asthma	Work Productivity and Activity Impairment: Asthma

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2. Introduction

This statistical analysis plan (SAP) is to describe the planned analyses and data presentation to be included in global Clinical Study Report (CSR) for GSK's protocol 219912 "A Phase 4, 52-Week (primary analysis at 24-weeks), randomized, stratified, open-label, active-controlled, parallel-group, effectiveness study, comparing FF/UMEC/VI with non-ellipta usual care (ICS/LABA) in adult participants with uncontrolled asthma". The SAP outlines the types of analyses that will address the study objectives and explains in detail how the data will be handled and analyzed for the planned Week 24 primary analysis, and the final analyses at Week 52 for overall study population. Any post-hoc, or unplanned, analyses performed not identified in this SAP will be clearly identified in the respective CSR.

According to country-specific requirement for Japan only (protocol amendment version 3.0, dated 20 March 2025), to enable the assessment of consistency of effect between study participants in Japan and the overall study population, following 24 weeks of treatment, the Primary and Key Secondary objectives, endpoints and estimands will be summarized and analyzed for the Japan population. In addition, following 52 weeks of treatment, the composite endpoints (stabilized and optimized) will be summarized and analyzed for the Japan population. Further details will be provided in the Japan supplementary SAP.

According to country-specific amendment for China (protocol amendment version 2.0, dated 17 December 2024), the country-level enrollment for mainland China will start separately from overall study population. The objectives, endpoints and estimands specified for China population are consistent with those specified for the overall study population. The primary and final analyses for China populations will be completed at different times due to recruitment in China starting later. General statistical consideration, study endpoint derivation details, data handling, reporting conventions, specifications for tables, listings and figures, unless specially described will follow the analysis descriptions for the global overall cohort. The SAP for China population is drafted in separate documents.

The global CSR will not include data from the China population and the Japan-specific outputs. Reporting of the China population and Japan-specific outputs will be provided separately from the global CSR.

Specifications for tables, listings and figures are contained in a separate document.

3. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effects of fluticasone furoate/umeclidinium bromide/vilanterol trifenate (FF/UMEC/VI) on lung function compared with inhaled corticosteroids/long-acting beta-2 agonists (ICS/LABA) after 24 weeks of treatment	○ Change from baseline in trough forced expiratory volume in 1 second (FEV ₁) at Week 24
Key Secondary	
To evaluate the effects of FF/UMEC/VI on asthma control compared with ICS/LABA after 24 weeks of treatment	○ Achieving ≥ 0.5 point improvement (decrease) from baseline for the ACQ-7 at Week 24

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Other Secondary	
To evaluate the effects of FF/UMEC/VI on a composite endpoint (optimized) compared with ICS/LABA after 52 weeks of treatment	○ Composite endpoint at Week 52. Occurrence of participants achieving the following criteria: ▪ Change from baseline in trough FEV₁ ≥ 100 mL at Week 52 ▪ Controlled asthma based on ACQ-5 total score <1.5 at Week 52 ▪ No severe asthma exacerbations over 52 weeks ▪ OCS-free over 52 weeks
To evaluate the effects of FF/UMEC/VI on lung function compared with inhaled corticosteroids/long-acting beta-2 agonists (ICS/LABA) after 24 and 52 weeks of treatment	○ Change from baseline in trough forced expiratory volume in 1 second (FEV₁) at Week 52 ○ Change from baseline in trough FEV₁ ≥ 100 mL at Week 24 and Week 52 ○ Change from baseline in trough FEV₁ ≥ 0 mL at Week 24 and Week 52
To evaluate the effects of FF/UMEC/VI on asthma control compared with ICS/LABA after 24 and 52 weeks of treatment	○ Achieving ≥0.5 point improvement (decrease) from baseline for the ACQ-7 at Week 52 ○ Achieving ≥0.5 point improvement (decrease) from baseline for the ACQ-6 at Week 24 and Week 52 ○ Achieving ≥0.5 point improvement (decrease) from baseline for the ACQ-5 at Week 24 and Week 52 ○ Change from baseline in the ACQ-7 total score (and derivatives: ACQ-6 and ACQ-5) at Week 24 and Week 52 ○ Change from baseline in the Asthma Control Test (ACT) score at Week 24 and Week 52
To evaluate the effects of FF/UMEC/VI on a composite endpoint (optimized) compared with ICS/LABA after 52 weeks of treatment for participants on ICS/LABA prior to randomization.	○ Composite endpoint at Week 52. Occurrence of participants achieving the following criteria: ▪ Change from baseline in trough FEV₁ ≥ 100 mL at Week 52 ▪ Controlled asthma based on ACQ-5 total score <1.5 at Week 52 ▪ No severe asthma exacerbations over 52 weeks ▪ OCS-free over 52 weeks
To evaluate the effects of FF/UMEC/VI on a composite endpoint (optimized) compared	○ Composite endpoint at Week 52. Occurrence of

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with ICS/LABA after 52 weeks of treatment for participants on no treatment prior to randomization.	participants achieving the following criteria: ▪ Change from baseline in trough FEV₁ ≥ 100 mL at Week 52 ▪ Controlled asthma based on ACQ-5 total score <1.5 at Week 52 ▪ No severe asthma exacerbations over 52 weeks ▪ OCS-free over 52 weeks
To evaluate the effects of FF/UMEC/VI on health-related quality of life compared with ICS/LABA after 24 and 52 weeks of treatment	○ Change from baseline in the Asthma Quality of Life Questionnaire (AQLQ-12) total and domain scores at Week 24 and Week 52
To evaluate the effects of FF/UMEC/VI on absenteeism, presenteeism, work productivity loss, activity impairment compared with ICS/LABA after 24 and 52 weeks of treatment	○ Change from baseline in the four domains of the asthma-specific adaptation of the Work Productivity and Activity Impairment Questionnaire (WPAI:Asthma) at Week 24 and Week 52
To evaluate the effects of FF/UMEC/VI on lung function compared with ICS/LABA after 24 weeks of treatment for participants on ICS/LABA prior to randomization.	○ Change from baseline in trough forced expiratory volume in 1 second (FEV₁) at Week 24
To evaluate the effects of FF/UMEC/VI on asthma control compared with ICS/LABA after 24 and 52 weeks of treatment for participants on ICS/LABA prior to randomization.	○ Achieving ≥0.5 points improvement (decrease) from baseline for ACQ-7 at Week 24 and Week 52 ○ Change from baseline in the ACQ-7 total score at Week 24 and Week 52
To evaluate the effects of FF/UMEC/VI on lung function compared with ICS/LABA after 24 weeks of treatment for participants on no treatment prior to randomization.	○ Change from baseline in trough forced expiratory volume in 1 second (FEV₁) at Week 24
To evaluate the effects of FF/UMEC/VI on asthma control compared with ICS/LABA after 24 and 52 weeks of treatment for participants on no treatment prior to randomization.	○ Achieving ≥0.5 points improvement (decrease) from baseline for ACQ-7 at Week 24 and Week 52 ○ Change from baseline in the ACQ-7 total score at Week 24 and Week 52
Exploratory	
To evaluate the effectiveness of FF/UMEC/VI compared with ICS/LABA over 24 and 52 weeks of treatment	○ Usage of short-acting beta-agonists (SABA) over Week 24 and 52 weeks of treatment ○ Usage of oral corticosteroids (OCS) over 24 and 52 weeks of treatment ○ Incidence of severe exacerbations over 24 and

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	52 weeks of treatment
To evaluate the effects of FF/UMEC/VI on a composite endpoint (optimized) compared with ICS/LABA after 24 weeks of treatment	○ Composite endpoint at Week 24. Occurrence of participants achieving the following criteria: ▪ Change from baseline in trough FEV₁ ≥ 100 mL at Week 24 ▪ Controlled asthma based on ACQ-5 total score < 1.5 at Week 24 ▪ No severe asthma exacerbations over 24 weeks ▪ OCS-free over 24 weeks
To evaluate the effects of FF/UMEC/VI on a composite endpoint (stabilized) compared with ICS/LABA after 24 weeks of treatment	○ Composite endpoint at Week 24. Occurrence of participants achieving the following criteria: ▪ Change from baseline in trough FEV₁ ≥ 0 mL at Week 24 ▪ Controlled asthma based on ACQ-5 total score <1.5 at Week 24 ▪ No severe asthma exacerbations over 24 weeks ▪ OCS-free over 24 weeks
To evaluate the effects of FF/UMEC/VI on a composite endpoint (stabilized) compared with ICS/LABA after 52 weeks of treatment	○ Composite endpoint at Week 52. Occurrence of participants achieving the following criteria: ▪ Change from baseline in trough FEV₁ ≥ 0 mL at Week 52 ▪ Controlled asthma based on ACQ-5 total score <1.5 at Week 52 ▪ No severe asthma exacerbations over 52 weeks ▪ OCS-free over 52 weeks
Safety	
To evaluate the safety and tolerability of FF/UMEC/VI compared with ICS/LABA over 24 and 52 weeks of treatment	• Incidence and type of study intervention-related adverse events (AEs) and all serious adverse events (SAEs)

4. Estimands

4.1 Primary estimand

The primary clinical question of interest is: what is the treatment effect on change from baseline in trough FEV₁ after 24 weeks of treatment with FF/UMEC/VI compared to non-Ellipta ICS/LABA usual care in participants aged 18 years or older with uncontrolled asthma? This question is to be addressed regardless of study intervention discontinuation unrelated to an unexpected worldwide disruptive event, regardless of the use of prohibited medication, regardless of any ICS dose escalation and in the absence of study intervention discontinuation due to an unexpected worldwide disruptive event.

The main estimand of the primary endpoint is defined by the following attributes:

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- **Target Population:** all randomized participants who are aged 18 years or older with uncontrolled asthma as defined by the inclusion/exclusion criteria and who received at least 1 prescription of study intervention excluding site(s) with falsified participants (Full Analysis Set – Modified 1).
- **Treatment condition:** FF/UMEC/VI versus ICS/LABA
- **Endpoint:** Change from baseline in trough FEV₁ at Week 24.
- **Population-level summary:** Difference in mean changes from baseline in trough FEV₁ after 24 weeks of treatment between FF/UMEC/VI and non-Ellipta ICS/LABA usual care.
- **Intercurrent events (IE):**
 - Study intervention discontinuation:
 - Due to an indirect impact of an unexpected worldwide disruptive event, the analysis will be handled with a hypothetical strategy (i.e., had the intercurrent event not occurred). In this situation, data collected after study intervention discontinuation (i.e., post-treatment) will not be included in the statistical analysis and will be treated as missing data.
 - Due to any other reason (e.g. AE, death, lack of efficacy etc.), then the analysis will be handled with a treatment policy strategy and all observed data will be included in the analysis regardless of the intercurrent events (i.e., on-treatment and post-treatment data at the scheduled time-point of the estimation will be included).
 - Use of prohibited medication or rescue medication: analysis will be handled by treatment policy strategy. All observed data will be included in the analysis regardless of the intercurrent events.
 - Escalation of ICS dose within randomized treatment group will be handled by treatment policy strategy (all data prior to ICS dose escalation and post-ICS dose escalation will be included).

Rationale for estimand:

The primary clinical question of interest lies in the treatment effect in the real-world application of the approved treatment, in the environment with approved competitors, irrespective of study intervention discontinuation unrelated to an unexpected worldwide disruptive event or use of a prohibited medication, as well as escalation of ICS dose, to reflect how participants may be treated in clinical practice, hence a treatment policy strategy is appropriate.

This study is designed to evaluate the benefit of FF/UMEC/VI compared to usual care and it is important that discontinuation of study intervention due to an indirect consequence of an unexpected worldwide disruptive event does not confound this. Therefore, to evaluate the benefit of FF/UMEC/VI compared to usual care in absence of this, a hypothetical strategy will be used.

A supplemental estimand will be defined where study intervention discontinuation will be handled using a while on treatment strategy, to evaluate the treatment effect prior to the occurrence of study intervention discontinuation. The intercurrent event of ICS dose escalation will be handled using treatment policy strategy.

A further supplemental estimand will be defined where all intercurrent events will be handled using a while on treatment strategy, except for the intercurrent event of escalation of ICS dose, which will be handled using a hypothetical strategy to estimate the treatment effect in the absence of ICS dose escalation (i.e. had the intercurrent event not occurred).

4.2 Secondary estimand(s)

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The key secondary clinical question of interest is: what is the treatment effect on achieving ≥ 0.5 points improvement (decrease) from baseline for the Asthma Control Questionnaire-7 (ACQ-7) at Week 24 with FF/UMEC/VI compared to non-Ellipta ICS/LABA usual care in participants aged 18 years or older with uncontrolled asthma? This question is to be addressed regardless of study intervention discontinuation unrelated to an unexpected worldwide disruptive event, regardless of the use of prohibited medication, regardless of any ICS dose escalation and in the absence of study intervention discontinuation due to an unexpected worldwide disruptive event.

The main estimand of the key secondary endpoint is defined by the following attributes:

- **Target Population:** all randomized asthma participants aged 18 years or older with uncontrolled asthma as defined by the inclusion/exclusion criteria and who received at least 1 prescription of study intervention excluding site(s) with falsified participants (Full Analysis Set – Modified 1).
- **Endpoint:** binary variable indicating the treatment response at Week 24 visit, whereby a responder is defined as participant who achieves ≥ 0.5 points improvement (decrease) from baseline for ACQ-7 at Week 24.
- **Treatment Condition:** FF/UMEC/VI versus ICS/LABA.
- **Population-level Summary:** Odds ratio on the percent of participants meeting the responder threshold at Week 24 visit of FF/UMEC/VI versus non-Ellipta ICS/LABA usual care.
- **Intercurrent Events (IE):**
 - Study intervention discontinuation:
 - Due to an indirect impact of an unexpected worldwide disruptive event, the analysis will be handled with a hypothetical strategy (i.e., had the intercurrent event not occurred). In this situation, data collected after study intervention discontinuation (i.e., post-treatment) will not be included in the statistical analysis and will be treated as missing data.
 - Due to any other reason (e.g. AE, death, lack of efficacy etc.), then the analysis will be handled by treatment policy strategy. All observed data will be included in the analysis regardless of the intercurrent event.
 - Use of prohibited medication or rescue medication: analysis will be handled by treatment policy strategy. All observed data will be included in the analysis regardless of the intercurrent events.
 - Escalation of ICS dose within randomized treatment group will be handled by treatment policy strategy (all data prior to dose escalation and post-ICS dose escalation will be included).

Rationale for estimand

Similar to the primary endpoint, the key secondary endpoint clinical question of interest lies in the treatment effect in the real-world application of the approved treatment, in the environment with approved competitors, irrespective of study intervention discontinuation unrelated to an unexpected worldwide disruptive event or use of a prohibited medication or escalation of ICS dose, to reflect how participants may be treated in clinical practice, hence a treatment policy strategy is appropriate.

This study is designed to evaluate the benefit of FF/UMEC/VI compared to usual care and it is important that discontinuation of study intervention due to an indirect consequence of an unexpected worldwide disruptive event does not confound this. Therefore, to evaluate the benefit of FF/UMEC/VI compared to usual care in absence of this, a hypothetical strategy will be used.

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Similar to the primary endpoint, for the key secondary endpoint, a supplemental estimand will be defined where the intercurrent event of study intervention discontinuation due to any reasons will be handled using a while on treatment strategy, to evaluate the treatment effect prior to the occurrence of study intervention discontinuation. The intercurrent event of ICS dose escalation will be handled using treatment policy strategy.

A further supplemental estimand will be defined where all intercurrent events will be handled using a while on treatment strategy, with the exception of the intercurrent event of escalation of ICS dose, which will be handled using a hypothetical strategy to estimate the treatment effect in the absence of ICS dose escalation (i.e. had the intercurrent event not occurred).

4.3 Additional estimand(s)

For the secondary endpoints of change from baseline in trough FEV₁ at Week 24 and achieving ≥ 0.5 points improvement (decrease) from baseline for the ACQ-7 at Week 24, subset on the participants on ICS/LABA prior to randomization the estimands will follow the same approach as the primary and key secondary estimands respectively, with the exception of the treatment attribute (which will be subset on participants on ICS/LABA prior to randomization). The estimands will use the same strategies for the intercurrent events. A similar approach will be taken for the no treatment prior to randomization subset.

For the other secondary endpoints and for the exploratory endpoints, the estimands will follow the same approach as the main estimand of the primary endpoint for continuous endpoints and the main approach of the key secondary estimand for binary endpoints (i.e., occurrence of participants meeting a responder threshold). The only difference is that the endpoint attribute will align with the endpoint of interest. The estimands will use the same strategies for intercurrent events.

Two supplemental estimands have been defined for the primary endpoint and key secondary endpoint only. However, if the supplementary estimand results are not consistent with the primary estimand and key secondary estimands respectively, further estimands for the other secondary endpoints and other endpoints may be explored.

Supportive sensitivity analyses will be performed for the primary endpoint and key secondary endpoint by using two supportive efficacy populations, full analysis set (FAS) and modified full analysis set 2 (FAS – Modified 2), which are defined in [section 7](#). The estimands for supportive analyses are defined by following the same attributes as the main estimand for the primary endpoint ([section 4.1](#)) and the main estimand for the key secondary estimand ([section 4.2](#)), respectively. The only difference is the target population of interest.

5. Study Design

Overview of Study Design and Key Features	
The diagram illustrates the study design timeline. It begins with a screening phase (S) at V1 (d0), followed by randomization (R) at V2 (d1). Participants are then assigned to one of two treatment groups: FF/UMEC/VI or ICS/LABA (non-Ellipta usual care). The treatment period lasts for 52 weeks, with a follow-up period of 7 days. Key visits are marked at V1 (d0), V2 (d1), V3 (w24), V4 (w52), and V5 (w53).	
Abbreviations: d=day; FF = fluticasone furoate; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; R = randomization; S = screening; UMEC = umeclidinium bromide; V = visit; VI = vilanterol trifenate; w = weeks.	
Design Features	This is a Phase 4, 52-week, randomized, stratified, open-label, active-controlled, parallel-group, global multicenter study, evaluating the effectiveness and safety of initiating once-daily FF/UMEC/VI compared to continuing or initiating usual care (ICS/LABA, administered via a non-Ellipta inhaler), in adult participants with uncontrolled asthma. This Phase 4 clinical trial aims to provide important information in a real-world setting on whether FF/UMEC/VI is superior to usual care (ICS/LABA) with regards to improvement in lung function and asthma control in adult participants with uncontrolled asthma.
Dosing and Treatment Assignment	FF/UMEC/VI (once a day) or ICS/LABA (in-line with dosing regimen in appropriate regulatory label) are administered, participants are randomized in a 1:1 ratio to each group (FF/UMEC/VI 100/62.5/25 mcg versus ICS/LABA). A subset of participants who are randomized within each group may also be prescribed FF/UMEC/VI 200/62.5/25 mcg or high-dose ICS/LABA (non-Ellipta). Inclusion in the high-dose ICS-containing therapy group will be at the discretion of the investigator and must comply with local treatment guidelines. The randomization will be stratified by pre-study asthma maintenance therapy (untreated, ICS alone, ICS/LABA) and pre-study ICS dose (low, high). ○ Untreated is defined as no exposure to ICS-containing therapy within the 3 months prior to randomization. For example, the use of budesonide/formoterol reliever therapy and/or ICS/SABA combination inhalers does not qualify as “untreated.” ○ Treated with daily maintenance ICS or ICS/LABA for at least 3 months prior to randomization with no changes to maintenance asthma medications during the 3 months immediately prior to randomization. Strata are:

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	• Untreated • ICS alone – Low • ICS alone – High • ICS/LABA – Low • ICS/LABA – High Note: throughout the text, term “study intervention” is used to denote study treatment of FF/UMEC/VI and ICS/LABA which are intended to be prescribed to a participant.
Time & Events	See Appendix 1: Schedule of Activities (SoA) The study includes 4 in-clinic study visits: a Screening Visit, a Randomization Visit, a Week 24 Visit, and a Week 52 Visit. The Safety Follow-up Visit is conducted via telephone.
Study Period	The total duration of the study is approximately 53 weeks, including a 52-week treatment period, and a 1-week safety follow-up.
End of Study	A participant is considered to have completed the study if the participant has completed all periods of the study including the Week 52 Visit or the Early Withdrawal Visit and the safety follow-up visit. The end of the study is defined as the date of the last visit of the last participant in the study.
Interim Analysis	No interim analyses are planned for this study.
Primary Analysis	The primary statistical analysis will be completed once all participants complete 24 weeks of treatment.
	The final analyses will be conducted after all participants complete the 52 week and safety follow-up visits (unless prematurely discontinued from the study). The final database release (DBR) and database lock (DBL) will be declared by Data Management.
Data Sources	Data will be collected by entry into an electronic Case Report Form (eCRF). In addition, external data transferred from third-party vendor(s) will be integrated into clinical database, e.g. IVRS treatment assignment, spirometry assessments, patient reported outcome questionnaires.

6. Statistical Hypotheses

The primary objective of this study is to evaluate the effectiveness of FF/UMEC/VI on lung function compared with non-Ellipta ICS/LABA in participants with uncontrolled asthma and the key secondary objective is to evaluate the effects of FF/UMEC/VI on asthma control compared with ICS/LABA.

The primary effectiveness endpoint is the change from baseline in trough FEV₁ at the end of the 24-week treatment period and the key secondary effectiveness endpoint is the proportion of participants with an improvement in ACQ-7 score of ≥ 0.5 at the end of the 24-week treatment period. The primary treatment comparison is FF/UMEC/VI versus non-Ellipta ICS/LABA for all participants with uncontrolled asthma.

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Secondary treatment comparisons also include the comparison between FF/UMEC/VI versus ICS/LABA in the subsets of participants on ICS/LABA prior to randomization as well as for participants on no treatment prior to randomization (defined as no exposure to ICS-containing therapy in the 3 months prior to randomization) for the change from baseline in trough FEV1 at Week 24. At the time of protocol amendment 3 it is anticipated that approximately 60% of participants will be taking ICS/LABA prior to randomization and approximately 35% of participants will be taking no treatment prior to randomization.

Significance levels for the confirmatory testing will be defined following the multiplicity strategy described in [Section 6.1](#).

For the test on each continuous effectiveness endpoint (including the primary and other secondary endpoints) the null hypothesis (H0) is that there is no difference between treatment groups:

$$H_0: T_1 - T_2 = 0$$

The alternative hypothesis (H1) is that there is a difference between treatment groups:

$$H_1: T_1 - T_2 \neq 0$$

where T1 and T2 represent the mean change from baseline for FF/UMEC/VI and non-Ellipta ICS/LABA respectively.

For the test on each binary effectiveness endpoint (including the key secondary effectiveness endpoint [and the derivatives of ACQ-7] and the 4-component composite endpoint at Week 52), the null hypothesis (H0) is that there is no difference between treatment groups:

$$H_0: T_1 = T_2$$

The alternative hypothesis (H1) is that there is a difference between treatment groups:

$$H_1: T_1 \neq T_2$$

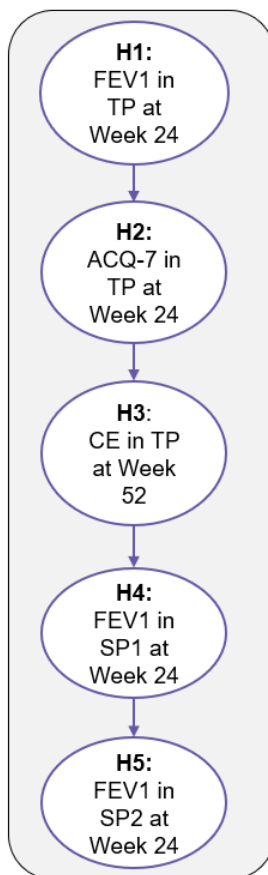
where T1 and T2 represent the proportion of participants who respond at Week 24 compared to baseline for FF/UMEC/VI and non-Ellipta ICS/LABA respectively.

6.1 Multiplicity adjustment

The primary, key secondary and other secondary endpoints as detailed [section 3](#) will be tested using a pre-specified testing procedure, in order to control the family-wise type I error rate at $\alpha=0.05$ within the multiple testing approach.

A step-down closed testing approach will be applied for the primary endpoint, key secondary endpoint, other secondary endpoint (composite endpoint at Week 52) and prior therapy subsets for the primary endpoint (participants on ICS/LABA prior to randomization and participants on no treatment prior to randomization).

Figure 1 Step-down closed testing approach to control for type I error rate



Note: TP: Total population, SP1: Sub-population 1 (participants on ICS/LABA prior to randomization), SP2: Sub-population 2 (participants on no treatment prior to randomization), CE: composite endpoint.

The testing strategy depicted in [Figure 1](#) will control for inflation of the overall 2-sided type I error rate of 5% for the testing of the following hypotheses in the below defined order:

- 1) H1: the primary endpoint (change from baseline in trough FEV₁ at Week 24) in total population.
- 2) H2: key secondary endpoint (achieving ≥ 0.5 point improvement (decrease) from baseline for the ACQ-7 at Week 24) in total population.
- 3) H3: Composite endpoint (optimized) at Week 52 in total population. (Occurrence of participants achieving change from baseline in trough FEV₁ ≥ 100 mL, ACQ-5 total score < 1.5 , no severe asthma exacerbations, OCS-free).
- 4) H4: change from baseline in trough FEV₁ at Week 24 in the population subset on the participants on ICS/LABA prior to randomization.
- 5) H5: change from baseline in trough FEV₁ at Week 24 in the population subset on the participants on no treatment prior to randomization.

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H1 and H2 will be part of the primary analysis at Week 24 and H3, H4 and H5 will be part of the final analysis at Week 52.

For the remaining effectiveness endpoints not mentioned above in the step-down closed testing approach, treatment comparisons will be made without adjusting for multiplicity.

Primary, key secondary and other secondary endpoints will be analyzed as detailed in [Section 8.3](#).

7. Analysis Sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened Set	All participants who were screened for eligibility.	Study population
Enrolled Set	All participants who entered the study (who were randomized or received at least 1 prescription of study intervention or underwent a post screening study procedure). Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the Enrolled Analysis Set as they did not enter the study.	Study population
Randomized Set	All participants who were randomly assigned to receive a prescription for study intervention in the study. The screened, enrolled, and randomized populations are nested, i.e., the enrolled population is a subset of the screened, the randomized population is a subset of the enrolled population.	Study population
Full Analysis Set (FAS)	All randomized participants who received at least 1 prescription of study intervention. Data will be reported according to the randomized study intervention.	Supportive analysis for primary and key secondary endpoints
Full Analysis Set – Modified 1 (FAS-Modified 1)	All randomized participants who received at least 1 prescription of study intervention excluding site(s) with falsified participants. Data will be reported according to the randomized study intervention.	Effectiveness (Primary and key secondary endpoint analysis)

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Full Analysis Set – Modified 2 (FAS-Modified 2)	All randomized participants who received at least 1 prescription of study intervention excluding site(s) with GCP non-compliance/significant data integrity concerns or falsified participants. Data will be reported according to the randomized study intervention.	Supportive analysis for primary and key secondary endpoints
Safety Analysis Set (SAF)	All randomized participants who received at least 1 prescription of study intervention. Data will be reported according to the actual ^a study intervention prescribed.	Supportive safety population
Safety Analysis Set – Modified 1 (SAF-Modified 1)	All randomized participants who received at least 1 prescription of study intervention excluding site(s) with falsified participants. Data will be reported according to the actual study intervention prescribed.	Primary safety population
Safety Analysis Set – Modified 2 (SAF-Modified 2)	All randomized participants who received at least 1 prescription of study intervention excluding site(s) with GCP non-compliance/significant data integrity concerns or falsified participants. Data will be reported according to the actual study intervention prescribed.	Supportive safety population

^a For participants who received the correct treatment throughout the study, the actual treatment will be the same as the planned treatment. For participants who received incorrect treatment, the actual treatment will be derived as follows:

- If the duration of exposure of an incorrect treatment since randomization is less than the duration of exposure of the planned treatment, then the actual treatment is assigned as planned treatment.
- If the duration of exposure of an incorrect treatment since randomization is greater than the duration of exposure of the planned treatment, then the actual treatment is assigned as the incorrect treatment.
- If the duration of exposure of an incorrect treatment and planned treatment are the same since randomization, the actual treatment is assigned as the treatment with the higher dose.

8. Statistical Methodology

8.1 Statistical and Analytical Issues

8.1.1 Statistical Methods

The FAS-Modified 1 population will be used for primary effectiveness analyses. The FAS and FAS–Modified 2 populations will be used for supportive effectiveness analyses. The SAF-Modified 1 population will be used for primary safety analyses. The SAF and SAF–Modified 2 populations will be used for supportive safety analyses.

Randomization is stratified by pre-study asthma maintenance therapy (untreated, ICS alone, ICS/LABA) and pre-study ICS dose (high, low) (see [section 5](#) study design). In the case of wrong stratification assigned at the time of randomization, the analyses will be performed based on the actual stratum per data collected in the eCRF.

All data for Randomized Set participants will be included in the data listings unless otherwise specified.

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Disposition will be presented for the primary efficacy population (**FAS-Modified 1**). Demographics summaries will be provided for **FAS**, **FAS-Modified 1** and primary safety population (**SAF-modified 1**). Baseline characteristics summaries will be performed for **FAS-Modified 1** population. All effectiveness summaries and analyses will be performed using the randomized study intervention. All safety analyses will be performed using actual study intervention prescribed. Participants who are randomized but not treated will be listed within the treatment group they are randomized to and will be flagged respectively. Listings will be sorted by treatment group, participant ID number and by visit.

In general, summary tables will include participants in the population set referenced in the title of the tables and will be provided by treatment group and scheduled visit, if applicable.

All study-collected data will be summarized by treatment group using descriptive statistics, graphs, and data listings. Continuous data will be summarized in terms of the number of participants (n), mean, SD, median, minimum (min) and maximum (max), unless otherwise stated, e.g., additional lower and upper quartiles (Q1 and Q3). Categorical data will be summarized in terms of the number of participants providing data at the relevant time point (n), number of participants with missing data, frequency counts and percentages.

In cases where an ANCOVA or a Mixed Model Repeated Measures (MMRM) analysis is performed, key results (LS means, LS means differences), corresponding standard errors (SE), 95% confidence intervals (CI) and p-values will be integrated into the summary table.

For the ordinal logistic regression models parameter estimates, corresponding SE, p-values, the odds ratios and corresponding 95% CIs will be integrated into the summary tables.

Confirmatory statistical comparisons will be performed for the primary and secondary effectiveness endpoints to test whether FF/UMEC/VI demonstrates an improvement in lung function and asthma control versus non-Ellipta ICS/LABA. If the statistical testing of one hypothesis in the hierarchical testing approach does not lead to a significant result, the p-value of this estimand and of all following estimands (in the hierarchical order) will be interpreted descriptively in an exploratory way. Significance levels for the confirmatory testing will be defined following the multiplicity strategy described in [Section 6.1](#).

Assumptions of the statistical tests used will be investigated graphically and will be displayed in the original statistical output for the primary efficacy variable. For data that is not normally distributed, sensitivity analysis might be explored.

All safety analyses will be performed in a descriptive manner. Adverse events and medical history will be coded according to Medical Dictionary for Regulatory Activities (MedDRA® Version 28.0 or later). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (March 2025 version or later).

Tabulations will be produced for appropriate demographic, baseline, safety, and effectiveness endpoint. In the tables, treatment group will be presented as “FF/UMEC/VI”, “ICS/LABA”, and “Total”.

By-subject data listings will be produced for data collected through the study. All data listings that contain an evaluation date will contain a relative study day (Study Day).

Statistical analyses will be carried out using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). Any deviations from the planned analysis as described in the SAP will be justified and recorded in the CSR.

8.1.2 Treatment Assignment and Blinding

Once eligibility and consent are confirmed, randomization will occur using the centralized, interactive web-based response system (IVRS/IWRS). Participants will be randomly assigned to FF/UMEC/VI or ICS/LABA in a 1:1 allocation ratio using a randomly permuted block randomization design, stratified by pre-study

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asthma maintenance therapy (untreated, ICS alone, ICS/LABA) and pre-study ICS dose (low, high) (refer to [Section 5](#) study design).

This is an open-label trial, however, to comply with ICH E9 Guideline for Good Clinical Practice and GSK standard operating procedure (SOP) which recommends the blinded review of planned analyses, and to minimize the risk of potential bias into primary analysis and maintain study integrity, blinding controls have been implemented on treatment arm. Statistics & Programming (S&P) teams from both Syneos Health and Sponsor remain blinded to study investigator prescribing of study intervention during the study until the S&P unblinding takes place at Week 24 and at Week 52 primary analyses, respectively. The other function teams including site personnel, coordinating center staff, clinical and data management remain unblinded and know whether the participant is receiving FF/UMEC/VI or ICS/LABA during the entire length of the study.

The unblinded clinical programmers/SDTM level programmers will process masking the treatment group and sensitive data in restricted area before supplying the data to S&P team. Therefore Syneos Health/GSK S&P team will only receive blinded/masked data for analysis before week 24 and week 52 primary analysis database release.

Planned and unplanned unblinding scenarios will be managed as per Syneos Health Work Instruction (WI 3101.W05) and detailed blinding plan document. The involved parties will ensure every effort is made to limit the number of blinded individuals becoming unblinded to treatment assignment in order to protect integrity and usability of the clinical data.

8.1.3 Handling of Dropouts and Missing Data

8.1.3.1 Safety

Analyses of safety endpoints will be based on available data, in addition, partial or missing data will be imputed by a “worst case approach”, for example, assume an AE is TEAE if AE onset / end dates are missing or inconclusively incomplete.

Similarly, if the start and/or stop date of a medication is missing or incomplete, it will be assumed that the medication is concomitant to study intervention, unless any available date information indicates otherwise.

Partial incomplete dates or totally missing dates will be imputed according to the most conservative approach. Missing day will be imputed as the first day of the month for all start dates and as the last day of the month for all stop dates. Missing month will be imputed as January for all starting dates and as December for all ending dates. Exceptions are given where the partial dates and the start and stop dates of the study for a participant confirm otherwise. For AEs, start or end dates which are completely missing (i.e. no year specified or captured as a date string of 'UNUNK0000') will remain missing, with no imputation applied. For concomitant medications, missing or partial dates for any concomitant medications recorded in the eCRF will be imputed with the widest possible dates (i.e. earliest possible start date and latest possible end date). For asthma diagnosis date, if date is completely missing (i.e. no year specified or captured as a date string of 'UNUNK0000') it will remain missing, with no imputation applied. Consequently, any calculation using this date will also be missing.

How partial dates will be handled are detailed in [Appendix 15.2](#). Partial dates will be displayed as captured in subject listing displays.

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8.1.3.2 Efficacy

Data collected on- or post-study intervention discontinuation will be included in the primary effectiveness analysis and no imputation of missing data are planned. Missing data will be assumed to be missing at random (MAR) by applying MMRM approach.

Missing items of the Asthma Control Questionnaires (ACQ) will be imputed. Imputation will only be performed if only one item is missing, e.g. if a participant does not complete 1 of the 5 questions of ACQ-5 at a visit, then the ACQ-5 score will be the mean of the responses to the remaining 4 questions at that visit. In case of two or more missing items, the ACQ score will be defined as missing.

Missing items of the Asthma Quality of Life Questionnaire with standardized activities (AQLQ +12) will be imputed. In case of one missing item the subscale will be calculated based on the available items. In case of two or more missing items, the respective AQLQ +12 subscale will be defined as missing.

All imputed values will be flagged in the subject data listings.

8.1.4 Determination of Sample Size

Approximately 1420 participants will be screened to achieve 1136 randomly assigned to study intervention (568 participants per arm). The sample size has been calculated to provide sufficient power for both the primary endpoint and key secondary endpoint at Week 24.

This is a superiority study to demonstrate the benefit of FF/UMEC/VI compared to usual care (ICS/LABA). The primary effectiveness analysis for the primary endpoint of change from baseline in trough FEV₁ at Week 24 in the FAS-Modified 1, will use a MMRM analysis, including all trough FEV₁ recorded post-randomization (i.e., on-treatment and post-treatment). The sample size is powered on the key secondary endpoint of achieving ≥ 0.5 points improvement (decrease) from baseline for ACQ-7 at Week 24, which will be analysed using a generalized linear model (logistic regression), including all data up to Week 24. This sample size also provides sufficient power for the primary endpoint of change from baseline in trough FEV₁ at Week 24.

There is no planned sample size re-estimation for this study.

8.1.5 Baseline Definition and Study Day

For endpoints measured at discrete timepoints, the baseline value is defined as the last pre-dose value obtained at the Randomization Visit (Visit 2), unless otherwise stated. If a value for Randomization Visit 2 is missing, then the baseline value will be taken from Visit 1 (screening).

Specifically, the baseline value of trough FEV₁ will be defined as the last acceptable/borderline acceptable pre-dose FEV₁ obtained at the Randomization Visit (Visit 2). If trough FEV₁ is missing at Randomization Visit, baseline is defined as the last acceptable/borderline acceptable FEV₁ either from the screening visit or from an unscheduled visit between screening and randomization (whichever is latest). This same approach applies to the other pulmonary function tests (PFTs).

For all other endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to the prescription date of study intervention and used as baseline.

Unless otherwise stated, if there is no pre-dose assessment, baseline data will be missing and no derivation will be performed.

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Study day for all assessments (efficacy, safety etc.) on or after start date of study intervention will be calculated as: Study day = Date of the assessment – Prescription date of study intervention + 1.

The prescription date of study intervention is study day 1. For events that occur before the prescription date of study intervention, remove the “+1” from the formula above.

Pre-treatment and on-treatment study days are numbered relative to the prescription date of study intervention, which is designated as Day 1.

8.1.6 Time Windows

Assessments and their timing to be performed are outlined in the schedule of assessments ([Appendix 1](#)). All data will be tabulated per the evaluation visit as recorded on the eCRF. There will be no derivation for visit windows in terms of summary of assessments. Nominal visits will be used for listings and tables. Unscheduled assessments will not be included in by visit summaries. All assessments, scheduled or unscheduled, will be included in summaries where best/worst and/or maximum/minimum post-baseline values are presented.

8.2 Patient Characteristics

8.2.1 Patient Disposition

The number of participants screened, the number of participants screened failed along with the distribution of reasons for failing screening, the number of participants enrolled and the number of participants met eligibility criteria but not needed will be summarized for all screened participants. Additionally, number and percentage of participants who are randomized, who are randomized but not taking prescription of study intervention and who received at least 1 prescription of study intervention will be presented by treatment group prescribed and overall in the **FAS-Modified 1** population.

A summary of study intervention status will be provided by treatment group and overall in the FAS-Modified 1. This display will show the number and percentage of participants who have completed the scheduled study intervention, are ongoing with study intervention, or have discontinued study intervention by Week 24 or Week 52, respectively, with primary reasons for discontinuation of study intervention.

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study by Week 24 or Week 52 will be provided by treatment group and overall. Reasons for study withdrawal will be summarized. For those who have neither completed nor withdrawn, they will be categorized as on study intervention or in follow up. A participant is considered to have completed the study if the participant has completed all periods of the study including the Week 52 Visit and the safety follow-up visit.

This is a global multicenter study. Enrollment will be presented by site and country. The number of participants will be summarized by Region, Country and Site ID. This summary is based on the **FAS-Modified 1**. Region is defined as North America, Asia and Rest of World and includes countries as below:

Region	Countries
Asia	Japan, South Korea, Taiwan
North America	Canada, US
Rest of World	Argentina, Australia

Participants' disposition data will be provided in a listing for all who are enrolled by treatment group. A listing of the inclusion/exclusion criteria deviation record for participants with deviations will be provided.

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8.2.2 Protocol Deviations

Clinical Trial Management System (CTMS) is utilized for entry of participant level protocol deviations (PD) and site level non-compliances. Study PD and major PD defined as part of the protocol deviation management plan for the study will be identified and assessed by the clinical research physician or designee following standard operational procedure on collection, evaluation, and reporting. The severity of PD will be determined in CTMS. The important PD will be presented in the table and listing.

The number and percentage of participants with an important deviation by type of deviation category will be presented by treatment group and overall based on **FAS-modified 1**. In addition, all important PD will be provided in a by-subject listing.

8.2.3 Demographic and Baseline Characteristics

Demographic data (age (year), age group (18 - 64, 65 - 84 and ≥ 85), sex, childbearing potential (for females), ethnicity, race details, smoking status and substance use, country and region) will be summarized by treatment group and overall on the **FAS**, **FAS-Modified 1** and **SAF-Modified 1** populations.

The following baseline disease characteristics will be summarized descriptively on **FAS-Modified 1** population:

- Pre-study asthma maintenance therapy (EDC) (ICS alone low, ICS alone high, ICS/LABA low, ICS/LABA high, untreated)
- Stratum Used for Randomization (IRT) (ICS alone low, ICS alone high, ICS/LABA low, ICS/LABA high, untreated)
- Asthma history (Yes, No, Unknown)
- Time since asthma diagnosis at time of study intervention prescribed (months)
- Participants on ICS/LABA prior to randomization (Yes, No)
- Pneumonia in past 12 month (Yes, No, Unknown)
 - Hospitalized due to pneumonia (Yes, No, Unknown)
- Oral corticosteroid (OCS) usage at Baseline (defined as taking OCS on the prescription date of study intervention) (note: Data collected by "Oral Corticosteroid (OCS) Usage Details" form will be considered)
- Trough FEV₁ (mL), percent predicted FEV₁ (%) at baseline
- FVC (mL) as baseline
- ACQ-5 score at baseline
- ACQ-6 score at baseline
- ACQ-7 score at baseline
- ACT total score category at baseline (Poorly controlled asthma (5 - 15), Somewhat controlled asthma (16 – 19), Well controlled asthma (20 - 25))
- Asthma exacerbation observed during the last 12 months (Yes, No) :
 - Number of severe asthma exacerbations treated with systemic corticosteroids for at least 3 days including single depo injection of systemic corticosteroids (0, 1, 2, 3, 4, 5);
 - Number of asthma exacerbations that required ER visits but did not include hospitalization (0, 1, 2, 3, 4, 5);
 - Number of asthma exacerbations that required hospitalization in general ward without ICU (0, 1, 2, 3, 4, 5);
 - Number of asthma exacerbations that required hospitalization in ICU (0, 1, 2, 3, 4, 5).

Demographics, substance use and disease characteristics will be listed on Enrolled Analysis Set.

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8.2.4 Prior and Concomitant Medications and Therapies

Concomitant medications will be coded using both the GSK Drug and WHO Drug dictionaries. However, the summary will be based on GSK Drug dictionaries only. The summary of concomitant medications will be provided by Anatomical Therapeutic Chemical (ATC) classifications level 1 and ingredients, i.e. multi-ingredient medications will be summarized under each individual ingredient rather than a combination of ingredients. The summary will be created using ingredient base names, e.g. ingredients with the same base name but different salt will appear under one base name in the summary.

Relevant prior and concomitant medications for asthma and non-asthma indications will be recorded at screening and updated throughout the duration of the study.

Start date and stop date for medications, in conjunction with the ongoing indicator, from the eCRF will be used to determine whether medication is prior or concomitant. Prior medications are defined as all medications recorded on the “Concomitant Medications” CRF taken prior to start of study intervention, whether continuing or not. Concomitant medications are defined as medications that are ongoing at the start of study intervention or started on or after the prescription date of study intervention; if the medication is ongoing, it is considered to be concomitant. Missing medication dates will be handled as described in [Section 8.1.3.](#)

The number and percentage of participants in **FAS-Modified 1** population for prior and concomitant asthma and/or non-asthma medication will be summarized by ATC classification level 1 and ingredient. The medications will be sorted in descending order of total incidence across treatment groups for the ATC level 1 and in descending order of total incidence for the ingredient within each ATC level. If the total incidence for any two or more ingredients is equal, the events will be presented in alphabetical order. The summary may also be performed by respiratory medication classes as determined by clinical review. The respiratory medication class includes inhaled corticosteroid (ICS), intravenous corticosteroid (IVCS), oral corticosteroid (OCS) and other asthma.

8.2.5 Medical Histories

The reported medical histories will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. The latest version available at the time of the database lock will be used.

Medical histories will be presented by primary system organ class (SOC) and preferred term (PT) in FAS-Modified 1.

8.3 Efficacy Analysis

Summary tables for all in-clinic assessments will be presented by treatment group for baseline and all post-baseline scheduled visits. Changes for study week (Week 24 and/or Week 52) during the treatment period from baseline will be presented by treatment group. Frequency tables (number and percentage) will be provided by treatment response evaluated based on asthma control assessments (OCS use, SABA use and asthma exacerbations) and patient reported outcome questionnaires (ACQs, ACT, AQLQ and WPAI). All efficacy summaries will be presented on **FAS-Modified 1** population unless otherwise specified. For all

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continuous efficacy parameters, figures may be provided containing mean values and the respective standard deviation by scheduled visits as applicable.

8.3.1 Primary Analysis – Change from baseline in Trough FEV₁ (Week 24)

8.3.1.1 Primary estimand analysis

The main estimand of the primary objective is the difference in mean change from baseline to Week 24 in trough FEV₁ between FF/UMEC/VI and ICS/LABA taken by participants with uncontrolled asthma. The analysis will be performed on FAS-Modified 1 population. Please refer to [section 4.1](#) for the definition of the primary estimand.

Descriptive statistics of observed data will be provided. The analysis of FF/UMEC/VI versus ICS/LABA will be performed using analysis of covariance (ANCOVA) with change from baseline in the trough FEV₁ at Week 24 as the summary measure, and randomized study intervention as a main factor, and pre-study asthma maintenance therapy (untreated, ICS alone, ICS/LABA), pre-study ICS dose (high, low), baseline trough FEV₁ value, age, sex and region (North America, Asia and Rest of World) as covariates. Actual pre-study asthma maintenance therapy and actual pre-study ICS dose as collected in the eCRF will be used, regardless of mis-stratification. The Kenward and Roger correction to the degrees of freedom will be used. The LS means (SE) and 95% CI for change from baseline in trough FEV₁ at Week 24 will be estimated for each treatment group, and the difference in LS means between FF/UMEC/VI versus ICS/LABA will be estimated along with 95% CI, and 2-sided p-values. SAS proc mixed procedure will be implemented to preserve all of the data that are present assuming that missing data are MAR and will not be imputed.

Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

8.3.1.2 Sensitivity analysis for missing data

Data collected on- or post-study intervention discontinuation (with the exception of data collected after study treatment discontinuation due to an indirect impact of an unexpected worldwide disruptive event) will be included in the primary effectiveness analysis and no imputation of missing data are planned. Missing data will be assumed to be MAR. No sensitivity analysis will be performed.

8.3.1.3 Supplementary analyses

In addition, a supplementary analysis is planned using while on-treatment estimand (as defined in [section 4.1](#)) to evaluate the treatment effect prior to the occurrence of study intervention discontinuation. Trough FEV₁ data observed following the study intervention discontinuation will not be used in the analysis. The intercurrent event of ICS dose escalation will be handled using treatment policy strategy (i.e., on-treatment and post-treatment data will be included).

A second supplemental estimand is defined where all intercurrent events will be handled using a while on treatment strategy, with the exception of the intercurrent event of escalation of ICS dose, which will be handled using a hypothetical strategy to estimate the treatment effect in the absence of ICS dose escalation (i.e. had the intercurrent event not occurred). Data will be set to missing following the study intervention discontinuation and/or escalation of ICS dose.

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Supportive sensitivity analyses for the primary endpoint will also be performed on **FAS** and **FAS-Modified 2** populations. The estimands for supportive analyses are defined by following the same attributes as the main estimand. The only difference is the target population of interest.

Same ANCOVA model as detailed for primary analysis will be used.

8.3.2 Key Secondary Variable – Achieving ≥ 0.5 Point Improvement for ACQ-7 (Week 24)

8.3.2.1 Estimands for key secondary variable

The ACQ-7 measures 7 attributes of asthma control and consists of 5 symptom related questions (ACQ-5) (nocturnal awakening, symptoms on waking in the morning, activity limitation, shortness of breath and wheeze with response options, ranging from 0 (no impairment/limitation) to 6 (total impairment/ limitation)), a question on rescue use and an additional item relating to lung function, which is calculated based on the collected pre-bronchodilator FEV₁ % predicted value and included via study visit spirometry assessment.

The FEV₁ % predicted value is scaled to 0-6 score as below:

FEV1 % Predicted	Scores
> 95 %	0
89.5 – 95 %	1
79.5 – 89.4 %	2
69.5 – 79.4 %	3
59.5 – 69.4 %	4
50 – 59.4 %	5
< 50 %	6

ACQ-7 total score is the mean of the responses of the 7 items. A score of ≤ 0.75 indicates well-controlled asthma, a score of between 0.75 and 1.5 indicates partially controlled asthma, and a score ≥ 1.5 indicates poorly controlled asthma. A change of 0.5 in score suggests a clinically important change in asthma control.

The key secondary estimand of interest is the difference in proportions of responders between FF/UMEC/VI and ICS/LABA treatment groups. A responder is defined as a participant who achieved ≥ 0.5 points improvement (decrease) from baseline to Week 24 in the ACQ-7 total score. The analysis will be performed on FAS-Modified 1 population. Please refer to [section 4.2](#) for definition of secondary estimand.

The ACQ-7 total score recorded at the Randomization visit will be defined as baseline value. All participants are expected to have ACQ-7 total score at baseline. Participants with a missing baseline will have responder status as missing if any. Participants with missing data at the timepoint of interest (i.e. Week 24), regardless of treatment status, are considered as non-responders and participants who withdrew from study prior to the timepoint of interest are considered as non-responders at the timepoint. The estimand analyzed will be the percent of participants who do not prematurely discontinue from study, have data available at the timepoint and meet the responder threshold.

The statistical testing of treatment group FF/UMEC/VI versus ICS/LABA will be performed using a generalized linear model (logistic regression) with binary responder as the summary measure, and

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treatment group, sex, region, pre-study asthma maintenance therapy at randomization (untreated, ICS alone, ICS/LABA), pre-study ICS dose (high, low), age, and baseline value as covariates. Actual pre-study asthma maintenance therapy and actual pre-study ICS dose as collected in the eCRF will be used, regardless of mis-stratification. The logit link function will be used. The number and percentage of responders and non-responders for each treatment group at Week 24 will be presented. The number of non-responders due to missing data will also be presented. The comparison of FF/UMEC/VI versus ICS/LABA will be expressed as an odds ratio. The odds ratio and associated 95% CI and 2-sided p-value will be presented.

The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. In the event the model fails to run using the KR method, then the residual method will be used instead. Computation of confidence intervals for the odds ratio is based on the individual Wald tests (CLPARM=WALD). The goodness of fit of the model will be assessed by examination of Pearson residual plots. These will not be included in the main set of outputs, although may be included in a Statistics Appendix if necessary.

8.3.2.2 Supplementary analyses

Two supplemental estimands will be defined.

In the first, the intercurrent event of study intervention discontinuation will be handled using a while on treatment strategy, to evaluate the treatment effect prior to the occurrence of study intervention discontinuation. Assessment data will be excluded and considered as missing following the study intervention discontinuation. The intercurrent event of ICS dose escalation will be handled using treatment policy strategy (i.e., on-treatment and post-treatment data will be included). Participants with a missing baseline will have responder status as missing. The endpoint analyzed will be the proportion of participants who do not discontinue study intervention before the analysis timepoint and meet the responder threshold. The same logistic regression model as detailed for key secondary estimand analysis will be used.

The second supplemental estimand will be defined where all intercurrent events will be handled using a while on treatment strategy, with the exception of the intercurrent event of escalation of ICS dose, which will be handled using a hypothetical strategy to estimate the treatment effect in the absence of ICS dose escalation (i.e. had the intercurrent event not occurred). Data will be set to missing following the study intervention discontinuation and/or escalation of ICS dose.

Supportive sensitivity analyses for the key secondary endpoint will also be performed on FAS and FAS-Modified 2 populations. The estimands for supportive analyses are defined by following the same attributes as the main estimand of key secondary endpoint. The only difference is the target population of interest.

8.3.3 Other Secondary Variable

8.3.3.1 Composite Endpoint (Optimized) (Week 52)

A 4-component composite endpoint will be evaluated at the end of the 52-week treatment period. The composite endpoint (optimized) evaluates the percentage of participants who achieve the following criteria after 52 weeks of treatment:

- Change from baseline in trough FEV₁ ≥ 100 mL at Week 52
- Controlled asthma based on ACQ-5 total score < 1.5 at Week 52
- No severe asthma exacerbations over 52 weeks (see protocol section 8.2.5.2 for the definition of a severe asthma exacerbation).

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- No OCS use for asthma over 52 weeks.

The composite estimand will be considered as a binary variable indicating the treatment responder defined as participant who achieves all four criteria after 52 weeks treatment, and non-response defined as participant who does not achieve all four criteria after 52 weeks treatment.

Baseline value for each component will be derived based on definition in [section 8.1.5](#). Participants with a missing baseline will have responder status as missing. Participants with missing data at the timepoint of interest (i.e. Week 52), regardless of treatment status, are considered as non-responders and participants who withdrew from study prior to Week 52 visit are considered as non-responders at Week 52.

The composite estimand is to test the difference in the proportions of treatment responders between FF/UMEC/VI and ICS/LABA after 52 weeks treatment. The analysis will be performed in FAS-Modified 1. The intercurrent event of study intervention discontinuation will be handled using strategy described in [section 4.3](#).

For the analysis of composite estimand at Week 52, generalized linear mixed model for binary response will be used to include both Week 24 and Week 52 data with the binary composite treatment responder as dependent variable, and treatment, treatment-by-visit interaction, sex, region, pre-study asthma maintenance therapy at randomization (untreated, ICS alone, ICS/LABA), pre-study ICS dose (high, low), age, baseline value of trough FEV₁, baseline value of ACQ-5, baseline value of trough FEV₁-by-visit interaction and baseline value of ACQ-5-by-visit as covariates. The Kenward and Roger correction to the degrees of freedom will be used. The number and percentage of responders and non-responders for each treatment at Week 52 will be presented. The comparison of FF/UMEC/VI versus ICS/LABA will be expressed as an odds ratio. The odds ratio and associated 95% CI and 2-sided p-values will be presented.

8.3.3.2 Secondary Variable – Change from Baseline in trough FEV₁ at Week 52

Change from baseline in trough FEV₁ at Week 52 will be analyzed using the MMRM approach. The estimand will use the same strategies for the intercurrent events as the main primary estimand.

MMRM approach will be used to include both Week 24 and Week 52 data with the change from baseline in the respective variable as dependent variable, and treatment, treatment-by-visit interaction, sex, region, pre-study asthma maintenance therapy at randomization (untreated, ICS alone, ICS/LABA), pre-study ICS dose (high, low), age, baseline value of trough FEV₁ and baseline value-by-visit interaction as covariates. The Kenward and Roger correction to the degrees of freedom will be used. An unstructured covariance matrix will be used to model the covariance of within-subject assessments. If the model with the unstructured covariance structure does not converge, simplified covariance structures will be used to fit the model, e.g. compound symmetry. In the event that the model still fails to converge, the list of covariates may be adjusted and/or reduced. If convergence is not possible with region as a covariate, the regions may be grouped or dropped from model. The LS means (SE) and 95% CI for change from baseline will be estimated for each treatment group, and the LS means difference between treatment groups will be estimated on the treatment-by-visit interaction at each visit, along with 95% CI and 2-sided p-values.

Line plots may be presented showing the LS mean change from baseline in trough FEV₁ and 95% CI for each treatment group at Week 24 and Week 52.

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8.3.3.3 Secondary Variable – Change from Baseline in trough FEV₁ ≥100 mL at Week 24 and Week 52

A binary variable indicating treatment responder will be defined by trough FEV₁ change from baseline ≥100 mL at the time point of interest (Week 24 or Week 52). The estimand will use the same strategies for the intercurrent events as the main primary estimand. Participants with missing data at the visit are considered as non-responders and participants who withdrew from study prior to the timepoint of interest are considered as non-responders at the timepoint.

The responder from baseline at visit Week 24 will be analyzed using the same analysis approach as for the key secondary estimand.

For the analysis of treatment responder at Week 52, generalized linear mixed model method for binary response will be used to include both Week 24 and Week 52 data with the binary treatment responder as dependent variable, and treatment, treatment-by-visit interaction, sex, region, pre-study asthma maintenance therapy at randomization (untreated, ICS alone, ICS/LABA), pre-study ICS dose (high, low), age, baseline value of the respective variable and baseline value-by-visit interaction as covariates. The number and percentage of responders and non-responders for each treatment at Week 24 and 52 will be presented. The number of participants missing responder status will also be presented. The comparison of FF/UMEC/VI versus ICS/LABA will be expressed as an odds ratio. The odds ratio and associated 95% CI and 2-sided p-values will be presented.

8.3.3.4 Secondary Variable – Change from Baseline in trough FEV₁ ≥ 0 mL at Week 24 and Week 52

A binary variable indicating treatment responder will be defined by trough FEV₁ change from baseline ≥ 0 mL at the time point of interest (Week 24 or Week 52). The estimand will use the same strategies for the intercurrent events as the main primary estimand. Participants with missing data at the visit are considered as non-responders and participants who withdrew from study prior to the timepoint of interest are considered as non-responders at the timepoint.

The same analysis approach as for binary variable defined by trough FEV₁ change from baseline ≥100 mL will be applied ([section 8.3.3.3](#)).

8.3.3.5 Secondary Variables – Change from Baseline in Patient Reported Outcome Questionnaires (ACQ, ACT, AQLQ+12 and WPAI) at Visit Week 24 and Week 52

Secondary variables of change from baseline for patient reported outcome questionnaires including ACQ, ACT, AQLQ+12 and WPAI will be summarized and analyzed.

ACQs:

The ACQ-7 measures are defined in [section 8.3.2](#). ACQ-6 and ACQ-5 are derived from ACQ-7 by removal of the lung function element (ACQ-6) and removal of lung function and rescue use elements (ACQ-5).

- Change from baseline in the ACQ-7 total score at Week 24 and Week 52
- Change from baseline in the ACQ-6 total score at Week 24 and Week 52
- Change from baseline in the ACQ-5 total score at Week 24 and Week 52

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ACT:

The ACT is a 5-item self-administered survey for assessing asthma control. The survey measures the elements of asthma control, including shortness of breath, general asthma symptoms, use of rescue medications, effect of asthma on daily functioning and overall self-assessment of asthma control as defined as important elements of asthma control by the National Heart, Lung, and Blood Institute [Nathan, 2004]. Each question is scored from 1 to 5 for a total score ranging from 5 to 25; with higher scores indicating better asthma control. The recall period is the past 4 weeks. Scores of 20 or higher indicate well controlled asthma, while scores ≤ 15 indicate poorly controlled asthma, and scores of 16-19 indicate somewhat controlled asthma [Schatz, 2006].

- Change from baseline in the ACT score at Week 24 and Week 52

AQLQ-12:

AQLQ-12 overall score is defined by the 15-item mini-AQLQ. The mini-AQLQ is a reduced version of the AQLQ which includes 15 items on a 7-point scale (7 = not impaired at all - 1 = severely impaired). The questions correspond to 4 dimensions of health: symptoms (5 items), limitation of usual activities (4 items), emotional function (3 items) and environmental stimuli (3 items). The overall AQLQ-12 score (in a range 1 to 7) is the mean of all responses and the individual domain scores are the means of the items in those domains.

- Change from baseline in the AQLQ-12 total score and domain scores at Week 24 and Week 52
- Change from baseline in the four domains scores at Week 24 and Week 52:
 - Total sub-score of Symptoms: (1, 4, 6, 8, 10)
 - Total sub-score of Activity Limitation: (12, 13, 14, 15)
 - Total sub-score of Emotional Function: (3, 5, 9)
 - Total sub-score of Environmental Stimuli: (2, 7, 11)

WPAI: Asthma

The Work Productivity and Activity Impairment Questionnaire (WPAI: Asthma) is an asthma-specific adaptation of the WPAI. The WPAI questionnaire measures impact due to poor health due to asthma on work and regular activities, described as absenteeism or percent of time missed from work; presenteeism or percent of impairment while working; percent overall work productivity impairment, which considers both absenteeism and presenteeism; and percent impairment in daily activities. The WPAI questionnaire score represents the percentage of impairment, from 0 to 100%. Higher percentages indicate greater impairment and less productivity.

Mean change from baseline in WPAI:Asthma composite scores expressed as percentages at Week 24 and Week 52:

- Change from Baseline in the WPAI-Asthma Overall Percentage Score at Week 24 and Week 52
- Change from baseline in the four domains of the asthma-specific adaptation of WPAI: Asthma at Week 24 and Week 52:
 - Percent work time missed due to asthma (absenteeism).
 - Percent impairment while working due to asthma (presenteeism).
 - Percent overall work impairment due to asthma (absenteeism plus presenteeism),.
 - Percent overall activity impairment due to asthma.

The estimands will use the same strategies for the intercurrent events as the main primary estimand.

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Descriptive statistics will be used to summarize patient reported outcomes scores at baseline, Week 24 and/or Week 52. The change from baseline at Week 24 will be analyzed using the same analysis approach as for the main estimand of primary endpoint.

For the analysis of change from baseline at Week 52, a MMRM approach will be used as described for secondary variable of change from baseline in trough FEV₁ at Week 52 ([section 8.3.3.2](#)).

8.3.3.6 Secondary Variables – Achieving ≥ 0.5 Point Improvement in ACQs from Baseline at Visit Week 24 and Week 52

The following secondary variables will be derived as binary variables indicating treatment responder if achieving the responder threshold of ≥ 0.5 point improvement (decrease) from baseline at the time point of interest for each respective assessment (ACQ-5, ACQ-6 or ACQ-7). Participants with missing data at the visit are considered as non-responders and participants who withdrew from study prior to the timepoint of interest are considered as non-responders at the timepoint.

- Achieving ≥ 0.5 point improvement (decrease) from baseline for the ACQ-7 at Week 52
- Achieving ≥ 0.5 point improvement (decrease) from baseline for the ACQ-6 at Week 24 and Week 52
- Achieving ≥ 0.5 point improvement (decrease) from baseline for the ACQ-5 at Week 24 and Week 52

The responder of each respective ACQ assessment from Baseline at visit Week 24 will be analyzed using the same analysis approach as for the key secondary estimand. The estimands will use the same strategies for the intercurrent events (treatment policy estimand for treatment discontinuation).

For the analysis of treatment responder at Week 52, generalized linear mixed model method for binary response will be used to include both Week 24 and Week 52 data with the binary treatment responder of the respective variable as dependent variable, and treatment, treatment-by-visit interaction, sex, region, pre-study asthma maintenance therapy at randomization (untreated, ICS alone, ICS/LABA), pre-study ICS dose (high, low), age, baseline value of the respective variable and baseline value-by-visit interaction as covariates. The number and percentage of responders and non-responders for each treatment at Week 24 and 52 will be presented. The number of participants missing responder status will also be presented. The comparison of FF/UMEC/VI versus ICS/LABA will be expressed as an odds ratio. The odds ratio and associated 95% CI and 2-sided p-values will be presented.

8.3.3.7 Secondary Variables – Subgroup Analysis at Week 24 and Week 52

Some secondary endpoints will be performed within a subgroup of participants. Subgroups which will be considered are:

- Participants on ICS/LABA prior to randomization
- Participants on no treatment prior to randomization.

The subgroup analysis will be carried out for following secondary variables:

- Change from baseline in trough FEV₁ at Week 24
- Change from baseline in trough FEV₁ at Week 52 (added analysis in addition to what protocol has specified, [section 8.3.3.2](#))
- Achieving ≥ 0.5 points improvement (decrease) from baseline for ACQ-7 at Week 24 and Week 52
- Change from baseline in the ACQ-7 total score at Week 24 and Week 52
- Composite endpoint (optimized) at Week 52

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The continuous change from baseline endpoints will use the same analysis approach as the main primary estimand and the binary responder endpoints (achieving a specified improvement from baseline) will follow the same approach as the key secondary estimand, with the exception of excluding pre-study asthma maintenance therapy at randomization (untreated, ICS alone, ICS/LABA), pre-study ICS dose (high, low) from the covariates in the model.

8.3.4 Exploratory Analysis

8.3.4.1 Usage of Short-acting Beta-agonists (SABA) Over 24 and 52 Weeks of Treatment

The number of SABA canisters used in the 12 months prior to randomization and during the study will be collected from the review of electronic/paper medical records and patient recall, and recorded in the eCRF, at the timepoints specified in the SoA ([Appendix 1](#)).

The SABA usage at baseline is defined as the number of canisters taken in the last 12 months collected on eCRF "Short-Acting Beta-2 Agonists (SABA) Usage Details – Randomization".

The SABA usage at timepoints of Week 24 and Week 52 will be defined by the annualized number of SABA canisters used, which will be calculated as number of canisters taken during time period divided by number of days that participant was on post-exposure period of interest and multiplied by 365.25. The post-exposure duration at Week 24 is measured from the prescription date of study intervention to the earliest of death, withdrawal of study, Week 24 visit date or 24 weeks post-exposure (prescription date of study intervention + 168 days) if Week 24 visit date is missing. The post-exposure duration at Week 52 is measured from the prescription date of study intervention to the earliest of death, withdrawal of study, Week 52 visit date or 52 weeks post-exposure (prescription date of study intervention + 364 days) if Week 52 visit date is missing. The SABA usage will be assigned 0 if participant reports not receiving SABA medication at the timepoint.

The annualized SABA usage at baseline, Week 24 and Week 52 and change from baseline will be summarized descriptively.

8.3.4.2 Usage of Oral Corticosteroids (OCS) Over 24 weeks and 52 weeks of Treatment

The participant's use of OCS (start date, end date and total daily dose), as reported by the participant or from the review of electronic/paper medical records will be collected at the time points specified in the SoA ([Appendix 1](#)). The total daily corticosteroid dose will be converted to prednisone equivalent dose by applying the conversion factors below. A review of the medications will take place prior to the DBL (Week 24 and Week 52) and any other conversions will be documented.

Drug	Conversion Factor to Equivalent of Prednisolone (mg) ^a
BETAMETHASONE	8.33
BETAMETHASONE DIPROPIONATE	8.33
BETAMETHASONE SODIUM PHOSPHATE	8.33
CORTISONE	0.2
CORTISONE ACERTATE	0.2
CORTIVAZOL	17
DEFLAZACORT	0.833
DEXAMETHASONE	6.67

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Drug	Conversion Factor to Equivalent of Prednisolone (mg) ^a
DEXAMETHASONE SODIUM PHOSPHATE	6.67
FLUDROCORTISONE ACETATE	0
HYDROCORTISONE	0.25
HYDROCORTISONE SODIUM SUCCINATE	0.25
HYDROCORTISONE HYDROGEN SUCCINATE	0.25
HYDROCORTISONE SODIUM PHOSPHATE	0.25
MEPREDNISONE	1
METHYLPREDNISOLONE	1.25
METHYLPREDNISOLONE ACETATE	1.25
METHYLPREDNISOLONE SODIUM SUCCINATE	1.25
MYTHYLPREDNISONE	1.25
MYTHYLPREDNISONE ACETATE	1.25
MYTHYLPREDNISONE SODIUM SUCCINATE	1.25
PREDNISOLONE	1
PREDNISOLONE ACETATE	1
PREDNISOLONE HEMISUCCINATE	1
PREDNISOLONE SODIUM SUCCINATE	1
PREDNISONE	1
PREDNISONE ACETATE	1
TRIAMCINOLONE	1.25
TRIAMCINOLONE ACETONIDE	1.25
DECADRON (NOS)	6.67
BUDESONIDE	3.33
KENALOG (NOS)	1.25

^a The factors might be adjusted based on clinical opinion. Any drugs which are not included will be consulted with clinical.

The OCS usage at post-baseline will be expressed as average total daily dose (mg/day) over the post-exposure period of interest. The average total daily dose (mg/day) is calculated as:

Average total daily dose (mg/day) = Cumulative dose (mg) during the time period / # of days on post-exposure period of interest, where # of days on post-exposure period of interest is calculated as [post exposure end date at Week 24 or Week 52 – prescription date of study intervention +1].

The post-exposure end date at Week 24 is defined as the earliest of death, withdrawal of study, 24 week visit date or 24 weeks post-exposure (prescription date of study intervention + 168 days) if Week 24 visit date is missing. The post-exposure end date at Week 52 is defined as the earliest of death, withdrawal of study, 52 weeks visit date or 52 weeks post-exposure (prescription date of study intervention + 364 days) if Week 52 visit date is missing.

Descriptive statistics for OCS usage over 24 weeks of treatment and over 52 weeks of treatment will be provided.

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8.3.4.3 Incidence of Severe Exacerbations Over 24 and 52 weeks of treatment

A severe asthma exacerbation is defined as (1) the deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection), or an increase from a stable maintenance dose, for at least 3 days, or (2) an inpatient hospitalization or emergency department visit because of asthma, requiring systemic corticosteroids. A single depo injection of systemic steroids will be considered to meet the definition of a severe exacerbation. Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation. Exacerbations collected with missing/partial start or end dates will not be collapsed into a single exacerbation event where it is possible for two distinct exacerbation events to have occurred more than 7 days apart.

The pre-exposure severe asthma exacerbations will be collected and recorded on exacerbation history eCRF page. All post-exposure severe asthma exacerbations will be collected and recorded on the severe asthma exacerbation eCRF page from the start of study intervention until Week 52 (Visit 4) or the Early Withdrawal Visit. The Incidence of severe exacerbations at Baseline is defined as total number of severe exacerbations recorded during the last 12 months prior to the start of study intervention. 24 weeks post-exposure exacerbations are measured from study intervention start date to the earliest of death, withdrawal of study, Week 24 visit date or 24 weeks post-exposure (prescription date of study intervention + 168 days) if Week 24 visit date is missing. 52 weeks post-exposure exacerbations are measured from prescription date of study intervention to the earliest of death, withdrawal of study, Week 52 visit date or 52 weeks post-exposure (prescription date of study intervention + 364 days) if Week 52 visit date is missing.

The total number of severe asthma exacerbations and number of subjects experienced severe asthma exacerbations at baseline and during post-exposure 24 weeks (or 52 weeks) will be presented by treatment group.

8.3.4.4 Composite Endpoint (Optimized) (Week 24) and Composite Endpoint (Stabilized) (Week 24 and Week 52)

The composite endpoint (optimized) evaluates the percentage of participants who achieve the following criteria after 24 weeks of treatment:

- Change from baseline in trough FEV₁ ≥ 100 mL at Week 24
- Controlled asthma based on ACQ-5 total score < 1.5 at Week 24
- No severe asthma exacerbations over 24 weeks (see protocol section 8.2.5.2 for the definition of a severe asthma exacerbation).
- No OCS use for asthma over 24 weeks.

The composite endpoint (stabilized) evaluates the percentage of participants who achieve the following criteria after 24 weeks and 52 weeks of treatment, respectively:

- Change from baseline in trough FEV₁ ≥ 0 mL
- Controlled asthma based on ACQ-5 total score < 1.5
- No severe asthma exacerbations (see protocol section 8.2.5.2 for the definition of a severe asthma exacerbation).
- No OCS use for asthma.

The composite endpoints will be considered as binary variable indicating the treatment responder defined as participant who achieves all four criteria after 24 or 52 weeks treatment, and non-response defined as participant who does not achieve all four criteria after 24 or 52 weeks treatment.

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Participants with a missing baseline will have responder status as missing. Participants with missing data at the timepoint of interest (i.e. Week 24, Week 52), regardless of treatment status, are considered as non-responders and participants who withdrew from study prior to the timepoint of interest are considered as non-responders.

The analysis will be performed in **FAS-Modified 1**. The estimand for this endpoint will follow the main approach of the key secondary estimand. Descriptive statistics for the occurrence of responders including each of the four components at the visit of interest will be provided by study intervention group and overall. The statistic testing for the composite estimand (optimized and stabilized) at Week 24 will be performed by using logistic regression model as described for key secondary estimand. For the analysis of composite endpoint (stabilized) at Week 52, generalized mixed linear model for binary response will be used to include both Week 24 and Week 52 data with the binary composite treatment responder as dependent variable, and treatment, treatment-by-visit interaction, sex, region, pre-study asthma maintenance therapy at randomization (untreated, ICS alone, ICS/LABA), pre-study ICS dose (high, low), age, baseline value of trough FEV₁, baseline value of ACQ-5, baseline value of trough FEV₁-by-visit interaction and baseline value of ACQ-5-by-visit as covariates. The Kenward and Roger correction to the degrees of freedom will be used. The number and percentage of responders and non-responders for each treatment at Week 52 will be presented. The comparison of FF/UMEC/VI versus ICS/LABA will be expressed as an odds ratio. The odds ratio and associated 95% CI and 2-sided p-values will be presented.

8.3.5 Other Exploratory Analysis

The following analyses are not specified in the protocol but added as exploratory analyses. They are country-specific required analyses for participants enrolled in Japan by using clinical remission criteria based on Japanese guidelines for adult asthma (JGL) 2024 and Practical Guidelines for Asthma Management (PGAM) 2024 and are added for global study cohort for completeness of analyses.

8.3.5.1 Achieving ACT Total Score ≥ 20 at Visit Week 52

Binary treatment responder endpoint is defined as of achieving ≥ 20 in ACT total score at visit Week 52 which indicates well controlled asthma. Participants with missing data at the visit are considered as non-responders and participants who withdrew from study prior to the timepoint of interest are considered as non-responders at the timepoint.

For the analysis of treatment responder at Week 52, generalized linear mixed model method for binary response will be used to include both Week 24 and Week 52 data with the binary treatment responder of the respective variable as dependent variable, and treatment, treatment-by-visit interaction, sex, pre-study asthma maintenance therapy at randomization (untreated, ICS alone, ICS/LABA), pre-study ICS dose (high, low), age, baseline value of ACT total score and baseline ACT total score-by-visit interaction as covariates. The number and percentage of responders and non-responders for each treatment at Week 24 and 52 will be presented. The number and percentage of non-responders due to missing will also be presented. The comparison of FF/UMEC/VI versus ICS/LABA will be expressed as an odds ratio. The odds ratio and associated 95% CI and 2-sided p-values will be presented. The estimand for this endpoint will follow the main approach of the key secondary estimand.

8.3.5.2 Achieving ACT Total Score ≥ 23 at Visit Week 52

Binary treatment responder endpoint is defined as of achieving ≥ 23 in ACT total score at visit Week 52 which indicates well controlled asthma. Participants with missing data at the visit are considered as non-responders and participants who withdrew from study prior to the timepoint of interest are considered as non-responders at the timepoint.

The similar analysis approach as described in [section 8.3.5.1](#) will be implemented .

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8.3.5.3 Composite Endpoint (3-Component) based on Practical Guidelines for Asthma Management (PGAM) at Week 52

Based on practical guidelines for asthma management (PGAM), a composite endpoint (3-component), which evaluates the clinical remission of asthma, is defined.

The composite endpoint evaluates the percentage of participants who achieve the following criteria after 52 weeks of treatment:

- Controlled asthma based on ACT total score ≥ 23 at Week 52
- No severe asthma exacerbations over 52 weeks
- No OCS use for asthma over 52 weeks.

The analysis will be performed on **FAS-Modified 1** population. The similar analysis approach as described in [section 8.3.4.4](#) will be implemented except appropriate covariates will be adjusted. The estimand will use the same strategies for the intercurrent events (treatment policy estimand for treatment discontinuation).

8.3.5.4 Composite Endpoints (4-Component) based on Japanese Guidelines for Adult Asthma (JGL) at Week 52

Based on Japanese guidelines for adult asthma (JGL), two composite endpoints, which evaluate the clinical remission of asthma, are defined:

The composite endpoint (optimized) evaluates the percentage of participants who achieve the following criteria after 52 weeks of treatment:

- Change from baseline in trough $FEV_1 \geq 100$ mL at Week 52
- Controlled asthma based on ACT total score ≥ 23 at Week 52
- No severe asthma exacerbations over 52 weeks
- No OCS use for asthma over 52 weeks.

The composite endpoint (stabilized) evaluates the percentage of participants who achieve the following criteria after 52 weeks of treatment:

- Change from baseline in trough $FEV_1 \geq 0$ mL at Week 52
- Controlled asthma based on ACT total score ≥ 23 at Week 52
- No severe asthma exacerbations over 52 weeks
- No OCS use for asthma over 52 weeks

The analysis will be performed on **FAS-Modified 1** population. The similar analysis approach as described in [section 8.3.4.4](#) will be implemented except appropriate covariates will be adjusted. The estimand will use the same strategies for the intercurrent events (treatment policy estimand for treatment discontinuation).

8.3.6 Compliance of Electronic Clinical Outcome Assessment (eCOA)

The ACQ eCOA data will be assessed at clinical visits and the compliance rate will be calculated at overall study and visit level for secondary endpoints of ACQ-5 and ACQ-6 by treatment group and overall. The compliance rate is defined as total number of complete questionnaires, divided by total number of questionnaires expected to be received at the visit multiplied by 100. The endpoint level compliance (ACQ-5 and ACQ-6, respectively) and study level compliance (ACQ-6) are detailed in [Appendix III](#).

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8.4 Safety Analysis

8.4.1 Treatment Exposure and Compliance

No measures outside of usual care will be taken to ensure and document treatment compliance.

A summary of randomized study intervention (FF/UMEC/VI or ICS/LABA) by low or high dose and a summary study intervention (drug, dose, frequency) will be produced. The extent of exposure to study intervention will be determined by duration of exposure in days calculated as: [(date of last dose) – (prescription date of study intervention) + 1]. The descriptive summary will be provided on primary safety population (**SAF-Modified 1**).

A by-subject listing of data on participant exposure to study intervention will be produced. The listing will include medication names, start and stop date, dose, frequency, any dose modification and reason for dose modification.

8.4.2 Adverse Events

AEs will be coded using MedDRA version 28.0 or later. All safety data summaries will be presented on primary safety population (**SAF-Modified 1**) unless otherwise specified.

All AEs considered related to study intervention or study procedures will be collected from randomization until study completion, as specified in the SoA. Any SAEs assessed as related to study participation (e.g., study intervention, protocol mandated- procedures, invasive tests, or change in existing therapy) or related to a GSK product (non-IMP) will be recorded from the time a participant consents to participate in the study. All SAEs (related and unrelated) will be collected from the start of study intervention until the safety follow-up visit. A treatment-emergent AE (TEAE) is defined as an AE with onset dates on or after the start of the study intervention and to 7 days after the last dose of study intervention. If the start date of an AE is partially or completely missing, the date will be compared as far as possible with the date of the start of administration of study intervention. The AE will be assumed to be treatment-emergent if it cannot be definitively shown that the AE did not occur or worsen during the treatment-emergent period (refer to section [8.1.3.1](#) handling of dropouts and missing data).

An overview of AE incidence summary table will be produced and will include number and percentage of participants with:

- Any TEAE
- Any study intervention related TEAE
- Serious TEAE (SAE)
- Serious study intervention related TEAE

The summary will be also conducted by sub-categories within each category of above:

- Result in an outcome of death.
- Leading to study intervention withdrawn .
- Leading to study intervention dose reduction.
- Leading to study intervention interruption.
- Recurred event when study intervention stopped temporarily and restarted.

The number and percentage of participants with TEAEs will be summarized by MedDRA SOC and PTs. Additional summaries will be provided by the maximum intensity (e.g. mild, moderate, severe, moderate/severe), relationship to the study intervention (i.e., study intervention related), seriousness, actions taken with study intervention (i.e., associated with study intervention dose reduction, study intervention interruption, study intervention withdrawn), and fatality. Adverse events will be sorted by SOC,

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in descending order from the SOC with the highest total incidence for any adverse event within the class to the SOC with the lowest total incidence based on FF/UMEC/VI treatment group. PT will be sorted in the same manner within each SOC.

If a participant reports more than one AE with the same PT, the AE with the maximum intensity will be presented. If a participant reports more than one AE within the same primary SOC, the participant will be counted only once with the maximum intensity at the SOC level, where applicable.

A summary of the number and percentage of participant with common TEAEs by overall frequency (e.g., incidence $\geq 1\%$) and a summary of the number and percentage of participant and the number of occurrences of common non-serious adverse events by SOC and PT will be created.

Additionally, supportive safety analyses will be performed on each of supportive safety populations of **SAF** and **SAF-Modified 2** for following summaries:

- Overview of AE incidence summary
- TEAE by SOC and PT
- Serious TEAE by SOC and PT

All AEs will be listed including, but not limited to, verbatim term, PT, SOC, intensity, relationship to study drug, start and end date, seriousness, action taken, and outcome on **SAF** population. Non-TEAEs will be flagged in the listing.

Separate listings may be provided for SAEs, AEs associated with death, AEs associated with study intervention withdrawn, AEs associated with study intervention interruption, AEs leading to death.

8.4.3 CV Events

The Cardiovascular effects (CV) eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information is recorded in the specific CV section of the eCRF.

The number and percentage of subjects with the specific CV event for the following AEs and SAEs will be summarized with all other AE summaries for **SAF-Modified 1** population:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

8.4.4 Death

The Death eCRF is provided immediately after the occurrence or outcome of death is reported.

All deaths will be summarized by primary cause of death on **SAF-Modified 1** population. All deaths including death details will be listed on **SAF** population, and those that occurred during the post-treatment period will be flagged in the listing.

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8.4.5 Analysis of Other Assessments

No analysis for other assessments which are not planned by protocol will be performed.

9. Planned Analyses

9.1 Primary Analysis

The primary analysis will be performed once all participants have completed their Week 24 visit (unless prematurely discontinued from the study).

This analysis will not lead to a decision to stop the study. This primary analysis will include baseline demographic and characteristics, subject disposition, safety and primary results for all Primary, Secondary and Exploratory endpoints at Week 24.

9.2 Final Analysis

The final analysis will be conducted after all participants complete 52 week and safety follow-up visits (unless prematurely discontinued from the study).

The final analysis will include all planned analysis including baseline demographic and characteristics, subject disposition, safety and results for all Primary, Secondary and Explorable endpoints up to Week 52. Analyses or periods reported previously at Week 24 analyses will be regenerated as part of this final analysis and will reflect all study periods of interest within the final study database [0-Week 24 visit, and 0-Week 52 visit post-exposure data]. The final planned analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database lock (DBL) has been declared by Data Management.

9.3 Changes to Protocol Defined Analyses

The following analyses are added:

1. The compliance analysis of eCOA data will be implemented and added in [section 8.3.6](#) and appendix III.
2. Additional exploratory analyses are added into [section 8.3.5](#), which are country-specific required analyses for participants enrolled in Japan and are added for global overall participants for completeness of analyses.
3. Supportive analyses excluding site(s) with GCP non-compliance/significant data integrity concerns or falsified participants according to sponsor clinical decision.
4. In the protocol, the cut-off for controlled asthma based on the ACQ-5 was specified as ≤ 1.5 . The composite endpoint has since evolved and has been updated to look at ACQ-5 < 1.5 . This has been updated across SAP text and mock shells.
5. Change from baseline in trough FEV1 at Week 52 was added as an endpoint to provide additional information on this endpoint at Week 52.

10. Tables, Figures and Listings

Table of contents is provided in a separate document.

This document is confidential.

11. References

1. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the Asthma Control Test. A survey for assessing asthma control. J Allergy Clin Immunol. 2004;113:59-65.
2. Schatz M, Sorkness CA, Li, JT, et al. Asthma Control Test: reliability, validity and responsiveness in patients not previously followed by asthma specialists. J Allergy Clin Immunol. 2006;117(3):549-556.

12. Programming Considerations

All TFLs and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA). The general programming conventions will be stated in the TLF shells document.

13. Quality Control

SAS programs are developed to produce output such as analysis datasets, summary tables, figures, and data listings, or statistical analyses. An overview of the development of programs is detailed in Developing Statistical Programs SOP (3922).

The Developing Statistical Programs and Conducting the Transfer of Biostatistical Deliverables SOP (3922) and the SAS Programming and Validation Plan (3920A) describe the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

14. Shells

Table, figure and listing shells are provided as a separate document.

15. Appendices

15.1 Appendix 1: Schedule of Activities

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Protocol Activity	Screening Day 0 Visit 1 ^a	Randomization Day 1 Visit 2 ^a	Treatment Period		Safety Follow-up Week 53	Notes
			Week 24 Visit 3	Week 52 Visit 4/ Early Withdrawal ^b		
Window (days)	n/a	+ 7	± 7	± 7	+ 7	
Written Informed Consent	X					Informed consent form (ICF) must be signed before any study procedures/assessments
Demography	X					
Medical history	X					
Asthma History	X					
Exacerbation History	X					
Concomitant Medications	X	X	X	X	X	
Inclusion/Exclusion Criteria	X	X				Recheck eligibility criteria before randomization and/or first prescription for study intervention.
Smoking History and Status	X		X	X		
Randomization		X				Participants must not be randomized prior to confirming their eligibility to participate in the study. IRT will be used for randomization. (Please refer to the IRT manual for more information).
Spirometry ^c		X	X	X		Visit 2 pre-bronchodilator assessments may be repeated within 7 days of Visit 2 (see protocol section 5.12 for details of the criteria to be met before a repeat of the assessment is permitted). Participants must not be randomized until spirometry criteria are met. Visit 3 and Visit 4 spirometry may be repeated within 7 days of the visit, if acceptable/repeatable maneuvers were

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						not achieved (see protocol section 8.2.1 for further details).
Asthma Control Questionnaire (ACQ)		X	X	X		Participants must have an ACQ score ≥ 1.5 at Visit 2 to be eligible for randomization
Asthma Control Test (ACT)		X	X	X		
Asthma Quality of Life Questionnaire for 12 years and older (AQLQ +12)		X	X	X		
Work Productivity and Activity Impairment: Asthma (WPAI: Asthma)		X	X	X		
Record Use of Short-Acting Beta-2 Agonists		X	X	X	X	The number of canisters prescribed in the 12 months before Visit 2 will be collected. Refer to protocol section 8.2.1 for time limit restrictions related to spirometry.
Record Use of Oral Corticosteroids		X	X	X	X	OCS use (start date, end date and total daily dose), as reported by the participant or from the review of electronic/paper medical records will be collected.
Exacerbation Assessment		X	X	X	X	Severe exacerbations will be recorded.
Adverse Events		X	X	X	X	The definition of and procedures for recording, evaluating, follow-up and reporting of adverse events is provided in protocol section 10.2 (Appendix 2).
Serious Adverse Events	X	X	X	X	X	
Urine Pregnancy Test		X	X	X		A WOCBP must have a negative highly sensitive urine pregnancy test (or serum if required by local regulations) ≤ 7 days prior to randomization.
Post-Randomization Medication Review			X	X		Reason for initiating a new treatment, or any changes to current treatment (such as an increase in dose of study intervention), including date, dose and frequency, must be recorded.
Provide Study Intervention prescriptions for FF/UMEC/VI or ICS/LABA		X	X			To ensure study intervention is provided in a minimally interventional routine clinical care setting it will not be possible to collect the start date of study intervention. Study prescriptions will be managed as per usual care procedures.

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Telephone Call					X	A safety follow-up telephone contact will be conducted approximately 7 days after the participant completes all protocol-defined procedures for Visit 4, or 7 days after study intervention is discontinued. A participant will be considered to have completed the study upon completion of all assessments, including a successful follow-up contact.
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- a. If it is local and routine medical practice to request that a participant withhold their ICS/LABA medication for at least 24 hours and SABA for at least 6 hours prior to a clinic visit then, provided that the participant complied with the request, Visit 1 and Visit 2 can occur on the same day.
- b. The Early Withdrawal Visit should only be conducted if the participant withdraws from the study. Participants that discontinue study intervention but remain in the study, should complete all study visits.
- c. Participants who are unable to achieve a minimum of 2 acceptable and 1 repeatable effort at Visits 3 and 4 can, at the discretion of the investigator, attend the clinic once more to attempt to perform the FEV1 maneuvers again. This must be within 7 days of the scheduled visit.

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15.2 Appendix II: Handling of Partial Dates

Element	Reporting Detail
General	- Partial dates will be displayed as captured in participants listing displays. - However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. - Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis).
Adverse Events	In the event of a missing/incomplete start or stop date associated with an adverse event, only the treatment-emergence will be imputed using the algorithm below. Dates will not be imputed. In general, if the missing/incomplete start date is not clearly prior to initiation of treatment, then the AE will be considered a TEAE. If the AE end date is prior to the initiation of treatment, the AE will not be considered a TEAE. If the AE end date is on or after the initiation of treatment: - If the AE start date is completely missing or if the year is missing, then the AE will be considered a TEAE - For partial AE start dates: - Known year, unknown month, and day (or known year and day, unknown month) - If the year is the same as or later than the year of the prescription date of study intervention, the AE will be considered a TEAE - Otherwise, the AE will not be considered a TEAE - Known year and month, unknown day - If the month and year are the same as or later than the month and year of the prescription date of study intervention, the AE will be considered a TEAE - Otherwise, the AE will not be considered a TEAE
Concomitant Medications/Medical History	A partial/missing start date recorded on the Prior and Concomitant Medications CRF will be handled as follows: - If only the day is missing, and the month and year match the month and year of the first treatment dose date, then the day of the first treatment dose date will be imputed. Otherwise, the first of the month will be used. - If both the day and month are missing, and the year matches the year of the first treatment dose date, then the month and the day of the first treatment dose date will be imputed. Otherwise, 01 January will be used. - If the start date is completely missing, the first treatment dose date will be imputed, unless the stop date is prior to the first treatment dose date, then

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Element	Reporting Detail
	the stop date of the medication will be imputed, and the medication will be considered to be a prior medication. A partial/missing end date recorded on the Prior and Concomitant Medications CRF will be handled as follows: • If only the day is missing, then the last day of the month will be imputed. • If both the day and month are missing, then 31 December will be imputed. • If the stop date is completely missing, or if the medication is ongoing, the missing date will not be used

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15.3 Appendix III: Electronic Clinical Outcome Assessment (eCOA) Compliance

The compliance of ACQ eCOA data will be assessed at clinical visits and will be derived at overall study and visit level for the secondary endpoint of ACQ and reported across all participants and by treatment group.

Endpoint Level Compliance

The assessments of ACQ will be performed as detailed within Section [8.3.2](#).

The compliance for ACQ eCOA (i.e. availability of a score) will be reported at each analysis timepoint using a frequency table, i.e. Baseline, Week 24 and Week 52. The denominator will be the number of expected completed questionnaires (i.e., the number of participants remaining in the study at the given timepoint).

Endpoint-level compliance will be restricted to key eCOA endpoints within the study (ACQ-5 and ACQ-6). eCOA compliance for key eCOA endpoints of ACQ-5 and ACQ-6 across all participants will be calculated separately. The target compliance is $\geq 90\%$ for each key endpoint. The endpoint eCOA compliance will be reported for each treatment group and overall.

Study Level Compliance

An ACQ eCOA will be considered as complete if the participant completes the ACQ-6 questionnaire on the electronic tablet/web application at the study visit and the ACQ-6 score can be derived.

- The overall study level eCOA compliance (based on completion of ACQ-6) will be assessed across all participants and across all visits between the date of the Randomization visit through to the date of the participant's study completion or study withdrawal.

The target compliance for the study level is $\geq 90\%$. The study ACQ eCOA compliance will be reported for each treatment group and overall.

Overall study level ACQ eCOA compliance is calculated as:

$$\frac{\text{Total number of complete eCOAs}}{\text{Expected number of complete eCOAs per participant} \times \text{Total number of participants}} \times 100$$

- Overall visit level ACQ eCOA compliance will be calculated across all ACQ eCOAs and across all participants for baseline (Day 1), Week 24 and Week 52, respectively. The target compliance is $\geq 90\%$. The study ACQ eCOA compliance will be reported for each treatment group and overall.

Overall visit level ACQ eCOA compliance is calculated as:

$$\frac{\text{Total number of complete eCOAs at that visit}}{\text{Expected number of complete eCOAs per participants} \times \text{Total number of participants at the visit}} \times 100$$

GSK Trelegy 219912 Statistical Analysis Plan v3.0_07Aug2025

Final Audit Report

2025-08-08

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Number of Documents:	1
Document page count:	49
Number of supporting files:	0
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