TITLE PAGE

Protocol Title:

A Phase III, 52-week, Open-label Study to Evaluate Long-term Safety of Fixed Dose Combination Therapy Fluticasone Furoate/Umeclidinium Bromide/Vilanterol Trifenatate in Japanese Patients with Asthma

Protocol Number: 207236 Amendment 02

Short Title:

A Long-term Safety Study of Fixed Dose Combination Therapy Fluticasone Furoate/Umeclidinium Bromide/Vilanterol Trifenatate in Japanese Patients with Asthma

Compound Number： GW685698/GW642444/GSK573719

Sponsor Name and Legal Registered Address:

GlaxoSmithKline K.K. (GSK)

8-1, Akasaka 1-chome Minato-ku, Tokyo 107-0052 Japan

Study Director: PPD , Medicines Development (Respiratory Therapy Area Office, Head)

Medical Monitor Name and Contact: See the Study Reference Manual (SRM)

Regulatory Agency Identifying Number(s): Not applicable

Approval Date: 25 Oct 2017

治験依頼者署名（SPONSOR SIGNATORY）：

PPD

25 Oct. 2017

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Date

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PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 02	25-Oct-2017
Amendment 01	24-May-2017
Original Protocol	13-Mar-2017

Amendment 02: 25-Oct-2017

Overall Rationale for the Amendment: Relocation of Sponsor, etc. (See below table)

Section # and Name	Description of Change	Brief Rationale
TITLE PAGE	***Changed from:*** **Sponsor Name and Legal Registered Address:** GlaxoSmithKline K.K. (GSK) 6-15, Sendagaya 4-chome Shibuya-ku, Tokyo 151-8566 Japan ***Changed to:*** **Sponsor Name and Legal Registered Address:** GlaxoSmithKline K.K. (GSK) 8-1, Akasaka 1-chome Minato-ku, Tokyo 107-0052 Japan	Relocation of Sponsor
2. SCHEDULE OF ACTIVITIES (SOA)	***Changed from:*** **Table 1. SCHEDULE OF ACTIVITIES** Procedure; Serum pregnancy test Visit 1, 4, 5, 7, Early Withdrawal; X^6 **Footnote 6.** Assessments at only Visit1 to be conducted in all females. Assessments at Visit except for the Visit 1 only to be conducted in females of	To align with on-going 205715 study

Section # and Name	Description of Change	Brief Rationale
	reproductive potential. ***Changed to:*** **Table 1. SCHEDULE OF ACTIVITIES** Procedure; Serum pregnancy test[6] Visit 1, 4, 5, 7, Early Withdrawal; X **Footnote 6.** Assessments are only to be conducted in females of reproductive potential.	
12.2. Appendix 2: Study Governance Considerations	**Study Period** ***Changed from:*** June 2017 ~ Mar 2019 ***Changed to:*** June 2017 ~ Sep 2019	Extension of recruitment periods
12.2. Appendix 2: Study Governance Considerations	**Sponsor Information Page** ***Changed from:*** **Sponsor Legal Registered Address**: GlaxoSmithKline K.K. (GSK) 6-15, Sendagaya 4-chome Shibuya-ku, Tokyo 151-8566 Japan Study Director: PPD , Head of Respiratory TA Office, Medicines Development **Sponsor Contact Address:** Leading Author : PPD , Respiratory TA Office, Medicines Development TEL : PPD FAX : PPD Sponsor's Contact Information (10:00-18:00, Monday to Friday, except national holidays,	Relocation of Sponsor

Section # and Name	Description of Change	Brief Rationale
	year-end and new-year holidays); 207236 team, JDMA, GlaxoSmithKline K.K. TEL: PPD (dial-in) FAX: PPD Sponsor's Medical Monitor: PPD, Head of Nurology Science TA Office, Medicines Development TEL : PPD FAX : PPD ***Changed to:*** **Sponsor Legal Registered Address**: GlaxoSmithKline K.K. (GSK) 8-1, Akasaka 1-chome Minato-ku, Tokyo 107-0052 Japan Study Director: PPD, Head of Respiratory TA Office, Medicines Development **Sponsor Contact Address:** Leading Author : PPD, Respiratory TA Office, Medicines Development TEL : PPD FAX : PPD Sponsor's Contact Information (10:00-18:00, Monday to Friday, except national holidays, year-end and new-year holidays); 207236 team, JDMA, GlaxoSmithKline K.K. TEL: PPD	

Section # and Name	Description of Change	Brief Rationale
	FAX: PPD Sponsor's Medical Monitor: PPD, Head of Nurology Science TA Office, Medicines Development TEL : PPD FAX : PPD	
12.2. Appendix 2: Study Governance Considerations	***Changed from:*** **Laboratory** **Clinical Laboratory** SRL Medisearch Inc. Shinjuku I-Land-Tower 10F, 6-5-1, Nishishinjuku, Shinjuku-ku, Tokyo, 163-1310, Japan Q2 Solutions LLC (Only items that can not be measured in SRL Medisearch in the laboratory test after liver event) ***Changed to:*** **Laboratory** **Clinical Laboratory** SRL Medisearch Inc. Shinjuku I-Land-Tower 10F, 6-5-1, Nishishinjuku, Shinjuku-ku, Tokyo, 163-1310, Japan	To be able to perform only in SRL Medisearch Inc.

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1. SYNOPSIS

Protocol Title:

A Phase III, 52-week, Open-label Study to Evaluate Long-term Safety of Fixed Dose Combination Therapy Fluticasone Furoate/Umeclidinium Bromide/Vilanterol Trifenatate in Japanese Patients with Asthma

Short Title:

A Long-term Safety Study of Fixed Dose Combination Therapy Fluticasone Furoate/Umeclidinium Bromide/Vilanterol Trifenatate in Japanese Patients with Asthma

Rationale:

Despite availability of treatments and published guidelines, patients may have asthma that is inadequately controlled. The prevalence of inadequately controlled asthma varies based on the definition used for control. In a sample of asthmatics visiting their healthcare provider for any reason, 58% of adult asthmatics were estimated to have uncontrolled asthma based on the Asthma Control Test (ACT, defined as an ACT score ≤19).

The Global Initiative for Asthma (GINA) guidelines recommend include a long-acting muscarinic antagonist (LAMA) as add-on treatment option for adults with asthma that are currently taking medium to high dose inhaled corticosteroid/long-acting β_2 agonist (ICS/LABA) treatment and have a history of exacerbations. Exacerbations are an important endpoint in asthma therapy; however, symptom control is also important in determining what patients could benefit from step-up therapy. Data from the GlaxoSmithKline (GSK) Phase IIb study 200699 demonstrated that the LAMA/umeclidinium (UMEC), when added to the ICS fluticasone furoate (FF), reduced salbutamol use and improved symptoms in a sub-group of subjects with the primary diagnosis of asthma.

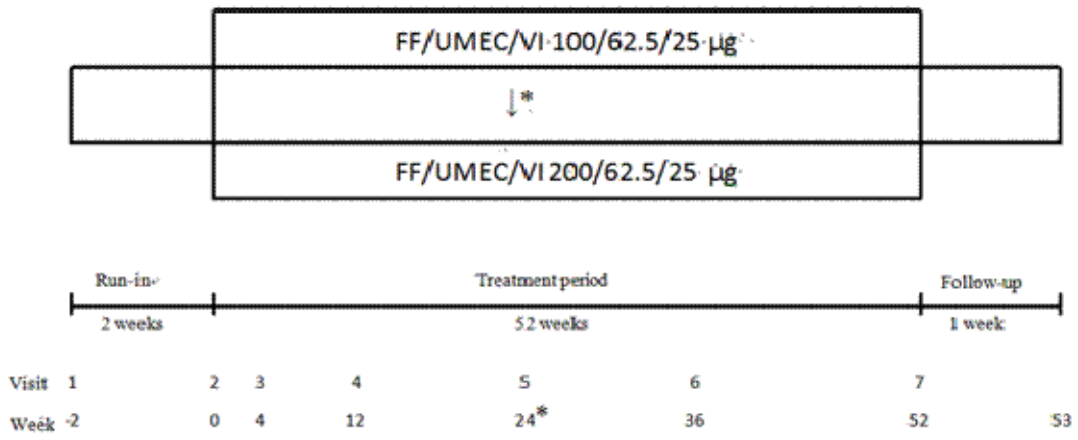
GSK is currently developing a once-daily ‘closed’ triple therapy of an ICS/LAMA/LABA combination [FF/UMEC/vilanterol (VI)] in a single device, with the aim of providing a new treatment option for the management of asthma by improving lung function, health-related quality of life (HRQoL) and symptom control over established combination therapies. The objective of this study is to evaluate long-term safety of fixed dose combination therapy FF/UMEC/VI in Japanese patients with asthma. A global study comparing FF/UMEC/VI with a standard of care ICS/LABA combination therapy (Study 205715) is ongoing in parallel with this study, which will provide important information to prescribers regarding the benefit of step-up to closed triple therapy to patients uncontrolled on ICS/LABA.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To evaluate the safety of long-term treatment with FF/UMEC/VI combination therapy	• Incidence and type of adverse events (AE)/serious adverse events (SAE)
Secondary	
• To evaluate the safety of FF/UMEC/VI combination therapy	Secondary Endpoints • Blood pressure/pulse measurements • 12-lead Electrocardiogram (ECG) • Clinical laboratory tests (hematology , biochemistry and urinalysis)
Other	
• To evaluate the efficacy of FF/UMEC/VI combination therapy	Other Endpoints • Mean change from baseline in trough Forced Expiratory Volume in 1 second (FEV1) at Week 24 and Week 52 • Mean change from baseline in Asthma Control Questionnaire – 7 (ACQ-7) total score at Week 24 and Week 52 • Mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 24 and Week 52 • Mean change from baseline in the Asthma Quality of Life Questionnaire (AQLQ) total score at Week 24 and Week 52 • Unscheduled asthma-related healthcare resource utilization over the 52 weeks of the treatment period • Annualized rate of severe asthma exacerbations • Annualized rate of moderate/severe asthma exacerbations

Overall Design:

The present study is a phase III, multicenter, non-comparator, non-randomized, open-label study in Japanese patients with asthma to evaluate long-term safety of FF/UMEC/VI 100/62.5/25 micrograms (mcg) and FF/UMEC/VI 200/62.5/25 mcg.



* Switching medication from FF/UMEC/VI 100/62.5/25 mcg to FF/UMEC/VI 200/62.5/25 mcg will be permitted in accordance with the control status of the subject assessed by ACQ-7 at Week 24 of the treatment period.

Eligible patients who meet the pre-defined criteria at screening (Visit 1) will enter into a 2-week run-in period. During the run-in period, the subjects will continue their pre-screening inhaled medications for asthma (ICS+LABA or ICS+ LABA+LAMA) until the day before Visit 2 without any change in regimen/dosage. After completion of the run-in period, subjects who meet pre-defined criteria at Visit 2 will be allocated to either FF/UMEC/VI 100/62.5/25 or FF/UMEC/VI 200/62.5/25 treatment depending on the asthma control status with inhaled asthma therapy during the run-in period as shown in the table below, and initiate a 52-week treatment period. Only at Week 24 of the treatment period (Visit 5), switching medication from FF/UMEC/VI 100/62.5/25 to FF/UMEC/VI 200/62.5/25 will be permitted if the control status of the subject assessed by ACQ-7 is not well controlled (i.e., ACQ score >0.75).

Correspondence between Asthma Control Status with inhaled Asthma Therapy during the run-in period and Allocated Study Treatment

Group	Asthma control status with inhaled asthma therapy[1]	Allocated study treatment
Group 1	Not well controlled with ICS (mid-dose)+LABA or Controlled with ICS (mid-dose)+LABA + LAMA	FF/UMEC/VI 100/62.5/25 mcg via ELLIPTA, once-daily, 1 puff/time, morning
Group 2	Not well controlled with ICS (high-dose)+LABA or Not well controlled with ICS (mid-dose)+LABA + LAMA or Controlled with ICS (high-dose)+LABA + LAMA	FF/UMEC/VI 200/62.5/25 mcg via ELLIPTA, once-daily, 1 puff/time, morning

1. Asthma Control Questionnaire (ACQ-6 at screening and ACQ-7 at Week 0, week 24, week52/Withdrawal) will be used for the assessment of control status of asthma, i.e.,≤0.75 points shows controlled and >0.75 shows not well controlled.

Number of Participants:

The number of asthmatic adult subjects (with the control status on inhaled asthma therapy with medium to high dose ICS + LABA or medium to high dose ICS + LAMA + LABA [as shown in the table above]) required to be enrolled in this study is 110 (a total number of subjects to be allocated in Group 1 [FF/UMEC/VI 100/62.5/25] and Group 2 [FF/UMEC/VI 200/62.5/25]). According to the ICH guidelines, the sample size of 110 subjects would allow 100 subjects to complete the 52-week treatment period, assuming a drop-out rate of approximately 10%.

Treatment Groups and Duration:

This is a 55-week study consisting of the following three study periods:

- Run-in period (2 weeks): Eligible patients who meet the pre-defined criteria at screening (Visit 1) will enter into a 2-week run-in period. During the run-in period, the subjects will continue their pre-screening inhaled medications for asthma (ICS+LABA or ICS+LABA+LAMA) until the day before Visit 2 without any change in regimen/dosage.
- Treatment period (52 weeks): subjects who meet pre-defined criteria at Visit 2 will be allocated to either FF/UMEC/VI 100/62.5/25 or FF/UMEC/VI 200/62.5/25 treatment depending on the asthma control status with inhaled asthma therapy during the run-in period, and initiate a 52-week treatment period.

Switching medication from FF/UMEC/VI 100/62.5/25 to FF/UMEC/VI 200/62.5/25 will be permitted in accordance with the control status of the subject assessed by ACQ-7 at Week 24 of the treatment period (Visit 5).

- Follow-up period (1 week): A safety follow-up telephone contact or clinic visit will be conducted at the end of the follow-up period.

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 SCHEDULE OF ACTIVITIES

Procedure	Pre-screen	Run-in	Treatment period							Follow-up
Visit	0	1 Screening	2 Baseline	3	4	5	6	7 End of Treatment (EOT)	Early Withdrawal (EW)	Safety follow-up contact
Day	-28 to -14	-14	1	29	85	169	253	365		
Week	-4 to -2	-2	0	4	12	24	36	52		
Window		-3		-5/+2d	-5/+2d	-5/+2d	-5/+2d	-5/+2d		
Informed consent[1]	X									
Genetics/Pharmacogenetic informed consent[2]	X									
Inclusion and exclusion criteria		X	X							
Demography	X									
Past and current medical conditions including asthma history[3] and exacerbation history		X								
Smoking history and status		X								
Concomitant medication review		X	X	X	X	X	X	X	X	X
Allocation/registration[4]			X							
Register visit in IRT (RAMOS NG)[5]	X	X	X	X	X	X	X	X	X	X
Safety Assessment										
Physical examination		X				X		X	X	
Weight/height		X								
Adverse events			X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X	X	X
Vital signs (blood pressure and pulse rate)		X	X	X	X	X	X	X	X	
ECG		X		X		X		X	X	
Hematology and clinical chemistry		X			X	X		X	X	
Urinalysis		X			X	X		X	X	
Serum pregnancy test[6]		X			X	X		X	X	
Urine pregnancy test [6]			X	X			X			

Procedure	Pre-screen	Run-in	Treatment period							Follow-up
Visit	0	1 Screening	2 Baseline	3	4	5	6	7 End of Treatment (EOT)	Early Withdrawal (EW)	Safety follow-up contact
Day	-28 to -14	-14	1	29	85	169	253	365		
Week	-4 to -2	-2	0	4	12	24	36	52		
Window		-3		-5/+2d	-5/+2d	-5/+2d	-5/+2d	-5/+2d		
Other Assessment										
ACQ[7]		X[8]	X[9]			X[9]		X[9]	X[9]	
SGRQ[7]			X			X		X	X	
AQLQ[7]			X			X		X	X	
Pre-dose spirometry [10]			X			X		X	X	
Moderate/severe asthma exacerbation			X	X	X	X	X	X	X	X
Genetics/Pharmacogenetic sampling [11]			X							
Dispense paper Medical Problems/Medications Taken worksheet	X	X	X	X	X	X	X	X	X	
Review paper Medical Problems/Medications Taken worksheet		X	X	X	X	X	X	X	X	X
Healthcare resource utilization			X	X	X	X	X	X	X	
Dispense investigational product			X	X	X	X	X			
Collect investigational product				X	X	X	X	X	X	
Dispense salbutamol (as required)		X	X	X	X	X	X			
Collect salbutamol (as required)			X	X	X	X	X	X	X	

1. The Informed Consent Form (ICF) must be signed before any study procedures, including medication cessation.
2. Genetics/Pharmacogenetic research consent may be obtained at the same time as the study Informed Consent and must be obtained prior to obtaining a Genetics/pharmacogenetic blood sample.
3. The assessment of asthma history will include: the age of the subject when they were first provided with an inhaler for asthma; completion of an asthma medical history questionnaire (a copy of this questionnaire and instructions for its use can be found in the SRM).
4. Subjects must not be allocated prior to confirming their eligibility to participate in the study.
5. The IRT will be used for allocation, and study treatment supply management (Please refer to the RAMOS NG IRT manual and SRM for more information).
6. Assessments are only to be conducted in females of reproductive potential.
7. Assessment(s) to be completed before any study procedures .Study treatment should be administered at the same time of day each applicable clinic visit,
8. Assessment to be conducted by using ACQ-6
9. Assessment to be conducted by using ACQ-7

10. Spirometry to be performed after withholding rescue medication for at least 6 hours and prior to taking the morning dose of study treatment. Pre-dose spirometry assessments should be performed at the same time of day at each applicable visit.
11. Pharmacogenetic sample may be drawn any time from Visit 2 onwards.

ACQ: Asthma Control Questionnaire, AQLQ: Asthma Quality of Life Questionnaire, IRT: Interactive Response Technology, SGRQ: St. George's Respiratory Questionnaire

3. INTRODUCTION

3.1. Study Rationale

The Global Initiative for Asthma guidelines [GINA, 2016] recommend include a long-acting muscarinic antagonist (LAMA) as add-on treatment option for adults (≥18 years) with asthma that are currently taking medium-to-high dose inhaled corticosteroid and long-acting beta2 agonist (ICS/LABA) maintenance therapy and have a history of exacerbations. Exacerbations are an important endpoint in asthma therapy; however, symptom control is also important in determining what patients could benefit from step-up therapy.

GSK is currently developing a once-daily 'closed' triple therapy of an ICS/LAMA/LABA combination [FF/UMEC/vilanterol (VI)] in a single device, with the aim of providing a new treatment option for the management of asthma by improving lung function, health-related quality of life (HRQoL) and symptom control over established combination therapies. The objective of this study is to evaluate long-term safety of fixed dose combination therapy FF/UMEC/VI in Japanese patients with asthma. A global study comparing FF/UMEC/VI with a standard of care ICS/LABA combination therapy (Study 205715) is ongoing in parallel with this study, which will provide important information to prescribers regarding the benefit of step-up to closed triple therapy to patients uncontrolled on ICS/LABA.

3.2. Background

Despite the availability of treatments and published guidelines, patients may have asthma that is inadequately controlled. The prevalence of inadequately controlled asthma varies based on the definition used for control. In a sample of asthmatics visiting their healthcare provider for any reason, 58% of adult asthmatics were estimated to have uncontrolled asthma based on the Asthma Control Test (ACT, defined as an ACT score ≤19) [Stanford, 2010].

Consistent with these observations, an analysis of asthma patients in the United States (US) found that 29%-31% of asthma patients treated with high dose ICS/LABA therapy experienced exacerbations [Schatz, 2014]. In a Dutch survey of 929 patients treated with high dose ICS/LABA or medium/high dose ICS/LABA and maintenance oral corticosteroid (OCS), who self-reported asthma or chronic obstructive pulmonary disease (COPD) with <10 smoking pack years, 74% of patients were classified as difficult to control (Asthma Control Questionnaire [ACQ] score >1.5, or experienced ≥3 exacerbations in a year, or ≥1 hospitalization in a year). Half (50.6%) of these patients had an ACQ score >1.5, 21.7% had ≥3 exacerbations in a year, and 21.7% had ≥1 hospitalization in a year. Based on this sample, an estimated 17.4% of the Dutch asthma population was estimated to be on high dose ICS/LABA or medium/high dose ICS/LABA and maintenance OCS and have difficult to control asthma [Hekking, 2015].

In summary, although patients with asthma can be effectively treated with available controller medications, a subset of patients do not adequately respond to current standard therapy, as measured by symptom questionnaires (ACT, ACQ) and exacerbations.

The goal of asthma treatment is to achieve and maintain asthma control and to reduce the future risk of exacerbations. ICSs are considered the most effective anti-inflammatory treatments for all severities of persistent asthma [National Institutes of Health (NIH), 2007; GINA, 2016]. Treatment with ICS controls asthma symptoms, improves quality of life and lung function, decreases airway hyper-responsiveness, controls airway inflammation, and reduces the frequency and severity of asthma exacerbations, thereby reducing asthma morbidity. The dose of ICS is selected based on the severity of the patient's asthma. In patients who are symptomatic on ICS alone, add-on therapy with another controller, in particular a LABA is preferred to increasing the dose of ICS to achieve asthma control. The addition of a LABA to an ICS improves symptom scores, decreases nocturnal asthma symptoms, improves lung function and reduces the number of asthma exacerbations [Ducharme, 2010]. Combination ICS/LABA inhalation products have been developed as a result of this need. In difficult to treat persistent asthma, some patients continue to be symptomatic despite treatment with ICS and LABA combination medications and the current guidelines [GINA, 2016; NIH, 2007; British Thoracic Society / Scottish Intercollegiate Guidelines Network (BTS/SIGN), 2014] recommend treatment with high-dose inhaled or oral glucocorticosteroids in combination with LABAs and/or additional controller medications.

In the European Union (EU), tiotropium bromide (LAMA) is licensed as an add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of ICS (≥800 micrograms (mcg) budesonide/day or equivalent) and LABA and who experienced one or more severe exacerbations in the previous year [Spiriva Respimat Summary of Product Characteristics (SPC), 2016]. In the US, tiotropium bromide was recently approved for the maintenance treatment of asthma, in patients 12 years of age and older [Spiriva Respimat United States Product Insert (USPI), 2016]. In Japan, tiotropium bromide is approved for use in patients with asthma aged 15 years or older if ICS or other medications fails in improving symptoms or if combination of tiotropium bromide with ICS is considered appropriate based on the disease severity of the patient [Spiriva Respimat Japan Product Insert (Tiotropium bromide), 2016]. The benefit of adding a LAMA to both ICS monotherapy and ICS/LABA fixed combination therapy was demonstrated in four Phase III confirmatory studies (416, 417 [Kerstjens, 2012]; 418 and 419 [Kerstjens, 2015]), in symptomatic asthma patients (ACQ score ≥1.5). The Phase III studies supporting the tiotropium application showed that addition of tiotropium bromide to ICS/LABA maintenance therapy significantly improved lung function and reduced the risk of severe asthma exacerbation.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GW685698/GSK573719/GW642444 (FF/UMEC/VI) may be found in the Investigator's Brochure (IB), Participant Information Leaflet.

Summaries of findings from both clinical and non-clinical studies of FF/UMEC/VI conducted by GSK can be found in the IB. The following section outlines the risk assessment and mitigation strategy for this protocol.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [FF/UMEC/VI]		
Cardiovascular effects of UMEC and VI	UMEC Cardiovascular effects are a potential class effect associated with anti-muscarinic therapies. In the UMEC/VI clinical development program in Chronic Obstructive Pulmonary Disease (COPD) patients, UMEC/VI was generally well tolerated. Overall, a low number of atrial arrhythmias were reported based on 12-lead ECGs, Holter ECGs, or AEs, of which some occurred with a higher incidence in active treatment groups compared to placebo. There was no additive effect with the combination over individual components. Few of these findings were reported as Serious Adverse Events (SAEs) and none were fatal. In a narrow* Major Adverse Cardiac Event (MACE) analysis , the incidence of non-fatal myocardial infarction (Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) of myocardial infarction and acute myocardial infarction) was low (<1%) across all treatment groups, although small imbalances in exposure adjusted frequency were observed between UMEC- and VI containing treatment groups when compared with placebo and tiotropium. There was no obvious dose relationship or additive effect from the combination. Whether this represents a true effect is difficult to determine due to the small numbers. During clinical studies in COPD (62.5 and 125mcg daily dose of UMEC) and in Healthy Volunteers (in the Thorough QT study, UMEC 500mcg daily dose), no effect was observed on heart rate, blood pressure or QT. VI In the FF/VI clinical development program in patients with COPD, the	Mitigation strategy for UMEC and VI: - Exclusion criteria as specified in Section 6.2. of the protocol - Collection of cardiovascular risk factors and medical history at baseline - ECGs as per schedule in the SoA (Table 1) - Vital sign assessments (blood pressure and pulse rate) as per schedule in the SoA (Table 1) - Cardiovascular AEs and Serious AEs (SAEs) will be captured on the electronic Case Report Form (CRF) (see Section 9.2.5.) - Protocol defined stopping criteria as per Section 8 - MACE analysis - Instream review .

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	cardiovascular safety profile of VI and FF/VI was broadly consistent with the known pharmacology of LABAs in patients with COPD. VI at doses up to 100mcg in healthy subjects and subjects with asthma or COPD was not consistently associated with clinically relevant or statistically significant effects on blood pressure after either single or repeat dose administration. Data from Thorough QT (TQT) studies with FF, FF/VI and UMEC/VI suggest that, at the doses to be used in phase III studies, the closed triple (FF/UMEC/VI) is unlikely to cause clinically relevant effects on QTc[1]. No difference in QTcF[2] was observed between UMEC/VI 125/25mcg or UMEC 500mcg and placebo. UMEC/VI 500/100mcg increased QTcF on average by 8.2msec (milliseconds) (90% Confidence Intervals (CI): 6.2, 10.2) at 30 minutes (min) only. A lack of effect was demonstrated for QTcF with FF/VI 200/25mcg (for 7 days). At a supratherapeutic dose of FF/VI (800/100mcg for 7 days), the largest mean time-matched difference from placebo was 9.6 msec (90% CI: 7.2, 12.0) at 30 min only. [1] QT interval corrected for heart rate [2] QT interval corrected for heart rate by Fridericia's formula	
Anticholinergic effects (including constipation nausea, dry mouth, glaucoma, raised intraocular pressure and blurred vision, urinary retention)	In clinical studies in COPD, few anticholinergic effects were associated with UMEC; those observed included dry mouth, constipation and cough. Based on post-marketing experience dysgeusia has been added as an Adverse Drug Reaction (ADR) for inhaled UMEC and UMEC/VI. 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.	- Patients with known narrow-angle glaucoma, prostatic hyperplasia or bladder outflow obstruction that, in the opinion of the Investigator, contraindicates study participation or use of an inhaled anticholinergic, will be excluded from participating in the study. - Review AEs/SAEs

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Systemic ICS effects - Adrenal suppression - Cataracts & glaucoma - 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 serum cortisol excretion, and multiple studies with COPD and asthma subjects which monitored urinary cortisol. During clinical development of FF & FF/VI no events of Adrenal Suppression were reported. 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 subjects 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. During studies in both subjects with asthma and COPD, no associated affect 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. In two replicate 12 month studies in the FF/VI clinical program, in a total of 3,255 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)	- Review AEs/SAEs - The occurrence of bone fractures will be recorded in the eCRF.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	occurred in <1% of the FF/VI and VI treatment arms. In an integrated analysis of 11 studies in asthma with FF/VI (7,034 patients) and 10 studies in asthma with FF (6,219), the incidence of fractures with FF/VI and FF was ≤1%, and usually associated with trauma.	
Pneumonia	While ICS use is a recognised 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. In an 18 study integration in the FF/VI asthma program, the incidence of pneumonia (adjusted for exposure) observed with FF/VI 100/25 and FF 100 (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 and FF 200 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 hospitalisation with either strength, and there were no observed differences in the incidence of serious events between the two treatment strengths. The risk of pneumonia in asthma patients is very low and is consistent with the risk of other ICS. <u>Pneumonia experience with UMEC</u> In the All Clinical Studies grouping, the incidence of on-treatment AEs in the Pneumonia and lower respiratory tract infection (LRTI) adverse events of special interest (AESI) category with UMEC 62.5 mcg (1%; 34.6/1000SY) was similar to placebo (1%; 34.8/1000SY) and lower than the incidence reported in the UMEC 125 mcg (3%; 72.6/1000SY). A higher incidence of AEs in the Pneumonia AESI category was reported for UMEC 125 mcg (2%; 37.4/1000SY) compared with UMEC 62.5 mcg (<1%; 19.8/1000SY) and	Exclusion criteria: - Immune suppression (e.g., Human Immunodeficiency Virus [HIV], Lupus) or other risk factors for pneumonia (e.g.,neurological disorders affecting control of the upper airway, such as Parkinson's Disease, Myasthenia Gravis). - Subjects at potentially high risk (e.g., very low body mass index [BMI] or severely malnourished) will only be included at the discretion of the Investigator. Medical history will also be taken for pneumonia in previous 12 months, including recording of any episodes resulting in hospitalisation. 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 subject has a suspected

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	placebo (<1%; 10.7/1000SY). The proportion of subjects with SAEs in the Pneumonia AESI category was similar between both UMEC treatment groups, UMEC 62.5 mcg (<1%; 4.9/1000SY) and UMEC 125 mcg (<1%; 17.6/1000SY) and placebo (<1%; 10.7/1000SY).	pneumonia. All reports of pneumonia (radiographically confirmed and unconfirmed) must be reported as an AE or SAE, if applicable. Instream review. Review of AESI relevant for pneumonia using pre-specified MedDRA preferred terms. AE terms relating to other Lower Respiratory Tract Infections (excluding pneumonia) will also be reviewed.
Hypersensitivity	There have been post-marketing reports of hypersensitivity reactions with FF/VI and UMEC/VI, including anaphylaxis, angioedema, rash, and urticaria. The formulation also contains lactose.	Subjects 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 6.2.) - Review AEs/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.	Patients will undergo regular medical assessments during clinical studies. - Review AEs/SAEs
Pregnancy and lactation	There are no 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.	Females who are pregnant or breast-feeding are not eligible for participating in the study. Females of child-bearing potential will

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	There is a limited amount of data from the use of umeclidinium 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 umeclidinium 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.	need to follow the contraceptive requirements that are specified in Appendix 5.

3.3.2. Benefit Assessment

The addition of UMEC to FF/VI in asthma has the potential to improve lung function, reduce moderate/severe exacerbations and improve quality of life in patients whose asthma is inadequately controlled on ICS/LABA alone. Current asthma treatment guidelines recommend the addition of a LAMA (tiotropium) for patients that are uncontrolled on ICS/LABA (GINA 2016 Steps 4 and 5); the availability of the FF/UMEC/VI combination would therefore be consistent with this approach. The combination in a closed triple combination would provide the convenience of once daily dosing and reduce the need for multiple inhalers.

3.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in the study, the potential risks identified in association with FF/UMEC/VI are justified by the anticipated benefits that may be afforded to subjects with asthma.

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 inadequately controlled on inhaled asthma therapy (ICS+LABA or ICS+LAMA+LABA).

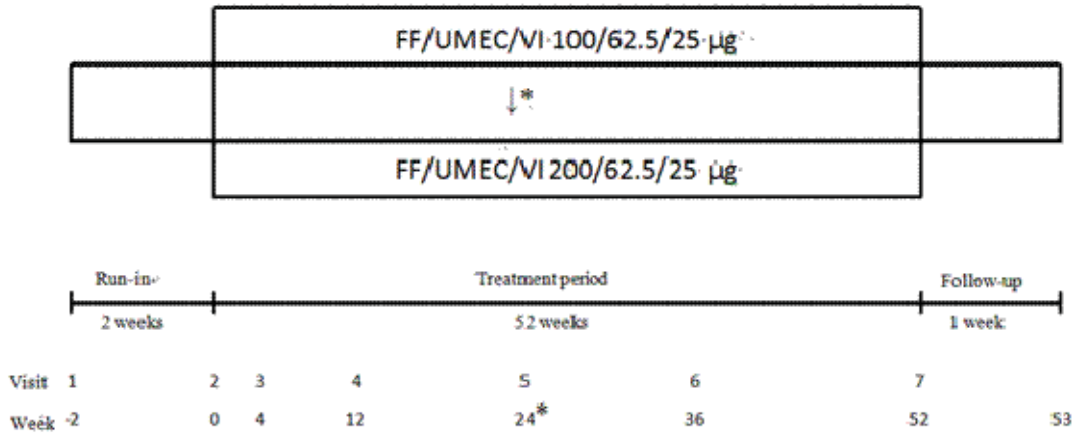
4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety of long-term treatment with FF/UMEC/VI combination therapy	• Incidence and type of adverse events (AE)/serious adverse events (SAE)
Secondary	
• To evaluate the safety of FF/UMEC/VI combination therapy	Secondary Endpoints • Blood pressure/pulse measurements • 12-lead electrocardiogram (ECG) • Clinical laboratory tests (hematology, biochemistry and urinalysis)
Other	
• To evaluate the efficacy of FF/UMEC/VI combination therapy	Other Endpoints • Mean change from baseline in trough Forced Expiratory Volume in 1 second (FEV1) at Week 24 and Week 52 • Mean change from baseline in Asthma Control Questionnaire–7 (ACQ-7) total score at Week 24 and Week 52 • Mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 24 and Week 52 • Mean change from baseline in the Asthma Quality of Life Questionnaire (AQLQ) total score at Week 24 and Week 52 • Unscheduled asthma-related healthcare resource utilization over the 52 weeks of the treatment period • Annualized rate of severe asthma exacerbations • Annualized rate of moderate/severe asthma exacerbations

5. STUDY DESIGN

5.1. Overall Design

The present study is a phase III, multicenter, non-comparator, non-randomized, open-label study in Japanese patients with asthma. This is a approximately 55-week study consisting of the run-in, treatment and follow-up periods.



* Switching medication from FF/UMEC/VI 100/62.5/25 mcg to FF/UMEC/VI 200/62.5/25 mcg will be permitted in accordance with the asthma control status of the subject assessed by ACQ-7 at Week 24 of the treatment period.

Figure 1 Study Schematic

Eligible patients who meet the pre-defined criteria at screening (Visit 1) will enter into a 2-week run-in period. During the run-in period, the subjects will continue their pre-screening inhaled medications for asthma (ICS+ LABA or ICS+LABA+ LAMA) until the day before Visit 2 without any change in regimen/dosage. After completion of the run-in period, subjects who meet pre-defined criteria at Visit 2 will be allocated to either FF/UMEC/VI 100/62.5/25 mcg (Group 1) or FF/UMEC/VI 200/62.5/25 mcg (Group 2) depending on the asthma control status with inhaled asthma therapy during the run-in period (see Table 2), and initiate a 52-week treatment period. Only at Week 24 of the treatment period (Visit 5), switching medication from FF/UMEC/VI 100/62.5/25 mcg to FF/UMEC/VI 200/62.5/25 mcg will be permitted if the control status of the subject assessed by ACQ-7 is inadequate (i.e., ACQ score >0.75). As a rescue medication, salbutamol is permitted throughout the run-in and treatment periods.

Table 2 Correspondence between Asthma Control Status with Inhaled Asthma Therapy during the run-in period and Allocated Study Treatment

Group	Asthma control status with inhaled asthma therapy[1]	Allocated study treatment
Group 1	Not well controlled with ICS (mid-dose)+LABA or Controlled with ICS (mid-dose)+LABA + LAMA	FF/UMEC/VI 100/62.5/25 mcg via ELLIPTA, once-daily, 1 puff/time, morning
Group 2	Not well controlled with ICS (high-dose)+LABA or Not well controlled with ICS (mid-dose)+LABA + LAMA or Controlled with ICS (high-dose)+LABA + LAMA	FF/UMEC/VI 200/62.5/25 mcg via ELLIPTA, once-daily, 1 puff/time, morning

1. Asthma Control Questionnaire (ACQ-6 at screening and ACQ-7 at week 0, week 24, week52/Withdrawal) will be used for the assessment of control status of asthma, i.e., ≤0.75 points shows controlled and >0.75 shows not well controlled.

Subjects will visit the clinic/hospital at screening (Visit 1), Week 0 (Visit 2), Week 4 (Visit 3), Week 12 (Visit 4), Week 24 (Visit 5), Week 36 (Visit 6), Week 52 (Visit 7/End of Treatment [EOT]) or Early Withdrawal (EW) , and about one week after Week 52 (Visit 7/EOT) or EW Visit as a safety follow-up visit.. Telephone contact can be selected for follow-up period.

This study consists of three periods as described below: run-in, treatment and follow-up periods. Details of study procedures and assessments in these periods are provided in the Study Reference Manual (SRM).

- Run-in period (2 weeks): Eligible patients who meet the pre-defined criteria at screening (Visit 1) will enter into a 2-week run-in period. During the run-in period, the subjects will continue their pre-screening inhaled medications for asthma (ICS+LABA or ICS+LABA+LAMA) until the day before Visit 2 without any change in regimen/dosage.
- Treatment period (52 weeks): subjects who meet pre-defined criteria at Visit 2 will be allocated to either FF/UMEC/VI 100/62.5/25 mcg or FF/UMEC/VI 200/62.5/25 mcg treatment depending on the asthma control status with inhaled asthma therapy during the run-in period, and initiate a 52-week treatment period.

  Switching medication from FF/UMEC/VI 100/62.5/25 mcg to FF/UMEC/VI 200/62.5/25 mcg will be permitted in accordance with the control status of the subject assessed by ACQ-7 at Week 24 of the treatment period (Visit 5).

- Follow-up period (1 week): A safety follow-up telephone contact or clinic visit will be conducted at the end of the follow-up period.

5.2. Number of Participants

The number of asthmatic adult subjects (with the control status on inhaled asthma therapy with medium to high dose ICS + LABA or medium to high dose ICS +LAMA + LABA [as shown in the table above]) required to be enrolled in this study is 110 (a total number of subjects to be allocated in Group 1 [FF/UMEC/VI 100/62.5/25 mcg] and Group 2 [FF/UMEC/VI 200/62.5/25 mcg]). According to the ICH guidelines, the sample size of 110 subjects would allow 100 subjects to complete the 52-week treatment period, assuming a drop-out rate of approximately 10% (Section 10.1.).

5.3. Participant and Study Completion

A subject is considered to have completed the study if he/she has completed all phases of the study including the safety follow-up telephone contact or clinic visit. The end of the study is defined as the date of the last safety follow-up telephone contact or clinic visit of the last subject in the study.

A subject who continues the study treatment until Visit 7/EOT is considered to have completed the study treatment.

5.4. Scientific Rationale for Study Design

The present study employs multicenter, non-comparator, non-randomized, open-label design. Eligible patients who meet pre-defined criteria will be allocated to either FF/UMEC/VI 100/62.5/25 mcg or 200/62.5/25 mcg which will be administrated in an open-label manner. As a step-up of the treatment during the treatment period, medication switching from FF/UMEC/VI 100/62.5/25 mcg to FF/UMEC/VI 200/62.5/25 mcg is permitted in accordance with the control status of the patient at Week 24. However, step-down is not permitted in order to ensure the long-term safety data of FF/UMEC/VI 200/62.5/25 mcg which contains higher dose of ICS (FF). Comparison between treatment groups is not planned and no stastistical tests will be performed because the purpose of this study is to evaluate mainly safety of overall FF/UMEC/VI containing UMEC 62.5 mcg. The duration of the treatment period is 52 weeks for the evaluation of long-term safety by reference to ICH E-1 guideline, “The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions”.

5.5. Dose Justification

At the moment, the candidate dosages of UMEC as a component of FF/UMEC/VI are 31.25 mcg and 62.5 mcg based on the result of Phase IIb study, 200699[1] and suggestions from the authorities (Food and Drug Administration [FDA] and the European Medicines Agency [EMA)]). The proposed marketed dosage of UMEC as a component of FF/UMEC/VI in Japan will be determined based on the results of the global phase III study (Study 205715). This safety study with FF/UMEC/VI 100/62.5/25 mcg and 200/62.5/25 mcg in Japanese subjects will add to the safety database in the Japanese sub-population of study 205715.The long-term safety of FF/UMEC/VI can be established with the data of FF/UMEC 62.5 mcg/ VI because the safety profile for FF/UMEC62.5 mcg/VI would cover all UMEC doses lower than 62.5 mcg as FF/UMEC/VI, thus, the only single higher dosage of UMEC as a component of FF/UMEC/VI will be employed in the present study. In addition, the doses of FF and VI as components of FF/UMEC/VI were selected based on the worldwide approved doses for the treatment of asthma (i.e., FF/VI 100/25 mcg and FF/VI 200/25 mcg). Therefore, FF/UMEC/VI 100/62.5/25 mcg and 200/62.5/25 mcg will be employed as the dose of FF/UMEC/VI in this study.

[1] Study 200699 is a dose-ranging study that evaluated the efficacy and safety of four doses of UMEC (15.6, 62.5, 125 and 250 mcg) in combination with FF (100 mcg) over a 4-week treatment period in irreversible subjects with fixed airway obstruction. The primary endpoint of Study 200699 was the change from baseline in trough FEV1. After 4 weeks of treatment in patients with a primary diagnosis of asthma, an increase in trough FEV1 of 136 mL was observed in those subjects treated with FF/UMEC (100/62.5 mcg) compared to those subjects treated with FF (100 mcg) alone. No safety signal was identified with any of the UMEC doses (15.6, 62.5, 125 and 250 mcg) evaluated in Study 200699. Based on these results, 62.5 mcg was selected as the dosage of UMEC as a component of FF/UMEC/VI.

6. STUDY POPULATION

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

Prior to screening, the Investigator will review each prospected subject's medical records and medical history to determine the subject's eligibility based on the inclusion/exclusion criteria at the time of informed consent (Visit 0) and at screening (Visit 1). The subject's eligibility should be confirmed again at the end of the run-in period based on the inclusion/exclusion criteria at Visit 2.

6.1. Inclusion Criteria

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

Age

1. Participant must be 18 years of age or older at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Ethnicity: Japanese
3. Diagnosis: Subjects with a diagnosis of asthma as defined by the National Institutes of Health [NIH, 2007] at least one year prior to providing informed consent.
4. Current Asthma Maintenance Therapy: Outpatients are eligible if they have received ICS+LABA with or without LAMA as inhaled medications for asthma in stable regimen and dosage for at least 4 weeks prior to screening visit (Visit 1) (with medium to high dose of ICS defined by the Japanese Guidelines [JGL Asthma, 2015]) and have control status as shown in Table 3. Asthma Control Questionnaire (ACQ-6) will be used for the assessment of control status of asthma at Visit 1 (screening Visit) (i.e., ≤0.75 points shows controlled and > 0.75 shows not well controlled).

Table 3 Asthma therapy and Control Status

Pre-screening inhaled asthma therapy	Control status of asthma[1]
ICS+LABA	Not well controlled with ICS (mid-dose) +LABA Not well controlled with ICS (high-dose) +LABA
ICS+LABA＋LAMA	Controlled with ICS (mid-dose) +LABA + LAMA Not well controlled with ICS (mid-dose) +LABA + LAMA Controlled with ICS (high-dose) +LABA + LAMA

1. Asthma Control Questionnaire (ACQ-6 at screening and ACQ-7 at week 0, week 24, week52/Withdrawal) will be used for the assessment of control status of asthma, i.e., ≤0.75 points shows controlled and >0.75 shows not well controlled.

5. Short-Acting β_2 Agonists (SABAs): All subjects must be able to replace their current SABA inhaler with salbutamol aerosol inhaler at Visit 1 as needed for the duration of the study. Subjects should be able to withhold salbutamol for at least 6 hours prior to clinic visit.

Sex

6. Male and/or female

A female participant is eligible to participate if she is not pregnant (see Appendix 4), not breastfeeding, and at least one of the following conditions applies:

(i)Not a woman of childbearing potential (WOCBP) as defined in Appendix 4.

or

(ii)A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 from the screening visit until after the last dose of study medication and completion of the follow-up visit.

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 2 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

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

Medical Conditions

1. Pneumonia: Chest X-ray documented pneumonia in the 6 weeks prior to Visit 1.
2. Asthma Exacerbation: Any asthma exacerbation requiring a change in maintenance asthma therapy in the 6 weeks prior to Visit 1.

   Note: Subjects requiring a temporary change in asthma therapy (e.g., oral corticosteroids or increased dose of ICS) to treat an exacerbation in the 6 weeks prior to Visit 1 are not explicitly excluded at Visit 1 provided that, at the Investigator's discretion, the subject's condition is stable after they have resumed their pre-exacerbation maintenance asthma therapy (without modification) and they are considered appropriate for enrolment into this study of up to 12 months' duration.

3. COPD: Subjects with the diagnosis of chronic obstructive pulmonary disease, as per Global Initiative for Chronic Obstructive Lung Disease (GOLD 2016) guidelines, including all of the following:

   - History of exposure to risk factors (i.e., especially tobacco smoke, occupational dusts and chemicals, smoke from home cooking and heating fuels) (for tobacco smoke, see Exclusion Criterion 16);

   and

   - A post- salbutamol FEV1/forced vital capacity (FVC) ratio of <0.70 and a post-salbutamol FEV1 of ≤70% of predicted normal values (diagnosis prior to Visit 1 acceptable);

   and

   - Onset of disease ≥40 years of age

4. Concurrent respiratory disorders: Subjects with current evidence of pneumonia, active tuberculosis, lung cancer, significant bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases or abnormalities other than asthma.

5. Risk Factors for Pneumonia: Immune suppression (e.g., HIV, lupus) or other risk factors for pneumonia (e.g., neurological disorders affecting control of the upper airway, such as Parkinson's disease, myasthenia gravis). Patients at potentially high risk (e.g., very low BMI, severely malnourished, or very low FEV1) will only be included at the discretion of the Investigator.

6. Other diseases/abnormalities: Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, gastrointestinal, urogenital, nervous system, musculoskeletal, skin, sensory, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.

7. Unstable liver disease as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices or persistent jaundice, cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

Note: Chronic stable hepatitis B and C are acceptable if the subject otherwise meets entry criteria.

8. Clinically significant ECG abnormality: Evidence of a clinically significant abnormality in the 12-lead ECG performed during screening. The Investigator will determine the clinical significance of each abnormal ECG finding in relation to the subject's medical history and exclude subjects who would be at undue risk by participating in the trial. An abnormal and clinically significant finding is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:

   - Atrial fibrillation (AF) with rapid ventricular rate >120 beats per minute (BPM)

- Sustained or nonsustained ventricular tachycardia (VT)
- Second degree heart block Mobitz type II and third degree heart block (unless pacemaker or defibrillator had been inserted)
- QTcF ≥500 msec in patients with QRS <120 msec and QTcF ≥530 msec in patients with QRS ≥120 msec

9. Unstable or life threatening cardiac disease: subjects with any of the following at screening (Visit 1) would be excluded:
   - Myocardial infarction or unstable angina in the last 6 months
   - Unstable or life threatening cardiac arrhythmia requiring intervention in the last 3 months
   - New York Heart Association (NYHA) Class IV heart failure [American Heart Association, 2016]
10. Antimuscarinic effects: Subjects with a medical condition such as narrow-angle glaucoma, urinary retention, prostatic hypertrophy or bladder neck obstruction should only be included if in the opinion of the Investigator the benefit outweighs the risk and that the condition would not contraindicate study participation.
11. Cancer: Subjects with carcinoma that has not been in complete remission for at least 5 years. Subjects who have had carcinoma in situ of the cervix, squamous cell carcinoma and basal cell carcinoma of the skin would not be excluded based on the 5 year waiting period if the subject has been considered cured by treatment.
12. Questionable validity of consent: Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation or other conditions that will limit the validity of informed consent to participate in the study.

Prior/Concomitant Therapy

13. Medication prior to spirometry: Subjects who are medically unable to withhold their salbutamol for the 6-hour period required prior to spirometry testing at each study visit.

Diagnostic assessments

14. Drug/alcohol abuse: Subjects with a known or suspected history of alcohol or drug abuse within the last 2 years.
15. Allergy or hypersensitivity: A history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, β_2-agonist, lactose/severe milk protein or magnesium stearate.
16. Tobacco use: Subjects who are:

- Current smokers (defined as subjects who have used inhaled tobacco products within the 12 months prior to Visit 1 [i.e., cigarettes, e-cigarettes/vaping, cigars or pipe tobacco]).
- Former smokers with a smoking history of ≥10 pack years (e.g., ≥20 cigarettes/day for 10 years).

Note: Refer to the SRM for the formula for calculating pack years.

Other Exclusions

17. Non-compliance: Subjects at risk of non-compliance, or unable to comply with the study procedures. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits.
18. Affiliation with Investigator site: Study Investigators, sub-Investigators, study coordinators, employees of a participating Investigator or study site, or immediate family members of the aforementioned that is involved with this study.
19. Inability to read: In the opinion of the Investigator, any subject who is unable to read and/or would not be able to complete study related materials.

Eligibility criteria at the end of the run-in period (Visit 2)

At the end of the run-in period, subjects must meet all of the additional criteria listed below in order to continue participation in the study. Subjects who meet these criteria can initiate a 52-week treatment period.

Inclusion criteria at the end of the run-in period (Visit 2)

Asthma maintenance therapy

1. Asthma maintenance therapy: No changes in asthma maintenance therapy (excluding salbutamol inhalation aerosol provided at Visit 1) and control status during the run-in period. Asthma Control Questionnaire (ACQ-6 at screening and ACQ-7 at the end of the run-in period) will be used for the assessment of control status of asthma, i.e., 0.75 points shows controlled and >0.75 shows not well controlled.

Concurrent conditions/medical history

2. Liver function test at Visit1
   - Alanine aminotransferase (ALT) <2 x upper limit of normal (ULN)
   - Alkaline phosphatase ≤1.5 x ULN

- Bilirubin ≤1.5 x ULN (isolated bilirubin >1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

Exclusion criteria at the end of the run-in period (Visit 2)

Concurrent conditions/medical history

1. Respiratory Infection: Occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear during the run-in period that led to a change in asthma management or, in the opinion of the Investigator, is expected to affect the subject's asthma status or the subject's ability to participate in the study.
2. Severe asthma exacerbation: Evidence of a severe exacerbation during screening or the run-in period, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days[2] or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.

Diagnostic assessments and other criteria

3. Laboratory test abnormalities: Evidence of clinically significant abnormal laboratory tests during screening or the run-in period which are still abnormal upon repeat analysis and are not believed to be due to disease(s) present. Each Investigator will use his/her own discretion in determining the clinical significance of the abnormality.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

There is no restriction on diet in this study.

6.3.2. Caffeine, Alcohol, and Tobacco

Use of tobacco products will not be allowed from screening until after the final follow-up visit. Caffeine and alcohol is allowed ad libitum.

6.3.3. Activity

There is no restriction on activity in this study.

[2] For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days is required.

6.4. Screen Failures

For the purpose of this study, pre-screen failures, screen failures and run-in failures will be defined as follows:

Pre-screen failures: Those subjects that sign the informed consent document but do not have a Visit 1 (screening) procedure.

Screen failures: Those subjects that complete at least one Visit 1 (screening) procedure but do not enter the run-in period. A subject who complete Visit 1 assessments is considered to have entered the run-in period.

Run-in failures: Those subjects that enter the run-in period but do not subsequently enter the treatment period, including those subjects that complete the run-in period and then meet the eligibility criteria but are not assigned to treatment at Visit 2.

The study interactive response technology (IRT) system (RAMOS NG) will be contacted to report pre-screen, screen and ruin-in failures.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened subjects should be assigned a subject number different from that for the initial screening. Advance written approval to proceed with rescreening a subject must be obtained from the Medical Monitor (see the SRM for contact details).

7. TREATMENTS

The term ‘study treatment’ is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

7.1. Treatments Administered

Study treatment will be administered via the ELLIPTA device. The ELLIPTA device is a molded plastic two-sided device that can hold two individual blister strips. Description of the study treatment administered via the ELLIPTA is provided in Table 4.

Table 4 Description of Study Treatment

Investigational product:	FF/UMEC/VI	
Dosage formulation:	ELLIPTA with 30 doses of inhalation powder (2 strips with 30 blisters per strip)	
Unit dose strengths/ dosage levels:	Strip 1: FF blended with lactose 100 or 200 mcg per blister	Strip 2: UMEC and VI blended with lactose and magnesium stearate UMEC 62.5 mcg and VI 25 mcg per blister
Route of administration	Inhaled	
Dosing instructions:	1 puff at approximately the same time in each morning	
Packaging and labelling	Each will be labeled as required per country requirement.	
Manufacturer	GSK	

Subjects will self-administer their first dose in the clinic and will continue to administer FF/UME/VI at approximately the same time each morning for the duration of the treatment period. Each subject will be instructed on the proper use of the ELLIPTA and will inhale once from the ELLIPTA each morning.

At Visit 1, an salbutamol metered-dose inhaler (MDI) as rescue medication will be provided for as-needed use throughout the study period starting at Visit 1. At the Investigator's discretion, more than one MDI may be provided at any one time. Salbutamol will be sourced from local commercial stock. The contents of the label will be in accordance with all applicable regulatory requirements in Japan.

All used and unused study treatment and salbutamol will be returned to GSK at the end of the study to be available for disposal. Detailed instructions for the return of the study drug can be found in the SRM.

If any ELLIPTA fails to function properly, the subject should return to the clinic as soon as possible to obtain a new inhaler.

In addition, any ELLIPTA that fails to function properly must be identified and returned to GSK for testing.

7.2. Dose Modification

During the run-in period, the subjects will continue their current (pre-screening) inhaled medications for asthma (ICS+LABA or ICS+LABA+LAMA) until the day before Visit 2 without any change in regimen/dosage.

At Visit 2, subjects will be assigned to study treatment as shown in Table 5 and will be provided with the assigned investigational product.

Table 5 Study Treatment Assignment

Group	Current inhaled therapy and control status of asthma during the run-in period[1]	Study treatment
Group 1	Not well controlled with ICS (mid-dose)+LABA or Controlled with ICS (mid-dose)+LABA + LAMA	FF/UMEC/VI 100/62.5/25 mcg via ELLIPTA, once-daily, 1 puff/time, morning
Group 2	Not well controlled with ICS (high-dose)+LABA or Not well controlled with ICS (mid-dose)+LABA + LAMA or Controlled with ICS (high-dose)+LABA + LAMA	FF/UMEC/VI 200/62.5/25 mcg via ELLIPTA, once-daily, 1 puff/time, morning

1. ACQ-7 score (Week 0) will be used for the assessment of control status of asthma, i.e., ≤0.75 points shows controlled and >0.75 shows not well controlled.

On the morning of scheduled clinic study visit at Visit 2, Visit 5 and Visit 7, subjects will refrain from taking their morning dose of study treatment until instructed to do so by clinic personnel.

Study treatment will be taken at the clinic at approximately the same time of day as taken at Visit 2. Each Investigator will be provided with sufficient supplies to conduct the trial. Additional treatment packs will be supplied as needed to the sites.

The last dose of the investigational product will be taken at the clinical at Visit 7/EOT (or at the early withdrawal visit as appropriate) and safety follow-up assessments will be performed approximately 1 weeks later.

At Week 24 of the treatment period (Visit 5), switching medication from FF/UMEC/VI 100/62.5/25 mcg to FF/UMEC/VI 200/62.5/25 mcg will be permitted if the control status of the subject assessed by ACQ-7 is inadequate (i.e., ACQ score >0.75).

7.3. Method of Treatment Assignment

Treatment will not be assigned by randomisation, but by current inhaled therapy and control status of asthma during the run-in period as described in Section 7.2.. Details of procedures of treatment assignment of subjects and study treatment supply management using RAMOS NG (including study drug supply) are provided in the RAMOS NG Manual and the SRM.

7.4. Blinding

This will be an open-label (non-blind) study.

7.5. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

When subjects are dosed at the study site, they will receive study treatment under medical supervision by the Investigator or designee. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person responsible for study treatment accountability.

When subjects self-administer study treatment at home, the Investigator or designee will assess compliance with study treatment by counting the remained doses of FF/UMEC/VI in ELLIPTA as appropriate at the clinic visits and by querying the subject during the clinic visits as necessary, and document it in the source documents and CRF. A record of the number of the investigational product dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records by the person responsible for study treatment accountability. Treatment start and stop dates will also be recorded in the CRF. Subjects should be ≥80% to ≤120% compliant on taking study treatment between each pair of scheduled and consecutive on-treatment clinic visits.

Subjects who fall outside this range should be re-educated on treatment compliance by their site. The Investigator should document this re-education in the source documents.

If the study treatment is withdrawn early or a subject is unable comply with the study treatment method and repeatedly falls outside the acceptable compliance range, the sponsor/monitor should be notified of it for discussion about appropriateness of continuation of the study in the subject.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the treatment period must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

All asthma medications used within approximately 4 weeks prior to screening should also be recorded in the CRF. Medications initiated after completion of the assessments at Visit 7/EOT or the Early Withdrawal Visit will not be recorded in the CRF unless taken to treat an AE or asthma exacerbation. Concomitant medications relating to a SAE need to be entered on the CRF, if SAE is occurred from informed consent until the initiation of treatment period.

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

Detailed information of permitted and prohibited medications is included in the SRM. Participants who have completed the Visit 7/EOT or Early Withdrawal Visit are allowed to use any medications prescribed by the Investigator or primary care physician.

7.7.1. Prohibited Concomitant Medications

Use of the medications listed in Table 6 is not permitted during the study.

Table 6 Concomitant Medications (○: permitted, X: prohibited)

Medication	Prior to Visit 1	Run-in period	Treatment period	Follow-up period
Inhaled short-acting anticholinergics	Prohibited within 6 hours	X	X	○
Inhaled short-acting anticholinergics + short-acting β_2 agonist combination	Prohibited within 6 hours	X	X	○
Inhaled long-acting anticholinergics	○	○[1]	X	○
Immunosuppressive medications including immunomodulators	Prohibited within 12 weeks	X	X	○
Inhaled LABA (e.g., salmeterol, formoterol, indacaterol, olodaterol) or combination products containing inhaled LABA (e.g., Adoaire, Symbicort)	○	○[1]	X	○
Non-Inhaled LABA (e.g., Hokunalin Tape)	Prohibited within 24 hours	X	X	○
Inhaled short-acting beta$_2$-agonist (rescue salbutamol will be provided and is permitted during the study)	Prohibited within 6 hours	X	X	○
ICS	○	○[1]	X	○
Theophyllines, slow-release bronchodilators, ketotifen, nedocromil sodium, sodium cromoglycate, roflumilast	Prohibited within 48 hours	X	X	○
Medicinal marijuana[2]	Prohibited within 6 months	X	X	X
Other investigational products	Within 30 days or within 5 drug half-lives of the investigational drug (whichever is longer)	X	X	X

1. Start of use is prohibited.
2. Use of inhaled medicinal cannabis is prohibited. Use of medicinal cannabis by any other route of administration is also prohibited unless written approval is obtained from the Medical Monitor prior to Visit 1.

7.7.2. Permitted Concomitant Medications

7.7.2.1. Permitted Asthma Medications

In addition to study treatment, the following medications are permitted during this study:

- Systemic corticosteroids (≤5 mg/day of prednisolone or equivalent) will be permitted provided that treatment was initiated at least 12 weeks prior to Visit 1, remains stable for the 8 weeks prior to Visit 1 and the subject remains in the maintenance phase throughout the study (the only exception being the treatment of moderate/severe asthma exacerbations [see below]).
- Anti-immunoglobulin E (IgE) (e.g. omalizumab) treatment will be permitted provided that treatment was initiated at least 16 weeks prior to Visit 1 and the subject remains in the maintenance phase throughout the study.
- Anti-interleukin (IL)-5 (e.g. mepolizumab) treatment will be permitted provided that treatment was initiated at least 16 weeks prior to Visit 1 and the subject remains in the maintenance phase throughout the study.
- Anti-leukotriene treatment will be permitted provided that treatment was initiated at least 12 weeks prior to Visit 1 and the subject remains in the maintenance phase throughout the study.
- Study-provided salbutamol will be dispensed at Visit 1 for use as rescue medication throughout the duration of the study. GSK will not provide any recue drug to the sites in principle.

Temporary additions of medications are permitted for the treatment of moderate asthma exacerbations at the Investigator's/treating physician's discretion. Asthma exacerbations should be treated in line with national and international recommendations and local medical standards. Asthma medications permitted on a temporary basis to treat a moderate asthma exacerbation include but are not limited to the following (the Medical Monitor may be contacted for additional guidance, see the Medical Monitor/Sponsor Information Page):

- An increase in ICS dose
- Systemic corticosteroids (tablets, suspension or injection) (or an increase in systemic corticosteroid dose for those subjects receiving maintenance systemic corticosteroids)
- Change in SABA use (i.e., routinely scheduled versus as needed use)
- Leukotriene receptor antagonists (LTRAs)
- Oral theophylline
- By definition, a severe asthma exacerbation will be treated with systemic corticosteroid (tablets, suspension or injection) for at least 3 consecutive days (or at

least double the existing maintenance dose of systemic corticosteroid, if applicable, for at least 3 consecutive days). See Section 9.5.4.2..

7.7.2.2. Permitted Non-Asthma Medications

The following medications are permitted during this study:

- Medications for rhinitis (e.g., intranasal corticosteroids, antihistamines [including ocular and intranasal], cromolyn, nedocromil, nasal decongestants)
- Antibiotics for short term treatment of acute infections. Long term treatment with topical or ophthalmic antibiotics are permitted.
- Decongestants: Subjects may take decongestants during the study, but these are disallowed for 24 hours prior to ECG measurements.
- Immunotherapy: Immunotherapy for the treatment of allergies is allowed during the study provided it was initiated 4 weeks prior to Visit 1 and subjects remain in the maintenance phase for the duration of the study.
- Topical and ophthalmic corticosteroids
- Systemic and ophthalmic β-blockers: Administer with caution as systemic β-blockers block the pulmonary effect of β-agonists and may produce severe bronchospasm in patients with reversible obstructive airways disease. Cardioselective β-blockers also should be administered with caution.
- Localized corticosteroid injections (e.g. intra-articular and epidural)
- Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). Administer with extreme caution as they may potentiate the effects of β-agonists on the cardiovascular system, including QTc prolongation.
- Diuretics. Caution is advised in the co-administration of β-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.
- Vaccinations (e.g., influenza vaccine, pneumonia vaccine, herpes zoster vaccine). Administration of influenza and pneumonia vaccines should be considered based on clinical discretion of the Investigator and local/national guidelines. Current influenza vaccines and pneumonia vaccines will be captured on the concomitant medication pages of the CRF.)

All medications for other disorders may be continued throughout the study provided their use would not be expected to affect the subjects' lung function or safety assessments (e.g., cardiac measurements). However, no systemic corticosteroids for other conditions will be permitted.

7.7.2.3. Permitted Non-Drug Therapies

Use of continuous positive airway pressure (CPAP) for treatment of obstructive sleep apnea syndrome will be permitted provided that the treatment was initiated at least 6 weeks prior to the screening visit (Visit 1) and the subject remains on CPAP throughout the study.

7.8. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because other treatment options are available.

The Investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

A subject may be withdrawn from study treatment at any time. A reason for premature discontinuation of study treatment (e.g., AE, lack of efficacy [including acute moderate or severe asthma exacerbation], protocol deviation, Investigator discretion, consent withdrawn) must be captured in the CRF.

A subject must be withdrawn from study treatment if any of the following stopping criteria are met:

- Liver Chemistry: Meets any of the protocol-defined liver chemistry stopping criteria (see Section 8.1.1. and Appendix 6).
- QTc: Meets any of the protocol-defined stopping criteria (see Section 8.1.2.).
- Pregnancy: Positive pregnancy test (see Section 9.2.7. and Appendix 4)

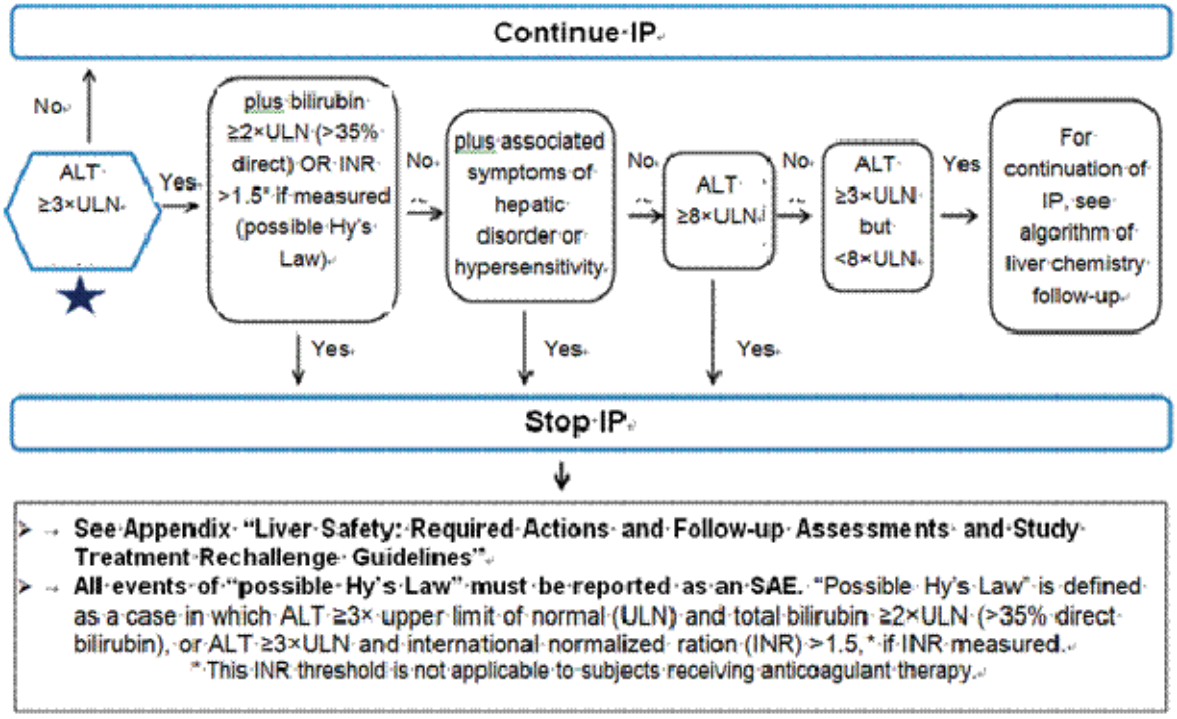
8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance:

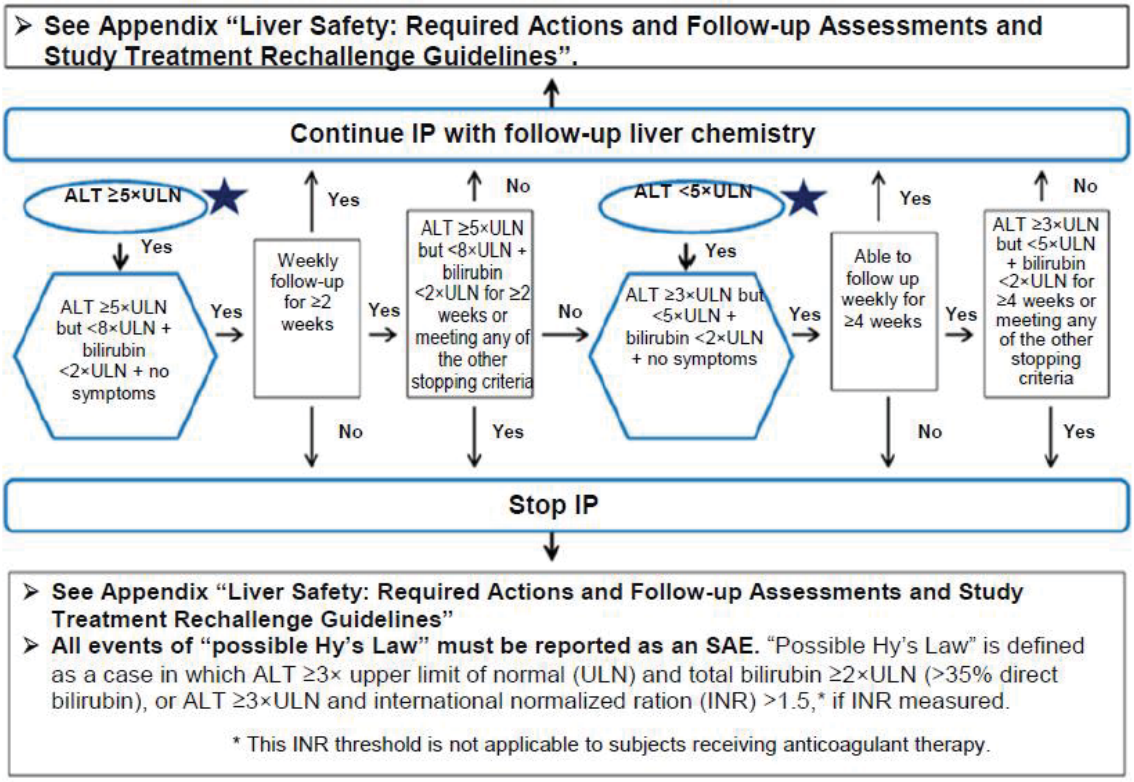
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm or if the investigator believes that it is in the best interest of the participant.

Algorithm A: Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Algorithm B: Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

8.1.2. QTc Stopping Criteria

Details on performing ECG assessments can be found in Section 9.4.3..

- The QTcF (QT interval corrected by Fridericia's formula) must be used for each individual participant to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
- The QTcF must be continued to be used for all QTc data being collected from all subjects for data analysis. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minutes) recording period.
- For this study, the following QTc stopping criteria will apply:
  - QTcF >500 msec or uncorrected QT >600 msec
  - For patients with bundle branch block: QTcF ≥ 530 msec

- Change from baseline in QTcF > 60 msec

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.3. Temporary Discontinuation

A subject who discontinue the study treatment must be withdrawn from the study.

8.1.4. Rechallenge

8.1.4.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- 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, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she 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 and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not 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, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (see Table 1).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- 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. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples

Screening and critical baseline assessments

No study related procedures may be performed until the informed consent form has been signed by the subject. A pre-screening visit (Visit 0) is required in order to administer the informed consent before any changes are made to the subject's current medical regimen. Selection and modification of the subject's medications prior to study participation is based on the physician's judgment according to sound medical practice, principles, and each subject's needs. A subject's treatment must not be changed merely for the purpose of enabling the subject's participation in the study.

At the pre-screening visit (Visit 0) the following information will be assessed for each subject:

- Date of ICF signature
- Demographic information including race, age and gender
- Subject number
- Serious Adverse Event information (only in the case assessed as related to study participation)

The following additional critical baseline assessments will be conducted at screening (Visit 1):

- Weight and height
- Asthma diagnosis history including:
  - The age of the subject when they were first provided with an inhaler for asthma
  - Completion of an asthma medical history questionnaire (A copy of this questionnaire and instructions for its use can be found in the SRM.)
- Smoking history and status
- Exacerbation history
- Asthma and other concurrent medications and non-drug therapies
- Medical history including previous and/or concurrent medical conditions, detailed cardiovascular risk factor history, pneumonia, and pneumonia vaccine status
- Reason for screen failure (if applicable)
- Vital signs
- ACQ-6
- Inclusion/Exclusion criteria assessment
- Physical examination
- 12-lead ECG
- Child bearing status assessment for all potential female subjects
- Clinical laboratory tests (including hematology, clinical chemistry, urinalysis and serum pregnancy test)
- SAE assessment

In addition, the following procedures must be completed at screening (Visit 1):

- Review/dispense Medical Problems/Medication Taken worksheet
- Dispense salbutamol

9.1. Efficacy Assessments

This is an open-label study and the efficacy will be assessed in an exploratory manner. Therefore, the efficacy endpoints are considered other endpoints and hence described in section 9.5. .

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment/study (see Section 8.).

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of study treatment until the follow-up visit at the time points specified in the SoA (Table 1). Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Table 1).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. 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 AE/SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3.). Further information on follow-up procedures is given in Appendix 3.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

9.2.6. Pneumonia

Medical history will also be taken for pneumonia in previous 12 months, including recording of any episodes resulting in hospitalization. Where possible a chest X-ray should be performed to confirm a diagnosis, whenever a subject has a suspected pneumonia. Suspected pneumonias will require confirmation as defined by the presence of new infiltrate(s) on chest X-ray AND at least 2 of the following signs and symptoms:

- Increased cough
- Increased sputum purulence (color) or production
- Auscultatory findings of adventitious sounds (e.g., egophony, bronchial breath sounds, rales)
- Dyspnea or tachypnea
- Fever (oral temperature >37.5°C)
- Elevated white blood cells (WBC) (>10,000/mm^3 or >15% immature forms)
- Hypoxemia (oxyhemoglobin [HbO2] saturation <88% or at least 2% lower than baseline value)

All pneumonias must be captured on the AE/SAE page of the CRF and on the pneumonia page of the CRF.

For all suspected cases of pneumonia, investigators are strongly encouraged to confirm the diagnosis (this includes obtaining a chest X-ray) and to initiate appropriate therapy as promptly as possible. All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable).

9.2.7. Pregnancy

- Details of all pregnancies in female will be collected after the start of dosing and until the safety follow-up contact/visit.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2.8. Adverse Events of Special Interest (AESIs)

AE groups of special interest have been defined as AEs which are associated with the already acknowledged pharmacological effects (class effects) of any of ICS, LAMA, and LABA. Some AE groups may have subgroups defined.

The following Table 7 presents the current special interest AE groups and subgroups. These may be updated prior to conclusion of the study reporting. The final list, including the preferred terms which contribute to each of the groups will be documented a priori in the study Reporting and Analysis Plan (RAP).

Table 7 The Special interest groups and subgroups

Special interest AE group	Special interest AE subgroup
Cardiovascular effects	Cardiac arrhythmia
	Cardiac failure
	Cardiac ischemia
	Stroke
Anticholinergic syndrome	-
Urinary retention	-
Dry mouth / drying of airway secretions	-
Gastrointestinal obstruction	-
Antimuscarinic ocular effects / Corticosteroids associated eye disorders	Glaucoma (antimuscarinic/corticosteroid)
	Cataracts (corticosteroid)
Pneumonia and LRTI	Pneumonia
	LRTI excluding pneumonia
Adrenal suppression	-
Decreased bone mineral density and associated fractures	-
Effects on glucose	-
Effects on potassium	-
Tremor	-
Asthma intubations, and deaths	-
Hypersensitivity	-
Local steroid effects	-

9.3. Treatment of Overdose

An overdose is defined as a dose greater than the total doses described above which results in clinical signs and symptoms. These should be recorded by the investigator on the AE/SAE pages. In the event of an overdose of study treatment, the investigator should use clinical judgment in treating the overdose and contact the GSK medical monitor.

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

9.4. Safety Assessments

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

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded. Height will be measured at Visit 1.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Pulse rate and blood pressure will be assessed.
- Blood pressure (systolic and diastolic) and pulse measurements will be assessed in the sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- A single set of values will be collected and recorded in the source documentation and CRF.

9.4.3. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (see Table 1) using an ECG machine of the site that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. A single 12-lead ECG and rhythm strip will be recorded after measurement of vital signs and spirometry.
- For subjects who meet the protocol defined QTc stopping criteria, triplicate ECGs (over a brief period of time) should be performed (Section 8.1.2.).
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.
- The Investigator, a designated sub-Investigator or other appropriately trained site personnel will be responsible for performing each 12-lead ECG. The Investigator must provide his/her dated signature on the original paper tracing, attesting to the authenticity of the ECG machine interpretation.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Table 8 for the list of clinical laboratory tests to be performed and to the SoA (Table 1) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Table 8, must be conducted in accordance with the laboratory manual and the SoA (Table 1).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE), then the results must be recorded in the CRF.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Laboratory Manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

All blood samples which will be taken pre-dose, will be sent to a central laboratory for analysis (details provided in the Laboratory Manual). Standard reference ranges will be used.

Refer to the Laboratory Manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 8.

Table 8 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count	RBC Indices:	WBC count with differential:	
	Red blood cell (RBC) count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry [1]	Blood urea nitrogen (BUN)	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total protein
	Glucose	Calcium	Alkaline phosphatise	Albumin
Routine Urinalysis	• pH, glucose, protein, blood and ketones by dipstick • Specific gravity, Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in females of non-reproductive potential only) • Serum/urine hCG pregnancy test (see the SoA in Table 1)			

NOTES :
1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 8.1.1. and Section 12.6. (Appendix 6).

BUN: Blood Urea Nitrogen, FSH: Follicle Stimulating Hormone, hCG: Human Chorionic Gonadotropin, MCH: Mean Corpuscular Hemoglobin, MCV: Mean Corpuscular Volume, SGOT: Serum glutamic-oxaloacetic tranaminase, SGPT: Serum glutamic-pyruvic tranaminase

9.4.5. Paper Medical Problems/Medications Taken Worksheet

Subjects will be issued with a Paper Medical Problems/Medications Taken Worksheet to record any medical problems and non-study specific medications used during the study. Subjects must also use this paper worksheet to record all emergency department visits and/or hospitalizations that occur during their participation in the study. Subjects will be asked to bring their paper worksheet to every study site visit as it will be used to assist subject recall in discussions with the Investigator (or designee), for site staff to then enter as appropriate in the CRF.

9.5. Other Assessments

9.5.1. Other endpoints

The exact timing of each of the following assessments is shown in the SoA (see Table 1).

- Change from baseline in trough FEV1 at Week 24 and Week 52
- Change from baseline in ACQ-7 total score at Week 24 and Week 52
- Change from baseline in SGRQ total score at Week 24 and Week 52
- Change from baseline in AQLQ total score at Week 24 and Week 52
- Unscheduled asthma-related healthcare resource utilization over the 52 weeks of the treatment period
- Annualized rate of severe asthma exacerbations
- Annualized rate of moderate/severe asthma exacerbations

9.5.2. Questionnaires

The questionnaires should be completed before any procedures are performed on the subject to avoid influencing the subject's response. To avoid biasing responses, the subjects 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. Adequate time must be allowed to complete all items on the questionnaires; the questionnaires must be reviewed for completeness and, if necessary, the subject must be encouraged to complete any missing assessments or items.

Instructions for completing the questionnaires can be found in the SRM.

9.5.2.1. Asthma Control Questionnaire (ACQ)

The ACQ measures seven attributes of asthma control [Juniper, 1999]. Six attributes are measured with a patient-completed questionnaire, and the questions are designed to be self-completed by the subject. Subjects will complete the ACQ at specified study visits. The six questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath, wheeze and rescue medication use) enquire about the frequency and/or severity of symptoms over the previous week. The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale. The recall period is the past week. The seventh attribute of the ACQ-7 is lung function (FEV1%-predicted) which will be included via study visit spirometry. Two shortened versions of the ACQ exist. The two shortened versions include the ACQ-5 (a five-item measure using only the symptoms items) and the ACQ-6 (six-item measures and rescue bronchodilator use). The measurement properties were very similar for all versions of the ACQ (original 7-item ACQ and shortened versions) [Juniper, 2005; Virchow, 2015]. For all versions, 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 score [Juniper, 2005].

9.5.2.2. St. George's Respiratory Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire is a well-established instrument, comprising 50 questions designed to measure Quality of Life in patients with diseases of airway obstruction, measuring symptoms, impact, and activity. The questions are designed to be self-completed by the subject [Jones, 1992] with a recall over the past 3 months. Higher scores indicate worse health status, and a change of 4 points is considered a clinically relevant change [Jones, 2005].

9.5.2.3. Asthma Quality of Life Questionnaire (AQLQ)

The Asthma Quality of Life Questionnaire (AQLQ) was developed to measure the functional impairments related to asthma experienced by adults 17+ years old. The AQLQ (+12), is a modified version of the original AQLQ and validated for use in asthma patients between the ages of 12 and 70 [Juniper, 2005]. 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 HRQoL, and a change of 0.5 is considered clinically important [Juniper, 1994].

9.5.2.4. Healthcare Resource Utilization

All unscheduled asthma-related healthcare utilization will be recorded in the CRF at the time points specified in the SoA (Table 1). Unscheduled asthma-related healthcare utilization includes telephone contacts, specialist nurse visits, visits to a physician's office, home visits (day and night time), outpatient visits, visits to urgent care, visits to the emergency department, and hospitalizations associated with the subject's worsening of symptoms. The Medical Problems/Medication Taken worksheet (see Section 9.4.5.) used by the subject to record all healthcare contacts experienced since the last visit will be presented to the Investigator (or designee) at the clinic visits. Subjects will be asked to bring their worksheet to every study site visit as it will be used to assist subject recall in discussions with the investigator, for site staff to then enter as appropriate in the CRF. The Investigator (or designee) should ask the subject if any of the healthcare contacts that are recorded on the worksheet were due to a worsening of asthma symptoms. The investigator can refer to his/her records to verify or supplement information given by the subject, if necessary.

9.5.3. Pulmonary Function Tests

Spirometry will be performed at the study site to assess FEV1 and FVC. At least 3 acceptable spirometry maneuvers (from a maximum of 8 attempts) should be achieved on each occasion that spirometry assessments are performed, in accordance with the American Thoracic Society (ATS) / European Respiratory Society (ERS) standards [Miller, 2005]. The highest of 3 technically acceptable measurements will be recorded at each visit:

- Pre-dose Spirometry: At Visit 2, Visit 5 and Visit 7/EOT (and the Early Withdrawal Visit, if applicable), subjects should withhold salbutamol for at least 6 hours prior to

study visits, if possible. Spirometry assessments must be performed at the following time points:

- At the same time of day (±1 hour) as the assessment performed at Visit 2 (the baseline assessment)
- At least 24 hours after the subject's last morning dose of study treatment on the day prior to the visit
- Before the subject's morning dose of study treatment on the day of the visit

9.5.4. Asthma Exacerbations

For the purposes of this study, moderate/severe asthma exacerbations will be collected and recorded on the asthma exacerbation eCRF page from the start of treatment period until Visit 7/EOT Visit or the Early Withdrawal Visit for those subjects that withdraw from participation in the study (see Section 8.1.). Moderate/severe asthma exacerbations should not be recorded as an adverse event unless:

- They meet the definition of an Adverse Event (see Appendix3) and occur:
  - After completion of the Visit 7/EOT Visit (or Early Withdrawal Visit) assessments until the follow-up contact.

OR

- They meet the definition of a Serious Adverse Event (see Appendix 3).
  Note: The SAE page of the eCRF should be completed in addition to the asthma exacerbation eCRF page if the exacerbation occurs after the start of treatment period but before completion of the Visit 7/EOT Visit or Early Withdrawal Visit assessments.

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

Subjects are also instructed to contact the investigator for signs of worsening asthma. Subjects will also complete a paper Medical Problems/Medications Taken worksheet to record medical problems experienced and medications used during the study, as well as all emergency department visits and/or hospitalizations that occur during their participation in the study. This paper worksheet must be reviewed by the Investigator (or designee) at each visit to the study site to assist the investigator in the identification of new asthma exacerbations.

All moderate/severe asthma exacerbations will be recorded in the eCRF by the Investigator (or designee).

9.5.4.1. Moderate Asthma Exacerbation

The investigator will utilize clinical discretion and available objective evidence (including a paper Medical Problems/Medications Taken worksheet) to determine if the patient is experiencing a moderate asthma exacerbation. Examples of key considerations include subject's past medical history, severity and duration of current symptoms, and

known asthma triggers. Guidance for identifying moderate exacerbations includes the following [Reddel, 2009, Virchow, 2015]:

- 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 will not be severe enough to warrant systemic corticosteroid use (or a doubling or more of the maintenance systemic corticosteroid dose, if applicable) for 3 days or more and/or hospitalisation.
- A moderate asthma exacerbation is an event that, when recognized, should result in a temporary change in treatment, in an effort to prevent the exacerbation from becoming severe.

Subjects are also instructed to contact the investigator for signs of worsening asthma. The paper Medical Problems/Medications Taken worksheet must also be reviewed by the Investigator (or appropriately trained designee) at each visit to the study site to assist the Investigator in the identification of new asthma exacerbations. At the Investigator's discretion, a temporary change in background asthma medication will be permitted in order to treat the symptoms of a moderate asthma exacerbation (see Section 7.7.2.1. for details). If a subject experiences a second moderate asthma exacerbation requiring a change in therapy, the Investigator may choose to continue the additional therapy for as long as medically appropriate.

9.5.4.2. Severe Asthma Exacerbation

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[1], for at least 3 days.

[1] *For subjects receiving maintenance systemic corticosteroids, at least double the maintenance systemic corticosteroid dose for at least 3 days is required.*

OR

An inpatient hospitalization or emergency department visit because of asthma, requiring systemic corticosteroids.

9.6. Pharmacokinetics

PK parameters are not evaluated in this study.

9.7. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.8. Genetics/Pharmacogenetics

In this study, genetics may be evaluated after review by the ethical review committee established by GSK in accordance with Japanese ethical guidelines for human genome/gene analysis research.

In conducting pharmacogenetics(PGx) research in this study, the objectives are as follows;

The objective of the PGx research is to understand the relationship between genetic factors and response to FF/UMEC/VI. To achieve this objective, the relationship between genetic variants and the followings are investigated.

- Response to medicine, including FF/UMEC/VI or any concomitant medicines;
- Asthma susceptibility, severity, and progression and related conditions

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetics research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in SRM.

9.9. Biomarkers

Biomarkers are not evaluated in this study.

9.10. Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

Sample size in this study is not based on statistical consideration. The number of asthmatic adult subjects (with the control status on inhaled asthma therapy with medium to high dose ICS + LABA or medium to high dose ICS +LABA +LAMA as shown in the Table 2) required to be enrolled in this study is 110 (a total number of subjects to be allocated in Group 1 [FF/UMEC/VI 100/62.5/25 mcg] and Group 2 [FF/UMEC/VI 200/62.5/25 mcg]). According to the ICH guidelines, the sample size of 110 subjects would allow 100 subjects to complete the 52-week treatment period, assuming a drop-out rate of approximately 10%.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All screened subjects. This population will be used for the summary of reasons for screening failures.
Enrolled	All subjects who are found to be eligible for the study based on the screening examination result. This population will be used for the summary tables required by EudraCT.
ITT	All subjects who take at least one dose of study treatment in the treatment period. Subjects will be analyzed according to the treatment they actually received. This population will be used for all safety and efficacy analyses.

EudraCT: European Drug Regulatory Authorities Clinical Trial, ITT: Intent to Treat

10.3. Statistical Analyses

10.3.1. Efficacy Analyses

This is an open-label study and its efficacy assessment has limitations. Therefore, the efficacy will be assessed in an exploratory manner as other endpoints.

10.3.2. Safety Analyses

All safety analyses will be performed on the ITT Population.

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint is incidence and type of AEs/SAEs. This endpoint will be summarized using the following two approaches: 1. Summary statistics will be provided for the integration of the groups and for each group separately (only FF/UMEC/VI 100/62.5/25 mcg, only FF/UMEC/VI 200/62.5/25 mcg and switching medication from FF/UMEC/VI 100/62.5/25 mcg to FF/UMEC/VI 200/62.5/25 mcg). 2. Summary statistics will be provided by the dose received at the time of experiencing the AE. (FF/UMEC/VI 100/62.5/25 mcg and FF/UMEC/VI 200/62.5/25 mcg) The number and proportion of subjects experiencing at least one AE will be calculated and presented by system organ class (SOC) and by preferred term (PT). Summary statistics will also be presented for all AEs, treatment-related AEs, SAEs, AEs leading to treatment or study discontinuation,.and AESI.
Secondary	Secondary endpoints will be summarized using the approach described in approach 1 above (i.e., provided for only FF/UMEC/VI 100/62.5/25 mcg, only FF/UMEC/VI 200/62.5/25 mcg and switching medication from FF/UMEC/VI 100/62.5/25 mcg to FF/UMEC/VI 200/62.5/25 mcg). Specific details will be provided in the Reporting and Analysis Plan (RAP).

10.3.3. Other Analyses

No statistical analysis will be performed for any of the other endpoints but only summary of them will be presented. The approach 1 described in the table above will be used for the other endpoints (i.e., summary statistics will be provided for only FF/UMEC/VI 100/62.5/25 mcg, only FF/UMEC/VI 200/62.5/25 mcg and switching medication from FF/UMEC/VI 100/62.5/25 mcg to FF/UMEC/VI 200/62.5/25 mcg). Specific details will be provided in the RAP.

10.3.4. Interim Analyses

No statistical interim analysis requiring hypothesis test is planned. However, the data will be summarized when all subjects (who have not withdrawn) have completed 24-week administration during treatment period and the CRF data up to Week 24 for all subjects is locked. It is used for JNDA submission.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ADR	Adverse Drug Reaction
ALT	Alanine aminotransferase
AQLQ	Asthma Quality of Life Questionnaire
AST	Aspartate Transaminase
BMI	Body Mass Index
BTS/SIGN	British Thoracic Society / Scottish Intercollegiate Guidelines Network
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous positive airway pressure
CPK	Creatine PhosphoKinase
(e)CRF	(Electronic) Case Report Form
CSR	Clinical Study Report
CV	Cardiovascular
CYP3A4	Cytochrome P450 3A4
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EMA	European Medicines Agency
EudraCT	European Drug Regulatory Authorities Clinical Trial
EOT	End of Treatment
EU	European Union
EW	Early Withdrawal
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FF	Fluticasone Furoate
FP	Fluticasone Propionate
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good clinical practice
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
HbO2	Oxyhemoglobin
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic Pituitary Axis
HRQoL	Health-Related Quality of Life
HRT	Hormone Replacement Therapy

IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
INR	International normalized ratio
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to Treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LABA	Long-Acting Beta-2-Agonists
LAMA	Long-Acting Muscarinic Antagonist
LDH	Lactate Dehydrogenase
LOCS III	Lens Opacities Classification System III
LRTI	Lower Respiratory Tract Infection
LTRA	Leukotriene Receptor Antagonist
MACE	Major Adverse Cardiac Event
MAOI	Monoamine Oxidase Inhibitors
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
MDI	Metered Dose Inhaler
MedDRA	Medicinal Dictionary for Regulatory Activities
mcg (μg)	Microgram
NIH	National Institutes of Health
OCS	Oral Corticosteroids
PGx	Pharmacogenetics
PK	Pharmacokinetic
PT	Preferrd Term
QOL	Quality of Life
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
SABA	Short-Acting Beta-2-Agonists
SGOT	Serum glutamic-oxaloacetic tranaminase
SGPT	Serum glutamic-pyruvic tranaminase
SGRQ	St. George's Respiratory Questionnaire
SoA	Schedule of Activities
SOC	System Organ Class
SPC	Summary of Product Characteristics
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions

ULN	Upper Limit of Normal
UMEC	Umeclidinium Bromide
US	United States
WBC	White Blood Cell

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ELIPTA

Trademarks not owned by the GlaxoSmithKline group of companies
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12.2. Appendix 2: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - The Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27th March, 1997)" and the Pharmaceuticals and Medical Devices Act.
- GSK will submit the CTN to the regulatory authorities in accordance with Pharmaceuticals and Medical Devices Act before conclusion of any contract for the conduct of the study with study sites.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - 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 SAE 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 ICH guidelines, the IRB/IEC, and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

Prior to participation in the study, the investigator (or subinvestigator) should fully inform the potential subject and/or the subject's legally acceptable representative of the study including the written information. The investigator (or subinvestigator) should provide the subject and/or the subject's legally acceptable representative ample time and opportunity to inquire about details of the study. The subject and/or the subject's legally acceptable representative should sign and personally date the consent form. The subject may consider the content of the written information at home. The person, who conducted the informed consent discussion and the study collaborator giving supplementary explanation, where applicable, should sign and personally date the consent form. If an impartial witness is required, the witness should sign and personally date the consent form. The investigator (or subinvestigator) should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the subject and/or the subject's legally acceptable representative. Participants who are rescreened are required to sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. 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.
- The participant must be informed that his/her personal 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.
- The participant must be informed that his/her 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.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- Disclosure of Clinical Study Reports (CSRs) after review by regulatory authorities.

- The posting of company-sponsored study information and tabular study results on the US National Institutes of Health's website www.ClinTrials.gov and other publically-accessible sites.
- Publication planning to peer-reviewed publications.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. 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.

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 reported on the CRF or 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 can be found in SRM.

Study and Site Closure

GSK or its 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:

- 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 recruitment of participants by the investigator
- Discontinuation of further study treatment development

Study Period

June 2017 ~ Sep 2019

Sponsor Information Page

Sponsor Legal Registered Address:

GlaxoSmithKline K.K. (GSK)

8-1, Akasaka 1-chome Minato-ku, Tokyo 107-0052 Japan

Study Director: PPD , Head of Respiratory TA Office, Medicines Development

Sponsor Contact Address:

Leading Author : PPD , Respiratory TA Office, Medicines Development

TEL : PPD

FAX : PPD

Sponsor's Contact Information (10:00-18:00, Monday to Friday, except national holidays, year-end and new-year holidays);

207236 team, JDMA, GlaxoSmithKline K.K.

TEL: PPD

FAX: PPD

Contact Inforamtion at Night and on Holidays (Monday to Friday: 18:00-10:00, Saturday, Sunday, national holidays, year-end and new-year holidays)

BI Medical, Inc.

TEL: PPD (local toll-free)

FAX: PPD (local toll-free)

Sponsor's Medical Monitor: PPD, Head of Nurology Science TA Office, Medicines Development

TEL : PPD

FAX : PPD

Laboratory

Clinical Laboratory

SRL Medisearch Inc.

Shinjuku I-Land-Tower 10F, 6-5-1, Nishishinjuku, Shinjuku-ku, Tokyo, 163-1310, Japan

Pharmacokinetic Measurement Facilities

York Bioanalytical Solutions Limited

Cedar House, Northminster Business Park, Upper Poppleton, York

YO26 6QR, UK

Contract Reserch Organization

Parexel International Inc.

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Gx/PGx Research Administration

Gx/PGx Sample Management

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709 Swedeland Road, King of Prussia, PA, 19406, USA

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12.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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 treatment, whether or not considered related to the study treatment. • 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 treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment 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. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from

lack of efficacy 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 which 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 (eg, 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).
- 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.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

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 detained (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 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require 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 in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF 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

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will then record all relevant AE/SAE information in the CRF.
- 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 AE/SAE CRF page.
- 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.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- 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 investigators always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK.

- The investigator may change his/her 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.

Follow-up of AE and SAE

- 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 post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF. After the study is completed at a given site, the electronic data collection tool will be taken off-line 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 off-line, then the site can report this information on a paper SAE form (see

next section) or via telephone to the sponcer.

- Contacts for SAE reporting can be found in Appendix 2.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponcer.
- In rare circumstances and in the absence of 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 CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in Appendix 2.

12.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 9.

Table 9 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • Oral
Highly Effective Methods That Are User Independent
• Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
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 drug. 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.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized from the screening visit until after the last dose of study medication and completion of the follow-up visit.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing should be performed from the screening visit until after the last dose of study medication and completion of the follow-up visit as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing, with a sensitivity of 25 mIU/mL will be performed and assayed in the central laboratory using the test kit provided by the central laboratory in accordance with instructions provided in its package insert.

Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, 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 participant and neonate, 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 treatment by the investigator, will be reported to GSK as described in Appendix 3. 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 will discontinue study treatment or be withdrawn from the study.

12.5. Appendix 5: Genetics/Pharmacogenomics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to FF/UMEC/VI or asthma and related diseases. They may also be used to develop tests/assays (including diagnostic tests) related to FF/UMEC/VI, and asthma. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to FF/UMEC/VI or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on FF/UMEC/VI (or study treatments of this class) or asthma continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

12.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event.

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR(International normalized ratio) measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4

	weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event

Actions	Follow Up Assessments
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments (see Follow Up Assessments) • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>**	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) and quantitative hepatitis B DNA • Blood sample for pharmacokinetic (PK) analysis, obtained within 72 hours after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential count of leukocytes to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE** (**excluding studies of hepatic impairment or cirrhosis**); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody or Hepatitis E RNA
5. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline. • If at any time participant meets the liver chemistry stopping criteria, proceed as described above. • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

References

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Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

12.7. Appendix 7: Country-specific requirements

No country-specific requirements

12.8 Appendix 8: Protocol Amendment History

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

Amendment 01: 24-May-2017

Overall Rationale for the Amendment: Correction of typographical errors and description adjustment

Section # and Name	Description of Change	Brief Rationale
4. OBJECTIVES AND ENDPOINTS	Secondary Objective ***Changed from:*** To evaluate the efficacy and safety of FF/UMEC/VI combination therapy ***Changed to:*** To evaluate the safety of FF/UMEC/VI combination therapy	Correction of a mistake
7.7.1. Prohibited Concomitant Medications	Table 6 Concomitant Medications Non-Inhaled LABA (e.g., Hokunalin Tape) Follow-up period ***Changed from:*** X ***Changed to:*** ○	Correction of a typographical error
12.1. Appendix 1: Abbreviations and Trademarks	UMEC ***Changed from:*** Umeclidinium ***Changed to:*** Umeclidinium Bromide	Description adjustment to add base of UMEC
12.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Foot note "b" in the Table 9 Highly Effective Contraceptive Methods ***Changed from:*** b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized from the treatment period until after the last dose of	Description adjustment to align with the contraceptive period defined in this study

Section # and Name	Description of Change	Brief Rationale
	study medication and completion of the follow-up visit. ***Changed to:*** b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized from the screening visit until after the last dose of study medication and completion of the follow-up visit.	