

Protocol 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

NCT ID: NCT06372496

Date of Document: 21-Mar-2025

CLINICAL STUDY PROTOCOL

Primary Study Intervention(s)	Fluticasone Furoate/Umecclidinium Bromide/Vilanterol (FF/UMEC/VI) in a Dry Powder Inhaler (Trelegy Ellipta)
Other Study Intervention(s)	Inhaled corticosteroid (ICS)/long-acting beta-2 agonist (LABA)
Study Identifier	219912
Approval Date	20 Mar 2025
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
Compound Number/Name	GW685698+GSK573719+GW642444
Brief Title	Pragmatic open - label randomized clinical trial of FF/UMEC/VI vs non-ellipta usual care ICS-LABA for adult participants with uncontrolled asthma.
Sponsor	GSK Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK
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Medical monitor name and contact can be found in local study contact information document

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Protocol Amendment 3 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with GCP and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- To cooperate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator(s)' ownership interest in the sponsor or the study intervention(s), and more generally about their financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.

Study identifier	219912
Approval date	20 Mar 2025
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
Investigator name	
Signature	
Date of signature (DD Month YYYY)	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	Date of Issue
Amendment 3	20 Mar 2025
Amendment 2	17 December 2024
Amendment 1	02 April 2024
Original Protocol	27 November 2023

Amendment 3 (20 Mar 2025)

Overall rationale for the current Amendment: To update the objectives, estimands and endpoints table as well as the statistical analysis section, due to the recruitment of a lower than anticipated number of participants taking budesonide/formoterol as maintenance asthma therapy and a higher than anticipated number of participants on no treatment, prior to joining the study.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale
1. Synopsis, Objectives, Endpoints and Estimands Table 2 Objectives and Endpoints Section 3 Additional Estimands	Objectives table and text updated to replace budesonide/formoterol with ICS/LABA.	Fewer participants than predicted were prescribed budesonide/formoterol prior to study start.
1. Synopsis, Objectives, Endpoints and Estimands Table 2 Objectives and Endpoints	Additional other secondary objective added 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 no treatment prior to randomization.	More participants were on no treatment prior to randomization than expected.
1. Synopsis, Objectives, Endpoints and Estimands	Additional exploratory objectives added to evaluate the effects of FF/UMEC/VI on a composite endpoint (stabilized) compared with	Recent guidelines recommend both optimized and stabilized lung function criteria are considered when assessing clinical remission.

Section # and title	Description of change	Brief rationale
Table 2 Objectives and Endpoints	ICS/LABA after 24 and 52 weeks of treatment. Composite endpoint (optimized) has replaced composite endpoint.	To differentiate optimized and stabilized composite endpoint objectives and associated endpoints.
1. Synopsis, Objectives, Endpoints and Estimands Table 2 Objectives and Endpoints	FEV1 responder analysis endpoints added to the other secondary objective to evaluate the effects of FF/UMEC/VI on lung function compared with inhaled corticosteroids/long-acting beta-2 agonists (ICS/LABA) after 52 weeks of treatment - Change from baseline in trough FEV1 ≥ 100 mL at Week 52 - Change from baseline in trough FEV1 ≥ 0 mL at Week 24	Change from baseline in trough FEV1 ≥ 100 mL at Week 24 and Week 52 was omitted from the protocol in error and change from baseline in trough FEV1 ≥ 0 mL at Week 24 and Week 52 has been added due to the addition of the stabilized composite endpoint at Week 24 and Week 52.
Table 1 Schedule of Activities and Section 8.2.1	Text added to allow participants to return to the clinic to repeat V3 and V4 spirometry, if acceptable/repeatable criteria were not met Prior SABA use within 12 months of V2 to be reported, not V1.	To ensure as many participants as possible have data available to meet the primary and key secondary objectives of the study. To align with other sections of the protocol.
9.1 Statistical hypotheses 9.5.2 Powered Key Secondary Endpoint 9.5 Sample size determination	Text updated to replace budesonide/formoterol with ICS/LABA and the subset of participants on no treatment prior to randomization was added. Sample size, power and minimum detectable treatment differences updated for the ICS/LABA and no treatment prior to randomization subsets.	Fewer participants than predicted were prescribed budesonide/formoterol prior to study start, whilst more participants were on no treatment prior to randomization than expected A consistency approach was originally planned for the participants on no treatment prior to randomization subset due to the expected smaller number of participants.
9.1.1 Multiplicity adjustment	Figure 2 and text updated to address availability of sub-populations and simplify the testing strategy. FEV1 sub-population analyses for budesonide/formoterol were replaced with ICS/LABA	Fewer participants than predicted were prescribed budesonide/formoterol prior to study start, whilst more participants were on no treatment prior to randomization than expected. ACQ-7 sub-population analyses were underpowered based on the number

Section # and title	Description of change	Brief rationale
	and no treatment sub-populations - ACQ-7 sub-population analyses were removed	of participants predicted to be in each group at the time of amendment 3.
9.5 Sample size determination	Text on the sample size assumptions for the asthma control subgroup endpoints was removed.	Asthma control subgroup objectives and analyses are no longer in the hierarchy.
10.1.7 Data Quality Assurance	Document retention updated to 15 years, instead of 25 years.	To align with current GSK guidelines.
10.2.6 Additional Adverse Event (AE) Reporting Requirements for Canadian Investigators	Table updated to remove reference to AEs leading to study withdrawal or study intervention discontinuation from the 'All Countries' column	Text was included in error. Non-serious AEs leading to study withdrawal or study intervention discontinuation are not reported in the eCRF.
Section 10.6: Appendix 6. Country-specific requirements	Description of the assessment of consistency of effect between study participants in Japan and the overall study population has been added.	Primary and Key Secondary objectives, endpoints and estimands will be summarized and analyzed for the Japan population, as well as the composite endpoints (stabilized and optimized) following 52 weeks of treatment.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACQ-5	Asthma Control Questionnaire-5
ACQ-6	Asthma Control Questionnaire-6
ACQ-7	Asthma Control Questionnaire-7
ACT	Asthma Control Test
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AQLQ	Asthma Quality of Life Questionnaire
ATS	American Thoracic Society
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CRF/eCRF	Case report form/electronic case report form
CSR	Clinical study report
CV	Cardiovascular
DRE	Disease-related event
DSUR	Development safety update report
ECG	Electrocardiogram
EMA	European Medicines Agency
EoS	End-of-study
ePRO	Electronic Patient-reported Outcome(s)
ERS	European Respiratory Society
FAS	Full analysis set
FEV ₁	Forced expiratory volume in 1 second
FF	Fluticasone furoate
FP	Fluticasone propionate
FSFV	First subject first visit
FVC	Forced vital capacity

Abbreviation	Definition
GCP	Good clinical practices
GINA	Global Initiative for Asthma
HIPAA	Health Insurance Portability and Accountability Act
HPA	Hypothalamic pituitary axis
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled corticosteroid
ICSR	Individual case safety reports
IEC	Independent ethics committee
IMP	Investigational medicinal product
IOP	Intraocular pressure
IRB	Institutional review board
IRT	Interactive response technology
IVRS/TWRS	Interactive voice/web response system
LABA	Long-acting beta-2 agonist
LAMA	Long-acting muscarinic antagonist
LSLV	Last Subject Last Visit
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Multiple inhaler triple therapy
MMRM	Mixed model repeated measures
OCS	Oral corticosteroid
PI	Personal information
PRO	Patient-reported outcomes
QTL	Quality tolerance limit
RSI	Reference safety information
SABA	Short-acting beta-2 agonist
SADE	Serious adverse device effect
SAE	Serious adverse event

Abbreviation	Definition
SAMA	Short-acting muscarinic antagonist
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SITT	Single inhaler triple therapy
SmPC	Summary of product characteristics
SMQ	Standardized MedDRA queries
SoA	Schedule of activities
SRT	Safety Review Team
UMEC	Umeclidinium bromide
USPI	United States Prescribing Information
VI	Vilanterol
WOCBP	Woman of childbearing potential
WPAI:Asthma	Work Productivity and Activity Impairment: Asthma

Term	Definition
Adverse Drug Reaction	An adverse reaction where a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. a. In the context of a clinical trial, an ADR can be serious or non-serious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). For marketed products, ADRs are subject to expedited reporting within the country where they are authorized.
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Term	Definition
Comparator	Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
Investigational Medicinal Product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a different way from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Participant number	A unique identification number assigned to each participant who consents to participate in the study.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.

Term	Definition
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Standard of Care	Medicine(s) for a specific indication, or a component of the standard care for a particular medicine indication, based on national and/or international consensus; there is no regulatory significance to this term. 1. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries.
Study completion date	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
Study intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
SUSAR	Suspected Unexpected Serious Adverse Reaction; in a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature of severity of which is not consistent with the reference safety information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting.

1. PROTOCOL SUMMARY

1.1. Synopsis

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

Brief Title: PERFORM: Pragmatic Evaluation of Randomized FF/UMEC/VI vs Open-label ICS-LABA for Regular asthma Management

Rationale: The majority of studies evaluating SITT in asthma recruit patients with a history of exacerbations, but the greatest unmet need is in patients with uncontrolled asthma [Price, 2014b]. While different patients with asthma may vary in their experience of symptoms versus exacerbations, exacerbation rates are 0.1 to 0.2 per patient per year whereas 80% of patients with asthma experience symptoms within the previous 7 days [Price, 2014a; Price, 2014b; Martin, 2020]. The CAPTAIN (NCT02924688) study compared two Ellipta inhaler products containing FF and VI with the only differences between the two products being the inclusion of UMEC (i.e., evaluating the effects of FF/UMEC/VI vs. FF/VI). There is a paucity of data comparing FF/UMEC/VI delivered via the Ellipta dry-powder inhaler, to non-Ellipta alternative ICS/LABA formulations, including budesonide-formoterol. Outcomes of interest in asthma have long been focused on prevention or delay of exacerbations [GINA, 2023; CHMP, 2015]. It is believed that increased symptom control is an outcome that benefits more patients and helps to prevent downstream events.

The use of SITT in asthma is increasing and there is a considerable need to optimize disease management in patients with uncontrolled asthma. Additional evidence is needed to establish FF/UMEC/VI delivered via the Ellipta dry-powder inhaler versus non-Ellipta ICS/LABA usual care comparators for patients with uncontrolled asthma where symptom control is assessed as an outcome of treatment impact. 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) in adult participants with uncontrolled asthma.

Objectives, Endpoints, and Estimands:

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 (FEV₁) 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
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 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

Objectives	Endpoints
	- 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 derivatives¹) 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 $FEV_1 \geq 100$ 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 with ICS/LABA after 52 weeks of treatment for participants on no treatment prior to randomization	- Composite endpoint at Week 52. Occurrence of participants achieving the following criteria: - Change from baseline in trough $FEV_1 \geq 100$ 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 ,	Change from baseline in the four domains of the asthma-specific

Objectives	Endpoints
presenteeism, work productivity loss, activity impairment compared with ICS/LABA after 24 and 52 weeks of treatment	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-2 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 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

Objectives	Endpoints
	- 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)

¹ ACQ-6 and ACQ-5 are derived from ACQ-7 by removal of the lung function element (ACQ-6) and lung function and rescue use elements (ACQ-5)

PRIMARY ESTIMAND

The primary endpoint is defined as change from baseline in trough FEV₁ after 24 weeks of treatment.

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:

- **Target Population:** all randomized patients aged 18 years or older with uncontrolled asthma as defined by the inclusion/exclusion criteria.
- **Endpoint:** Change from baseline in trough FEV₁ at Week 24
- **Treatment condition:** FF/UMEC/VI versus ICS/LABA.
- **Intercurrent events:**
 - a) 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, 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 will be included).
 - b) Use of prohibited medication: analysis will be handled by treatment policy strategy. All observed data will be included in the analysis regardless of the intercurrent events.
 - c) 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).
- **Population-level summary:** Difference in means.

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 patients 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.

For the primary endpoint, 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, 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).

Overall Design: 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 FF/UMEC/VI compared to continuing or initiating usual care (ICS/LABA, administered via a non-Ellipta inhaler), in adult participants with uncontrolled asthma. The primary statistical analysis will be completed once all participants complete 24 weeks of treatment, and the final analyses will be completed once all participants complete the 52 weeks of the study.

The total duration of the study will be approximately 53 weeks, including a 52-week treatment period, and a 1-week safety follow-up. The study will include 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 will be conducted via telephone.

Participants will be randomized to receive FF/UMEC/VI or ICS/LABA and will be stratified by pre-study asthma maintenance therapy (untreated [as defined in Section 5.1], ICS alone, ICS/LABA) and pre-study ICS dose (low, high). An overview of the study design is displayed in Figure 1.

Approximately 1420 participants will be screened to achieve 1136 randomly assigned to study intervention, with 568 participants randomized in a 1:1 ratio to each group (FF/UMEC/VI 100/62.5/25 mcg versus ICS/LABA). A subset of participants within each group may also be randomized to FF/UMEC/VI 200/62.5/25 mcg or high-dose ICS/LABA (non-Ellipta) if they were being treated with a high-dose ICS-containing inhaler at baseline. Inclusion in the high-dose ICS-containing therapy group will be at the discretion of the investigator and must comply with local treatment guidelines. At any time during the study (post-randomization), participants on FF/UMEC/VI 100/62.5/25 mcg or usual care ICS/LABA may be escalated to FF/UMEC/VI 200/62.5/25 mcg or high-dose ICS/LABA, respectively, if they demonstrate significant worsening of control (i.e., change in ACQ-7 score >0.5) after randomization **AND** their treating physician determines that an increased dose of ICS is necessary for ethical reasons.

Participants should continue to receive usual clinical care until randomization, according to the physician's discretion, and in line with local care guidelines. The Schedule of Activities (SoA) is provided in Table 1.

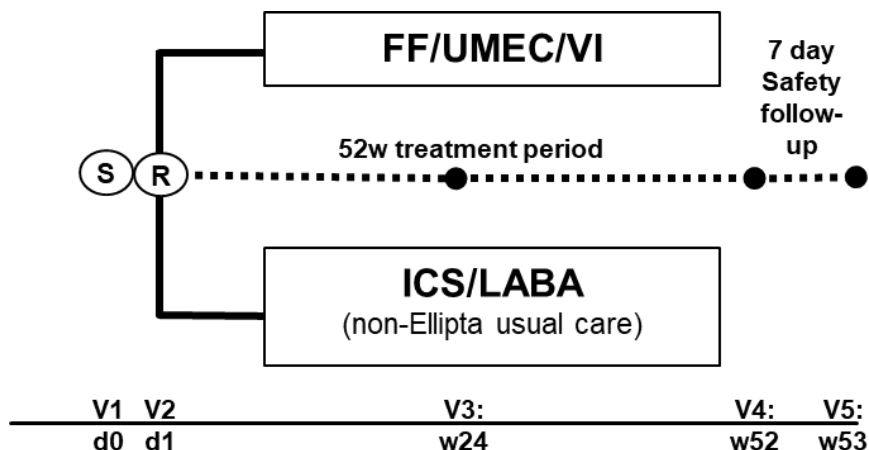
Number of Participants: Approximately 1420 participants will be screened to achieve 1136 randomly assigned to study intervention (568 participants per arm).

Data Monitoring/Other Committee: A SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new effectiveness and safety information.

A Steering Committee will be appointed. The committee may include a representative from each participating country, and they may provide scientific input and direction, in relation to the protocol and asset, to the GSK study team. In addition, the committee may assist with study conduct, including recruitment, protocol compliance and study challenges, for example. The scope and responsibilities of the Steering Committee will be detailed in the Steering Committee charter.

1.2. Schema

Figure 1 Study design overview



Abbreviations: d=day; FF = fluticasone furoate; ICS = inhaled corticosteroid; LABA = long-acting beta-2-agonist; R = randomization; S = screening; UMEC = umeclidinium bromide; V = visit; VI = vilanterol trifenate; w = weeks.

1.3. Schedule of activities (SoA)**Table 1 Schedule of activities**

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).

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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	
Spirometry		X	X	X		Visit 2 pre-bronchodilator assessments may be repeated within 7 days of Visit 2 (see Section 5.1 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 not achieved (see 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 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.

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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	
Exacerbation Assessment		X	X	X	X	Severe exacerbations will be recorded. Refer to Section 8.2.5.2 for the definition of a severe asthma exacerbation.
Adverse Events		X	X	X	X	The definition of and procedures for recording, evaluating, follow-up and reporting of adverse events is provided in 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.
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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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	

- 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.

2. INTRODUCTION

Asthma is a chronic inflammatory respiratory condition characterized by episodic and variable airflow limitation [Rennard, 2004; Demoly, 2012]. With a global prevalence of approximately 250 million people [World Health Organization, 2019], nearly 25 million Americans are affected by asthma [Lee, 2018]. Common symptoms of asthma include wheezing, shortness of breath, chest tightness, and cough [Demoly, 2012]. These symptoms may be exacerbated by exposure to allergens, respiratory tract infections, exercises, and cold air [Demoly, 2012]. Asthma exacerbations are a major driver of disease morbidity [Oppenheimer, 2022]. In addition to imposing considerable clinical burden on patients, asthma has also been associated with substantial economic burden [Pavord, 2017; GINA, 2023].

The current goal of asthma management is to control symptoms and mitigate exacerbations [Levy, 2023]. Treatment options for asthma include controller medications, such as ICS and LABAs, which help reduce inflammation and prevent symptom development; and reliever medications, such as SABAs, which provide rapid symptom relief [Levy, 2023; Reddel, 2022; Trelegy USPI, 2022]. The GINA guidelines recommend a stepwise treatment approach based on a patient's age, adherence status, and exacerbation risk [Levy, 2023]. The preferred initial treatment for adult patients with asthma is low-dose ICS-formoterol (i.e., ICS/LABA therapy), or alternatively, low-dose ICS along with as needed SABA. If symptoms worsen, increasing doses of maintenance ICS-formoterol or ICS/LABA with as needed SABA may be used; excessive use of oral steroids and/or SABAs are often key indicators of poor asthma control [Trelegy product monograph, 2022; Trelegy Australian PI, 2021; Lee, 2021]. For those with persistent symptoms or exacerbations despite good adherence to initial therapies, GINA recommends several add-on therapies, including LAMAs, azithromycin, biologics, and for patients with severely uncontrolled asthma, short course OCS.

2.1. Study rationale

The majority of studies evaluating SITT in asthma recruit patients with a history of exacerbations, but the greatest unmet need is in patients with uncontrolled asthma [Price, 2014b]. While different patients with asthma may vary in their experience of symptoms versus exacerbations, exacerbation rates are 0.1 to 0.2 per patient per year whereas 80% of patients with asthma experience symptoms within the previous 7 days [Price, 2014a; Price, 2014b; Martin, 2020]. The CAPTAIN (NCT02924688) study compared two Ellipta inhaler products containing FF and VI with the only differences between the two products being the inclusion of UMEC (i.e., evaluating the effects of FF/UMEC/VI vs. FF/VI). There is a paucity of data comparing FF/UMEC/VI delivered via the Ellipta dry-powder inhaler, to non-Ellipta alternative ICS/LABA formulations, including budesonide-formoterol. Outcomes of interest in asthma have long been focused on prevention or delay of exacerbations [GINA, 2023; Chen, 2008; CHMP, 2015]. It is believed that increased symptom control is an outcome that benefits more patients and helps to prevent downstream events.

The use of SITT in asthma is increasing and there is a considerable need to optimize disease management in patients with uncontrolled asthma. Additional evidence is needed to establish FF/UMEC/VI delivered via the Ellipta dry-powder inhaler versus non-Ellipta ICS/LABA usual care comparators for patients with uncontrolled asthma where symptom control is assessed as an outcome of treatment impact. 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) in adult participants with uncontrolled asthma.

2.2. Background

The fixed-dose triple combination of FF/UMEC/VI at doses of 100/62.5/25 mcg and 200/62.5/25 mcg, delivered via the Ellipta dry powder inhaler, has been approved in the US, Japan, Australia, Canada, and several other countries under the brand name Trelegy Ellipta, as a once-daily SITT for the maintenance treatment of asthma in adult patients aged 18 years and older.

The approvals for the adult asthma indication were based on data from a single pivotal GSK Phase 3 study 205715 (CAPTAIN, NCT02924688), which demonstrated that adult asthma participants who were uncontrolled on ICS/LABA gained additional bronchodilation and symptom control provided by FF/UMEC/VI compared to the fixed-dose dual combination of Ellipta-based FF/VI [Lee, 2021].

2.3. Benefit/risk assessment

Summaries of findings from both clinical and nonclinical studies conducted with GSK GW685698 +GSK573719+GW642444 (FF/UMEC/VI) can be found in the Investigator's Brochure (IB) and prescribing information [Trelegy Ellipta: US Prescribing Information, 2022]. Participants will continue their current asthma maintenance therapy products until randomization and marketed asthma products will be used for comparator treatments (ICS/LABA) during the randomized treatment period. These products will be used in accordance with the product labels and further details on experience with these products can be found in the Investigator Brochures and/or product labelling. Section 2.3.1 outlines the risk assessment and mitigation strategy for this protocol.

More detailed information about the known and expected benefits and risks and reasonable expected AEs of each study intervention and each auxiliary medicinal product may be found in the IB, participant information leaflet, package insert (e.g., Trelegy US Prescribing Information, [Advair, 2022] US Prescribing Information, 2023 and [SYMBICORT US Prescribing Information, 2017], DSUR, and summary of product characteristics (SmPC). Each participating country should use the product labels that have been approved by the appropriate regulatory authority, as RSI.

2.3.1. Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) [GW685698+GSK573719+GW642444]		
Cardiovascular effects	Cardiovascular effects, such as cardiac arrhythmias e.g., atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists or sympathomimetic agents, including umecclidinium or vilanterol, respectively. Vilanterol, like other beta2-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. In the completed pivotal study in asthma, 205715, which included 2439 participants and investigated the efficacy and safety of FF/UMEC/VI (100/31.25/25; 200/31.25/25; 100/62.5/25; 200/62.5/25 mcg) compared to FF/VI (100/25; 200/25 mcg) the percentage of participants with adverse events of special interest (AESIs) in the CV effects special interest group ranged from 4% to 7% across the treatment groups (highest in the FF/UMEC/VI 100/62.5/25 group). CV effects AESI reported in $\geq 1\%$ of participants in any treatment group were hypertension (range: 1% to 2%) and blood pressure increased (range: $<1\%$ to 1%). Few AESIs in the CV effects special interest group met the criteria of an SAE (range: 0-4 participants [$<1\%$ in all groups]).	Exclusion criteria as specified in Section 5.2 of the protocol Cardiovascular AEs and Serious AEs (SAEs) will be captured on the electronic Case Report Form (eCRF) (see Section 10.2)

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Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	0There were 2 CV deaths reported, 1 of circulatory collapse in the FF/VI 200/25 group and 1 of hypertrophic cardiomyopathy in FF/UMEC/VI 100/31.25/25. Neither CV death was considered drug-related. There were few participants with >1 on-treatment major adverse cardiac event (MACE; broad definition) in each of the treatment groups (range: 2 to 5 participants [$<1\%$ to 1%]). For both the FF 100 and FF 200 mcg containing treatment groups, there was a small difference in the number of narrow MACE in the UMEC 62.5-containing FF/UMEC/VI groups vs FF/VI (1 in both FF/VI 100/25 mcg and FF/UMEC/VI 100/31.25/25 mcg, and 3 in 100/62.5/25 mcg; 0 in both FF/VI 200/25 mcg and FF/UMEC/VI 200/31.25/25 mcg, and 2 in 200/62.5/25 mcg). No clinically meaningful differences were observed between FF/UMEC/VI and FF/VI for any electrocardiogram (ECG) parameters, vital signs or laboratory parameters.	
Anticholinergic effects (including constipation nausea, dry mouth, effects on the eye, urinary retention)	In the completed pivotal asthma study, 205715, the percentage of participants with AESIs in the Anticholinergic syndrome (standardized Medicinal Dictionary for Regulatory Activities [MedDRA] queries.[SMQ]) special interest group ranged from 1% to 3% across the treatment groups and the events occurring in ≥ 1 participant in any treatment group were dizziness (range: 1 to 4 participants [$<1\%$ in all groups]), pyrexia (range: 0 to 5 participants [$<1\%$ in all groups]), and tachycardia (range: 0 to 3 participants [$<1\%$ in all groups]). Dry mouth/drying of the airway secretions (broad focus) special interest group was the most frequently reported special interest group across all treatment groups (range: 22% to 24%), driven by nasopharyngitis (range: 13% to 15%). In the dry mouth/drying of the airway secretions (narrow focus) special interest group, 2 preferred terms were reported (dry throat and dry mouth), both occurring in few participants (4 participants and 3 participants, respectively). Dysgeusia is an adverse drug reaction (ADR) listed for FF/UMEC/VI.	Participants with medical history that, in the opinion of the Investigator, contraindicates study participation or use of an inhaled anticholinergic, will be excluded from participating in the study. Instream review of data, including AEs and SAEs.

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Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	ICS has a similar class risk of glaucoma and elevated intraocular pressure (IOP); however, these effects occur by a different mechanism that is not expected to be synergistic or additive when FF is used in combination with UMEC.	
Systemic ICS effects -Adrenal suppression -Effects on the eye -Reduced bone mineral density and associated fractures	No studies have shown a clinically relevant effect of FF/VI or FF on the hypothalamic pituitary axis (HPA). This includes a formal HPA study (HZA106851), which assessed the effects of FF/VI 100/25 and 200/25 on serum cortisol and 24-hour urinary cortisol excretion, and multiple studies with COPD and asthma participants which monitored urinary cortisol. During clinical development of FF& FF/VI no events of adrenal suppression were reported. No events were reported in the adrenal suppression AESI group in the completed pivotal asthma study, 205715. There has been no evidence for adrenal suppression based on post-marketing experience to date. In study HZA106839 (FF/VI, FF and fluticasone propionate (FP) in participants with asthma), formal ophthalmic assessments were conducted (including Lens Opacities Classification System III (LOCS III) evaluations for ocular opacities) throughout the study. This study showed no apparent effects on lens opacification, compared to baseline assessment. In the completed pivotal asthma study, 205715, 3 events of cataract were reported (1 event in FF/VI 200/25 mcg; 1 event in FF/UMEC/VI 100/62.5/25 mcg and 1 event in FF/UMEC/VI 200/62.5/25 mcg). During studies in both participants with asthma and COPD, no associated effect on ocular disorders was observed. Spontaneous data received to date does not alter the understanding of this risk. A decrease in bone mineral density and the risk of fractures is a class concern for any ICS-containing product for the treatment of COPD.	Participants will be informed about the risks in the informed consent. Investigators are made aware of the potential for these class effects in Section 6 (warnings and precautions) of the IB. The occurrence of bone fractures will be recorded in the eCRF if deemed related to study intervention. Instream review of data, including AEs and SAEs.

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Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In 2 replicate 12 month studies in the FF/VI clinical program, in a total of 3255 patients with COPD, the incidence of bone fractures overall was low in all treatment groups, with a higher incidence in all FF/VI groups (2%) compared with the VI 25 mcg group (<1%). Although there were more fractures in the FF/VI groups compared with the VI 25 mcg group, fractures typically associated with corticosteroid use (e.g., spinal compression/thoracolumbar vertebral fractures, hip and acetabular fractures) occurred in <1% of the FF/VI and VI treatment arms. In an integrated analysis of 11 studies in asthma with FF/VI (7034 patients) and 10 studies in asthma with FF (6219), the incidence of fractures with FF/VI and FF was ≤1%, and usually associated with trauma.	
Pneumonia	While ICS use is a recognized risk for pneumonia in patients with COPD a clear causal relationship between inhaled corticosteroid use and pneumonia in subjects with asthma has not been established. Pneumonia is a risk carried by the inhaled corticosteroid class of compounds. An increased incidence of pneumonia with higher doses of ICS cannot be ruled out, however the absolute risk of pneumonia with FF appears to be very small and consistent with other ICS. In the completed pivotal study in asthma, 205715, there was a similar and low incidence of pneumonia AESIs in the participants in the FF/UMEC/VI (range <1% to 2%) and FF/VI (2%) treatment groups. Thirty-six participants had an on-treatment event in the Infective pneumonia (SMQ) special interest group [<1% to 2%]). For 16 participants the infective pneumonia (SMQ) AESI was serious. There was a small increase in the number of serious pneumonia AESIs at FF 200 mcg dose groups (n=10 participants) compared with FF 100 mcg dose groups (n=6 participants). There were no pneumonia AESI with a fatal outcome. In the pneumonia eCRF, there was a similar incidence of on-	Participants are alerted to the potential risk of pneumonia in the informed consent. Investigators are informed of the risk in the warnings and precautions section of the IB (Section 6). Exclusion criteria as specified in Section 5.2 of the protocol. The occurrence of pneumonia will be recorded in the eCRF. Where possible a chest X-ray should be performed to confirm a diagnosis, whenever a participant has a suspected pneumonia. All reports of pneumonia (radiographically confirmed and unconfirmed) must be reported as an AE or SAE, if applicable. Instream review of data, including AEs and SAEs.

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Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	treatment pneumonia in the FF/UMEC/VI (<1%-2%) and FF/VI (2%) treatment groups. There was a small increase in the number of pneumonia events as FF dose increased, 16 participants at FF 100 mcg doses vs 20 participants at FF 200 doses. In an 18-study integration in the FF/VI asthma program, the incidence of pneumonia (adjusted for exposure) observed with FF/VI 100/25 mcg and FF 100 mcg (8.5/1000 patient years and 9.6/1000 patient years, respectively) was similar to that seen with placebo (9.3/1000 patient years). A higher incidence in the FF/VI 200/25 mcg and FF 200 mcg arms were observed (18.3/1000 patient years and 23.6/1000 patient years, respectively). However, the 95% CIs were wide and overlapped across all treatment groups, including placebo. Few of the pneumonia events led to hospitalization with either strength, and there were no observed differences in the incidence of serious events between the 2 treatment strengths. The risk of pneumonia in asthma patients is very low and is consistent with the risk of other ICS.	
Hypersensitivity	In the completed pivotal asthma study, 205715, AESI for hypersensitivity were balanced across treatment groups for FF/VI and FF/UMEC/VI (4% to 5%) There have been post-marketing reports of hypersensitivity reactions with FF/UMEC/VI, including anaphylaxis, angioedema, rash, and urticaria. The formulation also contains lactose.	Participants with a history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate are excluded from participation in this study (Section 5.2). Instream review of data, including AEs and SAEs.
Paradoxical bronchospasm	Rare reports of paradoxical bronchospasm (which may be life threatening) with other inhalational products have been reported. There have been rare post-marketing reports of paradoxical bronchospasm with FF/VI and UMEC/VI.	Instream review of data, including AEs and SAEs.

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Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Pregnancy and lactation	There are limited data from the use of FF/UMEC/VI in pregnant women. There has been limited pregnancy exposure to FF and FF/VI in humans. Animal studies have shown reproductive toxicity after administration of corticosteroids and beta2-agonists. There is a limited amount of data from the use of umecclidinium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There is limited information on the excretion of FF or VI or their metabolites in human milk. However, other corticosteroids and beta2-agonists are detected in human milk. It is unknown whether umecclidinium is excreted in human milk. The excretion of FF/UMEC/VI in breast milk has not been evaluated. A risk to breastfed newborns/infants cannot be excluded.	Females who are pregnant or breastfeeding are not eligible for participation in the study. Females of childbearing potential will need to follow the contraceptive requirements that are specified in Section 10.3.
Serious asthma related events	This is a risk carried by the class of LABA compounds. During the FF/VI studies for the asthma composite endpoint (asthma exacerbations leading to hospitalization, intubation and/or death), there was no significant difference between the FF/VI group and the ICS group or non-LABA group, demonstrating no increased risk when adding a LABA to an ICS. Three large completed studies with ICS/LABA compounds (one in pediatric participants) have shown no increased risk of serious asthma related events compared with ICS alone [Stempel, 2016a; Stempel, 2016b; Peters, 2016].	Participants with history of life-threatening asthma are excluded from the study. Participants will be advised to contact the investigator or their physician immediately.

2.3.2. Benefit assessment

Current asthma treatment guidelines recommend the addition of a LAMA for patients that are uncontrolled on ICS/LABA [GINA, 2023]; the availability of the FF/UMEC/VI combination would therefore be consistent with this approach. The combination as a SITT provides the convenience of once-daily dosing and reduces the need for multiple inhalers.

2.3.3. Overall benefit-risk conclusion

The clinical development program for FF/UMEC/VI demonstrated a favorable benefit/risk for patients with asthma. This has led to approval and marketing of FF/UMEC/VI delivered via the Ellipta dry-powder inhaler for an asthma indication in the US, Japan, Australia, Canada and several other countries for the maintenance treatment of asthma in patients aged 18 years and older.

The current experience with FF, UMEC, and VI and the lack of significant safety concerns relevant to the asthma population provides reassurance that the potential risks associated with the known pharmacology of these compounds is offset by the potential significant benefits that are afforded to patients with inadequately controlled asthma.

The ICS/LABA used in the comparator arm is marketed for the treatment of asthma. Each participating country should use the product labels that have been approved by the appropriate regulatory authority, as RSI.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 2 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 (FEV₁) 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
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 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 derivatives¹) 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

Objectives	Endpoints
	- 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 with ICS/LABA after 52 weeks of treatment for participants on no treatment 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 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-2 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 52 weeks of treatment

Objectives	Endpoints
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)

¹ ACQ-6 and ACQ-5 are derived from ACQ-7 by removal of the lung function element (ACQ-6) and lung function and rescue use elements (ACQ-5)

PRIMARY ESTIMAND

The primary endpoint is defined as change from baseline in trough FEV₁ after 24 weeks of treatment.

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:

- **Target Population:** all randomized patients aged 18 years or older with uncontrolled asthma as defined by the inclusion/exclusion criteria.
- **Endpoint:** Change from baseline in trough FEV₁ at Week 24
- **Treatment condition:** FF/UMEC/VI versus ICS/LABA.
- **Intercurrent events:**
 - a) 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, 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 will be included).
 - b) Use of prohibited medication: analysis will be handled by treatment policy strategy. All observed data will be included in the analysis regardless of the intercurrent events.
 - c) 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).
- **Population-level summary:** Difference in means.

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 patients 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.

For the primary endpoint, 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, 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).

SECONDARY ESTIMAND(S)

The key secondary endpoint is defined as achieving ≥ 0.5 points improvement (decrease) from baseline for the Asthma Control Questionnaire-7 (ACQ-7) at Week 24.

The key secondary clinical question of interest is:

What is the treatment effect on achieving ≥ 0.5 points improvement (decrease) from baseline for the 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 patients aged 18 years or older with uncontrolled asthma as defined by the inclusion/exclusion criteria.
- **Endpoint:** Achieving ≥ 0.5 points improvement (decrease) from baseline for the Asthma Control Questionnaire-7 (ACQ-7) at Week 24
- **Treatment condition:** FF/UMEC/VI versus ICS/LABA.
- **Intercurrent events:**
 - a) 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, then the analysis will be handled by treatment policy strategy. All observed data will be included in the analysis regardless of the intercurrent event.

- b) Use of prohibited medication: analysis will be handled by treatment policy strategy. All observed data will be included in the analysis regardless of the intercurrent events.
 - c) 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).
- **Population-level summary:** Odds ratio on the percent of participants.

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 patients 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.

Similar to the primary endpoint, for the key secondary endpoint, a supplemental estimand will be defined where 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. 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).

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 estimand 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.

4. STUDY DESIGN

4.1. Overall design

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. The primary statistical analysis will be completed once all participants complete 24 weeks of treatment, and the final analyses will be completed once all participants complete the 52 weeks of the study.

The total duration of the study will be approximately 53 weeks, including a 52-week treatment period, and a 1-week safety follow-up. The study will include 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 will be conducted via telephone.

Participants will continue their current asthma maintenance medication(s) until randomization.

Participants will be randomized to receive FF/UMEC/VI (once a day) or ICS/LABA (in-line with dosing regimen in appropriate regulatory label) and the randomization will be stratified by pre-study asthma maintenance therapy (untreated [as defined in Section 5.1], ICS alone, ICS/LABA) and pre-study ICS dose (low, high). An overview of the study design is displayed in [Figure 1](#).

Approximately 1420 participants will be screened to achieve 1136 randomly assigned to study intervention, with 568 participants randomized in a 1:1 ratio to each group (FF/UMEC/VI 100/62.5/25 mcg versus ICS/LABA). A subset of participants within each group may also be randomized to 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. At any time during the study (post-randomization), participants on FF/UMEC/VI 100/62.5/25 mcg or usual care ICS/LABA may be escalated to FF/UMEC/VI 200/62.5/25 mcg or high-dose ICS/LABA, respectively, if they demonstrate significant worsening of control (i.e., change in ACQ-7 score >0.5) after randomization **AND** their

treating physician determines that an increased dose of ICS is necessary for ethical reasons.

Participants should continue to receive usual clinical care until randomization, according to the physician's discretion, and in line with local care guidelines. The SoA is provided in [Table 1](#).

4.2. Scientific rationale for study design

This study is a 52-week, stratified, multicenter, pragmatic, open-label, randomized, controlled trial evaluating the effectiveness of initiating FF/UMEC/VI vs remaining or being initiated on non-Ellipta ICS/LABA comparators in patients with uncontrolled asthma who are not frequently exacerbating. Although the intention of this study is to assess FF/UMEC/VI in a minimally interventional routine clinical care setting, a randomized parallel group design has been chosen to provide the most robust evidence of clinical effectiveness. The comparison of randomized-treatment groups will enable a fair assessment of the effectiveness of FF/UMEC/VI relative to non-ELLIPTA ICS/LABA.

The study population is intended to be broad and reflect asthma patients that are uncontrolled and may be suitable for triple therapy.

The primary analysis will be completed once all participants receive study intervention for 24 weeks, and the final analyses will be completed once all participants complete the study (52 weeks). A treatment period of 24 weeks is considered to be of adequate duration in order to assess the effectiveness of FF/UMEC/VI, compared to ICS/LABA, in terms of lung function and other effectiveness endpoints. A 52-week treatment period is considered appropriate for the assessment of a composite endpoint that includes the assessment of lung function, asthma control, severe exacerbations and OCS use. A treatment period of 52 weeks is also considered to be of suitable duration to assess the safety of FF/UMEC/VI.

4.3. Justification for dose

The FF/UMEC/VI 100/62.5/25 mcg and 200/62.5/25 mcg doses are based on approvals received in the US and several other countries for the maintenance treatment of asthma in adult participants. The ICS/LABA doses are based on usual care as per the country specific regulatory labels.

4.4. End-of-study definition

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.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. **Age and Sex:** Male or female participants who are 18 to 75 years of age at the time of signing the informed consent.
2. **Informed Consent:** Capable of giving signed informed consent (further details are provided in Section 10.1.3).
3. **Type of Subject:** Has a diagnosis of asthma as defined by GINA 2023 guidelines prior to or at the screening visit (V1).
4. Participants who are either:
 - a) **Currently untreated.** 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.”
 - b) **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.
5. **Severity of symptoms:** ACQ-6 score ≥ 1.5 at randomization (V2).
6. **Study Questionnaires:** Participants must be able to complete the study questionnaires.
7. **Lung function testing:** Participants able to perform technically acceptable and repeatable FEV₁ maneuvers (i.e., a minimum of 2 acceptable and 1 repeatable effort) at V2.

NOTE: (please refer to the vendor manual for further details on performing spirometry assessments): Participants who are unable to perform FEV₁ maneuvers (i.e., a minimum of 2 acceptable and 1 repeatable efforts) at Visit 2 can, at the discretion of the investigator, attend the clinic once more after Visit 2 to attempt to perform the FEV₁ maneuvers again. This must be within 7 days of Visit 2.

5.2. Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

1. **Recent history of life-threatening asthma:** Defined as an asthma episode that required intubation and/or associated with hypercapnea, respiratory arrest or hypoxic seizures within the last 5 years.
2. **History of >1 severe exacerbation** of asthma within 12 months prior to randomization.

A severe exacerbation is defined as a deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. A single depo injection of systemic corticosteroids will be considered to meet the definition of a severe exacerbation.

3. **Women of childbearing potential that are not following at least one highly effective method of contraception.** This includes women who are pregnant or lactating or are planning on becoming pregnant during the study.

A female participant will be eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP)
OR
- Is a WOCBP and using an acceptable contraceptive method (see Section 10.3 for details) during the duration of the study. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

A WOCBP must have a negative highly sensitive urine pregnancy test (or serum if required by local regulations) ≤ 7 days prior to randomization.

NOTE: additional requirements for pregnancy testing during and after study intervention are defined in Section 8.3.2.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

4. **Exposure to inhaler triple therapy** (ICS+LAMA+LABA as SITT or MITT) and/or any **LAMA-containing therapy** within 12 months prior to randomization.
5. **Ongoing need for biologic therapy or recent use of a biologic therapy** (i.e., within 12 months of randomization or within 5 half-lives ($t_{1/2}$) of the prior investigational study, whichever is the longer duration).

6. **Chronic Obstructive Pulmonary Disease:** Participants with the diagnosis of chronic obstructive pulmonary disease, as per Global Initiative for Chronic Obstructive Lung Disease [[GOLD](#), 2024] guidelines.
7. **Other diseases/abnormalities:** Participants with historical or current evidence of uncontrolled or clinically significant disease. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the participant at risk through participation, or which would affect the effectiveness or safety analysis if the disease/condition exacerbated during the study.
8. Participants whose current medications include **RELVARELLIPTA** and **ARNUTY ELLIPTA** are not eligible to enter the study.
9. **Rescue Medication:** Participants who are medically unable to withhold their albuterol/salbutamol for 6 hours prior to spirometry testing at Visit 2 and the morning of each study visit with spirometry thereafter.
10. **Maintenance Medication:** Participants who are medically unable to withhold their morning maintenance ICS/LABA and/or ICS/LAMA/LABA for 24 hours prior to spirometry testing at Visit 2 and the morning of each study visit with spirometry thereafter.
11. **Changes in asthma medication** (e.g., maintenance ICS/LABA) within 3 months prior to randomization.
12. **Systemic corticosteroids:** Participants that require systemic corticosteroids for reasons other than the treatment of an asthma exacerbation.
13. **Drug/food allergy:** Participants with a history of hypersensitivity to any of the study medications (e.g., corticosteroid, anticholinergic/muscarinic receptor antagonist, beta-2-agonist) or components of the inhalation powder (e.g., lactose, magnesium stearate). Subjects that have lactose intolerance (an inability to digest lactose) are not excluded. Participants with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should be excluded.
14. **Participants taking any investigational drug treatment** within 3 months prior to randomization or within 5 half-lives ($t_{1/2}$) of the prior investigational study (whichever is the longer duration).
15. In the opinion of the investigator, any participant who is **unable to read** and/or would not be able to complete study-related materials.

5.3. Lifestyle considerations

Not applicable.

5.4. Screen failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomized to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened; however, written approval to proceed with rescreening must be obtained from the GSK Medical Monitor in advance (see the local study contact information document for contact details). Rescreened participants should be assigned a new participant number for every screening/rescreening event. Previously assigned participant numbers are to be recorded in the participants' eCRF.

Participants who are unable to perform technically acceptable and repeatable spirometry maneuvers, at Visit 2, can repeat these maneuvers at a separate visit (within 7 days), using the same participant number. Such participants are not screen failures and do not need a new participant number.

5.5. Criteria for temporarily delaying enrollment/randomization/administration of study intervention

Not applicable.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

The definition of study intervention is provided in the [list of abbreviations and definitions of terms](#).

6.1. Study interventions administered

All study interventions will be sourced from commercial supply. Descriptions of the study interventions are provided in [Table 3](#). The process for the payment/reimbursement of study intervention will be dependent on each country's regulations and guidelines. Study intervention will be provided with no cost to the participant (per local practice, if the participant is charged at the point of collection, this cost will be reimbursed to the participant at the earliest opportunity).

Table 3 Study intervention(s) administered

Intervention Label	Trelegy Ellipta		Inhaled corticosteroid (ICS)/ Long-acting beta-2 agonist (LABA) (non-Ellipta).
Intervention Name	fluticasone furoate/umeclidinium bromide/vilanterol trifenate (FF/UMEC/VI)		ICS/LABA (non-Ellipta)
Intervention Description	30 doses; the Ellipta Dry Powder Inhaler (DPI) is a molded plastic 2-sided device that can hold 2 individual blister strips (2 strips with 30 blisters per strip)		Based on usual care as per the country specific regulatory labels and investigator discretion
Type	Drug-Device Combination		Drug-Device Combination
Dose Formulation	Ellipta with 30 doses (2 strips with 30 blisters per strip)		Non-ellipta usual care as per the country specific regulatory labels
Unit Dose Strength(s)	FF 100 mcg/ UMEC 62.5 mcg/ VI 25 mcg	FF 200 mcg/ UMEC 62.5 mcg/ VI 25 mcg	
Dosage Level(s)	1 actuation once daily (QD)		
Route of Administration	Oral inhalation via a DPI		
Use	Experimental (marketed drug)		
Sourcing	Commerical supply via study intervention prescriptions		Commercial Supply via study intervention prescriptions
Packaging and Labelling	Packaged and labelled per country requirements		Packaged and labelled per country requirements

Table 4 Study arms

Arm Title	fluticasone furoate/umeclidinium bromide/vilanterol trifenate (FF/UMEC/VI)	Inhaled corticosteroid (ICS)/Long-acting beta-2 agonist (LABA)
Arm Type	Product under investigation	Active comparator
Arm Description	Participants will receive FF/UMEC/VI 100/62.5/25 mcg or 200/62.5/25 mcg once daily in the morning via the Ellipta dry powder inhaler (DPI) for 52 weeks, starting at the Randomization Visit (Visit 2)	Participants will receive ICS/LABA per the country specific regulatory labels, starting at the Randomization Visit (Visit 2)
Associated Intervention Labels	Trelegy Ellipta	Product label(s) of assigned ICS/LABA

6.1.1. Medical devices

The GSK manufactured medical device provided for use in this study is Ellipta.

Instructions for medical device use are provided in TRELEGY Ellipta Prescribing Information [[Trelegy Ellipta: US Package Insert, 2022](#)].

All device deficiencies (including malfunction and use error) shall be documented and reported by the investigator throughout the clinical investigation (see Section 10.4) and appropriately managed by GSK.

6.2. Preparation, handling, storage, and accountability

All randomized participants will receive study intervention prescriptions for FF/UMEC/VI or ICS/LABA, as per usual clinical practice.

6.3. Assignment to study intervention

Type of Study	
Study using IVRS/IWRS	All participants will be centrally assigned to randomized study intervention in accordance with the randomization schedule. The randomization number(s) will be generated using a validated computerized system. Randomization will occur via IVRS/IWRS. The study will use central-based randomization to allocate treatments. Once a randomization number is assigned to a participant it cannot be reassigned to any other participant in the study. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site. Study intervention prescriptions will be dispensed at the study visits as summarized in the SoA.

6.4. Blinding, masking

Blinding procedures will not be used in this open label study.

6.5. Study intervention compliance

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

6.6. Dose modification

ICS/LABA tapering is not prohibited but it is also not expected. ICS escalation is permissible. At any time during the study, participants on FF/UMEC/VI 100/62.5/25 mcg or usual care ICS/LABA may be escalated to FF/UMEC/VI 200/62.5/25 mcg or high-dose ICS/LABA, respectively, if they demonstrate significant worsening of control (i.e., change in ACQ-7 score [increase] >0.5) after randomization **AND** their treating physician determines that an increased dose of ICS is necessary for ethical reasons.

Refer to Section 7.1 for study intervention discontinuation criteria.

6.6.1. Retreatment criteria

Not applicable.

6.7. Continued access to study intervention after the end of the study

After completion of the study, the investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition. FF/UMEC/VI and usual care ICS/LABA are commercially available in all countries that are participating in this study and will be possible treatment options for patients following completion of the study.

6.8. Treatment of overdose

An overdose is defined as a dose greater than one dose of study intervention per day that results in clinical signs and symptoms. These should be recorded by the investigator on the AE/SAE eCRFs. In the event of an overdose of study intervention, the investigator should use clinical judgment in treating the overdose and contact the GSK Medical Monitor (see the local study contact information document for contact details).

GSK does not recommend specific treatment for an overdose and toxicity management. The investigator is advised to refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study drug being used in this study. Such documents may include, but not be limited to, the prescribing information or equivalent document provided by GSK.

6.9. Prior and concomitant therapy

All asthma medications used within approximately 3 months prior to randomization and during the study (including the Safety Follow-up Period) should be recorded in the eCRF (see Section 6.10 for rescue medication requirements).

All non-asthma medications taken during the study (after randomization including safety follow-up) and any changes to concomitant medications will be recorded in the eCRF. Note: The temporary use of asthma medication for asthma exacerbations will be recorded in the eCRF.

The minimum requirement is that the drug name, dose, route and the dates of administration are to be recorded.

Participants should be prescribed medications at the Investigator's discretion according to usual care, with reference to the Investigator Brochure/product label for potential interactions.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Asthma Medications

Asthma exacerbations should be treated in line with national and international recommendations and local medical standards. Medications used may include:

- An increase in ICS dose.
- Systemic corticosteroids.
- An investigator-advised change in SABA use (i.e., routinely scheduled versus as needed use).
- Leukotriene receptor antagonists (LTRAs) and leukotriene modifiers.
- Oral theophylline.

A severe asthma exacerbation is defined as a change in asthma symptoms requiring systemic corticosteroid (tablets, suspension or injection) for at least 3 consecutive days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. A single depo injection of systemic steroids will be considered to meet the definition of a severe exacerbation. Systemic corticosteroids for other conditions will be permitted.

6.9.2. Non-Asthma Medications

Guidance/caution is provided in relation to the use of the following:

- Systemic and ophthalmic beta-blockers: Administer with caution as systemic beta-blockers block the pulmonary effect of beta-agonists and may produce severe bronchospasm in patients with reversible obstructive airways disease. Cardio selective beta-blockers should be considered, although they also should be administered with caution.
- Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). (Administer with extreme caution as they may potentiate the effects of beta-agonists on the cardiovascular system, including QTc prolongation)
- Diuretics (Caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics as this may result in ECG changes and/or hypokalemia).
- Cytochrome P450 3A4 (CYP3A4) inhibitors (Caution should be exercised when considering the coadministration of long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur)

All medications for other disorders may be continued throughout the study provided their use would not be expected to affect the participants' lung function or safety assessments.

6.10. Rescue medicine

Participants should continue to take the rescue medication they were taking prior to participation in the study. LAMA-containing therapy should not be taken in the 12 months prior to the screening visit (Visit 1) and muscarinic antagonists (i.e., SAMA) cannot be used as rescue medication, throughout the study.

Rescue medication should be used, as required, throughout the study. The name of the rescue medication and the number of used canisters used within the 12 months prior to randomization, must be recorded in the eCRF. The number of used canisters may be obtained from patient recall and review of electronic medical records.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

Discontinuation of study intervention refers to any participant who has not received all planned doses of the study intervention. In rare instances, it may be necessary for a participant to permanently discontinue study intervention. Participants are required to return any unused study intervention prescriptions to sites, following the discontinuation of study intervention. Participants will be prescribed an appropriate medication, as determined by their treating physician and study intervention prescriptions (or reimbursement) will no longer be provided. FF/UMEC/VI and usual care ICS/LABA are commercially available in all countries that are participating in this study and will be possible treatment options for patients following the discontinuation of study intervention.

Participants randomized to the ICS/LABA group will discontinue randomized medication if their treating physician determines that escalation to SITT/MITT is necessary for ethical reasons. Participants randomized to FF/UMEC/VI will discontinue randomized medication if their treating physician determines that ICS/LABA or an alternative asthma maintenance medication would be more suitable.

Participants who permanently discontinue study intervention are not required to withdraw from the study. Discontinuation of study intervention does not impact a participant's participation in the study. Participants who have permanently discontinued study intervention and have not withdrawn consent should comply to the protocol schedule of assessments in the study protocol at the discretion of the investigator. The data for study assessments conducted after the participant has permanently discontinued study intervention will be recorded as "post-treatment". A Safety Follow-up Visit should also be completed 7 days after study intervention is discontinued. Refer to the SoA in [Table 1](#) for details.

The primary reason for premature discontinuation of the study intervention will be documented in the eCRF.

7.2. Participant withdrawal from the study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the investigator for safety reasons.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

At the time of early withdrawal from the study, an Early Withdrawal Visit should be conducted, if possible, as shown in the SoA. Refer to the SoA ([Table 1](#)) for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from the study intervention and withdrawn from the study at that time. Participants will be prescribed an appropriate medication, as determined by the treating physician. FF/UMEC/VI and usual care ICS/LABA are commercially available in all countries that are participating in this study and will be possible treatment options for patients following discontinuation of study intervention and withdrawal from the study.

All data and samples (for example, urine for pregnancy testing) collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this request in the site study records.

The primary reason for participant withdrawal from the study will be documented in the eCRF.

Participants who are withdrawn from the study because of aEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. The investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see [Section 10.2.5.5](#)).

7.3. Lost to follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the

assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study with a primary reason of lost to follow up.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA in [Table 1](#). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Participants who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of "screen failure".
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided that the procedures met the protocol-specified criteria and are performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, study intervention distribution, and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

8.1. Administrative and general/baseline procedures

8.1.1. Collection of demographic data

Record demographic data such as age, sex, race, and ethnicity in the participant's eCRF.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.1.2. Medical history

Obtain the participant's medical history by interviewing the participant and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the first dose of study intervention in the eCRF.

8.2. Effectiveness assessments

Planned time points for all effectiveness assessments are provided in the SoA.

8.2.1. Pulmonary function testing

Spirometry will be performed at the study site on the specified study visits to assess FEV₁ and FVC. At least 2 acceptable spirometry maneuvers (from a maximum of 8 attempts) should be achieved on each occasion that spirometry assessments are performed, in accordance with the ATS/ERS Task force: Standardization of Lung Function Testing [Graham, 2019].

At the Randomization Visit (V2), there must be a minimum of 2 acceptable and 1 repeatable spirometry effort for a participant to be eligible for the study. At Visits 2 through EoS (and the Early Withdrawal Visit, if applicable), participants should withhold SABAs for at least 6 hours and LABA for 24h prior to the clinic visit, if possible. Participants who have not withheld these medications will be asked to return to the clinic to perform the spirometry measures within 7 days of the original visit date, and within the study visit window (where possible). 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. Spirometry assessments should be performed at approximately the same time of day as the assessment performed at Visit 2 (the baseline assessment).

The baseline value of FEV₁ is defined as the highest acceptable/borderline acceptable pre-dose FEV₁ obtained at the Randomization Visit (Visit 2).

Spirometry equipment will be provided to all sites by a third-party vendor; the same third-party vendor will also centrally analyse the spirometry data from this study. Details on performing the spirometry assessments, including information on the equipment provided and its use as well as specific instructions on performing the spirometry maneuvers, are documented in the third-party vendor manual.

8.2.2. Patient Reported Outcome Questionnaires

Patient Reported Outcome Questionnaires, including the ACQ, ACT, AQLQ+12 and WPAI: Asthma should be completed before any procedures are performed on the participant to avoid influencing the participant's response. To avoid biasing responses, the participants should not be told the results of diagnostic tests prior to completing the questionnaires and it is recommended that the questionnaires be administered at the same time of day during each visit (as applicable) using the provided electronic device (unless otherwise specified). Adequate time must be allowed to complete all items on the questionnaire.

All Patient Reported Outcome Questionnaires will be self-administered using an ePRO device during specified visits as indicated in the SoA (Table 1).

8.2.2.1. Asthma Control Questionnaire (ACQ)

The ACQ-7 measures 7 attributes of asthma control [Juniper, 1999] and consists of 5 symptom related questions (nocturnal awakening, symptoms on waking in the morning, activity limitation, shortness of breath and wheeze with response options ranging from zero [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 FEV₁ (included via study visit spirometry). The recall period is the previous 7 days. A score of ≤ 0.75 indicates well-controlled asthma and a score ≥ 1.5 indicates poorly controlled asthma [Juniper, 2006]. A change of 0.5 in score suggests a clinically important change in asthma control.

Participants will complete the ACQ at specified Study Visits.

Two shorter versions of the ACQ are also included as endpoint measures: ACQ-5 (a 5-item measure using only the symptoms items) and the ACQ-6 (ACQ-5 symptom questions and rescue bronchodilator use). ACQ-6 and ACQ-5 are derived from ACQ-7 by the removal of the lung function element (ACQ-6) and lung function and rescue use elements (ACQ-5). The measurement properties were very similar for all versions of the ACQ (original 7-item ACQ and shortened versions) [Juniper, 2005a; Wyrwich, 2011].

The ACQ total score recorded at the Randomization Visit (Visit 2) will be the baseline value.

Instructions for completing the ACQ are provided in the vendor manual.

8.2.2.2. Asthma Control Test (ACT)

The ACT is a 5-question health survey used to measure asthma control in participants aged ≥ 12 years. 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]. The ACT is considered an efficient, reliable, and valid method of measuring asthma control, with or without lung functioning measures such as spirometry.

8.2.2.3. Asthma Quality of Life Questionnaire

The AQLQ was developed to measure the functional impairments related to asthma experienced by participants aged ≥ 17 years. There are 32 questions in the AQLQ assessing 4 domains including symptoms, activity limitation, emotional function and environmental stimuli. The AQLQ (+12), is a modified version of the original AQLQ with standardized activities and has been validated for use in asthma patients between the ages of 12 and 70 [Juniper, 2005b]. The response scale ranges from 1 (totally impaired) to 7 (not at all impaired). The questions are designed to be self-completed by the subject with a recall over the past 2 weeks. Higher scores indicate better asthma-related health-related quality of life, and a change of 0.5 is considered clinically important [Juniper, 1994].

8.2.2.4. Work Productivity and Activity Impairment Questionnaire: Asthma

The WPAI:Asthma is an asthma-specific adaptation of the WPAI. The WPAI:Asthma is a self-administered tool composed of 9 items representing 3 domains: work impairment (4 items), school impairment (4 items), and activity impairment (1 item). Participants will be asked to score the impact of their asthma on their ability to work, attend classes, and perform regular daily activity during the past 7 days. The work and school domains incorporate a skip pattern that allows subjects to respond only to relevant items depending on whether they are currently employed, taking classes, or both. WPAI:Asthma outcomes are scored as impairment percentages, with a higher percentage indicating greater impairment and less productivity [Chen, 2008].

8.2.3. Use of short-acting beta-2 agonist (SABA)

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 (Table 1).

8.2.4. Use of oral corticosteroid (OCS)

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 (Table 1).

8.2.5. Asthma exacerbations

For the purposes of this study, all severe asthma exacerbations will be collected and recorded on the asthma exacerbation eCRF page from the start of study intervention until Visit 4 or the Early Withdrawal Visit. Severe asthma exacerbations are disease-related events (DREs) and should not be reported as an AE/SAE, unless they meet the criteria specified in Section 8.4.8.

For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

8.2.5.1. Moderate Asthma Exacerbation

A moderate asthma exacerbation is considered to be a deterioration in asthma symptoms, deterioration in lung function, or increased rescue bronchodilator use lasting for at least 2 days or more but is not severe enough to warrant systemic corticosteroid use (or a doubling or more of the maintenance systemic corticosteroid dose) for 3 days or more and/or hospitalization.

A moderate asthma exacerbation is an event that, when recognized, should result in a temporary change in treatment, to prevent it from becoming severe.

This study's intention is to assess FF/UMEC/VI in a minimally interventional routine clinical care setting. This will make it difficult to detect and report moderate asthma exacerbations. For this reason, moderate asthma exacerbations will not be collected or recorded on the asthma exacerbation eCRF page.

8.2.5.2. Severe Asthma Exacerbations

A severe asthma exacerbation is defined as:

- 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

- 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.

8.2.6. Composite endpoint

A 4-component composite endpoint will be evaluated after 24 weeks of treatment (exploratory objective) at the end of the 52-week treatment period (secondary objective).

The composite endpoint (optimized) evaluates the percentage of participants that meet the following criteria:

- Change from baseline in trough FEV₁ ≥ 100 mL (see Section 8.2.1 for details on pulmonary function testing).
- Controlled asthma based on ACQ-5 total score ≤ 1.5 (see Section 8.2.2.1 for details on the ACQ).
- No severe asthma exacerbations see Section 8.2.5.2 for the definition of a severe asthma exacerbation).
- No OCS use for asthma.

The composite endpoint (stabilized) evaluates the percentage of participants that meet the following criteria:

- Change from baseline in trough FEV₁ ≥ 0 mL (see Section 8.2.1 for details on pulmonary function testing).
- Controlled asthma based on ACQ-5 total score ≤ 1.5 (see Section 8.2.2.1 for details on the ACQ).
- No severe asthma exacerbations (see Section 8.2.5.2 for the definition of a severe asthma exacerbation).
- No OCS use for asthma.

8.3. Safety assessments

Planned time points for all safety assessments are provided in the SoA.

8.3.1. Telephone follow-up

A safety follow-up telephone contact will be conducted within approximately 7 (+7) days (i.e., Visit 5) after the participant completes all protocol-defined procedures or following study intervention discontinuation. A participant will be considered to have completed the study upon completion of all assessments and procedures for Visit 4 and a successful safety follow-up contact.

8.3.2. Pregnancy testing

Female participants who are pregnant or breast-feeding are not eligible for the study.

Female participants of childbearing potential must perform a urine pregnancy test (or a serum test if required by local regulations) at the time points specified in the SoA (Table 1) and before the administration of any dose of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may be administered only if the pregnancy test is negative or the Investigator considers the continuation of study intervention to be of benefit to the participant.

Females of childbearing potential will need to follow the contraceptive requirements that are specified in Section 10.3.

Refer to Section 8.4.6 for the information on study continuation for participants who become pregnant during the study.

8.4. Adverse events (AEs) serious adverse events (SAEs), and other safety reporting

For definitions relating to safety information see Section 10.2

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and other safety information. The investigator and any qualified designees remain responsible for following up all AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention/study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.2.

8.4.1. Time period and frequency for collecting AE, SAE, and other safety information

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.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.2. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

All AEs considered related to study intervention or study procedures will be collected from randomization until study completion, as specified in the SoA. To ensure study intervention is provided in a minimally interventional routine clinical care setting study intervention prescriptions will be provided at randomization and study intervention will be collected, by the participant, from a pharmacy. It will not be possible to collect the start date of study intervention, therefore AEs considered to be related to study intervention or study procedures will be collected from the date of randomization.

A poststudy AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period as defined in the present section.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, after a participant has been discharged from the study, the investigator must record it in the medical records. If the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor and adhere to local requirements for the reporting of SAEs to the IRB/IEC.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

Country Specific Reporting Requirements

All participating countries must comply with local regulatory requirements, for the reporting of safety events.

To comply with Health Canada requirements, Canadian investigators are required to record unusual failure in efficacy events. A lack of efficacy is the failure to produce expected benefits. Please see Section 10.2.6 for details.

8.4.2. Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.2.

8.4.4. Pneumonia

Medical history will also be taken for pneumonia in the previous 12 months, including recording of any episodes resulting in hospitalization.

It is strongly recommended that all suspected pneumonias are confirmed by the presence of new infiltrates on a chest x-ray (preferably within 48 hour of the suspected event).

All pneumonias must be captured on the AE (if considered to be related to study intervention) or SAE page and on the pneumonia page of the eCRF.

8.4.5. Regulatory reporting requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. See Section 8.4.1 for reporting timeframes.
- For SAEs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in Section 10.2.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the prescribing information or other relevant documents and will notify the IRB/IEC, if appropriate according to local requirements.

Table 5 Timeframes for submitting SAE, pregnancy and other events reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours* ‡	AEs Report	24 hours*	AEs Report
Pregnancies	24 hours*	pregnancy notification report	24 hours *	pregnancy follow-up report

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.

‡ Paper AEs Report will be dated and signed by the investigator (or designee). For each SAE, the investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

8.4.6. Pregnancy

Female participants who become pregnant after randomization may continue in the study at the discretion of the investigator.

- Details of all pregnancies in female participants will be collected after the start of study intervention and until the Safety Follow-up Visit.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE (if considered to be related to study intervention or study procedures) or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and

the information will be forwarded to the sponsor. See [Table 5](#) and Section [10.3.3](#) for reporting timeframes and further details.

- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study may request continuation of study intervention.

Prior to continuation of study intervention following pregnancy, the following must occur:

- The participant gives signed informed consent.
- The investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.

8.4.7. CV and death events

For any CV events detailed in Section [10.2.4](#) (Appendix 2) and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the eCRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific CV section of the eCRF within one week of receipt of a CV event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

8.4.8. Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Asthma exacerbations are common disease-related events in participants with asthma and can be serious/life-threatening.

Severe asthma exacerbations will be recorded on the Exacerbation eCRF page.

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for reporting of SAEs even though the event may meet the definition of an SAE.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE/SAE in addition to reporting on the exacerbation eCRF page:

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

This study's intention is to assess FF/UMEC/VI in a minimally interventional routine clinical care setting. This will make it difficult to detect and report moderate asthma exacerbations. For this reason, moderate asthma exacerbations will not be collected or recorded on the asthma exacerbation eCRF page.

8.4.9. Contact information for reporting SAEs, and pregnancies

Refer to Section [10.2.5](#) for information on reporting SAEs and pregnancies.

Please contact the GSK Medical Monitor for questions regarding SAEs, AESIs and pregnancies. The GSK Medical Monitor contact details can be found in the local study contact information document.

8.4.10. Medical Device Deficiencies

Medical devices (e.g., Ellipta DPIs) will be used in this study as part of the study intervention. To fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definition of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section [10.4](#).

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section [10.4](#) of the protocol.

8.4.10.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Section [10.4](#).

8.4.10.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.10.3. Prompt Reporting of Device Deficiencies to the Sponsor

- Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- The medical device deficiency report form will be sent to the sponsor electronically. If this primary method is unavailable, then alternative method should be utilized (notification by telephone with a copy of the SAE paper data collection, see Section [10.4.5](#) for details).
- The sponsor will be the contact for the receipt of device deficiency reports.

8.4.10.4. Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.5. Pharmacokinetics

Not applicable.

8.6. Pharmacodynamics

Not applicable.

8.7. Genetics

Not applicable.

8.8. Biomarkers

Not applicable.

8.9. Immunogenicity assessments

Not applicable.

8.10. Health economics or medical resource utilization and health economics

Not applicable.

9. STATISTICAL CONSIDERATIONS**9.1. 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 patients 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 patients with uncontrolled asthma. Secondary treatment comparisons also include FF/UMEC/VI versus ICS/LABA for 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.

Inference will be restricted by the multiplicity strategy described in Section 9.1.1.

For the test on each continuous effectiveness endpoint (including the primary and other secondary endpoints) the null hypothesis (H_0) is that there is no difference between treatment groups:

$$H_0: T_1 - T_2 = 0$$

The alternative hypothesis (H_1) is that there is a difference between treatment groups:

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

where T_1 and T_2 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 (H_0) is that there is no difference between treatment groups:

$$H_0: T_1 = T_2$$

The alternative hypothesis (H_1) is that there is a difference between treatment groups:

$$H_1: T_1 \neq T_2$$

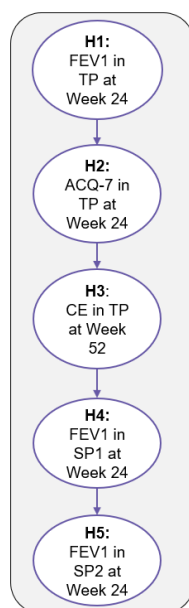
where T_1 and T_2 represent the proportion of participants who respond at Week 24 compared to baseline for FF/UMEC/VI and non-Ellipta ICS/LABA respectively.

9.1.1. Multiplicity adjustment

The primary, key secondary and other secondary endpoints as detailed in [Table 2](#) will be tested using a pre-specified testing procedure, in order to control the family-wise type I error rate at $\alpha=0.05$ from multiple testing.

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 2 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 2](#) will control for inflation of the overall 2-sided type I error rate of 5% for:

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

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-dose 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 9.3](#)

9.2. Analysis sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility.	Study population
Enrolled	- 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
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.	Effectiveness
Randomized	- All participants who were randomly assigned to receive a prescription for study intervention in the study. - The screened, enrolled, and randomized populations must be nested, i.e., the enrolled population must be a subset of the screened, the	Study population

Analysis Set	Definition / Criteria	Analyses Evaluated
	randomized population must be a subset of the enrolled population.	

9.3. Statistical analyses

The SAP will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Additional analytical conventions and details will be described in the SAP.

9.3.1. General considerations/definitions

The focus of the study is on the effectiveness of FF/UMEC/VI on asthma control compared with ICS/LABA after 24 and 52 weeks of treatment, in addition to safety.

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 subjects, 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 subjects providing data at the relevant time point (n), number of subjects with missing data, frequency counts and percentages.

Unless otherwise specified, disposition, demographics and baseline characteristics, compliance, and exposure will be presented for the FAS using the randomized treatment. All effectiveness summaries and analyses will be performed on the FAS using the randomized treatment. All safety analyses will be performed on the FAS.

9.3.2. Primary estimand analysis

The details of primary estimand are described in Section 3.

9.3.2.1. Main analytical approach

Descriptive statistics for the main primary estimand will be provided by treatment group. As described in the hypothesis Section 10.1, the primary estimand, the analysis of FF/UMEC/VI versus ICS/LABA will be performed using an analysis of covariance (ANCOVA) with change from baseline in the trough FEV₁ at Week 24 as the summary measure, and randomized study treatment as a main factor, and pre-study asthma maintenance therapy (untreated, ICS alone, ICS/LABA), pre-study ICS dose (high, low), baseline FEV₁ value, age, sex and region 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. Missing data will be assumed to be missing at random (MAR) and will not be imputed.

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

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.

9.3.2.2. Sensitivity analysis

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 missing at random (MAR) and will not be imputed.

9.3.2.3. Supportive analysis

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. Data will be set to 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).

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.

9.3.3. Key Secondary estimand analysis

The details of key secondary estimand, achieving ≥ 0.5 points improvement (decrease) from baseline for the ACQ-7 at Week 24 are described in Section 3.

9.3.3.1. Key Secondary analytical approach

Descriptive statistics for the key secondary estimand, occurrence of participants meeting the responder threshold will be provided by treatment group. The main analysis of the key secondary endpoint will be based on the FAS. The statistical testing of treatment group FF/UMEC/VI versus ICS/LABA will be performed using a generalized linear model (logistic regression), at Week 24 between treatment group with the percent of participants meeting the responder threshold at Week 24 as the summary measure, and 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 at Week 24 will be presented. The number of non-responders due to missing data will also be presented. The odds ratio and 95% CI difference and associated 2-sided p-values between FF/UMEC/VI versus ICS/LABA will be presented.

Participants with a missing baseline will have responder status as missing. Participants with missing data at the timepoint of interest, regardless of treatment status, will be considered as non-responders and participants who withdraw from the study prior to the timepoint of interest will be set as non-responders status at that timepoint. The endpoint analyzed will therefore essentially be the percent of participants who do not prematurely discontinue from the study, have data available at the timepoint and meet the responder threshold.

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

9.3.3.2. Supportive analysis

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. Data will be set to 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).

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.

Further details of these analyses will be described in the SAP.

9.3.4. Other Secondary analysis

The other secondary effectiveness endpoints (as described in [Table 2](#)) will be evaluated. For the analysis of change from baseline in trough FEV₁ at Week 52, a Mixed Model Repeated Measures (MMRM) will be used to include both Week 24 and Week 52 data. For the analysis of achieving ≥ 0.5 points improvement (decrease) from baseline for the ACQ-7 at Week 52, the generalised linear model will include the data from Week 24 and Week 52. In addition, for the analyses at Week 52, the interaction between baseline by time and treatment by time will be added as covariates in the analyses. Further details will be described in the SAP.

9.3.5. Exploratory analysis

The exploratory endpoints will be evaluated as described in Table 2. The change from baseline endpoints will use the same analysis approach as the primary endpoint and the responder endpoints (achieving a specified improvement from baseline) as well as the composite endpoint will follow the same approach as the key secondary endpoint. Further details will be given in the SAP.

9.4. Interim analyses

No interim analyses are planned for this study. The primary analysis will be performed once all participants have completed their Week 24 visit (unless prematurely discontinued from the study). The final analysis will be conducted after all participants complete 52 week and safety follow-up visits (unless prematurely discontinued from the study).

9.5. Sample size determination

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, will use a mixed model for repeated measures 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 analyzed 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.

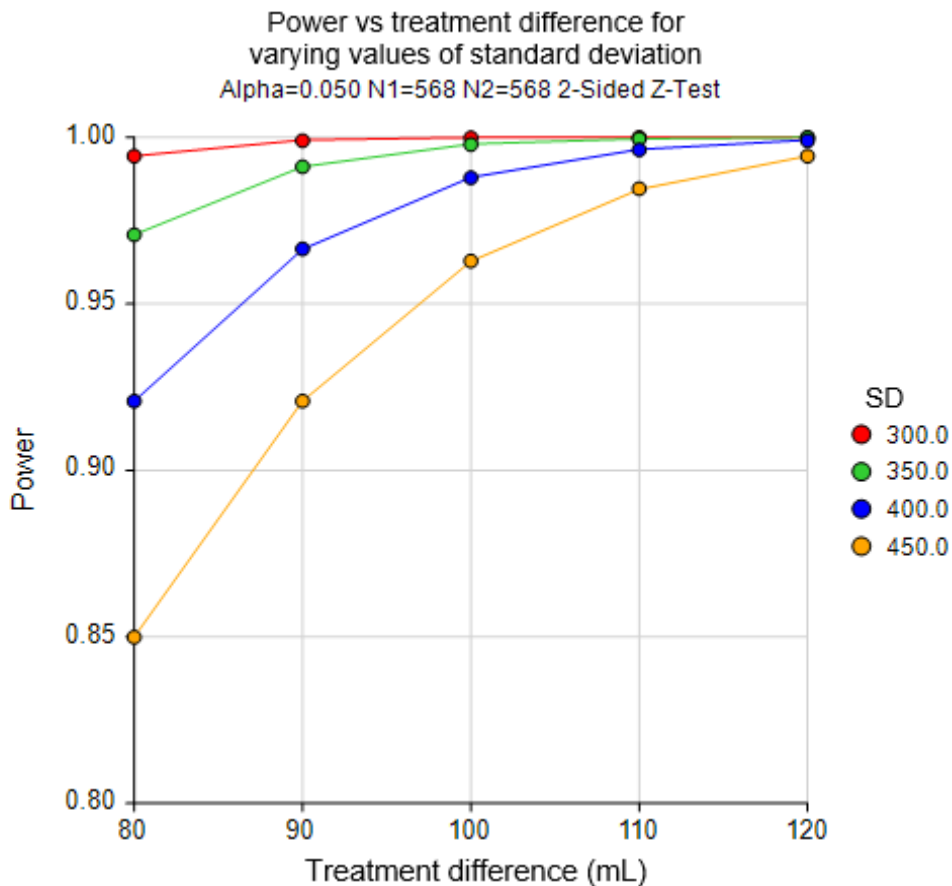
9.5.1. Primary Endpoint

The standard deviation (SD) for the primary endpoint of change from baseline in trough FEV₁ at the end of 24 weeks treatment is estimated to be 400 mL based on previous asthma studies (FF/VI studies). An SD of 400 mL was also assumed for the study 205715 study design (which comprised of similar estimands and missing data strategies to this study). Though, less variability was observed for this endpoint in the 205715 study (SD was approximately 310 mL at Week 24). However, as this study is a pragmatic study with minimal intervention carried out in normal clinical practice and participants may not be able to provide a true trough FEV₁ measurement it is expected that the variability of the data will be higher than a randomised controlled trial and so an SD of 400 mL is still a reasonable estimate for this study. Using the estimated SD of 400 mL, a 2-sided

significance threshold of 5%, 90% power, and assuming a true treatment difference of 100 mL, the study would need to have change from baseline in trough FEV₁ at Week 24 data for a minimum of 337 participants per treatment arm to detect a statistically significant difference between FF/UMEC/VI and ICS/LABA. With the study sample size of 568 participants per arm (please see Section 9.5.2 for details), there is 99% power to reject the null hypothesis at the 2-sided 5% significance level. The minimum detectable treatment difference is 46.5 mL.

To demonstrate the sensitivity of the primary estimand analysis, Figure 4 shows the power function for a fixed sample size of 568 participants per arm, varying the observed treatment difference and the estimated SD on the change from baseline in trough FEV₁ at Week 24.

Figure 3 Power Function for the Primary Endpoint fixed sample size



A secondary objective of the study is to evaluate the effects of FF/UMEC/VI on asthma control compared with ICS/LABA after 24 weeks of treatment for participants on ICS/LABA prior to randomization.

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 will also be evaluated. At the time of protocol amendment 3, about 60% of participants randomized so far were taking an ICS/LABA prior to randomization. Based on this it is anticipated that approximately 682 participants (341 participants per arm) will be taking ICS/LABA prior to randomization. For the change from baseline in trough forced expiratory volume in 1 second (FEV₁) at Week 24, for participants on ICS/LABA prior to randomization, a sample size of 341 participants per arm will have 90% power to reject the null hypothesis at the 2-sided 5% significance level. The minimum detectable treatment difference is 60.0 mL.

For the subset of participants taking no treatment prior to randomization, at the time of protocol amendment 3, about 35% of participants randomized so far were on no treatment prior to randomization. Based on this, a sample size of 199 participants per arm will have 70% power to reject the null hypothesis at the 2-sided 5% significance level. The minimum detectable treatment difference is 78.6 mL.

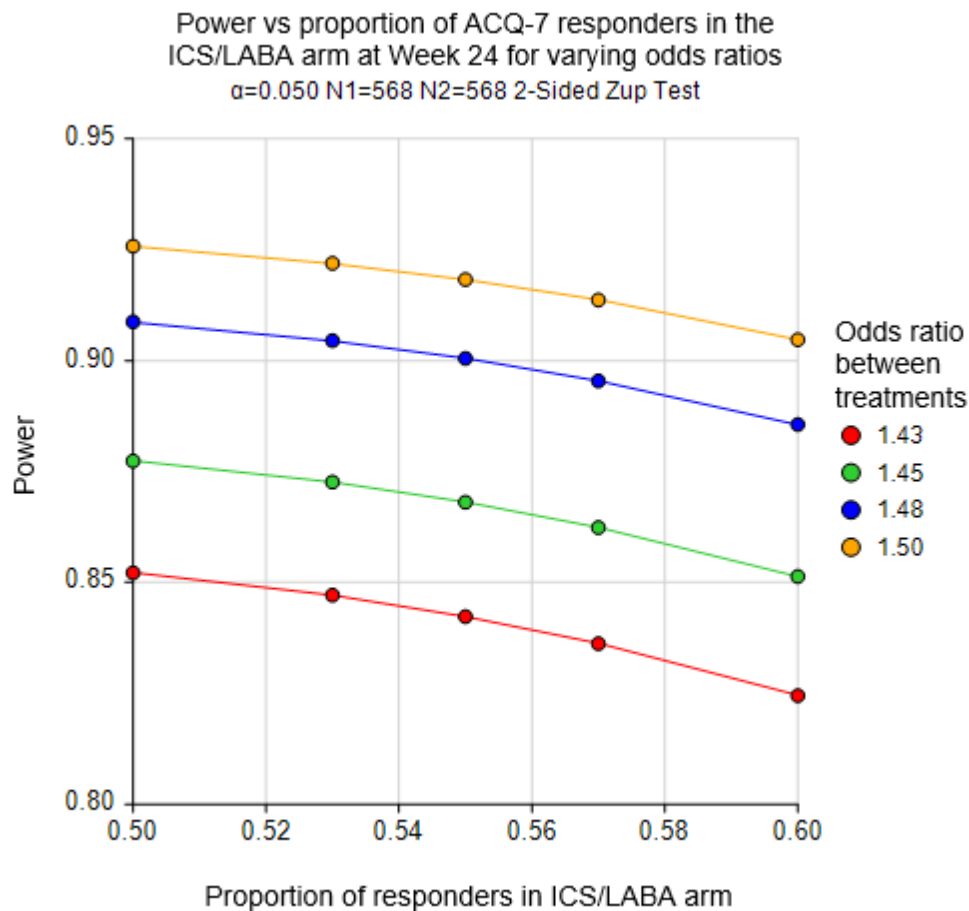
9.5.2. Powered Key Secondary Endpoint

The study sample size is 1136 participants (568 participants per arm) and is based on the key secondary endpoint of achieving ≥ 0.5 points improvement (decrease) from baseline for ACQ-7 at Week 24. In the pooled FF doses analysis of the 205715 study [FF/UMEC/VI (100+200)/62.5/25 vs FF/VI (100+200)/25], the proportion of participants meeting the responder threshold for improvement from baseline in ACQ-7 score in the FF/VI arm was 55%, and the odds ratio for being a responder vs. a non-responder for FF/UMEC/VI vs. FF/VI was 1.43 (95% CI: 1.16, 1.76). Given that it is anticipated that the FF/UMEC/VI treatment group will comprise 70% on FF/UMEC/VI 100/62.5/25 and 30% on FF/UMEC/VI 200/62.5/25, the 205715 study unpooled analysis is also relevant. In this analysis, the proportion of responders for FF/UMEC/VI 100/62.5/25 and FF/VI 100/25 was 62% and 52% respectively. The proportion of responders for FF/UMEC/VI 200/62.5/25 and FF/VI 200/25 was 64% and 58% respectively. The odds ratios for being a responder vs. a non-responder for FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 and for FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25 were 1.59 (95% CI: 1.18, 2.13) and 1.28 (95% CI: 0.95, 1.72), respectively. Based on these 205725 study results and considering the design of this study, it is reasonable to assume a true odds ratio of 1.48 for FF/UMEC/VI vs usual care (ICS/LABA). In addition, FF/VI has demonstrated superior effectiveness relative to the rest of the ICS/LABA class [Woodcock, 2017] and this study will build upon this molecule differentiation.

Assuming that the true odds ratio between treatments is 1.48 and that the proportion of ACQ-7 responders in the ICS/LABA arm at Week 24 is 55% (and the proportion of responders on FF/UMEC/VI is 65%), a sample size of 568 participants per arm would provide 90% power to reject the null hypothesis at the 2-sided 5% significance level. With this sample size, the minimum detectable effect is an odds ratio of 1.27.

To demonstrate the sensitivity of the sample size calculation for this study, for the key secondary endpoint, Figure 4 shows the power function for a fixed sample size of 568 participants per arm, varying the observed proportion of ACQ-7 responders in the ICS/LABA arm and odds ratio between treatments.

Figure 4 Power Function for Key Secondary Endpoint fixed sample size



10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
 - Applicable ICH GCP guidelines

- Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Substantial amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
 - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
 - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial disclosure

Not applicable.

10.1.3. Informed consent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to physically or digitally sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that physical or digital informed consent was obtained before the participant was enrolled in the study and the date the physical or digital consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

- A physical or digital copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

In case of unexpected pregnancy, participants that continue in the study must sign a pregnancy informed consent form, if required. Participant must be informed that PI such as date of birth, sex of the baby will be collected as part of safety follow-up. Consent for the baby may be obtained from the participant and/or their partner as per local regulations.

10.1.4. Data protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant must be informed that study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant, that their data will be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees structure

A SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new effectiveness and safety information.

A Steering Committee may be appointed. The committee may include a representative from each participating country, and they may provide scientific input and direction, in relation to the protocol and asset, to the GSK study team. In addition, the committee may assist with study conduct, including recruitment, protocol compliance and study challenges, for example. The scope and responsibilities of the Steering Committee will be detailed in the Steering Committee charter.

10.1.6. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocol summaries prior to study start and target results summaries submission within 12 months of

primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.

- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.

10.1.7. Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the Data Management Plan.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for a minimum period of 15 years from the issue of the final CSR/ equivalent summary, or in accordance with Applicable Law, whichever is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. In the event of a conflict between this Protocol and the fully executed clinical study agreement, the protocol shall prevail with respect to records retention.

10.1.8. Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the monitoring plan/guidelines.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and site start and closure**Start of study and first act of recruitment**

The start of study and the first act of recruitment are defined as FSFV (first ICF signature date) at a country-level.

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or temporarily suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or temporary suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication policy

The results of this study may be published in peer reviewed scientific literature and/or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice and as per the sponsor's internal policy. Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.2. Appendix 2: AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.2.1. Definition of AE

AE definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). Laboratory tests and ECGs will not be completed in this study. However, any changes/worsening in tests conducted as part of standard medical practice should be reported, if they meet the protocol definition of an Adverse Event.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen).
- "Lack of effectiveness" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the effectiveness assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of effectiveness will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, admission for routine examination.).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. Pre-existing diseases will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.2.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:	
a.	Results in death
b.	Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c.	Requires inpatient hospitalization or prolongation of existing hospitalization - In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d.	Results in persistent or significant disability/incapacity - The term disability means a substantial disruption of a person's ability to conduct normal life functions. - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e.	Is a congenital anomaly/birth defect in the offspring of a study participant
f.	Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)
g.	Is a suspected transmission of any infectious agent via an authorized medicinal product
h.	Other situations: - Possible Hy's Law case: ALT $\geq 3 \times$ ULN AND total bilirubin $\geq 2 \times$ ULN ($>35\%$ direct bilirubin) or INR >1.5 must be reported as SAE - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.2.3. Unsolicited AE

Definition of unsolicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.

10.2.4. Definition of CV events

CV definition:

Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs:

- 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

10.2.5. Recording, assessment and follow-up of AE, SAE and pregnancies

10.2.5.1. AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

10.2.5.2. Assessment of intensity

The investigator will make an assessment of intensity for each AE, SAE and device deficiency reported during the study and assign it to one of the following categories:

- **Mild:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate:** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe:** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.5.3. Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. The investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.2.5.4. Assessment of outcomes

The investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

10.2.5.5. Follow-up of AEs, SAEs, pregnancies or any other events of interest

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

After the initial AE/SAE/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, (as defined in the Section 8.4.1), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the electronic pregnancy report and the AE Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, the investigator must report any SAE occurring as a result of a poststudy pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.2.5.7

10.2.5.6. Updating of SAE, and pregnancy information after removal of write access to the participant's eCRF

When additional SAE or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the Study contact for reporting SAEs (refer to Section 8.4.3).

10.2.5.7. Reporting of SAEs, AESIs and pregnancies

SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone.

- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK non-IMP they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in local study contact information document.

SAE Reporting to GSK via Paper Data Collection Tool

- Secure email/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor or SAE coordinator.
- In rare circumstances and in the absence of email/facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in local study contacts information document.

10.2.6. Additional Adverse Event (AE) Reporting Requirements for Canadian Investigators

Health Canada requires pharmaceutical manufacturers to expeditiously report domestic cases of unusual failure in efficacy for new drugs to the Marketed Health Products Directorate (MHPD) within 15 days of first notification. This regulation applies to marketed drugs, and used as directed per the Canadian prescribing information, including those drugs used in Phase IV (non-CTA filed) clinical trials.

To comply with this Health Canada requirement, Canadian investigators are required to record study intervention related lack of efficacy events. A lack of efficacy is the failure to produce expected benefits. Lack of efficacy or "failure of expected pharmacological action" will be reported on a paper form as an AE or SAE as described below.

All paper forms are required to be faxed to GSK Canada's Drug Safety department at 1-866-903-4718 within 24 hrs of first awareness.

Adverse Event criteria	All countries: eCRF only	Canada only: Paper form only	Canada only: eCRF AND paper form
Non-serious	AEs considered related to study intervention/procedures	Study intervention related lack of efficacy reports without associated	Study intervention related lack of efficacy with associated signs or

Adverse Event criteria	All countries: eCRF only	Canada only: Paper form only	Canada only: eCRF AND paper form
		signs or symptoms or clinical sequelae	symptoms with clinical sequelae
Serious	All SAEs	Study intervention related lack of efficacy reports without associated signs or symptoms or clinical sequelae	Study intervention related lack of efficacy with associated signs or symptoms with clinical sequelae

10.3. Appendix 3: Contraceptive and barrier guidance

10.3.1. Definitions

10.3.1.1. Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

Adolescents of childbearing potential: Tanner stage ≥ 2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.

From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

Note: Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

10.3.2. Contraception guidance

CONTRACEPTIVES ^a ALLOWED DURING THE STUDY INCLUDE:
• Highly Effective Methods^b That Have Low User Dependency ○ Implantable progestogen-only hormone contraception associated with inhibition of ovulation^c ○ Intrauterine device (IUD) ○ Intrauterine hormone-releasing system (IUS)^c ○ Bilateral tubal occlusion ○ Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and

CONTRACEPTIVES^a ALLOWED DURING THE STUDY INCLUDE:
the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
• Highly Effective Methods^b That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation^c ○ oral ○ intravaginal ○ transdermal ○ injectable
Progestogen-only hormone contraception associated with inhibition of ovulation^c • oral • injectable
Sexual abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

10.3.3. Collection of pregnancy information

Investigator will collect pregnancy information on any female participants, who becomes pregnant while participating in this study

Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.

Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.

Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such.

Any SAE occurring as a result of a post-study pregnancy, which is considered reasonably related to the study intervention by the investigator, will be reported to GSK. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be able to continue study intervention at the discretion of the Investigator. Participants must provide consent, using the pregnancy informed consent form (where applicable), to continue in the study.

10.4. Appendix 4: Medical device AEs, ADEs, SAEs, SADEs, USADEs and device deficiencies: Definitions and procedures for recording, evaluating, follow-up, and reporting in medical device studies

- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to the Ellipta DPI. . See Section [6.1.1](#) for the list of sponsor medical devices.

10.4.1. Definition of medical device AE and ADE

Medical device AE and ADE definition
• A medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices. • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.4.2. Definition of medical device SAE, SADE and USADE

A Medical Device SAE is any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. • Chronic disease (MDR 2017/745).
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product

A Medical Device SAE is any serious adverse event that:
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report/ IB (see Section 2.3).

10.4.3. Definition of device deficiency

Device deficiency definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

10.4.4. Recording and follow-up of medical device AE and/or SAE and device deficiencies

10.4.4.1. Medical device AE, SAE, and device deficiency recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
 - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.
- If the site during the course of the study becomes aware of any serious, nonserious incident (including device deficiencies and malfunctions) related to any GSK non-IMP product they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

10.4.4.2. Assessment of intensity

Refer to Section [10.2.5.2](#)

10.4.4.3. Assessment of causality

Refer to Section [10.2.5.3](#)

10.4.4.4. Follow-up of medical device AE/SAE and device deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.4.5. Reporting of medical device SAEs

Medical Device SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next table) or to the medical monitor/SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the local study contacts information document. Refer to Section [8.4.9](#).

Medical Device SAE Reporting to GSK via Paper Data Collection Tool

- Email/Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor/SAE coordinator.
- In rare circumstances and in the absence of email/facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the local study contacts information document.

10.4.6. Reporting of SADEs

SADE reporting to GSK

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in the local study contacts information document.

10.4.7. Reporting of medical device deficiencies for associated person

Reporting to GSK
If an Associated Person (i.e., e.g., spouse, caregiver, site staff) experiences a device deficiency, the medical device deficiency information, and any associated AE/SAE information will be reported to GSK. The associated person will be provided with the authorization to contact physician letter. If follow-up information is required, authorization to contact physician (or other licensed medical practitioner) must be signed to obtain consent. • Medical device deficiencies that are not related to an AE or SAE should be reported via email to gsk-rd.complaints@gsk.com, using the medical device deficiency report form. • If the medical device deficiency is related to a nonserious AE and not linked to an SAE, please send the medical device deficiency report form with details of the associated AE via email to gsk-rd.complaints@gsk.com only. • If the device incident is linked to an SAE, please email the medical device deficiency report form, within 24 hours. Contacts for SAE reporting can be found in the local study contact information document. The associated SAE form should also be reported to OAX37649@gsk.com (or fax +44(0) 20 81814780). • GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

10.5. Appendix 5: Country-specific requirements for China only

Introduction

In China, FF/UMEC/VI 100/62.5/25 mcg is approved for the maintenance treatment of COPD in adult participants. FF/UMEC/VI has not yet been approved for the treatment of asthma in mainland China. In Hong Kong, FF/UMEC/VI 100/62.5/25 mcg and 200/62.5/25 mcg are approved for the maintenance treatment of asthma.

In 2020, the Central Government of China promulgated the Work Plan for Regulatory Innovation and Development of Pharmaceutical and Medical Device in the Guangdong-Hong Kong-Macao Greater Bay Area (Work Plan). According to the Work Plan, the Central Government allowed designated healthcare institutions operating in the nine Mainland cities of the Guangdong-Hong Kong-Macao Greater Bay Area (GBA) to use Hong Kong-registered drugs with urgent clinical use, and medical devices used in Hong Kong public hospitals with urgent clinical use and advanced clinical applications, subject to the approval of Guangdong Province. With this policy, local patients with asthma will have the opportunity to use FF/UMEC/VI in a compliant manner prior to China CDE approval.

Following approval by the CDE of Guangdong province (GD CDE), FF/UMEC/VI 100/62.5/25 mcg and 200/62.5/25 mcg will be shipped from Hong Kong to the Great Bay Area (GBA) in China. This approval will allow designated hospitals in the GBA to prescribe FF/UMEC/VI to participants with uncontrolled asthma. Should FF/UMEC/VI be approved for the treatment of Asthma in mainland China over the course of the study, and the recruitment needs of the study have not been met, the study sites may be expanded outside of the GBA. Although a Phase III China study has been conducted, that compared FF/UMEC/VI to FF/VI, in adult participants with inadequately controlled asthma (GSK Study number 214263), there is a paucity of data comparing FF/UMEC/VI to non-Ellipta alternative ICS/LABA formulations, including budesonide/formoterol, which are widely used therapies in the China population. The PERFORM study will provide data that directly compares the two treatments and will provide evidence for the effectiveness and safety of FF/UMEC/VI in China.

China will follow PERFORM protocol amendment 2 with the exception of the following sections:

Section 1 (Protocol Summary)

To enable the assessment of consistency of effect between China and the overall study population, following 24 and 52 weeks of treatment, the objectives, endpoints and estimands specified in the synopsis will be summarized and analyzed for the China population.

Section 2 (Schedule of activities)**Table 1 Schedule of activities**

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	
Urine Pregnancy Test		X	X	X		A WOCBP must have a negative highly sensitive urine pregnancy test (a serum test is not required by local regulations in China) ≤7 days prior to randomization.

Section 3 (Objectives, Endpoints and Estimands)

To enable the assessment of consistency of effect between China and the overall study population, following 24 and 52 weeks of treatment, the objectives, endpoints and estimands specified in Section 3 will be summarized and analyzed for the China population.

The primary and final analyses for the core study will be completed at different times to the China analyses, as recruitment in China will start later. For this reason, the main Clinical Study Report will not include data from China. Data from China will be reported in an addendum to the main Clinical Study Report.

Section 4 (Study design)**Section 4.1 Overall Design**

Participants will be randomized to receive FF/UMEC/VI (once a day, as described in the approved regulatory label for Hong Kong) or ICS/LABA (in-line with dosing regimen in the appropriate regulatory label in mainland China). Inclusion in the high-dose ICS-containing therapy group will be at the discretion of the investigator and must comply with local treatment guidelines.

If, during the study FF/UMEC/VI is approved for the treatment of asthma, in mainland China, the approved regulatory label for mainland China may be used.

Number of participants: Approximately 150 participants will be screened to achieve 120 randomly assigned to study intervention (60 participants per arm) in China. This is in addition to the 1136 participants to be randomized in the core study.

Section 4.1 Scientific rationale for study design

The China primary analysis will be completed once all participants in China receive study intervention for 24 weeks, and the China final analyses will be completed once all participants in China complete the study (52 weeks). The primary and final analyses for the core study will be completed at different times to the China analyses, as recruitment in China will start later. For this reason, the main Clinical Study Report will not include data from China. Data from China will be reported in an addendum to the main Clinical Study Report.

Section 4.3 Justification for dose

The FF/UMEC/VI 100/62.5/25 mcg and 200/62.5/25 mcg doses are based on the approval received in Hong Kong for the maintenance treatment of asthma. The ICS/LABA doses are based on usual care as per the China specific regulatory labels.

If, during the study FF/UMEC/VI is approved for the treatment of asthma, in mainland China, the approved regulatory label for mainland China may be used.

Section 5 (Study population)

Section 5.2 Exclusion criteria

A WOCBP must have a negative highly sensitive urine pregnancy test (serum tests are not required by local regulations in China) ≤ 7 days prior to randomization.

Section 6 (Study interventions and concomitant therapy)

Section 6.1 Study interventions administered

FF/UMEC/VI is not approved for the treatment of asthma in mainland China. Commercial supplies from Hong Kong will be imported to the Great Bay Area, following approval by the CDE of Guangdong province. FF/UMEC/VI will be shipped to designated hospital pharmacies.

If, during the study FF/UMEC/VI is approved for the treatment of asthma, in mainland China, FF/UMEC/VI may be sourced from mainland China commercial supplies.

ICS/LABA (comparator) study interventions will be sourced from local commercial supplies.

Section 6.2 Preparation, Handling, Storage and accountability

All randomized participants will receive study intervention prescriptions for FF/UMEC/VI or ICS/LABA as per usual clinical practice.

Section 6.3 Assignment to study intervention

Participants will be stratified by pre-study asthma maintenance therapy (untreated [as defined in Section 5.1], ICS alone, ICS/LABA) and pre-study ICS dose (low, high) and will be assigned to study treatment in accordance with a country specific randomization schedule (to ensure treatment balance within each stratum for participants in China). The randomization number(s) will be generated using a validated computerized system. Randomization will occur via IVRS/IWRS. Once a randomization number is assigned to a participant it cannot be reassigned to any other participant in the study.

Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

Study intervention prescriptions will be dispensed at the study visits as summarized in the SoA.

Section 6.7 Continued access to study intervention after the end of the study

After completion of the study, the investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition. After approval of Guangdong CDE, FF/UMEC/VI will be available in the GBA and can be prescribed to patients, following completion of the study. Usual care ICS/LABA and LAMA (MITT) or other SITT that are commercially available in China are also possible treatment options for patients following completion of the study.

Section 7 (Discontinuation of study intervention and participants discontinuation/withdrawal)**Section 7.1 Discontinuation of Study Intervention**

Following discontinuation of study intervention participants will be prescribed an appropriate medication, as determined by their treating physician and study intervention prescriptions will no longer be provided. Participants can still be prescribed FF/UMEC/VI at a designated medical institution in the Great Bay Area. ICS/LABA and LAMA (MITT) or other SITT that are commercially available in China are also possible treatment options.

Participants who permanently discontinue study intervention are not required to withdraw from the study. Participants who have permanently discontinued study intervention and have not withdrawn consent should comply to the protocol schedule of assessments.

Section 7.2 Participant Withdrawal from study

Participants that withdraw from the study will be prescribed an appropriate medication, as determined by their treating physician and study intervention prescriptions will no longer be provided. Participants can still be prescribed FF/UMEC/VI at a designated medical institution in the Great Bay Area. In addition, ICS/LABA and LAMA (MITT) or other SITT that are commercially available in China will be possible treatment options.

Section 8 (Study assessments and procedures)**Section 8.3.2 Pregnancy testing**

Serum pregnancy tests will not be required in China. Local regulations require a urine sample to be collected and tested.

Section 9 (Statistical considerations)**9.1 Statistical hypotheses**

The objective is to evaluate the consistency of effect between China and the overall study population. No formal hypotheses will be tested. All the summaries, analysis or comparisons conducted will be for descriptive purposes only.

9.2 China analysis Set	Definition / Criteria	Analyses Evaluated
Screened - China	All participants who were screened for eligibility in China.	Study population
Enrolled - China	- 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) in China. - 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
Full Analysis Set (FAS) - China	All randomized participants who received at least 1 prescription of study intervention in China. Data will be reported according to the randomized study intervention.	Effectiveness
Randomized - China	All participants who were randomly assigned to receive a prescription for study intervention in the study in China. The screened, enrolled, and randomized populations must be nested, i.e., the enrolled population must be a subset of the screened, the randomized population must be a subset of the enrolled population.	Study population

Section 9.3.2.1 Main analytical approach

To enable assessment of consistency of effect between China and the non-China study population (to be taken from study 219912 CSR), the primary, key secondary, secondary and exploratory efficacy endpoints will be summarised and analysed for the China FAS population. All the analyses on the China subgroup will be performed after the database is frozen for the China sites and statistical analysis for the non-China study population is completed. Further details will be provided in the China supplementary SAP (sSAP).

Section 9.5 Sample size determination

Sample size calculations were based on the same assumptions as described for both the primary endpoint and key secondary endpoint in Section 9.5. Approximately 60 participants per arm at sites in China would provide 91% probability of consistency of effect with the primary analysis and 84% for the key secondary endpoint of achieving ≥ 0.5 points improvement (decrease) from baseline for ACQ-7 at Week 24 according to basic principles on global clinical trials method 2 [000157900.pdf (pmda.go.jp)].

10.6. Appendix 6: Country-specific requirements for Japan only

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.

No formal hypotheses will be tested. All the summaries, analysis or comparisons conducted will be for descriptive purposes only.

Japan analysis Set

	Definition / Criteria	Analyses Evaluated
Screened - Japan	All participants who were screened for eligibility in Japan.	Study population
Enrolled - Japan	- 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) in Japan. - 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
Full Analysis Set (FAS) - Japan	All randomized participants who received at least 1 prescription of study intervention in	Effectiveness

	Definition / Criteria	Analyses Evaluated
	Japan. Data will be reported according to the randomized study intervention.	
Randomized - Japan	All participants who were randomly assigned to receive a prescription for study intervention in the study in Japan. The screened, enrolled, and randomized populations must be nested, i.e., the enrolled population must be a subset of the screened, the randomized population must be a subset of the enrolled population.	Study population

To enable assessment of consistency of effect between the Japanese population from the study and the overall study population, the primary, key secondary and composite endpoints will be summarised and analysed for the Japan FAS population. Further details will be provided in the Japan supplementary SAP (sSAP).

10.7. Appendix 7: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the TOC.

Amendment 2 (17 December 2024)

Overall rationale for the Amendment: This is a country-specific amendment for China. The amendment has no impact on any other participating country and will be issued and implemented in China, only. All other participating countries will continue to follow protocol amendment 1 (approved 02 April 2024). China-specific requirements have been added to the appendices.

Amendment 1 (02 April 2024)

Overall rationale for the Amendment: To update the inclusion criteria to allow the recruitment of untreated, recently diagnosed, asthma participants, in Japan, and to include specific safety reporting requirements for Canada.

Summary of changes table of previous amendments:

Section # and title	Description of change	Brief rationale
Section 1.1 Protocol Synopsis and Section 10.1.5 Committees Structure	Update to Data Monitoring/other committee to state that the steering committee may include a lead representative from each country and remove reference to a lead Principal Investigator from each country.	To reflect how steering committee members are being selected/invited.
1.3 Schedule of Activities	Update to the schedule of activities to reflect that Week 24 is defined as V3.	Week 24 was defined as V2, in error.
Table 2 Objectives and Endpoints	Update to evaluate the effects of FF/UMEC/VI on a composite endpoint compared with ICS/LABA after 52 weeks of treatment for participants on budesonide/formoterol prior to randomization	Omitted from the table in error. This objective and endpoints are included and described in the statistical analysis section of the protocol.
4.1 Overall Design	Remove the requirement for high-dose ICS participants to be treated with high-dose dose ICS at baseline.	To allow untreated participants to be randomized to the high-dose ICS subset, if deemed necessary by the Investigator.
5.1. Inclusion Criteria	Update to inclusion 3, to specify that participants must have a	To allow the inclusion of untreated participants into the study.

Section # and title	Description of change	Brief rationale
	diagnosis of asthma as defined by GINA 2023 guidelines prior to or at the screening visit (V1). Update to inclusion 7, to specify that 2 acceptable maneuvers are required at V2, not 3.	To correct a typo: 3 acceptable maneuvers are not required.
5.2 Exclusion Criteria	Update to specify that participants with COPD are excluded from the study. Update to specify that participants that require systemic corticosteroids for reasons other than the treatment of an asthma exacerbation.	To highlight the exclusion of participants with COPD and not rely on the exclusion of such participants as part of exclusion 6: other diseases/abnormalities. To align with section 6.9.2: Non-Asthma Medications.
6.9 Prior and Concomitant Therapy	Update to add that Investigators should also reference the relevant product label for potential interactions.	Reference to the product labels (for the comparator arm) was omitted from the protocol in error.
8.2.1 Pulmonary Function Testing	Update to reflect that 2 acceptable maneuvers are required, not 3. Text has been included to reflect that participants who did not withhold SABA/LABA medication for spirometry assessments, should return to the clinic within 7 days of the original visit, to perform spirometry. Update to define baseline FEV₁ as the highest acceptable/borderline acceptable pre-dose measurement, not the last acceptable/borderline acceptable measurement.	To correct a typo: 3 acceptable maneuvers are not required. To provide additional detail. To align with ATS/ERS guidelines.
8.4.1 Time period and frequency for collecting AE, SAE and other safety information	Update to specify that participating countries must comply with regulatory requirements for the reporting of safety events and to specify the specific requirements for Canada.	To provide specific requirements for sites in Canada.
10.1.2 Financial Disclosure	Amended to not applicable	Study is out of scope as will not be included in a US marketing application to the FDA.

Section # and title	Description of change	Brief rationale
10.2.6 Additional AE reporting requirements for Canadian investigators	Update to provide specific details for the reporting of unusual failure efficacy in Canada.	To document specific requirements for sites in Canada.
Section 10.5: Appendix 5. Country-specific requirements	Appendix 5 has been added to the protocol, to capture country-specific requirements for China.	To allow the recruitment of participants in China

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