Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A 6-month, open label, randomised, efficacy study to evaluate fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) Inhalation Powder delivered once daily via the Dry Powder Inhaler Ellipta™ compared with usual ICS/LABA maintenance therapy delivered by Dry Powder Inhaler in subjects with Persistent Asthma

Compound Number: GW685698 +GW642444

Development Phase: IIIB

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Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N190259_00	2015-FEB-27	Original
2014N190259_01	2015-AUG-14	Amendment No. 1
This protocol amendment has been created to correct mistakes in the wording of the inhaler errors questionnaires for the Ellipta™, Diskus™ and Turbuhaler inhalers, which are included in Section 7.3.1 of the protocol. All references to 'Type A errors' and 'overall errors' within the protocol, have been changed to 'critical' and 'non-critical' errors, respectively, for consistency with the inhaler errors questionnaire worksheets. Storage condition instructions for Seretide™ (fluticasone propionate/salmeterol) in Section 6.7 have been amended. The wording for the recommended number of spirometry efforts has been revised. New text has been included with regards to investigational product malfunction in Section 6.8. The secondary medical monitor contact information has been revised to include a new study physician. Other minor corrections and edits have been made.		
2014N190259_02	2016-APR-28	Amendment No. 2
This amendment has been written primarily to allow the addition of a new country/countries to the study. This includes: • Removing reference to France unless specifically required • Amending text to make language more applicable to participating countries • Updating the number of sites • Defining permitted 'usual ICS/LABA combinations' The endpoint associated with Inhaler Correct Use has been further defined. The objective and associated endpoint of adherence with study medication has been amended to compliance with study medication. Mepolizumab (Nucala™) has been added as a prohibited medication at screening and during the study. The option to rescreen a patient following approval by the medical monitor has been added.		

The section describing planned dose adjustments has been updated to clarify that dose increases are permitted but switching between treatments is not permitted, in accordance with the intention of the protocol. It has been clarified that GSK will not provide treatment following the study The T&E table has been updated to reflect that Screening, Visit6 and Withdrawal Visit should be logged on RAMOS NG. This was previously omitted in error. The description of the Per Protocol Population has been updated to reflect terminology now used as standard at GSK Other minor corrections and edits have been made

SPONSOR SIGNATORY

PPD

28 April 2016

Courtney Crim, MD
Project Physician Lead

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
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Regulatory Agency Identifying Number(s): EudraCT No: 2014-000551-81

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number HZA116492

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY HZA116492

Rationale

The pivotal phase III studies were key to demonstrate the safety and efficacy of Fluticasone Furoate/ Vilanterol in asthma. However, it is increasingly acknowledged that randomised clinical trials by definition tend to be highly controlled and enrol a more highly selected patient population than is expected to be prescribed the medication post-approval. The need for data in a more representative population in a close to 'real world' setting is increasingly being recognised as important to complement pivotal phase III safety and efficacy studies in order to establish the benefits and therefore the value of a medication in the context of clinical practice.

Moreover, double-blind comparison of once daily to twice daily medicines, while important for assessing efficacy, removes a potential source of difference in effectiveness derived from patient behaviour and experience. GlaxoSmithKline (GSK) has observed an increasing demand from payers who make reimbursement and policy decisions for data that enables the evaluation of a drug's effectiveness and impact on the health care system at launch, e.g. effectiveness data from a setting close to 'real world' in addition to traditional randomised clinical studies.

This open-label randomised clinical study will evaluate the efficacy and safety of FF/VI Inhalation Powder (FF 92mcg/VI 22mcg or FF 184mcg/VI 22mcg) compared with two fixed combinations ICS/LABA (Inhaled Corticosteroids/Long Acting Beta Agonists) inhalation powders, fluticasone propionate/salmeterol (FP/S) and budesonide/formoterol (BUD/F), for asthma maintenance therapy, in a "close to real life" manner in primary care and in respiratory specialist care/research sites. FF/VI will be administered once-daily (QD) via Ellipta™ and FP/S or BUD/F twice daily (BID) via Diskus™ and Turbuhaler respectively.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To compare the efficacy of FF/VI 92mcg/ 22mcg or FF 184mcg/22mcg with usual fixed combinations ICS/LABA for asthma maintenance therapy at Week 12 (Visit 4).	• Change from baseline in the Asthma Control Test (ACT) total score at Week 12 (Visit 4).
Secondary	
• To assess effect of FF/VI on asthma control compared with usual ICS/LABA fixed combination at Week 24 (Visit 6).	• Change from baseline in ACT score at Week 24 (Visit 6).
• To assess ELLIPTA inhaler correct use compared with other DPI (Diskus and Turbuhaler) at Week 12 (Visit 4) and at	• Percentage of subjects with correct use of device (defined as not making any

Objectives	Endpoints
Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).	critical error or non-critical error) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).
Other	
To assess effect of FF/VI on trough (pre-dose) FEV1 compared with usual ICS/LABA fixed combination at Week 12 (Visit 4)	Change from baseline in trough (pre-dose) FEV1 at Week 12 (Visit 4).
To assess the effect of FF/VI on response to treatment at Week 12 (Visit 4) and Week 24 (Visit 6)	ACT score ≥ 20 or 3 point increase from baseline in ACT at Week 12 (Visit 4) and Week 24 (Visit 6). Note: A 3 point increase in ACT total score was suggested as the Minimal Clinically Important Difference (MCID) in the literature [Schatz, 2009]. ACT score ≥ 20 at Week 12 (Visit 4) and Week 24 (Visit 6). Change from baseline in individual question scores for ACT at Weeks 12, 24
To assess the compliance with study medication and self-reported adherence to study medication at Week 12 (Visit 4) and Week 24 (Visit 6)	• Compliance with study medication from randomisation (Day 0) to Week 12 (Visit 4), from Week 12 (Visit 4) to Week 24 (Visit 6) and from randomisation (Day 0) to Week 24 (Visit 6). • Score of the MARS-A questionnaire (Medication Adherence Report Scale for asthma) at the randomisation (Day0), Week12 (Visit 4) and Week24 (Visit 6).
To assess the effect of FF/VI on severe asthma exacerbation over the study period	Number of subject with at least 1 severe asthma exacerbation*, number of severe asthma exacerbation and annual severe exacerbation rate over the study period.

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

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

Notes defining endpoints:

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

2. A prescription of systemic corticosteroid is defined as exacerbation-related if the reason the drug was given, in whole or in part, was to treat an acute worsening of asthma symptoms.
3. Exacerbation-related hospitalisation includes hospitalisation that is prolonged as a result of an asthma exacerbation.

Overall Design

This is a Phase IIIb multi-centre, randomised open label, parallel group study performed in subjects in primary care and in respiratory specialist care/research sites who have a diagnosis of asthma and regular treatment for asthma.

Approximately 422 asthmatic subjects who are taking an inhaled corticosteroid (ICS) alone without any other controller treatment will be randomised in a 1:1 ratio to receive either FF/VI (FF/VI 92mcg/22mcg or FF/VI 184mcg/22mcg) once daily or one ICS/LABA inhalation powder twice daily for asthma maintenance therapy.

As much as possible enrolment of subjects should be performed at a constant accrual rate throughout a full year in order to minimize a seasonality bias.

Subjects will visit the investigator site a minimum of 3 times as per protocol over a 6 month period while participating in the study. The first visit will be Visit 1 Screening Visit, which can take place between Day -7 and Day -1. At Visit 1, suitable subjects will be consented. The second visit will be Visit 2 (Day 0, Randomisation Visit) where subjects who meet all of the Inclusion Criteria and none of the Exclusion Criteria will be randomised. Visit 1 and Visit 2 can be combined, if the subject did not take his usual asthma medication before coming on site. If Visit 1 and Visit 2 are combined then this visit will be Day 0 and all baseline characteristics will be collected at this visit.

At Visit 2 (Day 0) subject will be asked to provide responses to the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires. Baseline pre-dose FEV1 will be assessed at this visit by the Investigator using a spirometer provided by GSK. At least three valid assessments should be performed with registration of the best value. On the morning of Visit 2 subjects will not take their usual asthma medication. Rescue medication (salbutamol) will be stopped 4 hours before baseline spirometry.

Subjects will self-administer their first dose of study drug at the investigator site at Visit 2 (or the combined Visit 1 and Visit 2 if appropriate) under supervision of the investigator or suitably qualified designee.

Thereafter, each subject randomised into the FF/VI arm will be instructed to self-administer one inhalation with Ellipta inhaler each day at the same time of the day, at a time that is convenient for the subject. Each subject will be advised to adhere to FF/VI dosing regimen throughout the study. The investigator may adjust the dose of FF/VI according to the subject's response. Dose adjustment is allowed and is not considered as a treatment failure in accordance with treatment failure definition.

In addition, each subject whose FF/VI (Ellipta) for asthma maintenance therapy is initiated at Visit 2 will be asked to read the information leaflet and will be instructed by

the investigator on the proper use of Ellipta. Each subject whose usual ICS/LABA DPI (Diskus or Turbuhaler) for asthma maintenance therapy is initiated at Visit 2 will follow the same procedure: reading of the information leaflet, demonstration of the proper use of the inhalers by the Investigator, and the correct dosing. This will be followed by an inhalation demonstration by the patient. Any critical error (defined as an error that is most likely to result in no or only minimal medication being inhaled) and/or non-critical error will be registered by the Investigator.

Randomisation at this visit will be performed on a 1:1 basis; to the FF/VI fixed dose combination delivered via Ellipta or the initiation with usual ICS/LABA inhalation powder for asthma maintenance therapy.

At Week 6 (Visit 3) and at Week 18 (Visit 5) subjects will be telephoned to enquire about whether the subject has experienced any serious adverse events or non serious adverse drug reactions. At these telephone calls subjects will also be asked to complete the ACT questionnaire (paper version) and to send it back to the Investigator.

Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation Visit). Subjects will be asked to withhold from taking study medication on the day of Visit 4. At this visit, subjects will be asked to provide responses to the ACT, MARS-A and PASAP questionnaires and the inhaler use will be assessed by recording critical and non-critical errors following the next procedure: self-administration of one dose of study drug ; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. At this visit, a trough (pre-dose) FEV1 will be assessed by the Investigator using a spirometer provided by GSK and subjects will also be interviewed about whether the subject has experienced any serious adverse events or non –serious adverse drug reactions. Female subjects of child bearing potential will also be reminded about the requirement for contraception throughout their study participation.

The final Visit 6 will occur at Week 24. The ACT, AQLQ(S), EQ-5D and MARS-A questionnaires will be conducted at this visit and critical and non-critical errors with inhaler will be recorded following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. At this visit, subjects will also be interviewed about whether they had experienced any serious adverse events or non –serious adverse drug reactions. The Investigator will be asked to make every effort to schedule Visit 6 at the same time of the day as Visit 2.

Although at least 3 formal scheduled visits and 2 phone calls are planned for this study (as per the Time and Events Table), subjects should continue to visit their physician for any routine standard of carevisits as per normal clinical practice. . An Early Withdrawal Visit should be performed in case of early withdrawal of the subject from the study, as per the Time and Events Table.

Treatment Arms and Duration

Two treatment arms: one FF/VI arm (FF/VI 92 mcg/22 mcg or FF/VI 184 mcg/22 mcg) once daily, and one arm ICS/LABA combination therapy in inhalation powder twice daily (FP/S 250 mcg/50 mcg or 500 mcg/50mcg, or BUD/F 200 mcg/6mcg or 400

mcg/12mcg) as decided by the investigator. The total duration of subject participation will be approximately 6 months (24 weeks).

Type and Number of Subjects

Subjects with documented physician's diagnosis of asthma ≥ 1 year, unsatisfactorily controlled asthma (ACT < 20) treated by ICS alone and intended to be treated by ICS/LABA maintenance therapy.

France Only: A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.

It is estimated that approximately 100 study centers will be required to have a total number of 422 randomised subjects so that at least 382 subjects will be evaluable. Assuming a 10% screen failure rate, approximately 466 subjects will have to be screened.

Analysis

The primary endpoint is defined as the change from baseline in the ACT total score assessed at Week 12 (Visit 4). The primary set of analysis is the ITT population.

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

Even though this study is open-label, the team will explore ways to ensure study blind is maintained during review of the data and pre-programming activities, prior to database lock. More information will be provided in the RAP.

2. INTRODUCTION

2.1. Study Rationale

Inhaled corticosteroids (ICS) are considered the most effective anti-inflammatory treatments for all severities of persistent asthma. This open-label randomised clinical study will evaluate the efficacy and safety of fluticasone furoate (FF)/vilanterol (VI) Inhalation Powder compared with nominated existing fixed combinations ICS/LABA (Inhaled Corticosteroids/Long Acting Beta Agonists) inhalation powders.

Fluticasone furoate (FF) is a glucocorticoid developed for use as a once daily inhaled treatment for asthma. Vilanterol is an orally inhaled long-acting agonist of the $beta_2$-adrenoceptor (LABA) and has been also developed for use in combination with ICS as a once-daily maintenance treatment of asthma.

The pivotal phase III studies demonstrated the safety and efficacy of FF/ VI. However, it is increasingly acknowledged that randomised clinical trials by definition tend to be highly controlled and enrol a more highly selected patient population than is expected to be prescribed the medication post-approval. The need for data in a more representative population in close to a 'real world' setting is increasingly being recognised as important

to complement pivotal phase III safety and efficacy studies in order to establish the benefits and therefore the value of a medication in the context of clinical practice. Indeed, in the close to 'real life' conditions, physicians have the ability to choose the best treatment in their view for any individual patient and adapt treatments to subjects' characteristics and response. Thus, double-blind comparison of once daily to twice daily medicines, while important for assessing efficacy, removes a potential source of difference in effectiveness derived from patient behaviour and experience. Moreover, a head-to-head study comparing Relvar 92mcg/22mcg Ellipta (FF/VI) once a day vs Seretide™/Viani™ 250mcg/50mcg Diskus (Fluticasone propionate/salmeterol) twice a day failed to demonstrate superiority on 24 hours weighted mean FEV1 after 6 months of treatment. However, 50% of subjects in both arms were uncontrolled (ACT score ≤ 19) at randomisation, after 4 weeks of Fluticasone propionate 250 mcg twice a day. For this sub-group of subjects, at the end of the 6 month-treatment period, 63% of subjects were controlled in the FF/VI arm vs 55% in the Seretide/Viani Diskus arm. The study was not powered on this criterion nor designed to include uncontrolled subjects only. Anyway, this trend justifies exploring if this difference would disappear or increase in a close to real life setting.

Subjects recruited into the study will be those currently taking an ICS alone without any other controller treatment with evidence of sub-optimal asthma control, corresponding to European Marketing Authorisation of FF/VI. These subjects will be randomised to receive FF/VI via Ellipta inhaler once daily or to receive usual ICS/LABA fixed combination in DPI (fluticasone propionate/salmeterol (FP/S)) via Diskus inhaler and budesonide/formoterol (BUD/F) via Turbuhaler twice daily for asthma maintenance therapy as per normal clinical practice. Ellipta is a new powder inhaler designed to be easy to use. Current powder inhalers have been associated with handling errors some of which may impact the ability of drug to reach the lung and hence impact clinical efficacy. Such errors deemed as critical will be evaluated in this study between different inhalers as well as overall inhaler preference and satisfaction.

2.2. Brief Background

Asthma is a chronic disease of the lungs characterised by airway inflammation, bronchoconstriction and increased airway responsiveness. Inhaled corticosteroids (ICS) are considered the most effective anti-inflammatory treatments for all severities of persistent asthma [GINA, 2009; NIH, 2007; British Thoracic Society, 2008]. The benefits of ICS include control of asthma symptoms, improvement in lung function, decrease in airway hyper-responsiveness and possibly, prevention of airway wall remodelling [Pedersen, 1997; Fanta, 2009].

Fluticasone furoate is a novel glucocorticoid developed for use as a once daily inhaled treatment for asthma. The drug consists of FF formulated in lactose for oral inhalation via the DPI Ellipta. Pre-clinical data and early phase clinical studies indicate that FF has a longer duration of action than fluticasone propionate (FP) and is therefore suitable for development for once daily administration.

Vilanterol is an orally inhaled long-acting agonist of the $beta_2$-adrenoceptor (LABA) and has been developed for use in combination with ICS as a once-daily maintenance

treatment of asthma. The drug consists of vilanterol formulated in lactose and magnesium stearate for oral inhalation via Ellipta.

The combination of these two agents has been developed as a once-daily combination therapy for the long-term maintenance treatment of asthma in adults and children ≥ 12 years of age. The availability of a once-daily ICS combined with a LABA would be expected to help to improve compliance and therefore improve asthma control.

Information on the physical, chemical and pharmaceutical properties of fluticasone furoate, vilanterol, and fluticasone furoate/vilanterol may be found in SmPC or Investigator Brochure.

3. OBJECTIVE(S) AND ENDPOINT(S)

This open-label randomised clinical study will evaluate the efficacy and safety of fluticasone furoate (FF)/vilanterol (VI) Inhalation Powder (FF 92mcg/VI 22mcg or FF 184mcg/VI 22mcg) compared with existing fixed combinations ICS/LABA (Inhaled Corticosteroids/Long Acting Beta Agonists) inhalation powders, fluticasone propionate/salmeterol (FP/S) and budesonide/formoterol (BUD/F), for asthma maintenance therapy, in a "close to real life" manner in primary care and in respiratory specialist care/research sites. FF/VI will be administered once-daily (QD) via Ellipta and FP/S or BUD/F twice daily (BID) via Diskus and Turbuhaler respectively.

Objectives	Endpoints
Primary	
• To compare the efficacy of FF/VI 92mcg/ 22mcg or FF 184mcg/22mcg with usual fixed combinations ICS/LABA for asthma maintenance therapy at Week 12 (Visit 4).	• Change from baseline in the Asthma Control Test (ACT) total score at Week 12 (Visit 4).
Secondary	
• To assess effect of FF/VI on asthma control compared with usual ICS/LABA fixed combination at Week 24 (Visit 6).	• Change from baseline in ACT score at Week 24 (Visit 6).
• To assess ELLIPTA inhaler correct use compared with other DPI (Diskus and Turbuhaler) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).	• Percentage of subjects with correct use of device (defined as not making any critical error or non-critical error) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).

Objectives	Endpoints
Other	
To assess effect of FF/VI on pre-dose trough FEV1 compared with usual ICS/LABA fixed combination at Week 12 (Visit 4)	Change from baseline in pre-dose trough FEV1 at Week 12 (Visit 4).
To assess the effect of FF/VI on response to treatment at Week 12 (Visit 4) and Week 24 (Visit 6)	ACT score ≥ 20 or 3 point increase from baseline in ACT at Week 12 (Visit 4) and Week 24 (Visit 6). Note: A 3 point increase in ACT total score was suggested as the Minimal Clinically Important Difference (MCID) in the literature [Schatz, 2009]. ACT score ≥ 20 at Week 12 (Visit 4) and Week 24 (Visit 6). Change from baseline in individual question scores for ACT at Weeks 12, 24
To assess the compliance with study medication and self-reported adherence to study medication at Week 12 (Visit 4) and Week 24 (Visit 6)	Compliance with study medication from randomisation (Day 0) to Week 12 (Visit 4), from Week 12 (Visit 4) to Week 24 (Visit 6) and from randomisation (Day 0) to Week 24 (Visit 6). Score of the MARS-A questionnaire (Medication Adherence Report Scale for Asthma) at the randomisation (Day0), Week12 (Visit 4) and Week24 (Visit 6).
To assess the effect of FF/VI on severe asthma exacerbation over the study period	Number of subject with at least 1 severe asthma exacerbation*, number of severe asthma exacerbation and annual severe exacerbation rate over the study period.
To assess the effect of FF/VI on Health Related Quality of Life at Week 24 (Visit 6)	Change from baseline in total score and domain scores of AQLQ(S) (Asthma Quality of Life Questionnaire) at Week 24 (Visit 6). An increase from baseline of ≥ 0.5 in AQLQ(s) total score at Week 24 (Visit 6). An increase from baseline of ≥ 0.5 in

Objectives	Endpoints
	AQLQ(s) environmental stimuli domain score at Week 24 (Visit 6). Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) Individual domain scores at Week 24 (Visit 6). Change from baseline in total score and domain scores of AQLQ(S) at Week 24 (Visit 6). Health status using the EuroQol Questionnaire (EQ-5D) at Week 24 (Visit 6).
To assess Patient Satisfaction and Preference assessment with different inhalers at Week 12 (Visit 4)	Score of PASAP Questionnaire (Patient Satisfaction and Preference) at Week 12 (Visit 4).
To evaluate the Safety of FF/VI compared with usual ICS/LABA (FP/S and Bud/F).	Serious Adverse Events (SAE) and non-serious Adverse Drug Reactions (ADR): Frequency and type of serious adverse events, Frequency and type of non-serious adverse drug reactions related to treatment.

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

Notes defining endpoints:

1. Contacts with a doctor or hospitalisation are defined as exacerbation-related contacts if these contacts were a direct result of an acute worsening of asthma symptoms.
2. A prescription of systemic corticosteroid is defined as exacerbation-related if the reason the drug was given, in whole or in part, was to treat an acute worsening of asthma symptoms.
3. Exacerbation-related hospitalisation includes hospitalisation that is prolonged as a result of an asthma exacerbation.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase IIIb multi-center randomised open label, parallel group study performed in subjects in primary care and in respiratory care specialist/research sites who have a diagnosis of asthma and a regular treatment for persistent asthma. Subjects with unsatisfactorily controlled asthma (defined as an ACT < 20) and intended to be treated by usual ICS/LABA maintenance therapy to seek a better control of their asthma will be randomised to receive either FF/VI (FF/VI 92mcg/22mcg or FF/VI 184mcg/22mcg) once daily or another usual ICS/LABA combination therapy in inhalation powder twice daily (FP/S or BUD/F) decided by the investigator. These medications are recorded in the e-CRF.

Investigators will be allowed during the treatment period to adapt prescription to different doses if necessary as well as to adapt doses of the comparative treatment according to products label. A table (Table 2, Section 6.3) of the indicative dosage equivalence between ICS and the other combination therapies will be provided to the investigators.

Note: To maintain consistency across countries the choice of usual inhaled dry powder ICS/LABA fixed combination will be limited to Seretide/Viani Diskus (FP/S 250mcg/50mcg or 500mcg/50mcg) or Symbicort Turbuhaler (BUD/F 200mcg/6mcg or 400mcg/12mcg). Some countries have other ICS/LABA fixed combinations and other generic versions of FP/S and BUD/F available for the treatment of patients with asthma, but these will not be permitted in this study. Additionally some countries have options for a lower dose of Viani Diskus (FP/S 100mcg/50mcg) and Symbicort Turbohaler (BUD/F 100mcg/6mcg) but these will not be permitted in this study.

For Study Schematic, see Appendix 2.

Investigators

General Practitioners and pulmonologists approved by an Ethics Commitee will be approached to participate in the study.

Screening, randomisation and follow-up

At the Screening Visit 1, eligible subjects will be consented to participate to the trial and the necessary examinations will be performed. The subjects will be asked to provide responses to the ACT. A screening log will be performed at this visit.

At a further visit (i.e V2, Day 0) occurring within 1 week after the screening visit (V1), subjects who meet all of the Inclusion Criteria, none of the Exclusion Criteria and who accept to give their consent will be randomised in the study. Randomisation at this visit will be on a 1:1 basis, to the FF/VI fixed dose combination delivered by Ellipta or to the initiation of the usual ICS/LABA DPI for asthma maintenance therapy chosen by the investigator. Visit 1 and Visit 2 can be combined, if the subject did not take his usual asthma medication before coming on site. If Visit 1 and Visit 2 are combined then this visit will be Day 0.

Patients who fail screening may be rescreened only upon approval by the medical monitor.

At Visit 2 (Randomisation visit, Day 0) baseline pre-dose FEV1 will be assessed by the Investigator using a spirometer provided by GSK. At least three assessments should be performed with registration of the best value. At least two of the spirometry efforts should be acceptable and repeatable. On the morning of Visit 2 subjects will not take their usual asthma medication. Rescue medication (salbutamol) will be stopped 4 hours before baseline spirometry.

In addition at Visit 2, subjects will be asked to read the written Ellipta package insert if randomised into the FF/VI arm, or Diskus or Turbuhaler package insert if randomised in the usual ICS/LABA therapy arm, and will be instructed by the investigator on the proper use of inhalers. Then the subject will self-administer their first dose of study drug under supervision of the investigator. Any critical error (defined as an error that is most likely to result in no or only minimal medication being inhaled) or non-critical error will be registered by the trained HCP. After completing the procedure, subjects will be instructed in the correct use of the device by the investigator or suitably qualified designee if needed. Thereafter, each subject randomised into the FF/VI arm will be instructed to self-administer one inhalation with Ellipta inhaler each day at the same time of the day, at a time that is convenient for the subject. Subject randomised into usual ICS/LABA therapy arm will be instructed to self-administer the inhalation with Diskus or Turbuhaler inhaler twice a day.

Subjects will be recommended to use salbutamol as needed throughout the study for relief of their asthma symptoms. At Visit 2 (randomisation, Day 0) subject will be asked to provide responses to the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires.

At Week 6 (Visit 3) and at Week 18 (Visit 5), subjects will be telephoned by the Investigator to enquire about whether the subject has experienced any adverse events (only the serious adverse events or non–serious adverse drug reactions will be recorded in eCRF). The Investigator makes the judgment as to whether it is related or not to study treatment. At these telephone calls, subjects will also be asked to complete the ACT questionnaire (paper version) and to send it back to the Investigator.

Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation Visit). Subjects will be asked to withhold from taking study medication on the day of Visit 4. At this visit, subjects will be asked to provide responses to the ACT, MARS-A and PASAP questionnaires and the inhaler use will be assessed by recording critical and non-critical errors following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. Pre-dose trough FEV1 will be assessed at this visit by the Investigator using the spirometer provided by GSK. Rescue medication (salbutamol) will be stopped 4 hours before the spirometry. At least three valid assessments should be performed with registration of the best value. At this visit, subjects will also be interviewed by the Investigator about whether the subject has experienced any adverse events (only the serious adverse events or non–serious adverse drug reactions will be recorded in eCRF). The Investigator makes the judgment as to whether it is related or not

to study treatment. Female subjects of child bearing potential will also be reminded about the requirement for contraception throughout their study participation.

The final Visit 6 will occur at Week 24. The ACT, AQLQ(S), EQ-5D and MARS-A questionnaires will be conducted at this visit and the inhaler use will be assessed by recording critical and non-critical errors following the next procedure: self-administration of one dose of study drug by subject; errors assessment by the Investigator; demonstration of correct use of inhaler in case of multiple errors detection. Subjects will be interviewed about whether the subject has experienced any serious adverse events or non –serious adverse drug reactions. The Investigator will be asked to make every effort to schedule Visit 6 at the same time of the day as Visit 2.

Although at least 3 formal scheduled visits and 2 phone calls are planned for this study, subjects should continue to visit their physician for any routine standard of care visits as per normal clinical practice, as per the Time and Events Table (Section 7.1). An Early Withdrawal Visit should be performed in case of early withdrawal of the subject from the study, as per the Time and Events Table (Section 7.1) and Section 5.4.2 Subject Withdrawal by Investigator or Self-withdrawal.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Reference Manual (SRM). The SRM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

Outcome description

One of the main challenges of this study performed in so-called ‘close to real life setting’ is to obtain data on subjects with minimal interference with the actual practice of medicine. Thus, during the 6 months treatment period of the study, all interventions will be recorded as per normal. They will be captured by several means:

1. Investigators participating in the study will be asked to fill in an electronic CRF (eCRF) focused on clinical data at screening visit (Visit 1), at randomisation (Visit2), at Week 12 (Visit 4), at the end of the study at Week 24 (Visit 6) and at two phone calls at Week 6 (Visit 3) and at Week 18 (Visit 5).
2. At Week 6 and at Week 18, subjects will be telephoned to enquire about whether the subject has experienced any adverse events and then the Investigator calling the patient must determine whether the event is related to study medication (either arm) and whether the event is serious. At these telephone calls, subjects will also be asked by the Investigator to complete the ACT questionnaire and to send it back to the Investigator.
3. When necessary and possible, information will be obtained from other medical sources: routine standard of care visits.

The variables of interest will be documented by a combination of information collected from all these sources.

Collected data

Eligible subjects will complete the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires at Randomisation Visit (Visit 2, Day 0) and at Visit 6 (Week 24), or at the Early Withdrawal visit. ACT questionnaire will be completed also by the subject at Screening visit (Visit 1), Week 6 (phone call 1 or Visit 3), at Week 12 (Visit 4) and Week 18 (phone call 2 or Visit 5). MARS-A questionnaire will be completed also at Week 12 (Visit 4). Inhaler use assessment will be performed at Randomisation Visit (Visit 2, Day 0), at Week 12 (Visit 4) and at Week 24 (Visit 6) / Early Withdrawal visit by recording the critical and non-critical errors. Patient's satisfaction and preference (PASAP-Q) will be evaluated at Week 12 (Visit 4).

Baseline spirometry will be performed at Randomisation Visit (Visit 2, Day 0) and at Week 12 (Visit 4) by the Investigator using the spirometer provided by GSK, in order to assess pre-dose trough FEV1 at Week 12 (Visit 4).

For the Study Schematic see Appendix 2 and Section 7.1 for the proposed time and events table.

4.2. Treatment arms and duration

Randomisation will be on a 1:1 basis with two treatment arms: one FF/VI arm (FF/VI 92 mcg/22 mcg or FF/VI 184 mcg/22 mcg) once daily, and one arm ICS/LABA combination therapy in inhalation powder twice daily (FP/S 250 mcg/50 mcg or 500 mcg/50mcg, or BUD /F 200 mcg/6mcg or 400 mcg/12mcg) as decided by the investigator. The total duration of subject participation will be approximately 6 months (24 weeks). As much as possible, enrolment of subjects should be performed at a constant accrual rate throughout a full year in order to minimize a seasonality bias.

4.3. Type and Number of Subjects

Subjects with documented physician's diagnosis of asthma ≥ 1 year, unsatisfactorily controlled asthma (ACT < 20) treated by ICS alone and intended to be treated by ICS/LABA maintenance therapy.

France Only: A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.

It is estimated that approximately 100 study centers will be required to have a total number of 422 randomised subjects so that at least 382 subjects will be evaluable. Assuming a 10% screen failure rate, approximately 466 subjects will have to be screened in the study.

Subjects withdrawn from the study will not be replaced.

4.4. Design Justification

An open label design is appropriate for such a study because it is a comparison of benefits and risks of FF/VI versus usual ICS/LABA asthma maintenance therapy in close to real life setting.

Previous studies have demonstrated that improvements in ACT score can be seen in periods of 3-6 months making this suitable time frame to assess ACT changes.

The treatment duration of 6 months (24 weeks) in this study is considered sufficient to demonstrate efficacy in the proposed study population.

The primary endpoint is defined as the change from baseline in the ACT total score assessed at Week 12 (Visit 4). The aim will be to prove non-inferiority of FF/VI to any other ICS/LABA comparator. The hypothesis of non-inferiority will be first tested at Week 12. If (and only if) non-inferiority is significantly achieved at Week 12, non-inferiority will then be tested at Week 24. If (and only if) non-inferiority is achieved at a visit, then superiority of FF/VI to any other comparator will be tested at this visit (Week 12 or Week 24).

4.5. Dose Justification

Two strengths of FF/VI have been approved, 100 mcg/25 mcg (delivered dose of 92 mcg/22 mcg) for moderate persistent asthma and 200 mcg/25 mcg (delivered dose of 184 mcg/22 mcg) for severe persistent asthma. The dose of 92 mcg/ 22 mcg is preferred in this study as this dose strength is likely to meet the needs of most subjects. However, investigators will be allowed to change the prescription to higher dose according to subject's response without exceeding the maximum allowed dose.

4.6. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with FF/VI can be found in the Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC). The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Serious Cardiovascular Events	This is a potential class effect of LABAs. In clinical studies, percentages of subjects with fatal events that were cardiovascular in nature were similar across all treatment groups (0 to <1%).	Subjects with historical or current evidence of uncontrolled or clinically significant disease are excluded from the study. Cardiovascular medical history, CV risk factors and exacerbation history will be assessed as described in the time and events table.
Asthma-related intubations and deaths	This is a potential class effect of LABAs. It was not observed in preclinical studies with FF/VI. During the FF/VI studies for the asthma composite endpoint (asthma exacerbations leading to hospitalization, intubation and/or death), there was no significant difference between the FF/VI group and the ICS group or non-LABA group, demonstrating no increased risk when adding a LABA to an ICS.	Subjects with a history of life-threatening asthma are excluded from this study. Subjects are excluded from this study if they have a severe and unstable asthma, with ACT score < 15, history of repeated severe exacerbations (3/year) and/or exacerbation in the previous 6 weeks. Subjects are excluded from this study if they are using LABA without an ICS as asthma maintenance therapy.

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Hypersensitivity	The reported hypersensitivity events in clinical trials, were not generally serious, did not lead to discontinuation in the studies, and were usually confounded, by either the subject's medical condition (such as COPD) or other factors at the time of the event. In spontaneous data, symptoms of hypersensitivity ranged from mild rash and pruritis to severe generalised rash and erythema and severe cases involving angiodema of the face, larynx and pharynx. These events were rare.	Subjects with a history of adverse reaction including immediate or delayed hypersensitivity to any intranasal, inhaled, or systemic corticosteroid and LABA therapy and to components of the inhalation powder (e.g., lactose, magnesium stearate) will be excluded. In addition, subjects with a history of severe milk protein allergy that, in the opinion of the Investigator, contraindicates the subject's participation will also be excluded.
Systemic effects of corticosteroids: adrenal suppression; eye disorders; decreased bone density and associated fractures	Adrenal suppression is a known class effect of corticosteroids. Preclinical studies showed that FF effects are comparable with other corticosteroids. No studies have shown a clinically relevant effect of FF/VI on the hypothalamic pituitary axis (HPA). This includes a formal HPA study (HZA106851), using 24 hour serum cortisol measurements, and multiple studies with COPD and asthma subjects which monitored urinary cortisol. During clinical	The mitigation in this study for all systemic effects of corticosteroids is that chronic users of systemic corticosteroids are excluded from this study: a subject who, in the opinion of the Investigator, is considered to be a chronic user of systemic corticosteroids for respiratory or other indications (if unsure discuss with the medical monitor prior to screening) will be excluded.

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	development, no events of Adrenal Suppression were reported. Eye disorders are a known class effect of corticosteroids. Preclinical studies showed FF at high dose comparable to other high dose corticosteroids. In study HZA106839 (FF/VI , FF and FP in subjects with asthma), formal ophthalmic assessments were conducted (including LOCS III evaluations for ocular opacities) throughout the study. This study showed no apparent effects on lens opacification, compared to baseline. During studies in both subjects with asthma and COPD, no associated affect on ocular disorders was observed. Decreased bone density is a known class effect of corticosteroids. Preclinical data showed that high dose corticosteroid effects of FF were comparable to other corticosteroids. Patients with Asthma In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of fractures with FF/VI was <=1%, and usually associated with trauma.	

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Study Procedures		
Spirometry procedures	Shortness of breath, coughing, light-headedness or fainting, and/or chest tightness	If any of these symptoms should happen to the subject, spirometry will be stopped and he/she will receive medical treatment
Other		
Summaries of findings from both clinical and non-clinical studies conducted with comparators (Seretide/Viani Diskus and Symbicort Turbuhaler) can be found in the Summary of Product Characteristics (SmPC).		

4.6.1.1. Benefit Assessment

Combined treatment with ICS and LABA has been shown to be more effective than the individual components in asthma, leading to the development of fixed dose combination inhalers. The use of ICS/LABA combinations is now well established in international treatment guidelines for moderate to severe persistent asthma patients for whom treatment with ICS alone is not sufficient.

Both fluticasone propionate/salmeterol and budesonide/formoterol fumarate are commercially available products for the treatment of persistent asthma and have recognized safety profiles. Both of these products are administered twice-daily.

4.6.2. Overall Benefit: Risk Conclusion

The investigational product (IP) FF/VI has an acceptable safety profile for clinical use and there are no significant associated risks. This conclusion is supported the results of previously performed clinical studies with the products in healthy volunteers and subjects with Asthma and COPD (GlaxoSmithKline Document Number RM2008/00012/06). Adverse effects that could be associated with the use of FF/VI, will be closely monitored. A safety criterion outlining details for subject withdrawal is included in the protocol (Section 5.4, Withdrawal Criteria). A thorough summary and evaluation of the available pre-clinical data can be found in the IB [GlaxoSmithKline Document Number RM2008/00012/06]. Routine safety analysis of this study will be conducted by the company. Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with FF/VI, are justified by the anticipated benefits that may be afforded to patients with asthma.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB/IB supplement(s) (or the SmPC), and other pertinent documents.

5.1. Inclusion Criteria

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. **Informed consent:** Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.
2. **Gender and Age**: Male or female subjects aged ≥18 and ≤ 75years of age at Visit 1.

Female subject: is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin [hCG] test), not lactating, and at least one of the following conditions applies:

a. Non-reproductive potential defined as:

- Pre-menopausal females with one of the following:
    - Documented tubal ligation
    - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
    - Hysterectomy
    - Documented Bilateral Oophorectomy
- Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

b. Reproductive potential and agrees to follow one of the options listed below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) requirements from 30 days prior to the first dose of study medication and until Week 24 (Visit 6).

GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

1. Contraceptive subdermal implant that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label
2. Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007a]
3. Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a]
4. Injectable progestogen [Hatcher, 2007a]
5. Contraceptive vaginal ring [Hatcher, 2007a]
6. Percutaneous contraceptive patches [Hatcher, 2007a]

7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007a].
8. Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2007b]
9. These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

3. **Type of subject:**
   a. Subjects with documented physician's diagnosis of asthma ≥ 1 year, unsatisfactorily controlled asthma (ACT < 20 at Visit 1 and Visit 2) treated by ICS alone and intended to be treated by ICS/LABA maintenance therapy.
   b. **France Only**: A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.
4. **Current Asthma Therapy:** All subjects must be prescribed maintenance therapy and receiving ICS alone without LABA for at least 4 weeks prior to Visit 2 (Randomisation visit).

Other background asthma medication such as anti-leukotrienes or theophylline is permitted as an alternative to ICS alone, if initiated at least 4 weeks prior to screening visit (Visit 1).

5. **Subject questionnaires:** Subjects must be able to complete the questionnaires themselves.

5.2. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study.

1. **History of Life-threatening asthma:** Defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnea, respiratory arrest or hypoxic seizures within the last 6 months before Visit 1 and Visit 2.
2. **Subjects having a severe and unstable asthma,** with ACT score < 15 at Visit 1 and at Visit 2, and/or a history of repeated severe exacerbations (3/year) and/or a severe exacerbation in the previous 6 weeks before Visit 1 and Visit 2.
3. **COPD Respiratory Disease**: A subject must not have current evidence or diagnosis of chronic obstructive pulmonary disease at Visit 1.
4. **Current or former cigarette smokers with a history of cigarette smoking of ≥ 10 pack-years** at screening (Visit 1) [number of pack years = (number of cigarettes per

day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)].

5. **Other diseases/abnormalities**: Subjects with historical or current evidence of uncontrolled or clinically significant disease at Visit 1 and at Visit 2. 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.
6. **Subjects with a history of adverse reaction** including immediate or delayed hypersensitivity to any intranasal, inhaled, or systemic corticosteroid and LABA therapy and to components of the inhalation powder (e.g., lactose, magnesium stearate) at Visit 1 and at Visit 2. In addition, subjects with a history of severe milk protein allergy that, in the opinion of the Investigator, contraindicates the subject's participation will also be excluded.
7. **Investigational Medications:** A subject must not have used any investigational drug within 30 days prior to Visit 2 or within five half-lives (t½) of the prior investigational study (whichever is longer of the two), (if unsure discuss with the medical monitor prior to screening).
8. **Chronic user of systemic corticosteroids:** A subject who, in the opinion of the Investigator, is considered to be a chronic user of systemic corticosteroids for respiratory or other indications (if unsure discuss with the medical monitor prior to screening) at Visit 1.
9. **Subjects treated by the monoclonal antibody omalizumab (Xolair) or mepolizumab (Nucala™) at Visit 1.** Treatment with Xolair or Nucala is not allowed during the study.
10. **Subjects involved in other clinical trials at Visit 1.**
11. **Affiliation with Investigator Site:** Is an investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member of the aforementioned that is involved in this study.
12. **Subjects who plan to move away from the geographical area where the study is being conducted during the study.**

5.3. Screening/Baseline/Failures

Approximately 466 subjects will be screened as 422 subjects are planned to be randomised and a 10% screen failure rate is expected.

- Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events related to study participation.

Patients that fail screening may be rescreened only upon approval by the medical monitor

5.4. Withdrawal/Stopping Criteria

5.4.1. Subjects Lost to Follow-up

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

5.4.2. Subject Withdrawal by Investigator or Self-withdrawal

Subjects may be withdrawn from study treatment at any time by the Investigator if it is considered to be detrimental for them to continue the study treatment or, may discontinue a subject from the study at his or her discretion. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the Investigator must document this in the site study records.

The following criteria will cause a subject to be withdrawn from investigational product(IP) but every effort should be made to keep the Subject in the study:

- A subject becomes pregnant.
- A subject meets the Liver Stopping Criteria as defined in Section 5.4.3.
- A subject meets the QTc stopping criteria as defined in Section 5.4.4.

If the subject chooses to withdraw from the study, all study-related medications and other study related materials should be returned to the site by the subject. An Early Withdrawal Visit should be conducted within 24 hours of the subject stopping study medication (Section 7.1 Time and Event Table). In the event a subject withdraws at or during a scheduled visit, an Early Withdrawal Visit is not required; however, all study procedures scheduled at an Early Withdrawal Visit must be performed at this visit instead.

The primary reason for study treatment discontinuation or study withdrawal will be recorded in the electronic Case Report Form (eCRF) and any data collected up until the point of withdrawal will be used in the data analyses.

Specific regard should be given to distinguishing withdrawals due to ADRs, SAEs and protocol deviation, following consultation with the medical monitor. The Investigator will record the primary reason in the eCRF.

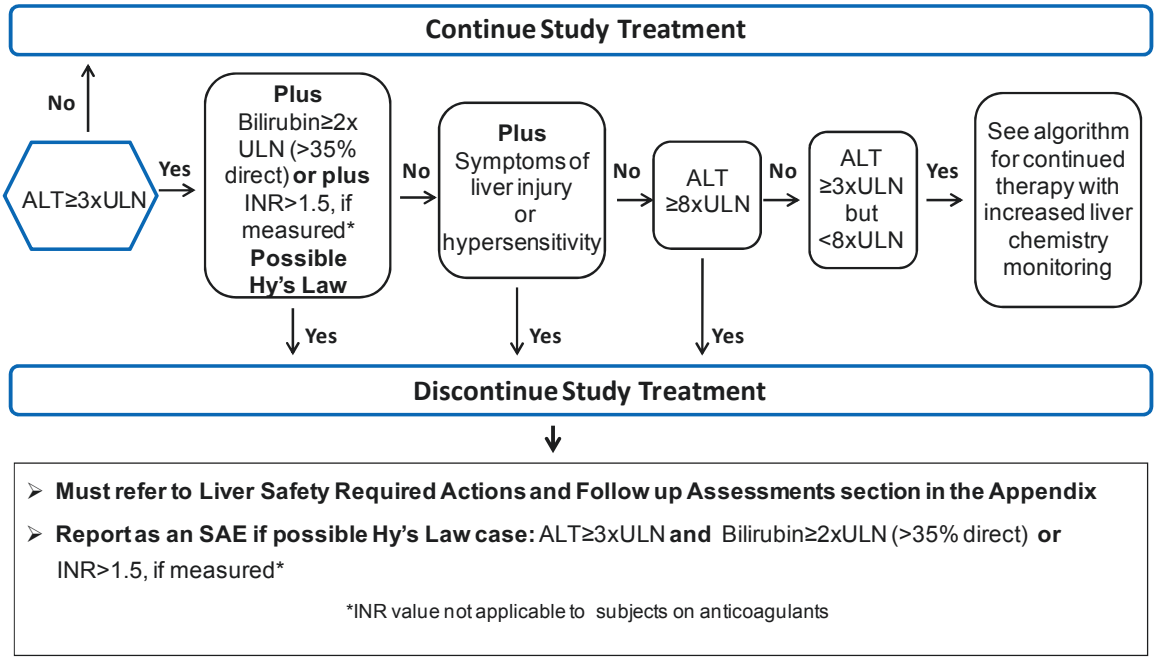
Subjects withdrawn from the study will not be replaced.

Subjects who experience an asthma exacerbation during the Treatment Period can continue in the study, at the discretion of their Investigator.

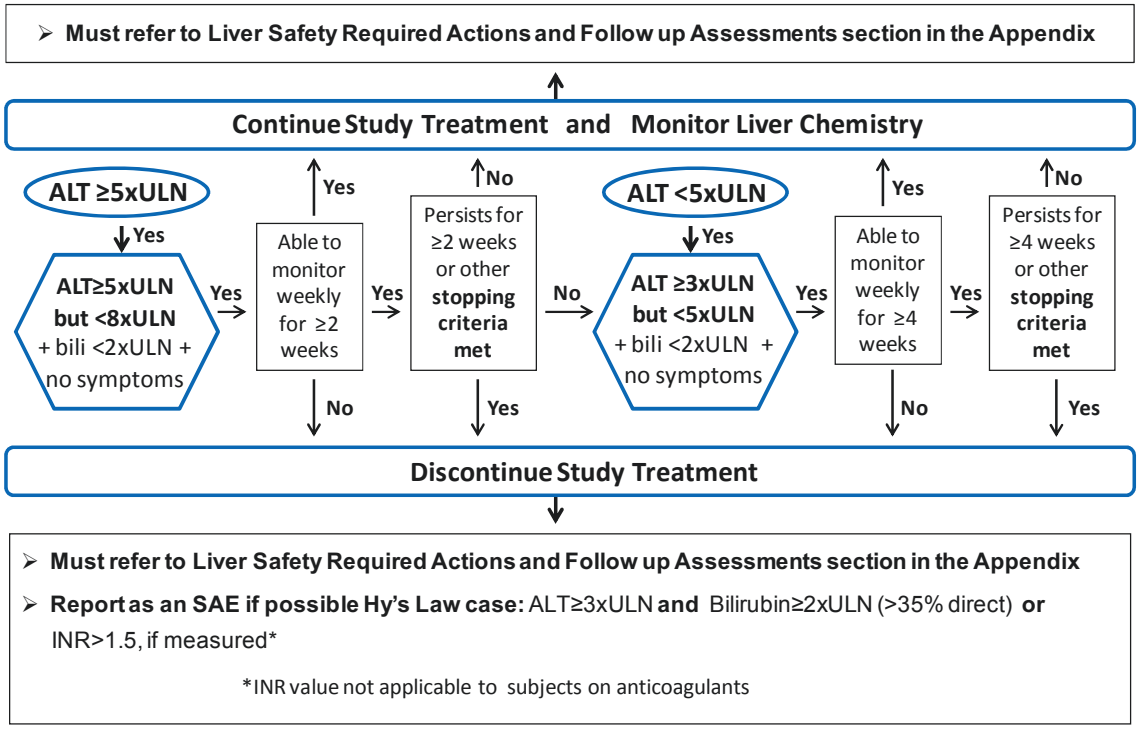
5.4.3. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



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 4.

5.4.3.1. Study Treatment Restart or Rechallenge

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

5.4.4. QTc Stopping Criteria

An ECG is not required prior to entering this study. There are no other regular ECGs required by this protocol. If, however, while a subject is receiving study medication, an ECG is performed as part of the normal clinical practice and a prolonged QT interval is detected, the following assessments for withdrawal from the study are required, after discussion between Investigator and the medical monitor:

For all subjects:

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

- QTc > 500 msec OR Uncorrected QT > 600 msec
- Increase in QTc >60msec detected compared to a previous ECG

For patients with underlying **bundle branch block**, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	**Discontinuation QTc with Bundle Branch Block**
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec

The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

5.5. Subject and Study Completion

A completed subject is one who has completed all study visits. The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

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.

All subjects will receive the asthma medication to be used during the study from the investigator site.

GlaxoSmithKline Clinical Trials Supplies will provide the investigational products (FF/VI: Relvar Ellipta and comparative treatments, i.e. Viani/Seretide Diskus, Symbicort Turbuhaler). Rescue medication (Salbutamol) will be provided locally by GSK in each country.

New ICS/LABA DPI or DPI copies of existing marketed ICS/LABA, if any at the time of the study, will not be considered in this trial.

Each subject randomised to the FF/VI arm will be instructed to administer the study medication once daily (by reading the leaflet and demonstration of it use), at the same time of the day, for the duration of the treatment period. Each subject will be advised to adhere to FF/VI dosing regimen throughout the study starting with FF/VI 92mcg/22 mcg. The investigator or appropriately qualified designee may increase the dose of FF/VI according to the subjects' response..

Each subject initiating other ICS/LABA maintenance therapy will be reminded about the techniques of how to use their maintenance medication (by reading the leaflet and demonstration of it use) and the correct dosing. Each subject will be advised to adhere to

ICS/LABA dosing regimen throughout the study, starting with FP/S 250mcg/50mcg or with BUD/F 200mcg /6mcg according to the Investigator's decision. The Investigator may increase the dose of each product according to the subjects' response.

A description of the investigational treatments is provided below:

Table 1 Description of Fluticasone Furoate/Vilanterol Inhalation Powder Dry Powder Inhaler and permitted comparative treatments

Compound Formulation	**Fluticasone Furoate/ Vilanterol** First strip: FF 92 mcg or 184 mcg blended with lactose Second strip: Vilanterol 22 mcg blended with lactose and magnesium stearate[1]
Dosage Form	DPI Ellipta – 30 doses per device
Unit Dose Strength	92 mcg/22 mcg or 184 mcg/22 mcg per actuation
Route of Administration	Inhaled
Compound Formulation	**Fluticasone propionate/ Salmeterol** FP 250 mcg or 500 mcg blended with lactose Salmeterol 50 mcg blended with lactose
Dosage Form	DPI Diskus – 60 doses per device
Unit Dose Strength	250 mcg/50 mcg or 500 mcg/50 mcg per actuation
Route of Administration	Inhaled
Compound Formulation	**Budesonide/Formoterol Fumarate** Budesonide 200 mcg or 400 mcg blended with lactose Formoterol Furoate 6 mcg or 12 mcg blended with lactose
Dosage Form	DPI Turbuhaler 60 or 120 doses (200 mcg/6 mcg or 400 mcg/12 mcg) per device
Unit Dose Strength	200 mcg/6mcg or 400 mcg/12 mcg per actuation
Route of Administration	Inhaled

1 magnesium stearate 1% w/w of total drug product

The subject's use of short/rapid acting beta$_2$-agonist bronchodilator will be assessed as it would be in routine care and if required, rescue medication will be prescribed to subjects to use as needed throughout the study for relief of asthma symptoms as per usual practice.

6.2. Medical Devices

Medical devices (spirometers) will be provided by GSK for use in this study. However, none of the devices provided are manufactured by, or on behalf of GSK.

6.3. Treatment Assignment

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

Subjects will be randomized (1:1) to one of the following treatment groups:

- FF/VI (as per dose guidance below)
- Usual inhaled dry powder ICS/LABA fixed combination for asthma maintenance therapy limited to Seretide/Viani Diskus or Symbicort Turbuhaler according to usual physician's prescription.
- Note: To maintain consistency across countries the choice of usual inhaled dry powder ICS/LABA fixed combination will be limited to Seretide/Viani Diskus (FP/S 250mcg/50mcg or 500mcg/50mcg) or Symbicort Turbuhaler (BUD/F 200mcg/6mcg or 400mcg/12mcg). Some countries have other ICS/LABA fixed combinations and other generic versions of FP/S and BUD/F available for the treatment of patients with asthma, but these will not be permitted in this study. Additionally some countries have options for a lower dose of Viani Diskus (FP/S 100mcg/50mcg) and Symbicort Turbohaler (BUD/F 100mcg/6mcg) but these will not be permitted in this study.

Dose Guidance:

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

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

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

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

Information extracted from GINA, 2012, refer to GINA for further guidance.

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

6.4. Planned Dose Adjustments

Subjects for whom it is considered appropriate/necessary to adjust treatment can have their dose increased from the starting dose as would be normal clinical practice at the Investigator's discretion. This will not require the subject to be withdrawn from the study.

It is not permitted for patients to be switched to a different treatment i.e. patients randomised to the usual ICS/LABA arm cannot change to a different ICS/LABA or receive FF/VI. Patients randomised to the FF/VI arm cannot receive usual ICS/LABA. If a switch between products is required the patient should be withdrawn from the study.

6.5. Blinding

This study is an open label randomised study.

6.6. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.7. Preparation/Handling/Storage/Accountability

All FF/VI and comparative ICS/LABA maintenance therapy prescribed throughout the study will be dispensed at, and collected from the investigator site.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. All DPIs containing FF/VI must be stored at a temperature of up to 25°C. Budesonide/Formoterol DPIs must be stored at a temperature of up to 30°C and Fluticasone Propionate/Salmeterol DPIs stored at 2-25°C.

Access to and administration of the investigational product will be limited to the investigator and authorised site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

All used and unused study medication inhalers (FF/VI or usual ICS/LABA asthma maintenance therapy) should be returned to the investigator site when the subjects attend for a visit.

At the end of the study, all study supplied study medication (used and unused) provided to investigator sites will be destroyed following local standard operating procedures, except where it is suspected that Ellipta or GSK DPI packaging is defective. The device and packaging should be returned to GSK. .

Details for both return and destruction and of study medication are found in the Study Reference Manual (SRM).

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

In accordance with local regulatory requirements, the Investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

6.8. Investigational Product Malfunction

Any investigational product inhaler that fails to function properly must be identified to GSK personnel. Details of the failure will be documented in the eCRF. Ellipta inhalers will be returned to GSK for testing. The subject should return the inhaler to the clinic as soon as possible to avoid missing any doses.

The site will then contact GSK's internal IWRS (also known as the Registration and Medication Ordering System [RAMOS] NG) and obtain a new treatment pack number for this subject and dispense a new study medication kit from the site's investigational product supply, as instructed per the IWRS.

6.9. Compliance with Study Treatment Administration

When the subjects attend the investigator site, they will be instructed to administer the study medication once daily at the same time of the day for the duration of the treatment, when randomised to FF/VI via Ellipta™ and twice daily (on the morning and evening) when randomised to ICS/LABA DPI (Diskus™ or Turbuhaler). All used and unused study medication inhalers (FF/VI or usual asthma maintenance therapy) should be returned to the investigator site when the subjects collect prescriptions of study medication.

Overall treatment compliance with study medication will be calculated for each type of inhaler separately as:

$$\text{Overall Compliance (\%)} = \left(\frac{\text{Total number of inhalations taken}}{\text{Expected Inhalations} \times (\text{Stop date} - \text{Start date} + 1)}\right) \times 100$$

- Total number of inhalations taken is the total number of doses taken from all inhalers during the time period (as assessed from dose counter data collected on the eCRF)
- Expected Inhalations is the expected number of inhalations per day (1 for ElliptaTM, 2 for DiskusTM and 2 or 4 for TurbuhalerTM depending on the dose)
- Start date and Stop date are the earliest treatment start date and the latest treatment stop date respectively for all inhalers used in the calculation.

Treatment compliance will be assessed for the period from randomisation (Day 0) until Week 12 (Visit 4), from Week 12 (Visit 4) until Week 24 (Visit 6) and also overall from randomisation (Day 0) until Week 24 (Visit 6).

Subject's self-reported adherence to medication will be evaluated based on analysis of Medication Adherence Report Scale for Asthma (MARS-A) questionnaires at randomisation Day 0, at Week 12 and at Week 24.

6.10. Treatment of Study Treatment Overdose

An overdose will be defined as the subject receiving any amount of IP greater than the maximum dose permitted by the protocol, which results in clinical signs or symptoms.

In the event of an overdose of study medication, the Investigator should use clinical judgment in treating the overdose and contact the study medical monitor.

GlaxoSmithKline (GSK) is not recommending specific treatment guidelines for overdose and toxicity management. The Investigator should 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(s) or equivalent document provided by GSK for study medications.

6.11. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition. GSK will not provide post study treatment.

6.12. Concomitant Medications and Non-Drug Therapies

All respiratory-related prescribed and dispensed concomitant medications taken during the study will be recorded. The minimum requirement is that drug trade name and the dates of prescribing, dispensing and collection will be recorded.

6.12.1. Permitted Medications and Non-Drug Therapies

All medications for asthma and other disorders that are not contraindicated in asthma, or listed as a prohibited medication (see Section 6.12.2), may be continued throughout the study.

At clinical doses, low plasma concentrations of FF and VI are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and/or liver, any clinically significant drug interactions mediated by FF or VI are unlikely.

A CYP3A4 drug interaction study was performed in healthy subjects with the FF/VI combination (200/25) and Ketoconazole. Co-administration increased mean FF AUC(0-24) and Cmax by 36% and 33%, respectively. The increase in FF exposure was associated with a 27% reduction in 0-24 h weighted mean serum cortisol. Co-administration increased mean VI AUC(0-t') and Cmax 65% and 22%, respectively. The increase in VI exposure was not associated with an increase in beta-agonist related systemic effects on heart rate, blood potassium or QTcF interval.

Care is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for an increased systemic exposure to both FF and VI. Consideration should be given to the clinical situation and the duration of treatment with such concurrent medications.

6.12.2. Prohibited Medications and Non-Drug Therapies

- **Systemic corticosteroids**, except in case of a severe asthma exacerbation.
- **Monoclonal antibodies omalizumab (Xolair) and mepolizumab (Nucala).**

7. STUDY ASSESSMENTS AND PROCEDURES

The Time and Events Table is provided in Section 7.1. All study assessments should be conducted by the Investigator or his/her qualified designee unless otherwise specified in the protocol or SRM. Please refer to the SRM for the suggested order of assessments.

7.1. Time and Events Table

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

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

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

Patients that fail screening may be rescreened only upon approval by the medical monitor

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

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

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

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

¥ Only for childbearing women.

Note: All adverse events will be recorded in the source documents but only information regarding non-serious adverse drug reactions (ADRs) and serious adverse events (SAEs) will be documented and reported in the eCRF.

7.2. Screening and Critical Baseline Assessments

The following demographic parameters will be captured: year of birth, sex, and ethnicity. Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5 and as indicated in the time and event table.

Cardiovascular medical history, CV risk factors and exacerbation history will be assessed as indicated in the time and event table.

Smoking status will be also captured as follows: non smoker, current or former cigarette smokers. Former smokers will be defined as those who have stopped smoking for at least 6 months prior to Visit 1 (or Visit 2 if the visit 1 and 2 are combined). Number of pack-years should be assessed at screening (Visit 1): number of pack years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years).

Procedures conducted as part of the subject's routine clinical management [e.g. blood count] and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

ACT will be assessed at screening (Visit 1) and randomisation (Visit 2). AQLQ(S), EQ-5D and MARS-A will be assessed at Visit 2 (Randomisation). These Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic investigator site visit, in the order specified. The correct use of inhaler will be assessed also at randomization visit (Visit 2):

1. after reading the package insert of product by the patient and
2. after demonstration of it use by the Investigator. Any critical errors will be registered by the Investigator when using each device.

Baseline pre-dose FEV1 will be assessed at this visit by the Investigator using a spirometer provided by GSK. Rescue medication (salbutamol) will be stopped 4 hours before baseline spirometry and usual asthma medication will be not be taken by the patient before coming on site.

No study related procedures may be performed until the informed consent form document has been reviewed with and signed by the subject.

7.3. Efficacy

See Section 3 for the efficacy endpoints and Section 7.1 for the proposed time and events table.

7.3.1. Inhaler Correct Use Assessment

Correct use of the inhaler will be assessed as outlined in the Time and Events Table (Section 7.1).

Table 3 Critical and Non-critical errors for Ellipta

Instructions: Critical Errors are identified in **bold text** in the list below. A critical error is defined as an error that is most likely to result in no or only minimal medication being inhaled. Check only one box.					
Did the subject make an error while using the device? [ ] No [ ]Yes *if yes, tick appropriate options below*					
Critical Errors for Ellipta	**yes**	**no**	**Non-critical Errors for Ellipta**	**yes**	**no**
Failed to open cover			No exhalation before an inhalation		
Shook the device upside down after dose preparation			Inhalation manoeuvre was not: - long - steady - deep		
Exhaled directly into mouthpiece			Blocked air inlet during inhalation manoeuvre		
No seal by the lips around the mouthpiece during the inhalation			Did not hold breath		
			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
Any other comments: [free text box]					

Table 4 Critical and Non-critical errors for Diskus

<table>
<tr><td colspan="6">Instructions: Critical Errors are identified in bold text in the list below. A critical error is defined as an error that is most likely to result in no or only minimal medication being inhaled. Check only one box.</td></tr>
<tr><td colspan="6">Did the subject make an error while using the device?
[ ] No
[ ]Yes if yes, tick appropriate options below</td></tr>
<tr><td>Critical Errors for Diskus</td><td>yes</td><td>no</td><td>Non-critical Errors for Diskus</td><td>yes</td><td>no</td></tr>
<tr><td>Failed to open cover</td><td></td><td></td><td>No exhalation before an inhalation</td><td></td><td></td></tr>
<tr><td>Lever is not pushed back</td><td></td><td></td><td>Inhalation manoeuvre was not:
- steady
- deep</td><td></td><td></td></tr>
<tr><td>Shook the device after dose preparation</td><td></td><td></td><td>Did not hold breath</td><td></td><td></td></tr>
<tr><td>Exhaled directly into mouthpiece</td><td></td><td></td><td rowspan="2">Did not close the device (Note: this is an error but one which does not affect the medication that is inhaled)</td><td></td><td></td></tr>
<tr><td>No seal by the lips round the mouthpiece during the inhalation</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="6">Any other comments: [free text box]</td></tr>
</table>

Table 5 Critical and Non-critical errors for Turbuhaler

Instructions: Critical Errors are identified in **bold text** in the list below. A critical error is defined as an error that is most likely to result in no or only minimal medication being inhaled. Check only one box.					
Did the subject make an error while using the device? [ ] No [ ]Yes *if yes, tick appropriate options below*					
Critical Errors for Turbuhaler	**yes**	**no**	**Non-critical Errors for Turbuhaler**	**yes**	**no**
Failed to remove cap			Device tipped downwards after dose preparation		
Did not hold device upright (±45% OK) during dose preparation			No exhalation before an inhalation		
Base not twisted fully backwards and forwards, no click heard			Inhalation manoeuvre was not: - forceful - deep Note to *HCP: it is important that the inhalation is forceful and deep from the start for this inhaler*		
Shook the device after dose preparation			Blocked air inlet during inhalation manoeuvre		
Exhaled directly into mouthpiece			Did not hold breath		
No seal by the lips round the mouthpiece during the inhalation			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
Any other comments: [free text box]					

7.3.2. Trough (pre-dose) FEV1 assessment

FEV1 will be measured to assess lung function at Visit 2 (Randomisation) and Visit 4 (Week 12), as outlined in the Time and Events Table. Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation visit). Measurements should be taken pre-dose and subjects should be instructed not to take their asthma medication/study drug prior to coming into the clinic at these visits. Subjects should also

withhold from using their rescue medication for at least 4 hours prior to Visit 2 (Randomisation) and Visit 4 (Week 12).

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

The Investigator will be asked to make every effort to perform the spirometry at the same time of the day at Visit 2 and at Visit 4.

7.3.3. Questionnaires

7.3.3.1. Asthma Control Test (ACT)

The ACT is a validated self-administered questionnaire utilising 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5). Subjects will complete the ACT at Screening (Visit 1), at Randomisation (Visit 2), at Week 6 (Phone Call 1 or Visit 3), at Week 12 (Visit 4), at Week 18 (Phone Call 2 or Visit 5) and at Week 24 (Visit 6) / Early Withdrawal visit.

An ACT score of 5 to 19 suggests that the subject's asthma is unlikely to be well controlled. A score of 20 to 25 suggests that the subject's asthma is likely to be well controlled.

Please refer to Appendix 3 and the Study Procedures Manual for further details.

7.3.3.2. Asthma Quality of Life Questionnaire (AQLQ-S)

The AQLQ is a disease-specific, self-administered quality of life questionnaire developed to evaluate the impact of asthma treatments on the quality of life of asthma sufferers, over the last 2 weeks [Juniper, 1993]. AQLQ(S) will be measured at Randomisation (Visit 2), at Week 24 (Visit 6) / Early Withdrawal visit. Please refer to Appendix 3 and the Study Procedures Manual for further details.

7.3.3.3. EuroQol Questionnaire (EQ-5D)-5 Level

General health status will be assessed with the EuroQol (EQ-5D)-5 Level Questionnaire at Randomisation (Visit 2) and at Week 24 (Visit 6) / Early Withdrawal visit.

Please refer to Appendix 3 and the Study Procedures Manual for further details.

7.3.3.4. Medication Adherence Report Scale for Asthma (MARS-A)

Subject's self- reported adherence to medication will be assessed with the Medication Adherence Report Scale for Asthma (MARS-A) questionnaire at Visit 2, Week 12 (Visit 4) and Week 24 (Visit 6) / Early Withdrawal visit.

The MARS-A is a 10-item questionnaire where medication use is rated on a 5-point Likert scale (1 indicating 'always' to 5 indicating 'never'). It has been validated as a self-

reported measure of adherence with ICS for subjects with asthma and includes generic ("I use it regularly every day") and lung condition-specific questions about medication use ("I only use it when I feel breathless") [Cohen, 2009]. There is no specified timeframe on which responses should be based.

The Investigator should ensure the subject completes the MARS-A at the same time at the specified visits and before any study procedures. The MARS-A have no specified timeframe on which responses should be based.

7.3.3.5. Patients Satisfaction and Preference with the device (PASAP Questionnaire)

The Patient Satisfaction and Preference Questionnaire (PASAPQ) [Kozma, 2005], is a multi-item measure of respiratory inhalation device satisfaction and preference designed to be easily understood and administered to patients with asthma and COPD. Patient satisfaction with each device and device preference will be assessed at Week 12 (Visit 4) / Early Withdrawal visit if subject is withdrawn before Week 12 (Visit 4).

The Investigator should ensure the subject completes the PASAP-Q at the same time at the specified visits and before any study procedures. The PASAP-Q has no specified timeframe on which responses should be based.

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (see Section 7.1).

Serious Adverse Events (SAE) and non-serious Adverse Drug Reactions (ADR) will be collected in this study.

Safety endpoints will include:

- Frequency and type of serious adverse events,
- Frequency and type of non serious adverse drug reactions related to treatment.

7.4.1. Adverse Events (AE), Adverse Drug Reactions (ADRs) and Serious Adverse Events (SAEs)

The definitions of an AE, ADR or SAE can be found in Appendix 5.

The Investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. All adverse events will be recorded in the source documents but only information regarding non-serious adverse drug reactions (ADRs) and serious adverse events (SAEs) will be documented and reported in the eCRF.

7.4.1.1. Time period and Frequency for collecting non serious ADRs and SAE information

- All non-serious ADRs and SAEs will be collected from the start of Study Treatment until the end of the study (see Section 7.4.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- 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 SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 5.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 5.

7.4.1.2. Method of Detecting non serious ADRs and SAEs

The Investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of a non-serious adverse drug reaction (ADR) or serious adverse events (SAE).

The method of detecting, recording, evaluating and follow-up of SAEs and non-serious ADRs plus procedures for completing and transmitting SAE reports to GSK are provided in the SRM. Procedures for post-study SAEs/non-serious ADRs are provided in the SRM.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

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

Potential SAEs and non serious ADRs may be identified by hospitalisation alerts through the medical record. The Investigator will have the ultimate responsibility for determining causality and seriousness.

7.4.1.3. Follow-up of non serious ADRs and SAEs

After the initial non serious ADRs/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious ADRs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 5.

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 5 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.

7.4.1.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Any clinically significant safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition, are **not** to be reported as non-serious ADRs or SAEs.

7.4.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the Investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met. This will also include potential SAEs identified by hospitalisation alerts through the medical record.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority/Independent Ethics Committee (IEC) and Investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An Investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IEC, if appropriate according to local requirements.

The method of detecting, recording, evaluating and follow-up of SAEs and non-serious ADRs plus procedures for completing and transmitting SAE reports to GSK are provided in the SRM. Procedures for post-study SAEs/non-serious ADRs are provided in the SRM.

Procedures for documenting, transmitting and follow-up of medical device incidents along with the regulatory reporting requirements for medical devices are provided in the SRM.

7.4.2. Pregnancy

- Details of all pregnancies in female subjects will be collected from the time the informed consent is signed (Visit 1) and until the end of the study (Visit 6).
- Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 7.
- Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

7.4.3. Medical Device Incidents (Including Malfunctions)

Medical devices (spirometers) will be provided by GSK for use in this study. However, none of the devices provided are manufactured by, or on behalf of GSK.

7.4.4. Physical Exams

A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.4.5. Vital Signs

Vital sign measurements will include height, weight, pulse rate, systolic and diastolic blood pressure.

Vital signs will be measured and recorded in the eCRF at Screening visit (Visit 1), at the Randomisation Visit 2 (Day 0), at Week 12 (Visit 4), at Week 24 (Visit 6) and at Early Withdrawal Visit except for height and weight that will be collected at Visit 1 only.

7.4.6. Electrocardiogram (ECG)

An ECG is not required prior to entering this study. There are no other regular ECGs required by this protocol.

7.4.7. Clinical Safety Laboratory Assessments

There are no clinical safety laboratory assessment requirements for this study.

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) recorded during a routine clinic visit, including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the Investigator are to be recorded as non-serious ADRs or SAEs as appropriate.

7.5. Genetics

Information regarding genetic research is included in Appendix 6.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary (GSKDrug).
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The objective of the study is to compare the efficacy of fluticasone furoate (FF)/vilanterol (VI) Inhalation Powder (FF/VI 92 mcg/22mcg or FF/VI 184 mcg/22mcg) with usual ICS/LABA inhalation dry powder for asthma maintenance therapy over six months in a large population of subjects with asthma.

The primary endpoint is defined as the change from baseline in the ACT total score assessed at Week 12 (Visit 4). Regarding the primary efficacy endpoint (i.e. the change from baseline in the ACT total score assessed at Week 12 [Visit 4]), the primary analysis will show that the fixed combination FF/VI (92mcg/22mcg or 184mcg/22mcg) is non-inferior to any other ICS/LABA combinations in inhalation powder assuming a non-inferiority margin of 1.5. Non-inferiority will be claimed if the 95% two-sided confidence interval on the difference in mean primary efficacy endpoints (FF/VI minus Comparator) precludes the non-inferiority margin of -1.5.

If (and only if) non-inferiority is significantly achieved at Week 12 (Visit 4) with regard to the primary endpoint, then non-inferiority of the fixed combination FF/VI (92mcg/22mcg or 184mcg/22mcg) to any other ICS/LABA combinations will be tested at Week 24 (Visit 6) considering the same non-inferiority margin of 1.5. Non-inferiority will be claimed if the 95% two-sided confidence interval on the difference in mean primary efficacy endpoints (FF/VI minus Comparator) at Week 24 (Visit 6) precludes the non-inferiority margin of -1.5.

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

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

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

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

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

9.2.2. Sample Size Sensitivity

To demonstrate the sensitivity of the sample size calculation for this study, the following table presents the power of the study under different circumstances in terms of the standard deviation.

The assumption used is shaded.

Standard deviation	Power for the subjects evaluable (N = 382)
3.8	97.0%
4.2	93.6%
4.5	90.1%
4.7	87.5%
4.9	84.7%

9.2.3. Sample Size Re-estimation or Adjustment

Not planned

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Populations considered for analysis are as follows:

Intent to treat (ITT) population: All randomized subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy). The ITT population will be used to analyze the primary efficacy endpoint analysis, the secondary efficacy endpoint and other efficacy endpoints. Subjects will be assigned to the treatment group as randomized for the ITT population.

Per-protocol (PP) population: ITT subjects without any protocol deviations specifically defined in the RAP. Protocol deviations will be reviewed and will be classified as important or not important during data review meetings that will be held before database lock. Deviations classified as important will be further defined according to whether they require the patient to be excluded from the PP population. Deviations that would exclude a patient from the PP population will be defined in the RAP. **Safety population:** All enrolled subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy) and considered as-treated. The Safety population will be the basis for safety analyses. Subjects will be assigned to the treatment group as treated for the Safety population.

Details of the analysis datasets to be created will be specified in the Report Analysis Plan (RAP).

9.3.2. Interim Analysis

Not applicable

9.4. Key Elements of Analysis Plan

The primary comparison of interest is the comparison of the change from baseline (Visit 2) in the total ACT score assessed at Week 12 (Visit 4) between FF/VI (92mcg/22mcg or 184mcg/22mcg) and usual ICS/LABA inhalation powder for asthma maintenance therapy.

The primary set for analysis will be performed on the intent to treat population. A sensitivity analysis will be performed in the PP population.

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

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

Of note, this step-down testing procedure still strongly controls the overall type I error at the 0.05 two-sided level.

Definition of the treatment failure will be as follow:

- Treatment withdrawal,
- Change of treatment,
- Dose increase beyond the maximum allowed daily dose in the EU license (for FF/VI > 184mcg/22mcg, for FP/S > 500mcg twice daily, for BUD/F > 800 mcg twice daily.

Other Comparisons of Interest: Other efficacy endpoints and safety endpoints will be described. Estimated differences between groups with 95% confidence intervals will be provided when applicable.

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the Reporting Analysis Plan (RAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report Descriptive summaries will be provided by treatment group.

Demographic and baseline characteristics will be summarized.

Continuous variables will be summarized using descriptive statistics (number of observed and missing data, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum).

Categorical variables will be summarized as numbers of observed and missing data, counts and percentage for each category (reported to the number of non-missing values). For binary variables, 95% confidence intervals for proportions will be estimated based on the Clopper-Pearson method.

The contrast between FF/VI and usual ICS/LABA asthma maintenance therapy in inhalation powder will be of primary interest for all efficacy endpoints.

Non-inferiority of FF/VI versus usual ICS/LABA asthma therapy will be first tested at Week 12 (Visit 4). If and only if significance is achieved at Week 12 (Visit 4), then non-inferiority will be tested at Week 24 (Visit 6) at the two-sided 0.05 level of significance. This step-down testing procedure strongly controls the overall type I error at the 0.05 two-sided level.

If non-inferiority is achieved at Week 12 (Visit 4), then superiority of FF/VI versus usual ICS/LABA asthma therapy will be tested at the same two-sided nominal significance level of 0.05. If non-inferiority is achieved at Week 24 (Visit 6), then superiority of FF/VI versus usual ICS/LABA asthma therapy will be tested at the same two-sided nominal significance level of 0.05.

Baseline ACT score will be included in the primary efficacy analyses. Gender, age, study site and potentially season at randomization will be further investigated in sensitivity analyses when appropriate. Other covariates may be considered and if so it will be detailed in the RAP.

Treatment by prognostic factors interactions will be specifically investigated in secondary models.

Handling of treatment withdrawal: treatment withdrawal will be considered as a failure and the primary endpoint at the treatment withdrawal time will be assessed based on the last available ACT post randomization score before withdrawal. Of note, a change in the dose regimen will not be considered as a treatment failure.

Handling of missing data: as a general rule, missing data will not be replaced. Nevertheless sensitivity analyses regarding the primary and key secondary endpoint will replace missing ACT assessments by the last available post randomization ACT value (i.e. based on the last observation carried forward method).

The study is adequately powered for the primary and the key secondary endpoint, i.e. to show non-inferiority of FF/VI to current ICS/LABA at Week 12 (Visit 4) and at Week 24 (Visit 6) considering a non-inferiority margin of 1.5. Other secondary endpoints are not necessarily adequately powered and a descriptive analysis will only be proposed for these endpoints.

The primary efficacy analysis population set is defined as all subjects belonging to the Intent-to-Treat population (ITT), which include all subjects who have been randomised and received at least one prescription of study medication (e.g. FF/VI or usual ICS/LABA inhalation powder for asthma maintenance therapy).

Each subject will complete the ACT at Visit 2 (Randomisation), Week 12 (Visit 4) and Week 24 (Visit 6). ACT scores will also be assessed at Week 6 (Visit 3) and at Week 18 (Visit 5) and at the withdrawal time, if any.

9.4.1. Primary Analyses

The primary endpoint is defined as the change from baseline (Visit 2) in the ACT total score assessed at Week 12 (Visit 4).

The primary population of analysis will be the ITT population.

If treatment is withdrawn, then the missing ACT score at the nearest visit after treatment withdrawal will be replaced by the ACT score assessed at withdrawal time. If no ACT

score is assessed at withdrawal time, then the ACT missing score at the nearest visit after treatment withdrawal will not be replaced.

1) Non-inferiority testing.

The non-inferiority of FF/VI versus any other ICS/LABA DPI comparator will be primarily tested in a mixed model repeated measures (MMRM) approach. The model will include factors and covariates as follow: treatment, scheduled visit time point (Week 6 and Week 12), baseline ACT, treatment by visit interaction, baseline ACT by visit interaction, gender, age and patient will be fitted as a random factor. The Restricted Maximum Likelihood (REML) estimation approach will be used, and the default covariance structure will be unstructured. Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point will be performed. The 95% confidence interval on the treatment effect (FF/VI vs ICS/LABA comparator) will be estimated at Week 12 (Visit 4) in this model. Non-inferiority will be achieved if the non-inferiority margin of -1.5 is lower than the lower bound of the confidence interval on the difference between FF/VI and any other comparator (positive values of the difference favour FF/VI).

Sensitivity analyses:

a) Handling missing data

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

1. Missing values at Week 12 (Visit 4) will be replaced by the post-randomization last available value (either the week 6-based ACT score or the ACT score at treatment withdrawal time, if any), i.e. based on the Last Observation Carried Forward method. The change from baseline in ACT at Week 12 (Visit 4) will be analyzed in an ANCOVA model adjusting for treatment and baseline ACT score. The treatment effect (FF/VI versus any other ICS/LABA comparator) and its corresponding 95% confidence interval will be estimated in this model to test the non-inferiority hypothesis.

2. Multiple imputation (MI) analyses utilizing covariates known to be predictive of response: season at randomization, observed value of ACT at Week 6, observed value of ACT at Week 12 (Visit 4). Other covariates may be considered and if so it will be detailed in the RAP.

Step 1: For each treatment group separately, missing measurements are imputed for subjects with a baseline measurement where there are missing observations (at either Week 6 or Week 12) using the above covariates and regression-based imputation method. The Markov Chain Monte Carlo (MCMC) method for MI will be used and ten such sets

of imputed data will be created each with the observed values or imputed values for subjects with missing observations.

Step 2: Each imputed data set will be analyzed using the primary MMRM model. The treatment effect from these 10 analyses will then be pooled using standard MI theory to make an overall inference. The difference in the least squares means between the two groups at Week 12 (Visit 4) and the corresponding 95% confidence interval for the difference will be presented.

b) A sensitivity analysis based on the semi parametric Hodges-Lehmann (HL) approach will be proposed to assess the robustness of the MMRM Model-based non-inferiority results. The HL difference between groups with the corresponding 95% confidence interval will be provided.

c) Sensitivity analyses for handling treatment withdrawal: when treatment withdrawal occurs, an alternative method for imputing the missing value at the nearest visit after withdrawal time will be proposed: the primary endpoint missing value will be estimated by the worst ACT score observed between baseline visit (included) and withdrawal time (included).

d) The primary analysis (i.e. based on the MMRM approach) and the same sensitivity analyses presented here above will be performed on the Per Protocol population.

Model assumptions checking:

a) Assumptions underlying the MMRM (resp. ANCOVA for the sensitivity analysis) model (residual normality, linear relationship between response and baseline ACT, etc) will be checked with graphical methods (plots of studentized residuals, etc)

b) Baseline ACT will be categorized according the distribution quartiles and the same MMRM model (resp. ANCOVA for the sensitivity analysis) adjusting for categorized Baseline ACT will be fitted again.

c) Possible treatment by covariates (baseline ACT, baseline Asthma therapy, season at randomisation) interaction will be investigated MMRM (resp. ANCOVA for the sensitivity analysis) adjusting for these additional interaction terms

d) The influence of the covariates and potential additional covariates on the outcome will be investigated.

2) Superiority testing.

If non-inferiority is statistically achieved at Week 12 (Visit 4), then superiority of FF/VI to any other comparator will be tested at the usual 0.05 two-sided nominal level of significance.

The same models and analyses mentioned above will be used to assess the superiority hypothesis.

9.4.2. Secondary Analyses

Key secondary analysis

The key secondary endpoint is defined as the change from baseline (Visit 2) in the ACT total score assessed at Week 24 (Visit 6).

1) Non-inferiority testing

If non-inferiority is statistically achieved at Week 12 (Visit 4), then non-inferiority will be tested at Week 24 at the 0.05 two-sided nominal level. If non-inferiority is not accepted at Week 12 (Visit 4), non-inferiority will not be tested at Week 24 (Visit 6) and assessed on a descriptive basis only

More precisely, the key secondary endpoint assessed at Week 24 (Visit 6) will also be analyzed using a mixed model repeated measures (MMRM) approach where data up to and including Week 24 (Visit 6) will be used in the model. The model will include factors and covariates as follow: treatment, scheduled visit time point (Week 6, Week 12, Week 18 and Week 24), baseline ACT, treatment by visit interaction, baseline ACT by visit interaction, gender, age and patient will be fitted as a random factor. The Restricted Maximum Likelihood (REML) estimation approach will be used, and the default covariance structure will be unstructured. Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point will be performed. The 95% confidence interval on the treatment effect (FF/VI vs ICS/LABA comparator) will be estimated at Week 24 in this model. Non-inferiority will be achieved if the non-inferiority margin of -1.5 is lower than the lower bound of the confidence interval on the difference between FF/VI and any other comparator (positive values of the difference favour FF/VI).

Sensitivity analyses: the same sensitivity analyses as those described above for the primary endpoint will be performed for the key secondary efficacy endpoint.

Model assumptions checking: the analyses proposed to check model assumptions for the analysis of the key secondary efficacy endpoint will be the same as those described above for the primary endpoint.

2) Superiority testing.

If non-inferiority is statistically achieved at Week 24 (Visit 6), then superiority of FF/VI versus any other comparator will be tested at the usual 0.05 two-sided nominal level of significance.

The same models and analyses mentioned above will be used to assess the superiority hypothesis.

Other secondary analyses

Proper use of the medical device

The other key secondary endpoint will be the correct use of the inhaler device assessed at randomisation (Visit 2), at Week 12 (Visit 4) and at Week 24 (Visit 6). The device will be considered as adequately used if the patient didn't make any critical error or non-critical error at the corresponding visits (randomisation [Visit 2], week 12 [Visit 4] and week 24 [Visit 6]). Percentages of subjects correctly using the device will be calculated within each group. A corresponding 95% confidence interval of the difference in percentages will also be provided. Furthermore, the percentage of subjects with overall error, at least one critical error, and at least one non-critical error will be presented by treatment group, along with the percentage making each specific error. Additional exploratory analyses could be performed and will be detailed in the RAP. Even if tests will be performed, no causal association will be inferred from these analyses.

9.4.3. Other Analyses

Other Analyses

The analysis of the other endpoints defined in this section will be provided for exploratory purposes only. Additional exploratory analyses could be performed and will be detailed in the RAP. Even if tests will be performed and 95% confidence intervals will be provided, no causal association will be inferred from these analyses.

Change from baseline in pre-dose trough FEV1

Results will be summarized for each group at Week 12 (Visit 4). More detail will be provided in the RAP.

Response to treatment

- Binary response defined as an ACT score ≥ 20 at a given visit OR a 3 point increase from baseline in ACT change.

The responder analyses will be conducted using a logistic regression model at a given Visit or Phone Call adjusting for treatment and stratification factors (baseline ACT score categorized into two classes, baseline asthma therapy, and potentially season at randomization). Treatment by stratification factors interaction effects will be further investigated in additional logistic models adjusting for these specific effects.

- Binary response defined as an ACT score ≥ 20 at a given visit.

The frequency and the percentage of subjects with ACT score ≥ 20 at a given visit will be described by treatment group. More detail will be provided in the RAP.

- Change from baseline in individual question scores for ACT at a given visit

For each question the statistical parameters of the changes will be summarized by treatment group. More detail will be provided in the RAP.

Compliance with study medication and self-reported adherence to study medication

- Overall treatment compliance with study medication from randomisation (Day 0) to Week 12 (Visit 4), from Week 12 (Visit 4) to Week 24 (Visit 6) and from randomisation (Day 0) to Week 24 (Visit 6) will be described by treatment group.
- The score for Medication Adherence Report Scale for Asthma (MARS-A) at Day0, Week 12 and Week 24 will be described by treatment group.

Severe asthma exacerbations

Number of subjects with at least one severe exacerbation, number of severe asthma exacerbation and annual exacerbation rate over the study period.

A severe asthma exacerbation is defined as deterioration of asthma requiring the use of systemic corticosteroids[2] (tablets, suspension, or injection) with or without antibiotics prescribed or an inpatient hospitalisation or emergency department visit due to asthma that required systemic corticosteroids or antibiotics[1,2,3] .

The number and percentage of subjects experiencing an asthma exacerbation during the study period will be summarized for each treatment group. Listing will be provided to include the primary causes of the exacerbation.

If feasible (i.e. if the number of exacerbation events is high enough), mean annual rate of asthma exacerbation will be analysed using a generalised linear model, assuming the negative binomial distribution, with the logarithm of time on treatment as an offset variable. The adjusted mean rates per year, treatment ratio and associated p-value and 95% confidence interval will be presented.

Health Related Quality of Life and Health status

- An increase from baseline of ≥ 0.5 in AQLQ(s) total score at Week 24 (Visit 6).
- An increase from baseline of ≥ 0.5 in AQLQ(s) environmental stimuli domain score at Week 24 (Visit 6).
- Change from baseline in total score and domain scores of AQLQ(S) at Week 24 (Visit 6).
- Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) Individual domain scores at Week 24 (Visit 6).
- Health status using the EuroQol Questionnaire (EQ-5D) at Week 24 (Visit 6).

Patients Satisfaction and Preference with the inhaler (PASAP Questionnaire) (see Appendix 3)

The overall inhaler satisfaction and preference will be measured at Week 12 (Visit 4). The PASAP score will be summarised by treatment group.

Further analyses will be specified in the Report Analysis Plan.

Subgroup Analyses

Subgroup summaries and/or analyses will also be provided, when appropriate, for efficacy and safety endpoints based on baseline disease characteristics.

Additional analyses could be carried out using appropriate methods to account for changes in treatment during the course of the study. Further details will be provided in the analysis plan.

The details will be provided in the RAP.

Safety Analyses

Safety data will be summarized and/or listed by treatment group and by visit for the Safety population.

Extent of Exposure

Extent of exposure to study treatment (i.e., number of days on randomised treatment) will be summarised by treatment group using mean, standard deviation, median, minimum, and maximum. In addition, duration of subject exposed to study drug will be summarised across treatment groups.

Adverse Drug Reactions

Adverse drug reactions during the treatment period and during the post treatment period will be summarised and displayed by treatment group. Adverse drug reactions during the treatment period include those with a date of onset on the date of study treatment initiation to one day after study treatment termination.

The adverse drug reactions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and will be reported using the primary System Organ Class (SOC) and Preferred Term. Preferred Terms will be summarised within the primary SOC. The relationship of primary SOC, preferred terms, and verbatim text will be listed.

The number of subjects with one or more events of any type will be calculated. Results will be displayed in the order of decreasing frequency, both across primary SOC and within primary SOC.

Adverse drug reactions during the study period will also be listed. The demographic details (e.g., age, sex) and the details on individual adverse events will be included in these listings. Listings will be sorted within subject by the adverse drug reaction date of onset.

Similar summaries and listings will be provided for adverse events leading to withdrawal from study.

Deaths and Serious Adverse Events

Deaths and serious adverse events during the study period will be listed. Serious adverse events during the study period will also be summarised by treatment group.

Any pregnancies, serious adverse events and deaths reported during this study will also be summarised in case narratives written by GSK GCSP personnel.

Other safety parameters

All others safety parameters will be listed and summarized.
More specifically the vital signs (BMI, pulse rate, systolic blood pressure and diastolic blood pressure) will be summarized by visit and treatment group.

Genetic research

Information regarding genetic research is included in Appendix 6.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2013 including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which medical records will serve as the source document.

GSK will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The Investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

Upon completion or termination of the study, the GSK monitor will conduct site closure activities with the Investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the Investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all Investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by

applicable regulations, the Investigator or head of the medical institution must inform the IEC promptly and provide the reason(s) for the suspension/termination.

10.6. Records Retention

Following closure of the study, the Investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The Investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The Investigator and GSK must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the Investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The GP/Investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the Investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator signatory will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 8 months after the last subject's last visit (LSLV) [this applies to each data analysis phase for studies with multiple phases, e.g., primary analysis, follow up analysis etc]. In addition, the aim is to submit a manuscript to a peer-

reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11. REFERENCES

British Guideline on the Management of Asthma. British Thoracic Society: A national clinical guideline. 2008 63: iv1-iv121

Cohen JL, Mann DM, Wisnivesky JP, Horne R, Leventhal H, Musumeci-SzaboTJ, Halm EA. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. Ann Allergy Asthma Immunol. 2009: 103: 325-31

Dolan P. Modeling valuations for EuroQol health states. Med Care 1997; 35(11):1095-1108.

Fanta CH. Drug Therapy: Asthma. *New Engl J Med.* 2009;360(1):1002-1014.

GINA 2012, http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf

GlaxoSmithKline Document Number RM2008/00012/06. Fluticasone Furoate + Vilanterol Investigator's Brochure. 25-Jun-2014

Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention.* GINA, www.ginasthma.org; 2009.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. *Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(a): 24. Table 3-2.*

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. *Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(b): 28*

James LP et al. Pharmacokinetics of Acetaminophen-Protein Adducts in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37(8): 1779-1784.

Juniper EF et al. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol. 1994 Jan;47(1):81-7.

Juniper EF et al. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax. 1992 Feb;47(2):76-83

Juniper EF, Guyatt GH, Williams A, Griffith LE. Measuring quality of life in asthma. *Am Rev Respir Dis.* 1993;147:832-838.

Juniper EF. Asthma quality of life questionnaires (AQLQ, AQLQ(S) and MiniAQLQ): Background information and interviewing tips. QOL Technologies Inc. 1998.

Kozma CM et al. Development and Validation of a Patient Satisfaction and Preference Questionnaire for Inhalation Devices (PASAPQ). Treat Respir Med 2005

Le Gal F et al. 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.

Nathan RA, Sorkness CA, Kosinski M et al, Development of the Asthma Control Test: A survey for assessing asthma control, J Allergy Clin Immunol January 2004.

NIH, 2007, Asthma Guidelines Summary, http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.pdf

Pedersen S, O'Byrne P. A comparison of efficacy and safety of inhaled corticosteroids in asthma. *Allergy.* 1997;52(39):1-34.

Schatz M et al. The minimally important difference of the Asthma Control Test, The Journal of allergy and clinical immunology (2009)

The EuroQol Group, 1990. The EuroQol Group. EuroQol- a new facility for the measurement of health-related quality of life. Health Policy 1990; 199-208

12. APPENDICES

12.1. Appendix 1: Abbreviation and Trademarks

ACT	Asthma Control Test
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Co-variance
AQLQ(S)	Asthma Quality of Life Questionnaire
AST	Aspartate Aminotransferase
BID	Twice daily
BUD	Budesonide
°C	Celsius
CRF	Case Record Form
eCRF	Electronic Case Record Form
CV	Cardiovascular
DNA	Deoxyribonucleic acid
DPI	Dry Powder Inhaler
FP	Fluticasone Propionate
ECG	Electrocardiogram
EPI	Epidemiology
EQ-5D	EuroQol 5D
F	Formoterol
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in one second
FF	Fluticasone Furoate
FP	Fluticasone Propionate
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GINA	Global Initiative for Asthma
GP	General Practitioner
GSK	GlaxoSmithKline
HPA	Hypothalamic pituitary axis
HL	Hodges-Lehmann
IB	Investigators Brochure
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IgG	Immunoglobulin G
INR	International Normalised Ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IVD	In Vitro Diagnostic
IRT	Interactive Response Technology
LABA	Long Acting Beta Agonist

LDH	Lactate Dehydrogenase
LSLV	Last Subject Last Visit
MARS-A	Medication Adherence Report Scale in Asthma questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
Mcg	Microgram
MI	Multiple imputation
MID	Minimally Important Difference
MDI	Metered Dose Inhaler
MCID	Minimally Clinically Important Difference
ml	Millilitre
MSDS	Material Safety Data Sheet
MMRM	Mixed effects model with repeated measures
NDPI	Novel Dry Powder Inhaler
PASAP-Q	Patients Satisfaction and Preference Questionnaire
PK	Pharmacokinetics
PP	Per-protocol
PRO	Patient Reported Outcomes
pg	Picogram
pmol	Picomoles
QD	Once Daily
QoL	Quality of Life
QTc	Corrected QT interval
RAP	Reporting Analysis Plan
REML	Restricted maximum likelihood
RNA	Ribonucleic Acid
S	Salmeterol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
S&P	Statistics and Programming
SRM	Study Reference Manual
ULN	Upper Limit of Normal
VI	Vilanterol
WHO	World Health Organisation

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RELVAR
SERETIDE
VIANI

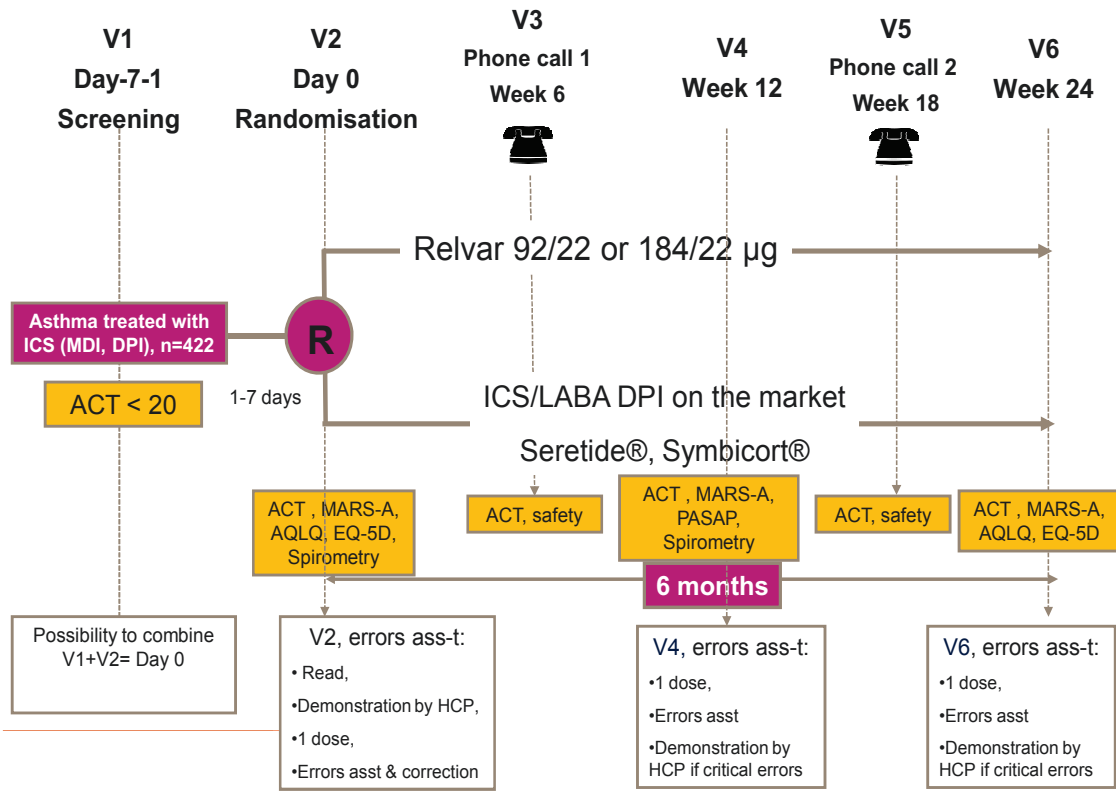
Trademarks not owned by the GlaxoSmithKline group of companies
ACT
Asthma Quality of Life Questionnaire - AQLQ(S)
EQ-5D
MARS-A questionnaire
PASAP Questionnaire
Symbicort Turbuhaler
TURBOHALER[1]
TURBUHALER[1]
XOLAIR

1-Turbuhaler and Turbohaler are both trade names for the inhaler device used for Symbicort. They are used interchangeably in this document.

12.2. Appendix 2: Study Schematic

FF/VI open- label or usual asthma maintenance treatment

HZA 116492: study design



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

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

12.3. Appendix 3: Questionnaires

Asthma Control Test (ACT)

The ACT is a validated self-administered questionnaire utilising 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5). By answering all 5 questions a subject with asthma can obtain a score that may range between 5 and 25, with higher scores indicating better control. An ACT score of 5 to 19 suggests that the subject's asthma is unlikely to be well controlled. A score of 20 to 25 suggests that the subject's asthma is likely to be well controlled. The total score is calculated as the sum of the scores from all 5 questions. [Nathan, 2004]. The minimally important difference (MID) for ACT is 3 [Schatz, 2009].

Subjects will complete the ACT at Screening (Visit 1), at Randomisation (Visit 2), at Week 12 (Visit 4) and at Week 24 (Visit 6) on site. Two telephone calls are provided at Week 6 and 18 and subjects will be asked to provide responses to the ACT questionnaire and to send it back to the Investigator.

The ACT has been developed as a measure of subjects' asthma control that can be quickly and easily completed in clinical practice. The questions are designed to be self-completed by the subject. It is recommended that the ACT be administered at the same time during each visit. The ACT should be completed before any procedures are performed on the subject to avoid influencing the subject's response. Adequate time should be allowed to complete all items on the ACT.

The subject should complete the questionnaire in a quiet area.

The Investigator should ask the subject to complete the questions as accurately as possible. If the subject requests help or clarification with any of the questions, he/she will be asked to re-read the instructions and give the answer that best reflects how he/she felt over the previous 4 weeks. The subject should be reassured that there are no right or wrong answers. The Investigator should not provide the subject with any answer or attempt to interpret any portion of a question.

Please refer to the Study Reference Manual (SRM) for further details.

Asthma Quality of Life Questionnaire (AQLQ-S)

The AQLQ (S) is a modified version of the original AQLQ in which all the activity questions are generic and it has been validated for use in asthma subjects between the ages of 17 and 70. The AQLQ is a disease-specific, self-administered quality of life questionnaire developed to evaluate the impact of asthma treatments on the quality of life of asthma sufferers, over the last 2 weeks [Juniper, 1993]. AQLQ(S) will be measured at Randomisation and at Week 24 / Early Withdrawal visit.

The AQLQ, which is available in numerous languages, has a demonstrated validity, reliability and reproducibility [Juniper, 1992; Juniper, 1998]. The AQLQ contains 32 items in four domains: activity limitation (11 items), symptoms (12 items), emotional function (5 items), and environmental stimuli (4 items). In addition, the 32 items of the

questionnaire are also averaged to produce an overall quality of life score. The response format consists of a seven-point scale where a value of 1 indicates “total impairment” and 7 indicates “no impairment”. Assuming a statistically significant result ($p < 0.05$), the minimal clinically meaningful change in overall quality of life, or in quality of life for any of the individual domains, is 0.5 points [Juniper, 1994].

It is recommended that the AQLQ (S) be administered at the same time during each visit. The AQLQ (S) must be administered before inquiring about AEs and any study assessments. Adequate time should be allowed to complete all items on the AQLQ (S). No stated or implied time for completing the AQLQ (S) will be given, though the survey typically takes 10 to 20 minutes to complete.

Subjects should complete all the questions from the AQLQ (S). The Investigator will ask the subject to complete all questions as accurately as possible. If the subject requests help or clarification of any question in the AQLQ (S) he or she should be asked to reread the instructions and give the answer that best reflects how he/she feels over the previous two weeks. The subject should be reassured that there are no right or wrong answers. The Investigator will not provide the subject with any answer or attempt to interpret any portion of a question. Please refer to the Study Reference Manual (SRM) for further details.

EuroQol Questionnaire (EQ-5D)-5 Level

General health status will be assessed with the EuroQol (EQ-5D)-5 Level Questionnaire at Randomisation and Week 24 / Early Withdrawal visit.

The EQ-5D is a standardised instrument for use as a measure of health status that asks subjects questions about their health status “today” [The EuroQol Group, 1990]. It is designed for self-completion and is cognitively simple. The EQ-5D is a two-part self-assessment questionnaire. The first part consists of five items covering five dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a three-point Likert scale (1-no problem, 2-some/moderate problem[s], and 3-unable/extreme problem[s]).

Respondents are asked to choose one level that reflects their "own health state today" for each of the five dimensions. Respondents can then be classified into one of 243 distinct health states. EQ-5D health states can be converted to a single summary index by applying a formula that attaches weights to each of the levels in each dimension. The formula is based on the valuation of EQ-5D health states from general population samples [Dolan, 1997].

The second part of the questionnaire consists of a vertical visual analogue scale (EQ-5D VAS) that has endpoints of "The best health you can imagine" (anchored at 100) and "The worst health you can imagine" (anchored at 0). Respondents are asked to indicate how they rate their current health state by drawing a line from the box marked “your health status today” to the appropriate point on the EQ-5D VAS scale.

The Investigator should ensure the subject completes the EQ-5D at the same time at the specified visits and before any study procedures. The EQ-5D will be administered at Randomisation (Visit 2) and Week 24 (Visit 6) / Early Withdrawal visit.

Medication Adherence Report Scale for Asthma (MARS-A)

Subject self-reported adherence to medication will be assessed with the Medication Adherence Report Scale for Asthma (MARS-A) questionnaire at Visit 2, Visit 4 and Visit 6/Early Withdrawal visit.

The MARS-A is a 10-item questionnaire where medication use is rated on a 5-point Likert scale (1 indicating ‘always’ to 5 indicating ‘never’). It has been validated as a self-reported measure of adherence with ICS for subjects with asthma and includes generic (“I use it regularly every day”) and lung condition-specific questions about medication use (“I only use it when I feel breathless”) [Cohen, 2009]. There is no specified timeframe on which responses should be based.

The Investigator should ensure the subject completes the MARS-A at the same time at the specified visits and before any study procedures. The MARS have no specified timeframe on which responses should be based.

Patient Satisfaction and Preference Questionnaire (PASAP-Q)

The Patient Satisfaction and Preference Questionnaire (PASAP-Q) [Kozma, 2005], is a multi-item measure of respiratory inhalation device satisfaction and preference designed to be easily understood and administered to patients with asthma and COPD. Patient satisfaction with each device and device preference will be assessed at Visit 4/ Early Withdrawal visit.

The Investigator should ensure the subject completes the PASAP-Q at the same time at the specified visits and before any study procedures. The PASAP-Q has no specified timeframe on which responses should be based.

12.4. Appendix 4: Liver Chemistry Stopping and Follow-up Criteria

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase III-IV liver chemistry stopping criteria and required follow up assessments

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 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 • Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is**	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for pharmacokinetic (PK) analysis, obtained within after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN

granted (refer to Appendix 4) • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Obtain complete blood count with differential 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 **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • 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 subject 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 subjects 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
5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].

6. PK sample may not be required for subjects 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 subject'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 subject safety. • Subject can continue study treatment • Subject 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 subject 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 subjects twice monthly until liver chemistries normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

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.

12.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.5.1. Definition of Adverse Events and ADRs

Adverse Event and ADRs Definition:
An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The definition of an ADR is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, for which there is a reasonable possibility that the untoward occurrence is causally related to the medicinal product. ADRs are a subset of AEs for a given medicinal product. 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 medicinal product.

Events <u>meeting</u> AE definition include:
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. 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 prior to the start of the study. Signs, symptoms, or the clinical sequelae of a suspected 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 this is an intentional overdose taken with possible suicidal/self-harming intent. This 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. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events NOT meeting definition of an AE include:
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 subject'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 subject's condition. Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. Situations where 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.

12.5.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 hospitalization or prolongation of existing hospitalization NOTE: In general, hospitalization signifies that the subject 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 out-patient setting. Complications that occur during hospitalization are AEs. 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 disability/incapacity NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere 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 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are 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
g) Is associated with liver injury <u>and</u> impaired liver function defined as: ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.
Refer to Appendix 4 for the required liver chemistry follow-up instructions

12.5.3. 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

12.5.4. Recording of AEs (ADRs) and SAEs

AEs and SAE Recording:
When an AE (ADRs) /SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE (ADRs) /SAE in the CRF It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE (ADRs) /SAE CRF page. There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE (ADRs) /SAE and not the individual signs/symptoms. Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE (ADRs) data are independent components of the study. Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer. The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE (ADRs) is inappropriate.

12.5.5. Evaluating AEs (ADRs) and SAEs

Assessment of Intensity

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

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities

Severe: An event that prevents normal everyday activities. - an AE (ADRs) that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs (ADRs) and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.

A "reasonable possibility" is meant to convey that there are facts/evidence 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 natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.

The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of 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 when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**

The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. If a subject 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 the designated reporting time frames.

12.5.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the SAE coordinator Site will enter the serious adverse event data into the electronic system as soon as it becomes available. The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) 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 subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the SAE coordinator by telephone. Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.6. Appendix 6: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;
- Asthma susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 2 ml saliva sample will be taken for Deoxyribonucleic acid (DNA) extraction. A saliva sample is collected at the baseline visit (Visit 2), after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the saliva sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The saliva sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or “coded”) with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the

subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any saliva being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample

reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.7. Appendix 7: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of foetal 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 5. 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 subject who becomes pregnant while participating

- will be withdrawn from the study
- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner’s pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.

Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

12.8. Appendix 8: Protocol Changes

Protocol Changes for Amendment 1 (14AUG2015) from Original Protocol (27FEB2015)

This protocol amendment has been created to correct mistakes in the wording of the inhaler errors questionnaires for the ELLIPTA™, DISKUS™ and Turbuhaler inhalers, which are included in Section 7.3.1 of the protocol. All references to 'Type A errors' and 'overall errors' within the protocol, have been changed to 'critical' and 'non-critical' errors, respectively for consistency with the inhaler errors questionnaire worksheets.

Storage condition instructions for Seretide (fluticasone propionate/salmeterol) in Section 6.7 have been amended. Section 6.7 of the protocol states that the storage conditions of Seretide (fluticasone propionate/salmeterol) must be stored at temperatures up to 30°C. At the point at which the protocol was approved it was intended that Seretide commercial stock would be provided for use in this study. However, due to labelling requirements this was not possible and the clinical trial image needed to be used instead. All Seretide (fluticasone propionate/salmeterol) DPIs should be stored at temperatures between 2-25°C.

The wording for the recommended number of spirometry efforts has been revised.

New text has been included with regards to investigational product malfunction in Section 6.8.

The secondary medical monitor contact information has been revised to include a new study physician.

Other minor corrections and edits have been made.

Method of Amendment

Original and amended texts are specified as follows:

Original text: as written in the original protocol

Revised text: as written in Amendment No. 01 with revisions in bold font.

Protocol synopsis for study HZA116492 and Section 3: Secondary Objectives and Endpoints

Original table:

Secondary	
• To assess effect of FF/VI on asthma control compared with usual ICS/LABA fixed combination at Week 24 (Visit 6).	• Change from baseline in ACT score at Week 24 (Visit 6).

Secondary	
• To assess ELLIPTA™ inhaler correct use compared with other DPI (Diskus™ and Turbuhaler) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).	• Percentage of subjects making at least 1 Type A error (likely to be critical) and overall errors at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).
Other	
• To assess effect of FF/VI on trough (pre-dose) FEV1 compared with usual ICS/LABA fixed combination at Week 12 (Visit 4)	Change from baseline in trough (pre-dose) FEV1 at Week 12 (Visit 4).
To assess the effect of FF/VI on response to treatment at Week 12 (Visit 4) and Week 24 (Visit 6)	ACT score ≥ 20 or 3 point increase from baseline in ACT at Week 12 (Visit 4) and Week 24 (Visit 6). Note: A 3 point increase in ACT total score was suggested as the Minimal Clinically Important Difference (MCID) in the literature [Schatz, 2009].
To assess the adherence with study medication at Week 12 (Visit 4) and Week 24 (Visit 6)	• Number of medications dispensed and collected during the study at Week12 (Visit 4) and Week 24 (Visit 6), • Score of the MARS-A questionnaire (Medication Adherence Report Scale) at the randomisation (Day0), Week12 (Visit 4) and Week24 (Visit 6).
To assess the effect of FF/VI on severe asthma exacerbation over the study period	Number of subject with at least 1 severe asthma exacerbation*, number of severe asthma exacerbation and annual severe exacerbation rate over the study period.
To assess the effect of FF/VI on Health Related Quality of Life at Week 24 (Visit 6)	Change from baseline in total score and domain scores of AQLQ(S) (Asthma Quality of Life Questionnaire) at Week 24 (Visit 6). An increase from baseline of ≥ 0.5 in AQLQ(s) total score at Week 24 (Visit 6). An increase from baseline of ≥ 0.5 in AQLQ(s) environmental stimuli domain

Secondary	
To assess Patient Satisfaction and Preference assessment with different inhalers at Week 12 (Visit 4) To evaluate the Safety of FF/VI compared with usual ICS/LABA (FP/S and Bud/F).	score at Week 24 (Visit 6). Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) Individual domain scores at Week 24 (Visit 6). Change from baseline in total score and domain scores of AQLQ(S) at Week 24 (Visit 6). Health status using the EuroQol Questionnaire (EQ-5D) at Week 24 (Visit 6). Score of PASAP Questionnaire (Patient Satisfaction and Preference) at Week 12 (Visit 4). Serious Adverse Events (SAE) and non-serious Adverse Drug Reactions (ADR): Frequency and type of serious adverse events, Frequency and type of non-serious adverse drug reactions related to treatment.

Revised table:

Secondary	
• To assess effect of FF/VI on asthma control compared with usual ICS/LABA fixed combination at Week 24 (Visit 6). • To assess ELLIPTA™ inhaler correct use compared with other DPI (Diskus™ and Turbuhaler) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).	• Change from baseline in ACT score at Week 24 (Visit 6). • Percentage of subjects making at least 1 **critical error and non-critical error** at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).
Other	
• To assess effect of FF/VI on trough (pre-	Change from baseline in trough (pre-dose)

Secondary	
dose) FEV1 compared with usual ICS/LABA fixed combination at Week 12 (Visit 4)	FEV1 at Week 12 (Visit 4).
To assess the effect of FF/VI on response to treatment at Week 12 (Visit 4) and Week 24 (Visit 6)	ACT score ≥ 20 or 3 point increase from baseline in ACT at Week 12 (Visit 4) and Week 24 (Visit 6). Note: A 3 point increase in ACT total score was suggested as the Minimal Clinically Important Difference (MCID) in the literature [Schatz, 2009]. **ACT score ≥ 20 at Week 12 (Visit 4) and Week 24 (Visit 6).** **Change from baseline in individual question scores for ACT at Weeks 12, 24**
To assess the adherence with study medication at Week 12 (Visit 4) and Week 24 (Visit 6)	• Number of medications dispensed and collected during the study at Week12 (Visit 4) and Week 24 (Visit 6), • Score of the MARS-A questionnaire (Medication Adherence Report Scale) at the randomisation (Day0), Week12 (Visit 4) and Week24 (Visit 6).
To assess the effect of FF/VI on severe asthma exacerbation over the study period	Number of subject with at least 1 severe asthma exacerbation*, number of severe asthma exacerbation and annual severe exacerbation rate over the study period.
To assess the effect of FF/VI on Health Related Quality of Life at Week 24 (Visit 6)	Change from baseline in total score and domain scores of AQLQ(S) (Asthma Quality of Life Questionnaire) at Week 24 (Visit 6). An increase from baseline of ≥ 0.5 in AQLQ(s) total score at Week 24 (Visit 6). An increase from baseline of ≥ 0.5 in AQLQ(s) environmental stimuli domain score at Week 24 (Visit 6).

Secondary	
To assess Patient Satisfaction and Preference assessment with different inhalers at Week 12 (Visit 4) To evaluate the Safety of FF/VI compared with usual ICS/LABA (FP/S and Bud/F).	Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) Individual domain scores at Week 24 (Visit 6). Change from baseline in total score and domain scores of AQLQ(S) at Week 24 (Visit 6). Health status using the EuroQol Questionnaire (EQ-5D) at Week 24 (Visit 6). Score of PASAP Questionnaire (Patient Satisfaction and Preference) at Week 12 (Visit 4). Serious Adverse Events (SAE) and non-serious Adverse Drug Reactions (ADR): Frequency and type of serious adverse events, Frequency and type of non-serious adverse drug reactions related to treatment.

Protocol synopsis for study HZA116492: Overall Design

Original text:

In addition, each subject whose FF/VI (Ellipta™) for asthma maintenance therapy is initiated at Visit 2 will be asked to read the information leaflet and will be instructed by the investigator on the proper use of Ellipta™. Each subject whose usual ICS/LABA DPI (Diskus™ or Turbuhaler) for asthma maintenance therapy is initiated at Visit 2 will follow the same procedure: reading of the information leaflet, demonstration of the proper use of the inhalers by the Investigator, and the correct dosing. This will be followed by an inhalation demonstration by the patient. Any mistakes (Type A errors, corresponding to critical errors) and overall errors will be registered by the Investigator. For the definition of Type A errors and overall errors see Section 7.3.1

Randomisation at this visit will be performed on a 1:1 basis; to the FF/VI fixed dose combination delivered via Ellipta™ or the initiation with usual ICS/LABA inhalation powder for asthma maintenance therapy.

At Week 6 (Visit 3) and at Week 18 (Visit 5) subjects will be telephoned to enquire about whether the subject has experienced any serious adverse events or non serious adverse drug reactions. At these telephone calls subjects will also be asked to complete the ACT questionnaire (paper version) and to send it back to the Investigator.

Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation Visit). Subjects will be asked to withhold from taking study medication on the day of Visit 4. At this visit, subjects will be asked to provide responses to the ACT, MARS-A and PASAP questionnaires and the inhaler use will be assessed by recording Type A errors and overall errors following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. At this visit, a trough (pre-dose) FEV1 will be assessed by the Investigator using a spirometer provided by GSK and subjects will also be interviewed about whether the subject has experienced any serious adverse events or non –serious adverse drug reactions. Female subjects of child bearing potential will also be reminded about the requirement for contraception throughout their study participation.

The final Visit 6 will occur at Week 24. The ACT, AQLQ(S), EQ-5D and MARS-A questionnaires will be conducted at this visit and Type A errors and overall errors with inhaler will be recorded following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. At this visit, subjects will also be interviewed about whether they had experienced any serious adverse events or non –serious adverse drug reactions. The Investigator will be asked to make every effort to schedule Visit 6 at the same time of the day as Visit 2.

Revised text:

In addition, each subject whose FF/VI (Ellipta™) for asthma maintenance therapy is initiated at Visit 2 will be asked to read the information leaflet and will be instructed by the investigator on the proper use of Ellipta™. Each subject whose usual ICS/LABA DPI (Diskus™ or Turbuhaler) for asthma maintenance therapy is initiated at Visit 2 will follow the same procedure: reading of the information leaflet, demonstration of the proper use of the inhalers by the Investigator, and the correct dosing. This will be followed by an inhalation demonstration by the patient. **Any critical error (defined as an error that is most likely to result in no or only minimal medication being inhaled) and/or non-critical error** will be registered by the Investigator.

Randomisation at this visit will be performed on a 1:1 basis; to the FF/VI fixed dose combination delivered via Ellipta™ or the initiation with usual ICS/LABA inhalation powder for asthma maintenance therapy.

At Week 6 (Visit 3) and at Week 18 (Visit 5) subjects will be telephoned to enquire about whether the subject has experienced any serious adverse events or non serious adverse drug reactions. At these telephone calls subjects will also be asked to complete the ACT questionnaire (paper version) and to send it back to the Investigator.

Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation Visit). Subjects will be asked to withhold from taking study medication on the day of Visit 4. At this visit, subjects will be asked to provide responses to the ACT, MARS-A and PASAP questionnaires and the inhaler use will be assessed by recording **critical and non-critical** errors following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. At this visit, a trough (pre-dose) FEV1 will be assessed by the Investigator using a spirometer provided by GSK and subjects will also be interviewed about whether the subject has experienced any serious adverse events or non –serious adverse drug reactions. Female subjects of child bearing potential will also be reminded about the requirement for contraception throughout their study participation.

The final Visit 6 will occur at Week 24. The ACT, AQLQ(S), EQ-5D and MARS-A questionnaires will be conducted at this visit and **critical and non-critical errors** with inhaler will be recorded following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. At this visit, subjects will also be interviewed about whether they had experienced any serious adverse events or non –serious adverse drug reactions. The Investigator will be asked to make every effort to schedule Visit 6 at the same time of the day as Visit 2.

Protocol synopsis for study HZA116492: Analysis

Original text:

The primary endpoint is defined as the change from baseline in the ACT total score assessed at Week 12 (Visit 4). The primary set of analysis is the ITT set.

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

Revised text:

The primary endpoint is defined as the change from baseline in the ACT total score assessed at Week 12 (Visit 4). The primary set of analysis is the ITT set.

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

Even though this study is open-label, the team will explore ways to ensure study blind is maintained during reviews of the data and pre-programming, prior to database lock. More information will be provided in the RAP.

Section 4.1 – Overall Design: Screening, randomisation and follow-up

Original text:

At the Screening Visit 1, eligible subjects will be consented to participate to the trial and prescribed the necessary examinations. The subjects will be asked to provide responses to the ACT. A screening log will be performed at this visit.

At a further visit (i.e V2, Day 0) occurring within 1 week after the screening visit (V1), subjects who meet all of the Inclusion Criteria, none of the Exclusion Criteria and who accept to give their consent will be randomised in the study. Randomisation at this visit will be on a 1:1 basis, to the FF/VI fixed dose combination delivered by Ellipta™ or to the initiation of any usual ICS/LABA DPI for asthma maintenance therapy chosen by the physician. Visit 1 and Visit 2 can be combined, if the subject did not take his usual asthma medication before coming on site. If Visit 1 and Visit 2 are combined then this visit will be Day 0.

At Visit 2 (Randomisation visit, Day 0) baseline pre-dose FEV1 will be assessed by the Investigator using a spirometer provided by GSK. At least three valid assessments should be performed with registration of the best value. On the morning of Visit 2 subjects will not take their usual asthma medication. Rescue medication (salbutamol) will be stopped 4 hours before baseline spirometry.

In addition at Visit 2, subjects will be asked to read the written Ellipta™ package insert if randomised into the FF/VI arm, or Diskus™ or Turbuhaler if randomised in the usual ICS/LABA therapy arm and will be instructed by the investigator on the proper use of inhalers. Then the subject will self-administer their first dose of study drug under supervision of the investigator. Any mistakes (Type A errors, likely to be critical and overall errors) will be registered by the trained HCP. After completing the procedure, subjects will be instructed in the correct use of the device by the trained physician if needed. Thereafter, each subject randomised into the FF/VI arm will be instructed to self-administer one inhalation with Ellipta™ inhaler each day at the same time of the day, at a time that is convenient for the subject. Subject randomised into usual ICS/LABA therapy arm will be instructed to self-administer the inhalation with Diskus™ or Turbuhaler inhaler twice a day.

Subjects will be recommended to use Salbutamol as needed throughout the study for relief of their asthma symptoms. At Visit 2 (randomisation, Day 0) subject will be asked to provide responses to the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires.

At Week 6 (Visit 3) and at Week 18 (Visit 5), subjects will be telephoned by the Investigator to enquire about whether the subject has experienced any adverse events (only the serious adverse events or non–serious adverse drug reactions will be recorded in eCRF). The Investigator makes the judgment as to whether it is related or not to study treatment. At these telephone calls, subjects will also be asked to complete the ACT questionnaire (paper version) and to send it back to the Investigator.

Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation Visit). Subjects will be asked to withhold from taking study medication on the day of Visit 4. At this visit, subjects will be asked to provide responses to the ACT, MARS-A

and PASAP questionnaires and the inhaler use will be assessed by recording Type A errors and overall errors following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. Pre-dose trough FEV1 will be assessed at this visit by the Investigator using the spirometer provided by GSK. Rescue medication (salbutamol) will be stopped 4 hours before the spirometry. At least three valid assessments should be performed with registration of the best value. At this visit, subjects will also be interviewed by the Investigator about whether the subject has experienced any adverse events (only the serious adverse events or non–serious adverse drug reactions will be recorded in eCRF). The Investigator makes the judgment as to whether it is related or not to study treatment. Female subjects of child bearing potential will also be reminded about the requirement for contraception throughout their study participation.

The final Visit 6 will occur at Week 24. The ACT, AQLQ(S), EQ-5D and MARS-A questionnaires will be conducted at this visit and the inhaler use will be assessed by recording Type A errors and overall errors following the next procedure: self-administration of one dose of study drug by subject; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. Subjects will be interviewed about whether the subject has experienced any serious adverse events or non –serious adverse drug reactions. The Investigator will be asked to make every effort to schedule Visit 6 at the same time of the day as Visit 2.

Revised text:

At the Screening Visit 1, eligible subjects will be consented to participate to the trial and prescribed the necessary examinations. The subjects will be asked to provide responses to the ACT. A screening log will be performed at this visit.

At a further visit (i.e V2, Day 0) occurring within 1 week after the screening visit (V1), subjects who meet all of the Inclusion Criteria, none of the Exclusion Criteria and who accept to give their consent will be randomised in the study. Randomisation at this visit will be on a 1:1 basis, to the FF/VI fixed dose combination delivered by Ellipta™ or to the initiation of **the** usual ICS/LABA DPI for asthma maintenance therapy chosen by the physician. Visit 1 and Visit 2 can be combined, if the subject did not take his usual asthma medication before coming on site. If Visit 1 and Visit 2 are combined then this visit will be Day 0.

At Visit 2 (Randomisation visit, Day 0) baseline pre-dose FEV1 will be assessed by the Investigator using a spirometer provided by GSK. At least three assessments should be performed with registration of the best value. **At least two of the spirometry efforts should be acceptable and repeatable.** On the morning of Visit 2 subjects will not take their usual asthma medication. Rescue medication (salbutamol) will be stopped 4 hours before baseline spirometry.

In addition at Visit 2, subjects will be asked to read the written Ellipta™ package insert if randomised into the FF/VI arm, or Diskus™ or Turbuhaler if randomised in the usual ICS/LABA therapy arm and will be instructed by the investigator on the proper use of inhalers. Then the subject will self-administer their first dose of study drug under

supervision of the investigator. Any **critical error (defined as an error that is most likely to result in no or only minimal medication being inhaled) or non-critical error** will be registered by the trained HCP. After completing the procedure, subjects will be instructed in the correct use of the device by the trained physician if needed. Thereafter, each subject randomised into the FF/VI arm will be instructed to self-administer one inhalation with Ellipta™ inhaler each day at the same time of the day, at a time that is convenient for the subject. Subject randomised into usual ICS/LABA therapy arm will be instructed to self-administer the inhalation with Diskus™ or Turbuhaler inhaler twice a day.

Subjects will be recommended to use Salbutamol as needed throughout the study for relief of their asthma symptoms. At Visit 2 (randomisation, Day 0) subject will be asked to provide responses to the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires.

At Week 6 (Visit 3) and at Week 18 (Visit 5), subjects will be telephoned by the Investigator to enquire about whether the subject has experienced any adverse events (only the serious adverse events or non–serious adverse drug reactions will be recorded in eCRF). The Investigator makes the judgment as to whether it is related or not to study treatment. At these telephone calls, subjects will also be asked to complete the ACT questionnaire (paper version) and to send it back to the Investigator.

Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation Visit). Subjects will be asked to withhold from taking study medication on the day of Visit 4. At this visit, subjects will be asked to provide responses to the ACT, MARS-A and PASAP questionnaires and the inhaler use will be assessed by recording **critical and non-critical** errors following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. Pre-dose trough FEV1 will be assessed at this visit by the Investigator using the spirometer provided by GSK. Rescue medication (salbutamol) will be stopped 4 hours before the spirometry. At least three valid assessments should be performed with registration of the best value. At this visit, subjects will also be interviewed by the Investigator about whether the subject has experienced any adverse events (only the serious adverse events or non–serious adverse drug reactions will be recorded in eCRF). The Investigator makes the judgment as to whether it is related or not to study treatment. Female subjects of child bearing potential will also be reminded about the requirement for contraception throughout their study participation.

The final Visit 6 will occur at Week 24. The ACT, AQLQ(S), EQ-5D and MARS-A questionnaires will be conducted at this visit and the inhaler use will be assessed by recording **critical and non-critical** errors following the next procedure: self-administration of one dose of study drug by subject; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. Subjects will be interviewed about whether the subject has experienced any serious adverse events or non –serious adverse drug reactions. The Investigator will be asked to make every effort to schedule Visit 6 at the same time of the day as Visit 2.

Section 4.1 – Overall Design: Collected data

Original text:

Eligible subjects will complete the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires at Randomisation Visit (Visit 2, Day 0) and at Visit 6 (Week 24), or at the Early Withdrawal visit. ACT questionnaire will be completed also by the subject at Screening visit (Visit 1), Week 6 (phone call 1 or Visit 3), at Week 12 (Visit 4) and Week 18 (phone call 2 or Visit 5). MARS-A questionnaire will be completed also at Week 12 (Visit 4). Inhaler use assessment will be performed at Randomisation Visit (Visit 2, Day 0), at Week 12 (Visit 4) and at Week 24 (Visit 6) / Early Withdrawal visit by recording the Type A errors and the overall errors. Patient's satisfaction and preference (PASAP-Q) will be evaluated at Week 12 (Visit 4).

Revised text:

Eligible subjects will complete the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires at Randomisation Visit (Visit 2, Day 0) and at Visit 6 (Week 24), or at the Early Withdrawal visit. ACT questionnaire will be completed also by the subject at Screening visit (Visit 1), Week 6 (phone call 1 or Visit 3), at Week 12 (Visit 4) and Week 18 (phone call 2 or Visit 5). MARS-A questionnaire will be completed also at Week 12 (Visit 4). Inhaler use assessment will be performed at Randomisation Visit (Visit 2, Day 0), at Week 12 (Visit 4) and at Week 24 (Visit 6) / Early Withdrawal visit by recording the **critical and non-critical** errors. Patient's satisfaction and preference (PASAP-Q) will be evaluated at Week 12 (Visit 4).

Section 4.3 – Type and Number of Subjects

Original text:

Subjects with documented physician's diagnosis of asthma ≥ 1 year, unsatisfactorily controlled asthma (ACT < 20) treated by ICS alone and intended to be treated by ICS/LABA maintenance therapy. A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.

It is estimated that approximately 70 study centers in France will be required to have a total number of 422 randomised subjects so that at least 382 subjects will be evaluable. Assuming a 10% of screen failure, 466 subjects will have to be screened in the study with 6 subjects /center.

Revised text:

Subjects with documented physician's diagnosis of asthma ≥ 1 year, unsatisfactorily controlled asthma (ACT < 20) treated by ICS alone and intended to be treated by ICS/LABA maintenance therapy. A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.

It is estimated that approximately 70 study centers in France will be required to have a total number of 422 randomised subjects so that at least 382 subjects will be evaluable. Assuming a 10% screen failure **rate**, **approximately** 466 subjects will have to be screened in the study with 6 subjects /center.

Section 4.6.1 – Risk Assessment

Original text:

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Hypersensitivity	The reported hypersensitivity events in clinical trials, were not generally serious, did not lead to discontinuation in the studies, and were usually confounded, by either the subject's medical condition (such as COPD) or other factors at the time of the event. In spontaneous data, symptoms of hypersensitivity ranged from mild rash and pruritis to severe generalised rash and erythema and severe cases involving angiodema of the face, larynx and pharynx. These events were rare.	Subjects with a history of adverse reaction including immediate or delayed hypersensitivity to any intranasal, inhaled, or systemic corticosteroid and LABA therapy and to components of the inhalation powder (e.g., lactose, magnesium stearate). In addition, subjects with a history of severe milk protein allergy that, in the opinion of the Investigator, contraindicates the subject's participation will also be excluded.

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Systemic effects of corticosteroids: adrenal suppression; eye disorders; decreased bone density and associated fractures	Adrenal suppression is a known class effect of corticosteroids. Preclinical studies showed that FF effects are comparable with other corticosteroids. No studies have shown a clinically relevant effect of FF/VI on the hypothalamic pituitary axis (HPA). This includes a formal HPA study (HZA106851), using 24 hour serum cortisol measurements, and multiple studies with COPD and asthma subjects which monitored urinary cortisol. During clinical development, no events of Adrenal Suppression were reported. Eye disorders are a known class effect of corticosteroids. Preclinical studies showed FF at high dose comparable to other high dose corticosteroids. In study HZA106839 (FF/VI , FF and FP in subjects with asthma), formal ophthalmic assessments were conducted (including LOCS III evaluations for ocular opacities) throughout the study. This study showed no apparent effects on lens opacification, compared to baseline. During studies in both subjects with asthma and COPD, no associated affect on ocular disorders	The mitigation in this study for all systemic effects of corticosteroids is that chronic users of systemic corticosteroids are excluded from this study: a subject who, in the opinion of the Investigator, is considered to be a chronic user of systemic corticosteroids for respiratory or other indications (if unsure discuss with the medical monitor prior to screening).

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	was observed. Decreased bone density is a down class effect of corticosteroids. Preclinical data showed that high dose corticosteroid effects of FF were comparable to other conrticosteroids. Patients with Asthma In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of fractures with FF/VI was <=1%, and usually associated with trauma.	

Revised text:

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Hypersensitivity	The reported hypersensitivity events in clinical trials, were not generally serious, did not lead to discontinuation in the studies, and were usually confounded, by either the subject's medical condition (such as COPD) or other factors at the time of the event. In spontaneous data, symptoms of hypersensitivity ranged from mild rash and pruritis	Subjects with a history of adverse reaction including immediate or delayed hypersensitivity to any intranasal, inhaled, or systemic corticosteroid and LABA therapy and to components of the inhalation powder (e.g., lactose, magnesium stearate) **will be excluded**. In addition, subjects with a history of severe milk protein allergy that, in the opinion of the Investigator, contraindicates the subject's

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	to severe generalised rash and erythema and severe cases involving angiodema of the face, larynx and pharynx. These events were rare.	participation will also be excluded.
Systemic effects of corticosteroids: adrenal suppression; eye disorders; decreased bone density and associated fractures	Adrenal suppression is a known class effect of corticosteroids. Preclinical studies showed that FF effects are comparable with other corticosteroids. No studies have shown a clinically relevant effect of FF/VI on the hypothalamic pituitary axis (HPA). This includes a formal HPA study (HZA106851), using 24 hour serum cortisol measurements, and multiple studies with COPD and asthma subjects which monitored urinary cortisol. During clinical development, no events of Adrenal Suppression were reported. Eye disorders are a known class effect of corticosteroids. Preclinical studies showed FF at high dose comparable to other high dose corticosteroids. In study HZA106839 (FF/VI , FF and FP in subjects with asthma), formal ophthalmic assessments were conducted (including LOCS III evaluations for ocular	The mitigation in this study for all systemic effects of corticosteroids is that chronic users of systemic corticosteroids are excluded from this study: a subject who, in the opinion of the Investigator, is considered to be a chronic user of systemic corticosteroids for respiratory or other indications (if unsure discuss with the medical monitor prior to screening) **will be excluded**.

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	opacities) throughout the study. This study showed no apparent effects on lens opacification, compared to baseline. During studies in both subjects with asthma and COPD, no associated affect on ocular disorders was observed. Decreased bone density is a **known** class effect of corticosteroids. Preclinical data showed that high dose corticosteroid effects of FF were comparable to other conrticosteroids. Patients with Asthma In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of fractures with FF/VI was <=1%, and usually associated with trauma.	

Section 5.3 – Screening/Baseline/Failures

Original text:

A total of 466 subjects will be screened as 422 subjects are planned to be randomised and 10% of screen failure is expected.

Revised text:

Approximately 466 subjects will be screened as 422 subjects are planned to be randomised and **a** 10% of screen failure **rate** is expected.

Section 6.7 – Preparation/Handling/Storage/Accountability

Original text:

All FF/VI and comparative ICS/LABA maintenance therapy prescribed throughout the study will be dispensed at, and collected from the investigator site.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. All DPIs containing FF/VI must be stored at a temperature of up to 25°C. Budesonide/Formoterol and Fluticasone Propionate/Salmeterol DPIs must be stored at a temperature of up to 30°C.

Revised text:

All FF/VI and comparative ICS/LABA maintenance therapy prescribed throughout the study will be dispensed at, and collected from the investigator site.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. All DPIs containing FF/VI must be stored at a temperature of up to 25°C. Budesonide/Formoterol DPIs must be stored at a temperature of up to 30°C **and Fluticasone Propionate/Salmeterol DPIs stored at 2-25°C**.

Section 6.7 – Investigational Product Malfunction

New Text:

Any investigational product inhaler that fails to function properly must be identified to GSK personnel. Details of the failure will be documented in the eCRF. Ellipta inhalers will be returned to GSK for testing. The subject should return the inhaler to the clinic as soon as possible to avoid missing any doses. The site will then contact GSK's internal IWRS (also known as the Registration and Medication Ordering System [RAMOS] NG) and obtain a new treatment pack number for this subject and dispense a new study medication kit from the site's investigational product supply, as instructed per the IWRS.

Section 7.1 – Time and Events Table

Original table:

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

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

* Visit 1 and Visit 2 can be combined if the subject did not take his usual asthma medication before coming on site. Then this visit will be Day 0 and all baseline characteristics will be collected at this visit. Written Informed Consent must be obtained prior to initiation of study procedures or initiating changes in medications.
** Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation visit).
***PGx saliva sample collected at Visit 2 (Randomisation) or any scheduled clinic visit thereafter.
**** Only if early withdrawal occurs before Week 12.
¥ Only for childbearing women.

Revised table:

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

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

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

* Visit 1 and Visit 2 can be combined if the subject did not take his usual asthma medication before coming on site. Then this visit will be Day 0 and all baseline characteristics will be collected at this visit. Written Informed Consent must be obtained prior to initiation of study procedures or initiating changes in medications.
** Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation visit).
***PGx saliva sample collected at Visit 2 (Randomisation) or any scheduled clinic visit thereafter.
**** Only if early withdrawal occurs before Week 12.
¥ Only for childbearing women.
Note: All adverse events will be recorded in the source documents but only information regarding non-serious adverse drug reactions (ADRs) and serious adverse events (SAEs) will be documented and reported in the eCRF.

Section 7.3.1: Inhaler Correct Use Assessment

Original text:

Correct use of the inhaler will be assessed as outlined in the Time and Events Table (Section 7.1).

Table 6 List of Type A (likely to be critical) and overall errors for Ellipta™

Type A errors for Ellipta™	**yes**	**no**	**Overall errors for Ellipta™**	**yes**	**no**
Failed to open cover			No exhalation before an inhaling		
Exhaled directly into mouthpiece			Blocked air inlet during inhalation manoeuvre		
Shook the device upside down after dose preparation			Inhalation manoeuvre: - long - steady		

Type A errors for Ellipta™	**yes**	**no**	**Overall errors for Ellipta™**	**yes**	**no**
			- deep		
Inhalation from mouthpiece (kept between lips)			Blocked air inlet during inhalation manoeuvre		
			Did not hold breath		
			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
			Any other comments: [free text box]		

Table 7 List Type A (likely to be critical) and overall errors for Diskus™

Type A errors for Diskus™	**yes**	**no**	**Overall errors for Diskus™**	**yes**	**no**
Failed to open cover			No exhalation before an inhalation		
Lever is not pushed back			Inhalation manoeuvre: - steady - deep		
Exhaled directly into mouthpiece			Did not hold breath		
No seal by the lips round the mouthpiece during the inhalation			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
			Any other comments: [free text box]		

Table 8 List of Type A (likely to be critical) errors and overall errors for Turbuhaler

Type A errors for Turbuhaler	**yes**	**no**	**Overall errors for Turbuhaler**	**yes**	**no**
Failed to remove cap			No exhalation before an inhalation		
Did not hold device upright (±45% OK) during dose preparation			Inhalation manoeuvre: - forceful - deep Note to *HCP: it is important that the inhalation is forceful*		

Type A errors for Turbuhaler	**yes**	**no**	**Overall errors for Turbuhaler**	**yes**	**no**
			and deep from the start for this inhaler		
Base not twisted fully backwards and forwards, no click heard			Blocked air inlet during inhalation manoeuvre		
Shook the device after dose preparation			Did not hold breath		
Exhaled directly into mouthpiece			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
No seal by the lips round the mouthpiece during the inhalation			Any other comments: [free text box]		

Revised text:

Correct use of the inhaler will be assessed as outlined in the Time and Events Table (Section 7.1).

Table 9 Critical and Non-critical errors for Ellipta™

Instructions: Critical Errors are identified in bold text in the list below. A critical error is defined as an error that is most likely to result in no or only minimal medication being inhaled. Check only one box.					
Did the subject make an error while using the device? [ ] No [ ]Yes if yes, tick appropriate options below					
Critical Errors for Ellipta™	**yes**	**no**	**Non-critical Errors for Ellipta™**	**yes**	**no**
Failed to open cover			No exhalation before an inhalation		
Shook the device upside down after dose preparation			Inhalation manoeuvre was not: - long - steady - deep		
Exhaled directly into mouthpiece			Blocked air inlet during inhalation manoeuvre -		
No seal by the lips around the			Did not hold breath		

mouthpiece during the inhalation					
			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
Any other comments: [free text box]					

Table 10 Critical and Non-critical errors for Diskus™

Instructions: Critical Errors are identified in bold text in the list below. A critical error is defined as an error that is most likely to result in no or only minimal medication being inhaled. Check only one box.					
Did the subject make an error while using the device? [ ] No [ ]Yes if yes, tick appropriate options below					
Critical Errors for Diskus™	**yes**	**no**	**Non-critical Errors for Diskus™**	**yes**	**no**
Failed to open cover			No exhalation before an inhalation		
Lever is not pushed back			Inhalation manoeuvre was not: - steady - deep		
Shook the device after dose preparation			Did not hold breath		
Exhaled directly into mouthpiece			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
No seal by the lips round the mouthpiece during the inhalation					
Any other comments: [free text box]					

Table 11 Critical and Non-critical errors for Turbuhaler

Instructions: Critical Errors are identified in **bold text** in the list below. A critical error is defined as an error that is most likely to result in no or only minimal medication being inhaled. Check only one box.					
Did the subject make an error while using the device? [ ] No [ ]Yes *if yes, tick appropriate options below*					
Critical Errors for Turbuhaler	**yes**	**no**	**Non-critical Errors for Turbuhaler**	**yes**	**no**
Failed to remove cap			Device tipped downwards after dose preparation		
Did not hold device upright (±45% OK) during dose preparation			No exhalation before an inhalation		
Base not twisted fully backwards and forwards, no click heard			Inhalation manoeuvre was not: - forceful - deep Note to *HCP: it is important that the inhalation is forceful and deep from the start for this inhaler*		
Shook the device after dose preparation			Blocked air inlet during inhalation manoeuvre		
Exhaled directly into mouthpiece			Did not hold breath		
No seal by the lips round the mouthpiece during the inhalation			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
Any other comments: [free text box]					

Section 7.3.2: Trough (pre-dose) FEV1 assessment

Original text:

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

Revised text:

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

Section 7.4.7: Clinical Safety Laboratory Assessment

Original text:

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the Investigator are to be recorded as non-serious ADRs or SAEs as appropriate.

Revised text:

There are no clinical safety laboratory assessment requirements for this study.

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) **recorded during a routine clinic visit**, including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the Investigator are to be recorded as non-serious ADRs or SAEs as appropriate.

Section 9.3.1 – Analysis Population

Original text:

Populations considered for analysis are as follows:

Intent to treat (ITT) set: All randomized subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy). The ITT set will be used to analyze the primary efficacy endpoint analysis, the secondary efficacy endpoint and other efficacy endpoints. Subjects will be assigned to the treatment group as randomized for the ITT set.

Per-protocol (PP) set: all ITT subjects without any major violations of study procedures. Major protocol violations will be identified prior to database lock. Protocol deviations

will be reviewed and classified as minor or major during a data review meeting that will be held before database lock. The exclusion of subjects from the PP set will be specified and documented in the RAP.

Safety set: All enrolled subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy) and considered as-treated. The Safety set will be the basis for safety analyses. Subjects will be assigned to the treatment group as treated for the Safety set.

Revised text:

Populations considered for analysis are as follows:

Intent to treat (ITT) population: All randomized subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy). The ITT **population** will be used to analyze the primary efficacy endpoint analysis, the secondary efficacy endpoint and other efficacy endpoints. Subjects will be assigned to the treatment group as randomized for the ITT **population**.

Per-protocol (PP) population: all ITT subjects without any major violations of study procedures. Major protocol violations will be identified prior to database lock. Protocol deviations will be reviewed and classified as minor or major during a data review meeting that will be held before database lock. The exclusion of subjects from the PP **population** will be specified and documented in the RAP.

Safety population: All enrolled subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy) and considered as-treated. The Safety **population** will be the basis for safety analyses. Subjects will be assigned to the treatment group as treated for the Safety **population**.

Section 9.4 – Key Elements of Analysis Plan

Original text:

The primary comparison of interest is the comparison of the change from baseline (Visit 2) in the total ACT score assessed at Week 12 (Visit 4) between FF/VI (92mcg/22mcg or 184mcg/22mcg) and usual ICS/LABA inhalation powder for asthma maintenance therapy.

The primary set for analysis is the intent to treat set. A sensitivity analysis will be performed in the PP set.

Revised text:

The primary comparison of interest is the comparison of the change from baseline (Visit 2) in the total ACT score assessed at Week 12 (Visit 4) between FF/VI (92mcg/22mcg or

184mcg/22mcg) and usual ICS/LABA inhalation powder for asthma maintenance therapy.

The primary set for analysis **will be performed on** the intent to treat **population**. A sensitivity analysis will be performed in the PP **population**.

Section 9.4.1 – Primary Analysis

Original text:

The primary endpoint is defined as the change from baseline (Visit 2) in the ACT total score assessed at Week 12 (Visit 4).

The primary set of analysis is the ITT set.

1) **Non-inferiority testing.**

The non-inferiority of FF/VI versus any other ICS/LABA DPI comparator will be primarily tested in a mixed model repeated measures (MMRM) approach. The model will include factors and covariates as follow: treatment, scheduled visit time point (Week 6 and Week 12), baseline ACT, treatment by visit interaction, baseline ACT by visit interaction, gender, age and patient will be fitted as a random factor. The Restricted Maximum Likelihood (REML) estimation approach will be used, and the default covariance structure will be unstructured. Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point will be performed. The 95% confidence interval on the treatment effect (FF/VI vs ICS/LABA comparator) will be estimated at Week 12 (Visit 4) in this model. Non-inferiority will be achieved if the non-inferiority margin of -1.5 is lower than the lower bound of the confidence interval on the difference between FF/VI and any other comparator (positive values of the difference favour FF/VI).

Sensitivity analyses:

e) Handling missing data

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

1. Missing values at Week 12 (Visit 4) will be replaced by the post-randomization last available value (either the week 6-based ACT score or the ACT score at treatment withdrawal time, if any), i.e. based on the Last Observation Carried Forward method. The change from baseline in ACT at Week 12 (Visit 4) will be analyzed in an ANCOVA model adjusting for treatment and baseline ACT score. The treatment effect (FF/VI versus any

other ICS/LABA comparator) and its corresponding 95% confidence interval will be estimated in this model to test the non-inferiority hypothesis.

2. Multiple imputation (MI) analyses utilizing covariates known to be predictive of response: season at randomization, observed value of ACT at Week 6, observed value of ACT at Week 12 (Visit 4). Other covariates may be considered and if so it will be detailed in the RAP.

   Step 1: For each treatment group separately, missing measurements are imputed for subjects with a baseline measurement where there are missing observations (at either Week 6 or Week 12) using the above covariates and regression-based imputation method. The Markov Chain Monte Carlo (MCMC) method for MI will be used and ten such sets of imputed data will be created each with the observed values or imputed values for subjects with missing observations.

   Step 2: Each imputed data set will be analyzed using the primary MMRM model. The treatment effect from these 10 analyses will then be pooled using standard MI theory to make an overall inference. The difference in the least squares means between the two groups at Week 12 (Visit 4) and the corresponding 95% confidence interval for the difference will be presented.

f) A sensitivity analysis based on the semi parametric Hodges-Lehmann (HL) approach will be proposed to assess the robustness of the MMRM Model-based non-inferiority results. The HL difference between groups with the corresponding 95% confidence interval will be provided.

g) Sensitivity analyses for handling treatment withdrawal: when treatment withdrawal occurs, an alternative method for imputing the missing value at the nearest visit after withdrawal time will be proposed: the primary endpoint missing value will be estimated by the worst ACT score observed between baseline visit (included) and withdrawal time (included).

h) The primary analysis (i.e. based on the MMRM approach) and the same sensitivity analyses presented here above will be performed in the Per Protocol set.

Revised text:

The primary endpoint is defined as the change from baseline (Visit 2) in the ACT total score assessed at Week 12 (Visit 4).

The primary **population** of analysis **will be** the ITT **population**.

1) Non-inferiority testing.

The non-inferiority of FF/VI versus any other ICS/LABA DPI comparator will be primarily tested in a mixed model repeated measures (MMRM) approach. The model will include factors and covariates as follow: treatment, scheduled visit time point (Week 6 and Week 12), baseline ACT, treatment by visit interaction, baseline ACT by visit

interaction, gender, age and patient will be fitted as a random factor. The Restricted Maximum Likelihood (REML) estimation approach will be used, and the default covariance structure will be unstructured. Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point will be performed. The 95% confidence interval on the treatment effect (FF/VI vs ICS/LABA comparator) will be estimated at Week 12 (Visit 4) in this model. Non-inferiority will be achieved if the non-inferiority margin of -1.5 is lower than the lower bound of the confidence interval on the difference between FF/VI and any other comparator (positive values of the difference favour FF/VI).

Sensitivity analyses:

i) Handling missing data

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

3. Missing values at Week 12 (Visit 4) will be replaced by the post-randomization last available value (either the week 6-based ACT score or the ACT score at treatment withdrawal time, if any), i.e. based on the Last Observation Carried Forward method. The change from baseline in ACT at Week 12 (Visit 4) will be analyzed in an ANCOVA model adjusting for treatment and baseline ACT score. The treatment effect (FF/VI versus any other ICS/LABA comparator) and its corresponding 95% confidence interval will be estimated in this model to test the non-inferiority hypothesis.

4. Multiple imputation (MI) analyses utilizing covariates known to be predictive of response: season at randomization, observed value of ACT at Week 6, observed value of ACT at Week 12 (Visit 4). Other covariates may be considered and if so it will be detailed in the RAP.

   Step 1: For each treatment group separately, missing measurements are imputed for subjects with a baseline measurement where there are missing observations (at either Week 6 or Week 12) using the above covariates and regression-based imputation method. The Markov Chain Monte Carlo (MCMC) method for MI will be used and ten such sets of imputed data will be created each with the observed values or imputed values for subjects with missing observations.

   Step 2: Each imputed data set will be analyzed using the primary MMRM model. The treatment effect from these 10 analyses will then be pooled using standard MI theory to make an overall inference. The difference in the least squares means between the two groups at Week 12 (Visit 4) and the corresponding 95% confidence interval for the difference will be presented.

j) A sensitivity analysis based on the semi parametric Hodges-Lehmann (HL) approach will be proposed to assess the robustness of the MMRM Model-based non-inferiority results. The HL difference between groups with the corresponding 95% confidence interval will be provided.

k) Sensitivity analyses for handling treatment withdrawal: when treatment withdrawal occurs, an alternative method for imputing the missing value at the nearest visit after withdrawal time will be proposed: the primary endpoint missing value will be estimated by the worst ACT score observed between baseline visit (included) and withdrawal time (included).

l) The primary analysis (i.e. based on the MMRM approach) and the same sensitivity analyses presented here above will be performed **on** the Per Protocol **population**.

Section 9.4.2 – Secondary Analyses: Other Secondary Analyses

Original text:

Proper use of the medical device

The other key secondary endpoint will be the correct use of the inhaler device assessed at randomisation (Visit 2), at Week 12 (Visit 4) and at Week 24 (Visit 6). The device will be considered as adequately used if the patient didn't make any Type A error (all critical items correct) at the corresponding visits (randomisation [Visit 2], week 12 [Visit 4] and week 24 [Visit 6]). Proportions of subjects correctly using the device will be estimated within each group. A corresponding 95% confidence interval of the difference in proportions will also be provided. Additional exploratory analyses could be performed and will be detailed in the RAP. Even if tests will be performed, no causal association will be inferred from these analyses.

Revised text:

Proper use of the medical device

The other key secondary endpoint will be the correct use of the inhaler device assessed at randomisation (Visit 2), at Week 12 (Visit 4) and at Week 24 (Visit 6). The device will be considered as adequately used if the patient didn't make any **critical error** at the corresponding visits (randomisation [Visit 2], week 12 [Visit 4] and week 24 [Visit 6]). Proportions of subjects correctly using the device will be estimated within each group. A corresponding 95% confidence interval of the difference in proportions will also be provided. Additional exploratory analyses could be performed and will be detailed in the RAP. Even if tests will be performed, no causal association will be inferred from these analyses.

Section 9.4.3 – Other Analyses: Change from baseline in pre-dose trough FEV1

Original text:

The analysis of the other endpoints defined in this section will be provided for exploratory purposes only. Additional exploratory analyses could be performed and will be detailed in the RAP. Even if tests will be performed and 95% confidence intervals will be provided, no causal association will be inferred from these analyses.

Change from baseline in pre-dose trough FEV1

Results will be summarized for each group and the results of the difference between groups will be presented with the corresponding 95% confidence interval at Week 12 (Visit 4).

Response to treatment

- Binary response defined as an ACT score ≥ 20 at a given visit OR a 3 point increase from baseline in ACT change.

The responder analyses will be conducted using a logistic regression model at a given Visit or Phone Call adjusting for treatment and stratification factors (baseline ACT score categorized into two classes, baseline asthma therapy, and potentially season at randomization). Treatment by stratification factors interaction effects will be further investigated in additional logistic models adjusting for these specific effects.

Revised text:

The analysis of the other endpoints defined in this section will be provided for exploratory purposes only. Additional exploratory analyses could be performed and will be detailed in the RAP. Even if tests will be performed and 95% confidence intervals will be provided, no causal association will be inferred from these analyses.

Change from baseline in pre-dose trough FEV1

Results will be summarized for each group at Week 12 (Visit 4). **More detail will be provided in the RAP.**

Response to treatment

- Binary response defined as an ACT score ≥ 20 at a given visit OR a 3 point increase from baseline in ACT change.

The responder analyses will be conducted using a logistic regression model at a given Visit or Phone Call adjusting for treatment and stratification factors (baseline ACT score categorized into two classes, baseline asthma therapy, and potentially season at randomization). Treatment by stratification factors interaction effects will be further investigated in additional logistic models adjusting for these specific effects.

- **Binary response defined as an ACT score ≥ 20 at a given visit.**

The frequency and the percentage of subjects with ACT score ≥ 20 at a given visit will be described by treatment group. More detail will be provided in the RAP.

- **Change from baseline in individual question scores for ACT at a given visit**

For each question the statistical parameters of the changes will be summarized by treatment group. More detail will be provided in the RAP.

Protocol Changes for Amendment 2 (28-APR-2016) from Amendment 1 (14AUG2015)

This amendment has been written to allow the addition of a new country/countries to the study, and to clarify text to make the intention of the protocol more clear. Changes are to text are listed in this appendix.

In addition minor administrative updates have been made. These will not be listed below but include:

- Reference to Study Reference Manual (SRM) in place of Study Procedures Manual (SPM)
- Adding trademark (™) where applicable
- Amending text to make language more generic to cover participation outside of France
- Other minor corrections to text

Where the Amendment Applies

Amendment 2 is applicable to all investigator sites.

Method of Amendment

Original and revised texts are specified as follows:

Original text: as written in the original protocol

Revised text: as written in Amendment No. 02 with revisions in ~~strikethrough~~ (deleted text) and **bold font** or **bold underline** (additional text).

Title Page and Sponsor Signatory Page

Updated to reflect current authors and signatory.

Section 1 Protocol Synopsis for Study HZA116492

Original Text:

Objective(s)/Endpoint(s)

Objectives	Endpoints
Secondary	
• To assess ELLIPTA™ inhaler correct use compared with other DPI (Diskus™ and	• Percentage of subjects making at least 1 critical error and non-critical error at

Objectives	Endpoints
Turbuhaler) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).	Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).
Other	
To assess the adherence with study medication at Week 12 (Visit 4) and Week 24 (Visit 6)	• Number of medications dispensed and collected during the study at Week12 (Visit 4) and Week 24 (Visit 6), • Score of the MARS-A questionnaire (Medication Adherence Report Scale) at the randomisation (Day0), Week12 (Visit 4) and Week24 (Visit 6).

Text changed to:

Objective(s)/Endpoint(s)

Objectives	Endpoints
Secondary	
• To assess ELLIPTA inhaler correct use compared with other DPI (Diskus and Turbuhaler) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).	• Percentage of subjects **with correct use of device (defined as not making any critical error or non-critical error)** ~~making at least 1 critical error and non-critical error~~ at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).
Other	
To assess the ~~adherence~~ **compliance** with study medication **and self-reported adherence to study medication** at Week 12 (Visit 4) and Week 24 (Visit 6)	~~• Number of medications dispensed and collected during the study at Week12 (Visit 4) and Week 24 (Visit 6),~~ • **Compliance with study medication from randomisation (Day 0) to Week 12 (Visit 4), from Week 12 (Visit 4) to Week 24 (Visit 6) and from randomisation (Day 0) to Week 24 (Visit 6).** • Score of the MARS-A questionnaire (Medication Adherence Report Scale **for Asthma**) at the randomisation (Day0), Week12 (Visit 4) and Week24 (Visit 6).

Rationale for Change:

Correction to the definition of Inhaler Correct Use and replacement of Adherence with Compliance in line with the data being collected and the analyses planned.

Section 1 Protocol Synopsis for Study HZA116492

Original text:

Type and Number of Subjects

A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.

It is estimated that approximately 70 study centers in France will be required to have a total number of 422 randomised subjects so that at least 382 subjects will be evaluable. Assuming a 10% screen failure rate, approximately 466 subjects will have to be screened in the study iwth 6 subjects/center.

Text changed to:

France Only: A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.

It is estimated that approximately ~~70~~ **100** study centers ~~in France~~ will be required to have a total number of 422 randomised subjects so that at least 382 subjects will be evaluable. Assuming a 10% screen failure rate, approximately 466 subjects will have to be screened ~~in the study with 6 subjects/center~~.

Rationale for Change:

Updated to reflect the addition of another country/countries to the study

Section 2.1 Study Rationale

Original text:

Inhaled corticosteroids (ICS) are considered the most effective anti-inflammatory treatments for all severities of persistent asthma. This open-label randomised clinical study will evaluate the efficacy and safety of fluticasone furoate (FF)/vilanterol (VI) Inhalation Powder compared with existing fixed combinations ICS/LABA (Inhaled Corticosteroids/Long Acting Beta Agonists) inhalation powders.

Text changed to:

Inhaled corticosteroids (ICS) are considered the most effective anti-inflammatory treatments for all severities of persistent asthma. This open-label randomised clinical study will evaluate the efficacy and safety of fluticasone furoate (FF)/vilanterol (VI) Inhalation Powder compared with **nominated** existing fixed combinations ICS/LABA (Inhaled Corticosteroids/Long Acting Beta Agonists) inhalation powders.

Rationale for Change:

Updated to recognise the fact that other countries have other ICS/LABA combinations but only nominated combinations will be permitted in the study to reflect those available in France.

Section 3 Objective(s) and Endpoints

Original Text:

Objective(s)/Endpoint(s)

Objectives	Endpoints
Secondary	
• To assess ELLIPTA™ inhaler correct use compared with other DPI (Diskus™ and Turbuhaler) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).	• Percentage of subjects making at least 1 critical error and non-critical error at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).
Other	
To assess the adherence with study medication at Week 12 (Visit 4) and Week 24 (Visit 6)	• Number of medications dispensed and collected during the study at Week12 (Visit 4) and Week 24 (Visit 6), • Score of the MARS-A questionnaire (Medication Adherence Report Scale) at the randomisation (Day0), Week12 (Visit 4) and Week24 (Visit 6).

Text changed to:

Objective(s)/Endpoint(s)

Objectives	Endpoints
Secondary	
• To assess ELLIPTA inhaler correct use compared with other DPI (Diskus and Turbuhaler) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).	• Percentage of subjects **with correct use of device (defined as not making any critical error or non-critical error)** ~~making at least 1 critical error and non-critical error~~ at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).
Other	
To assess the ~~adherence~~ **compliance** with study medication **and self-reported**	~~• Number of medications dispensed and collected during the study at Week12~~

Objectives	Endpoints
adherence to study medication at Week 12 (Visit 4) and Week 24 (Visit 6)	~~(Visit 4) and Week 24 (Visit 6),~~ • **Compliance with study medication from randomisation (Day 0) to Week 12 (Visit 4), from Week 12 (Visit 4) to Week 24 (Visit 6) and from randomisation (Day 0) to Week 24 (Visit 6).** • Score of the MARS-A questionnaire (Medication Adherence Report Scale **for Asthma**) at the randomisation (Day0), Week12 (Visit 4) and Week24 (Visit 6).

Rationale for Change:

Correction to the definition of 'Correct Use' and replacement of Adherence with Compliance in line with the data being collected and the analyses planned.

Section 4.1 Overall Design

Added Text:

Note: To maintain consistency across countries the choice of usual inhaled dry powder ICS/LABA fixed combination will be limited to Seretide/Viani Diskus (FP/S 250mcg/50mcg or 500mcg/50mcg) or Symbicort Turbohaler (BUD/F 200mcg/6mcg or 400mcg/12mcg). Some countries have other ICS/LABA fixed combinations and other generic versions of FP/S and BUD/F available for the treatment of patients with asthma, but these will not be permitted in this study. Additionally some countries have options for a lower dose of Viani Diskus (FP/S 100mcg/50mcg) and Symbicort Turbohaler (BUD/F 100mcg/6mcg) but these will not be permitted in this study.

Rationale for Change:

Updated to recognise the fact that other countries have other ICS/LABA combinations but only nominated combinations will be permitted in the study to reflect those available in France.

Section 4.1 Overall Design

Added Text:

Patients who fail screening may be rescreened only upon approval by the medical monitor.

Rationale for Change:

To formalise the option to rescreen patients as per Study Reference Manual.

Section 4.3 Type and Number of Subjects

Original text:

A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.

It is estimated that approximately 70 study centers in France will be required to have a total number of 422 randomised subjects so that at least 382 subjects will be evaluable

Assuming a 10% screen failure rate, approximately 466 subjects will have to be screened in the study with 6 subjects/center.

Text changed to:

France only: A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.

It is estimated that approximately ~~70~~ **100** study centers ~~in France~~ will be required to have a total number of 422 randomised subjects so that at least 382 subjects will be evaluable

Assuming a 10% screen failure rate, approximately 466 subjects will have to be screened in the study~~ with 6 subjects/center~~.

Rationale for Change:

Updated to reflect the addition of another country/countries to the study.

Section 5.2 Exclusion Criteria

Original text:

2. Subjects having a severe and unstable asthma, with ACT score < 15 at Visit 1 and at Visit 2, history of repeated severe exacerbations (3/year) and/or a severe exacerbation in the previous 6 weeks before Visit 1 and Visit 2.

Text changed to:

2. Subjects having a severe and unstable asthma, with ACT score < 15 at Visit 1 and at Visit 2, **and/or a** history of repeated severe exacerbations (3/year) and/or a severe exacerbation in the previous 6 weeks before Visit 1 and Visit 2.

Rationale for Change:

To clarify the intent of this exclusion criteria.

Section 5.2 Exclusion Criteria

Original text:

9. Subjects treated by the monoclonal antibody omalizumab (Xolair) at Visit 1. Treatment with Xolair is not allowed during the study.

Text changed to:

9. Subjects treated by the monoclonal antibody omalizumab (Xolair) or mepolizumab (Nucala™) at Visit 1. Treatment with Xolair or **Nucala** is not allowed during the study.

Rationale for Change:

Mepolizumab (Nucala) is a new licensed treatment that should be excluded.

Section 5.3 Screening/Baseline/Failures

Added Text:

Patients that fail screening may be rescreened only upon approval by the medical monitor.

Rationale for Change:

To formalise the option to rescreen patients as per Study Reference Manual.

Section 6.1 Investigational Product and Other Study Treatment

Original text:

GlaxoSmithKline Clinical Trials Supplies will provide the investigational products (FF/VI: Relvar™ Ellipta™ and comparative treatments, i.e. Seretide™ Diskus™, Symbicort™ Turbuhaler) as well as rescue medication (Salbutamol) for use in this study.

New ICS/LABA DPI or DPI copies of existing marketed ICS/LABA if any in France at the time of the study will not be considered in this trial.

Each subject randomised to the FF/VI arm will be instructed to administer the study medication once daily (by reading the leaflet and demonstration of it use), at the same time of the day, for the duration of the treatment period. Each subject will be advised to adhere to FF/VI dosing regimen throughout the study. The investigator may adjust the dose of FF/VI according to the subjects' response starting with FF/VI 92mcg/22mcg.

Each subject initiating other ICS/LABA maintenance therapy will be reminded about the techniques of how to use their maintenance medication (by reading the leaflet and demonstration of it use) and the correct dosing. Each subject will be advised to adhere to ICS/LABA dosing regimen throughout the study, starting by FP/S 250mcg/50mcg or by

BUD/F 200mcg /6mcg according to the Investigator's decision. The Investigator may adjust the dose of each product according to the subjects' response.

Text changed to:

GlaxoSmithKline Clinical Trials Supplies will provide the investigational products (FF/VI: Relvar Ellipta and comparative treatments, i.e. Seretide Diskus, Symbicort Turbuhaler)**.** ~~as well as r~~**R**escue medication (Salbutamol) ~~for use in this study~~ **will be provided locally by GSK in each country**.

New ICS/LABA DPI or DPI copies of existing marketed ICS/LABA if any ~~in France~~ at the time of the study will not be considered in this trial.

Each subject randomised to the FF/VI arm will be instructed to administer the study medication once daily (by reading the leaflet and demonstration of it use), at the same time of the day, for the duration of the treatment period. Each subject will be advised to adhere to FF/VI dosing regimen throughout the study **starting with FF/VI 92mcg/22mcg**. The investigator **or appropriately qualified designee** may ~~adjust~~ **increase** the dose of FF/VI according to the subjects' response.~~ starting with FF/VI 92mcg/22mcg~~.

Each subject initiating other ICS/LABA maintenance therapy will be reminded about the techniques of how to use their maintenance medication (by reading the leaflet and demonstration of it use) and the correct dosing. Each subject will be advised to adhere to ICS/LABA dosing regimen throughout the study, starting ~~by~~ **with** FP/S 250mcg/50mcg or ~~by~~ **with** BUD/F 200mcg /6mcg according to the Investigator's decision. The Investigator may ~~adjust~~ **increase** the dose of each product according to the subjects' response.

Rationale for Change:

To clarify the starting dose and the option only to increase the dose of study medication.

Section 6.3 Treatment Assignment

Original text:

Subjects will be randomized (1:1) to one of the following treatment groups:

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

Text changed to:

Subjects will be randomized (1:1) to one of the following treatment groups:

- FF/VI (as per dose guidance below)

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

Note: To maintain consistency across countries the choice of usual inhaled dry powder ICS/LABA fixed combination will be limited to Seretide/Viani Diskus (FP/S 250mcg/50mcg or 500mcg/50mcg) or Symbicort Turbohaler (BUD/F 200mcg/6mcg or 400mcg/12mcg). Some countries have other ICS/LABA fixed combinations and other generic versions of FP/S and BUD/F available for the treatment of patients with asthma, but these will not be permitted in this study. Additionally some countries have options for a lower dose of Viani Diskus (FP/S 100mcg/50mcg) and Symbicort Turbohaler (BUD/F 100mcg/6mcg) but these will not be permitted in this study.

Rationale for Change:

Updated to recognise the fact that other countries have other ICS/LABA combinations but only nominated combinations will be permitted in the study to reflect those available in France.

Section 6.4 Planned Dose Adjustments

Original text:

Subjects randomised to the usual ICS/LABA asthma maintenance therapy arm can have their treatment adjusted as would be normal clinical practice at the Investigator's discretion. This will not require the subject to be withdrawn from the study. These subjects should not receive FF/VI, if the medication is marketed during the study period.

Subjects randomized to the FF/VI arm and for whom it is considered appropriate/ necessary to adjust treatment, can have their regimen changed as required as per normal clinical practice at any point in the study and the subject could remain in the study. Subjects on FF/VI arm can also change between the two FF/VI doses as appropriate and at the Investigator's discretion.

Text changed to:

Subjects **for whom it is considered appropriate/necessary to adjust treatment** ~~randomised to the usual ICS/LABA asthma maintenance therapy arm~~ can have their ~~treatment adjusted~~ **dose increased from the starting dose** as would be normal clinical practice at the Investigator's discretion. This will not require the subject to be withdrawn from the study. ~~These subjects should not receive FF/VI, if the medication is marketed during the study period.~~

~~Subjects randomized to the FF/VI arm and for whom it is considered appropriate/ necessary to adjust treatment, can have their regimen changed as required as per normal clinical practice at any point in the study and the subject could remain in the study. Subjects on FF/VI arm can also change between the two FF/VI doses as appropriate and at the Investigator's discretion.~~

It is not permitted for patients to be switched to a different treatment i.e. patients randomised to the usual ICS/LABA arm cannot change to a different ICS/LABA or receive FF/VI. Patients randomised to the FF/VI arm cannot receive usual ICS/LABA. If a switch between products is required the patient should be withdrawn from the study.

Rationale for Change:

Text adjusted to clarify that dose increases are permitted but switching treatments is not.

Section 6.9 Compliance with Study Treatment Administration

Original Text:

Treatment adherence with study medication will be assessed based on analysis of medications (dispensed and collected) during the study and on Medication Adherence Report Scale for Asthma (MARS-A) questionnaire at randomisation Day 0, at Week 12 and at Week 24.

Text changed to:

Overall ~~T~~treatment ~~adherence~~ **compliance** with study medication will be ~~assessed~~ **calculated for each type of inhaler separately as**

$$\textbf{Overall Compliance (\%)} = \left(\frac{\textbf{Total number of inhalations taken}}{\textbf{Expected Inhalations} \times (\textbf{Stop date} - \textbf{Start date} + \mathbf{1})}\right) \times \mathbf{100}$$

- **Total number of inhalations taken is the total number of doses taken from all inhalers during the time period (as assessed from dose counter data collected on the eCRF)**
- **Expected Inhalations is the expected number of inhalations per day (1 for Ellipta™, 2 for Diskus™ and 2 or 4 for Turbuhaler™ depending on the dose)**
- **Start date and Stop date are the earliest treatment start date and the latest treatment stop date respectively for all inhalers used in the calculation.**

Treatment compliance will be assessed for the period from randomisation (Day 0) until Week 12 (Visit 4), from Week 12 (Visit 4) until Week 24 (Visit 6) and also overall from randomisation (Day 0) until Week 24 (Visit 6).

Subject's self-reported adherence to medication will be evaluated based on analysis of ~~and on~~ Medication Adherence Report Scale for Asthma (MARS-A) questionnaire**s** at randomisation Day 0, at Week 12 and at Week 24.

Rationale for Change:

Replacement of the term Adherence with the term Compliance in line with the data being collected and the analyses planned. A description of how this will be assessed has been added.

Section 6.11 Treatment after the End of the Study

Original text:

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

Text changed to:

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition**.** ~~whether or not~~ GSK ~~is providing specific~~ **will not provide** post study treatment.

Rationale for Change:

Clarification that GSK will not provide post study treatment.

Section 6.12.2 Prohibited Medications and Non-Drug Therapies

Original text:

- **Systemic corticosteroids**, except in case of a severe asthma exacerbation.
- **Monoclonal antibody omalizumab (Xolair).**

Text changed to:

- **Systemic corticosteroids**, except in case of a severe asthma exacerbation.
- **Monoclonal antibodies omalizumab (Xolair) and mepolizumab (Nucala).**

Rationale for Change:

Mepolizumab (Nucala) is a new licensed treatment that should be prohibited.

Section 7.1 Time and Events Table (Header row & Footnote)

Original text:

Study Visits	Visit 1* Screening	Visit 2* Randomisation	Visit 3 Phone call 1	Visit 4**	Visit 5 Phone call 2	Visit 6	Early Withdrawal

Text changed to:

Study Visits	Visit 1* Screening#	Visit 2* Randomisation	Visit 3 Phone call 1	Visit 4**	Visit 5 Phone call 2	Visit 6	Early Withdrawal

Patients that fail screening may be rescreened only upon approval by the medical monitor

Rationale for Change:

To formalise the option to rescreen patients as per Study Reference Manual.

Section 7.1 Time and Events Table (RAMOS NG Row and Footnote)

Original text:

Study Visits	Visit 1* Screening	Visit 2* Randomisation	Visit 3 Phone call 1	Visit 4**	Visit 5 Phone call 2	Visit 6	Early Withdrawal
Study week (± specified no. of days)	Day -7 to -1	Day 0	Week 6 (±3 days)	Week 12 (±7 days)	Week 18 (±3 days)	Week 24 (±14 days)	Early Withdrawal
RAMOS/eCRF							
RAMOS NG		x		x			

Text changed to:

Study Visits	Visit 1* Screening	Visit 2* Randomisation	Visit 3 Phone call 1	Visit 4**	Visit 5 Phone call 2	Visit 6	Early Withdrawal
Study week (± specified no. of days)	Day -7 to -1	Day 0	Week 6 (±3 days)	Week 12 (±7 days)	Week 18 (±3 days)	Week 24 (±14 days)	Early Withdrawal
RAMOS/eCRF							
RAMOS NG	x	x		x		x	x

≠ France Only

Rationale for Change:

RAMOS NG at Screening, Visit 6 and Early Withdrawal was missed from the Time and Events Table in error.

Section 7.3.3.4 Medication Adherence Report Scale for Asthma (MARS-A)

Original Text:

Reported adherence to medication will be assessed with the Medication Adherence Report Scale for Asthma (MARS-A) questionnaire at Visit 2, Week 12 (Visit 4) and Week 24 (Visit 6) / Early Withdrawal visit.

Amended Text:

Subject's self-r~~R~~eported adherence to **study** medication will be assessed with the Medication Adherence Report Scale for Asthma (MARS-A) questionnaire at Visit 2, Week 12 (Visit 4) and Week 24 (Visit 6) / Early Withdrawal visit.

Rationale for change:

To ensure clarity that the MARS-A questionnaire is self reported adherence.

Section 9.4.2 Secondary Analyses

Original Text:

Other secondary analyses

Proper use of the medical device

The other key secondary endpoint will be the correct use of the inhaler device assessed at randomisation (Visit 2), at Week 12 (Visit 4) and at Week 24 (Visit 6). The device will be considered as adequately used if the patient didn't make any critical error at the corresponding visits (randomisation [Visit 2], week 12 [Visit 4] and week 24 [Visit 6]). Proportions of subjects correctly using the device will be estimated within each group. A corresponding 95% confidence interval of the difference in proportions will also be provided. Additional exploratory analyses could be performed and will be detailed in the RAP. Even if tests will be performed, no causal association will be inferred from these analyses.

Text changed to:

Other secondary analyses

Proper use of the medical device

The other key secondary endpoint will be the correct use of the inhaler device assessed at randomisation (Visit 2), at Week 12 (Visit 4) and at Week 24 (Visit 6). The device will be considered as adequately used if the patient didn't make any critical error **or non-critical error** at the corresponding visits (randomisation [Visit 2], week 12 [Visit 4] and week 24 [Visit 6]). ~~Proportions~~ **Percentages** of subjects correctly using the device will be ~~estimated~~ **calculated** within each group. A corresponding 95% confidence interval of the

difference in ~~proportions~~ **percentages** will also be provided. **Furthermore, the percentage of subjects with overall error, at least one critical error, and at least one non-critical error will be presented by treatment group, along with the percentage making each specific error.** Additional exploratory analyses could be performed and will be detailed in the RAP. Even if tests will be performed, no causal association will be inferred from these analyses.

Rationale for Change:

Clarification of analyses for 'Inhaler Correct Use' assessment.

Section 9.4.3 Other Analyses

Original Text:

Adherence with study medication

- Number of percentage of medications (dispensed and collected) during the study will be tabulated for each visit and by treatment group.
- The score for Medication Adherence Report Scale for Asthma (MARS-A) at Day0, Week 12 and Week 24 will be described by treatment group.

Text changed to:

~~Adherence~~ Compliance with study medication and self-reported adherence to study medication

- ~~Number of percentage of medications (dispensed and collected) during the study will be tabulated for each visit and by treatment group.~~
- **Overall treatment compliance with study medication from randomisation (Day 0) to Week 12 (Visit 4), from Week 12 (Visit 4) to Week 24 (Visit 6) and from randomisation (Day 0) to Week 24 (Visit 6) will be described by treatment group.**
- The score for Medication Adherence Report Scale for Asthma (MARS-A) at Day0, Week 12 and Week 24 will be described by treatment group.

Rationale for change:

Replacement of the term Adherence with the term Compliance in line with the data being collected and the analyses planned.

Section 9.3.1 Analysis Populations

Original text:

Per-protocol (PP) population: all ITT subjects without any major violations of study procedures. Major protocol violations will be identified prior to database lock. Protocol deviations will be reviewed and classified as minor or major during a data review meeting that will be held before database lock. The exclusion of subjects from the PP population will be specified and documented in the RAP.

Text changed to:

Per-protocol (PP) population: ~~all~~ ITT subjects without any **protocol deviations specifically defined in the RAP** ~~major violations of study procedures. Major protocol violations will be identified prior to database lock.~~
Protocol deviations will be reviewed and **will be** classified as ~~minor or major~~ **important or not important** during ~~a~~ data review meeting**s** that will be held before database lock. ~~The exclusion of subjects from the PP population will be specified and documented in the RAP.~~ **Deviations classified as important will be further defined according to whether they require the patient to be excluded from the PP population. Deviations that would exclude a patient from the PP population will be defined in the RAP.**

Rationale for Change:

Updated to reflect correct terminology.

Appendix 1: Abbreviation and Trademarks

Original text:

Trademarks of the GlaxoSmithKline group of companies
DISKUS
ELLIPTA
RELVAR
SERETIDE
TURBUHALER

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

Text changed to:

Trademarks of the GlaxoSmithKline group of companies
DISKUS
ELLIPTA
NUCALA
RELVAR
SERETIDE
VIANI
~~TURBUHALER~~

Trademarks not owned by the GlaxoSmithKline group of companies
ACT
Asthma Quality of Life Questionnaire - AQLQ(S)
EQ-5D
MARS-A questionnaire
PASAP Questionnaire
Symbicort Turbuhaler
XOLAIR
TURBUHALER[1]
TURBOHALER[1]

1. Turbuhaler and Turbohaler are both trade names for the inhaler device used for Symbicort. They are used interchangeably in this document.

Rationale for Change:

Trade names outside of France and trade name for mepolizumab added.

TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A 6-month, open label, randomised, efficacy study to evaluate fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) Inhalation Powder delivered once daily via the Dry Powder Inhaler Ellipta™ compared with usual ICS/LABA maintenance therapy delivered by Dry Powder Inhaler in subjects with Persistent Asthma

Compound Number: GW685698+GW642444

Development Phase: IIIB

Effective Date: 14-AUG-2015

Protocol Amendment Number: 01

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N190259_00	2015-FEB-27	Original
2014N190259_01	2015-AUG-14	Amendment No. 1

This protocol amendment has been created to correct mistakes in the wording of the inhaler errors questionnaires for the Ellipta™, Diskus™ and Turbuhaler inhalers, which are included in Section 7.3.1 of the protocol. All references to 'Type A errors' and 'overall errors' within the protocol, have been changed to 'critical' and 'non-critical' errors, respectively, for consistency with the inhaler errors questionnaire worksheets.

Storage condition instructions for Seretide (fluticasone propionate/salmeterol) in Section 6.7 have been amended.

The wording for the recommended number of spirometry efforts has been revised.

New text has been included with regards to investigational product malfunction in Section 6.8.

The secondary medical monitor contact information has been revised to include a new study physician.

Other minor corrections and edits have been made.

SPONSOR SIGNATORY

PPD

11th August 2015

Richard Tomiak, MD Date

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MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD (Clinical Development Physician, RD Respiratory R&D)	Phone: PPD Email: PPD	PPD		GlaxoSmithKline Research & Development Limited 1-3 Iron Bridge Road, Stockley Park West, Uxbridge, Middlesex, UB11 1BT, UK
Secondary Medical Monitor	PPD PPD	Phone: PPD Email: PPD	PPD		GlaxoSmithKline Stockley Park West 1-3 Ironbridge Road Uxbridge, Middlesex, UB11 1BT
SAE coordinator	PPD PPD (OSL)	Phone : PPD Email: PPD			GSK France, 100 Route de Versailles, Marly-le-Roi, 78163, France

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Regulatory Agency Identifying Number(s): EudraCT No: 2014-000551-81

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number: HZA116492

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY HZA116492

Rationale

The pivotal phase III studies were key to demonstrate the safety and efficacy of Fluticasone Furoate/ Vilanterol in asthma. However, it is increasingly acknowledged that randomised clinical trials by definition tend to be highly controlled and enrol a more highly selected patient population than is expected to be prescribed the medication post-approval. The need for data in a more representative population in a close to 'real world' setting is increasingly being recognised as important to complement pivotal phase III safety and efficacy studies in order to establish the benefits and therefore the value of a medication in the context of clinical practice.

Moreover, double-blind comparison of once daily to twice daily medicines, while important for assessing efficacy, removes a potential source of difference in effectiveness derived from patient behaviour and experience. GlaxoSmithKline (GSK) has observed an increasing demand from payers who make reimbursement and policy decisions for data that enables the evaluation of a drug's effectiveness and impact on the health care system at launch, e.g. effectiveness data from a setting close to 'real world' in addition to traditional randomised clinical studies.

This open-label randomised clinical study will evaluate the efficacy and safety of FF/VI Inhalation Powder (FF 92mcg/VI 22mcg or FF 184mcg/VI 22mcg) compared with two fixed combinations ICS/LABA (Inhaled Corticosteroids/Long Acting Beta Agonists) inhalation powders, fluticasone propionate/salmeterol (FP/S) and budesonide/formoterol (BUD/F), for asthma maintenance therapy, in a "close to real life" manner in French primary and respiratory specialist care. FF/VI will be administered once-daily (QD) via Ellipta™ and FP/S or BUD/F twice daily (BID) via Diskus™ and Turbuhaler respectively.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To compare the efficacy of FF/VI 92mcg/ 22mcg or FF 184mcg/22mcg with usual fixed combinations ICS/LABA for asthma maintenance therapy at Week 12 (Visit 4).	• Change from baseline in the Asthma Control Test (ACT) total score at Week 12 (Visit 4).
Secondary	
• To assess effect of FF/VI on asthma control compared with usual ICS/LABA fixed combination at Week 24 (Visit 6).	• Change from baseline in ACT score at Week 24 (Visit 6).
• To assess ELLIPTA™ inhaler correct use compared with other DPI (Diskus™ and Turbuhaler) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the	• Percentage of subjects making at least 1 critical error and non-critical error at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12

Objectives	Endpoints
use at Week 12 (Visit 4).	(Visit 4).
Other	
• To assess effect of FF/VI on trough (pre-dose) FEV1 compared with usual ICS/LABA fixed combination at Week 12 (Visit 4)	• Change from baseline in trough (pre-dose) FEV1 at Week 12 (Visit 4).
• To assess the effect of FF/VI on response to treatment at Week 12 (Visit 4) and Week 24 (Visit 6)	• ACT score ≥ 20 or 3 point increase from baseline in ACT at Week 12 (Visit 4) and Week 24 (Visit 6). Note: A 3 point increase in ACT total score was suggested as the Minimal Clinically Important Difference (MCID) in the literature [Schatz, 2009]. • ACT score ≥ 20 at Week 12 (Visit 4) and Week 24 (Visit 6). • Change from baseline in individual question scores for ACT at Weeks 12, 24
• To assess the adherence with study medication at Week 12 (Visit 4) and Week 24 (Visit 6)	• Number of medications dispensed and collected during the study at Week12 (Visit 4) and Week 24 (Visit 6), • Score of the MARS-A questionnaire (Medication Adherence Report Scale) at the randomisation (Day0), Week12 (Visit 4) and Week24 (Visit 6).
• To assess the effect of FF/VI on severe asthma exacerbation over the study period	• Number of subject with at least 1 severe asthma exacerbation*, number of severe asthma exacerbation and annual severe exacerbation rate over the study period.
• To assess the effect of FF/VI on Health Related Quality of Life at Week 24 (Visit 6)	• Change from baseline in total score and domain scores of AQLQ(S) (Asthma Quality of Life Questionnaire) at Week

Objectives	Endpoints
	24 (Visit 6). • An increase from baseline of ≥ 0.5 in AQLQ(s) total score at Week 24 (Visit 6). • An increase from baseline of ≥ 0.5 in AQLQ(s) environmental stimuli domain score at Week 24 (Visit 6). • Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) Individual domain scores at Week 24 (Visit 6). • Change from baseline in total score and domain scores of AQLQ(S) at Week 24 (Visit 6). • Health status using the EuroQol Questionnaire (EQ-5D) at Week 24 (Visit 6).
• To assess Patient Satisfaction and Preference assessment with different inhalers at Week 12 (Visit 4)	• Score of PASAP Questionnaire (Patient Satisfaction and Preference) at Week 12 (Visit 4).
• To evaluate the Safety of FF/VI compared with usual ICS/LABA (FP/S and Bud/F).	Serious Adverse Events (SAE) and non-serious Adverse Drug Reactions (ADR): • Frequency and type of serious adverse events, • Frequency and type of non-serious adverse drug reactions related to treatment.

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

Notes defining endpoints:

1. Contacts with a doctor or hospitalisation are defined as exacerbation-related contacts if these contacts were a direct result of an acute worsening of asthma symptoms.
2. A prescription of systemic corticosteroid is defined as exacerbation-related if the reason the drug was given, in whole or in part, was to treat an acute worsening of asthma symptoms.

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

Overall Design

This is a Phase IIIb multi-centre, randomised open label, parallel group study performed in subjects in primary and respiratory specialist care who have a diagnosis of asthma and regular treatment for asthma in France.

Approximately 422 asthmatic subjects who are taking an inhaled corticosteroid (ICS) alone without any other controller treatment will be randomised in a 1:1 ratio to receive either FF/VI (FF/VI 92mcg/22mcg or FF/VI 184mcg/22mcg) once daily or one ICS/LABA inhalation powder twice daily for asthma maintenance therapy.

As much as possible enrolment of subjects should be performed at a constant accrual rate throughout a full year in order to minimize a seasonality bias.

Subjects will visit the HCP (general practitioner or pulmonologist) a minimum of 3 times as per protocol over a 6 month period while participating in the study. The first visit will be Visit 1 Screening Visit, which can take place between Day -7 and Day -1. At Visit 1, suitable subjects will be consented. The second visit will be Visit 2 (Day 0, Randomisation Visit) where subjects who meet all of the Inclusion Criteria and none of the Exclusion Criteria will be randomised. Visit 1 and Visit 2 can be combined, if the subject did not take his usual asthma medication before coming on site. If Visit 1 and Visit 2 are combined then this visit will be Day 0 and all baseline characteristics will be collected at this visit.

At Visit 2 (Day 0) subject will be asked to provide responses to the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires. Baseline pre-dose FEV1 will be assessed at this visit by the Investigator using a spirometer provided by GSK. At least three valid assessments should be performed with registration of the best value. On the morning of Visit 2 subjects will not take their usual asthma medication. Rescue medication (salbutamol) will be stopped 4 hours before baseline spirometry.

Subjects will self-administer their first dose of study drug in the clinic at Visit 2 (or the combined Visit 1 and Visit 2 if appropriate) under supervision of the site staff.

Thereafter, each subject randomised into the FF/VI arm will be instructed to self-administer one inhalation with Ellipta™ inhaler each day at the same time of the day, at a time that is convenient for the subject. Each subject will be advised to adhere to FF/VI dosing regimen throughout the study. The investigator may adjust the dose of FF/VI according to the subject's response. Dose adjustment is allowed and is not considered as a treatment failure in accordance with treatment failure definition.

In addition, each subject whose FF/VI (Ellipta™) for asthma maintenance therapy is initiated at Visit 2 will be asked to read the information leaflet and will be instructed by the investigator on the proper use of Ellipta™. Each subject whose usual ICS/LABA DPI (Diskus™ or Turbuhaler) for asthma maintenance therapy is initiated at Visit 2 will follow the same procedure: reading of the information leaflet, demonstration of the proper use of

the inhalers by the Investigator, and the correct dosing. This will be followed by an inhalation demonstration by the patient. Any critical error (defined as an error that is most likely to result in no or only minimal medication being inhaled) and/or non-critical error will be registered by the Investigator.

Randomisation at this visit will be performed on a 1:1 basis; to the FF/VI fixed dose combination delivered via Ellipta™ or the initiation with usual ICS/LABA inhalation powder for asthma maintenance therapy.

At Week 6 (Visit 3) and at Week 18 (Visit 5) subjects will be telephoned to enquire about whether the subject has experienced any serious adverse events or non serious adverse drug reactions. At these telephone calls subjects will also be asked to complete the ACT questionnaire (paper version) and to send it back to the Investigator.

Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation Visit). Subjects will be asked to withhold from taking study medication on the day of Visit 4. At this visit, subjects will be asked to provide responses to the ACT, MARS-A and PASAP questionnaires and the inhaler use will be assessed by recording critical and non-critical errors following the next procedure: self-administration of one dose of study drug ; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. At this visit, a trough (pre-dose) FEV1 will be assessed by the Investigator using a spirometer provided by GSK and subjects will also be interviewed about whether the subject has experienced any serious adverse events or non –serious adverse drug reactions. Female subjects of child bearing potential will also be reminded about the requirement for contraception throughout their study participation.

The final Visit 6 will occur at Week 24. The ACT, AQLQ(S), EQ-5D and MARS-A questionnaires will be conducted at this visit and critical and non-critical errors with inhaler will be recorded following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. At this visit, subjects will also be interviewed about whether they had experienced any serious adverse events or non –serious adverse drug reactions. The Investigator will be asked to make every effort to schedule Visit 6 at the same time of the day as Visit 2.

Although at least 3 formal scheduled visits and 2 phone calls are planned for this study, subjects should continue to visit their physician for any routine (naturalistic) visits as per normal clinical practice, as per the Time and Events Table. An Early Withdrawal Visit has to be considered in case of early withdrawal of the subject from the study, as per the Time and Events Table.

Treatment Arms and Duration

Two treatment arms: one FF/VI arm (FF/VI 92 mcg/22 mcg or FF/VI 184 mcg/22 mcg) once daily, and one arm ICS/LABA combination therapy in inhalation powder twice daily (FP/S 250 mcg/50 mcg or 500 mcg/50mcg, or BUD/F 200 mcg/6mcg or 400 mcg/12mcg) as decided by the physician. The total duration of subject participation will be approximately 6 months (24 weeks).

Type and Number of Subjects

Subjects with documented physician's diagnosis of asthma ≥ 1 year, unsatisfactorily controlled asthma (ACT < 20) treated by ICS alone and intended to be treated by ICS/LABA maintenance therapy. A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.

It is estimated that approximately 70 study centers in France will be required to have a total number of 422 randomised subjects so that at least 382 subjects will be evaluable. Assuming a 10% screen failure rate, approximately 466 subjects will have to be screened in the study with 6 subjects /center.

Analysis

The primary endpoint is defined as the change from baseline in the ACT total score assessed at Week 12 (Visit 4). The primary set of analysis is the ITT population.

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

Even though this study is open-label, the team will explore ways to ensure study blind is maintained during review of the data and pre-programming activities, prior to database lock. More information will be provided in the RAP.

2. INTRODUCTION

2.1. Study Rationale

Inhaled corticosteroids (ICS) are considered the most effective anti-inflammatory treatments for all severities of persistent asthma. This open-label randomised clinical study will evaluate the efficacy and safety of fluticasone furoate (FF)/vilanterol (VI) Inhalation Powder compared with existing fixed combinations ICS/LABA (Inhaled Corticosteroids/Long Acting Beta Agonists) inhalation powders.

Fluticasone furoate (FF) is a glucocorticoid developed for use as a once daily inhaled treatment for asthma. Vilanterol is an orally inhaled long-acting agonist of the $beta_2$-adrenoceptor (LABA) and has been also developed for use in combination with ICS as a once-daily maintenance treatment of asthma.

The pivotal phase III studies demonstrated the safety and efficacy of FF/ VI. However, it is increasingly acknowledged that randomised clinical trials by definition tend to be highly controlled and enrol a more highly selected patient population than is expected to be prescribed the medication post-approval. The need for data in a more representative population in close to a 'real world' setting is increasingly being recognised as important to complement pivotal phase III safety and efficacy studies in order to establish the benefits and therefore the value of a medication in the context of clinical practice. Indeed, in the close to 'real life' conditions, physicians have the ability to choose the best treatment in their view for any individual patient and adapt treatments to subjects'

characteristics and response. Thus, double-blind comparison of once daily to twice daily medicines, while important for assessing efficacy, removes a potential source of difference in effectiveness derived from patient behaviour and experience. Moreover, a head-to-head study comparing Relvar 92mcg/22mcg Ellipta™ (FF/VI) once a day vs Seretide 250mcg/50mcg Diskus™ (Fluticasone propionate/salmeterol) twice a day failed to demonstrate superiority on 24 hours weighted mean FEV1 after 6 months of treatment. However, 50% of subjects in both arms were uncontrolled (ACT score ≤ 19) at randomisation, after 4 weeks of Fluticasone propionate 250 mcg twice a day. For this sub-group of subjects, at the end of the 6 month-treatment period, 63% of subjects were controlled in the FF/VI arm vs 55% in the Seretide Diskus™ arm. The study was not powered on this criterion nor designed to include uncontrolled subjects only. Anyway, this trend justifies exploring if this difference would disappear or increase in a close to real life setting.

Subjects recruited into the study will be those currently taking an ICS alone without any other controller treatment with evidence of sub-optimal asthma control, corresponding to European Marketing Authorisation of FF/VI. These subjects will be randomised to receive FF/VI via Ellipta™ inhaler once daily or to receive usual ICS/LABA fixed combination in DPI (fluticasone propionate/salmeterol (FP/S)) via Diskus™ inhaler and budesonide/formoterol (BUD/F) via Turbuhaler twice daily for asthma maintenance therapy as per normal clinical practice. Ellipta™ is a new powder inhaler designed to be easy to use. Current powder inhalers have been associated with handling errors some of which may impact the ability of drug to reach the lung and hence impact clinical efficacy. Such errors deemed as critical will be evaluated in this study between different inhalers as well as overall inhaler preference and satisfaction.

2.2. Brief Background

Asthma is a chronic disease of the lungs characterised by airway inflammation, bronchoconstriction and increased airway responsiveness. Inhaled corticosteroids (ICS) are considered the most effective anti-inflammatory treatments for all severities of persistent asthma [GINA, 2009; NIH, 2007; British Thoracic Society, 2008]. The benefits of ICS include control of asthma symptoms, improvement in lung function, decrease in airway hyper-responsiveness and possibly, prevention of airway wall remodelling [Pedersen, 1997; Fanta, 2009].

Fluticasone furoate is a novel glucocorticoid developed for use as a once daily inhaled treatment for asthma. The drug consists of FF formulated in lactose for oral inhalation via the DPI Ellipta™. Pre-clinical data and early phase clinical studies indicate that FF has a longer duration of action than fluticasone propionate (FP) and is therefore suitable for development for once daily administration.

Vilanterol is an orally inhaled long-acting agonist of the beta$_2$-adrenoceptor (LABA) and has been developed for use in combination with ICS as a once-daily maintenance treatment of asthma. The drug consists of vilanterol formulated in lactose and magnesium stearate for oral inhalation via Ellipta™.

The combination of these two agents has been developed as a once-daily combination therapy for the long-term maintenance treatment of asthma in adults and children ≥ 12 years of age. The availability of a once-daily ICS combined with a LABA would be expected to help to improve compliance and therefore improve asthma control.

Information on the physical, chemical and pharmaceutical properties of fluticasone furoate, vilanterol, and fluticasone furoate/vilanterol may be found in SmPC or Investigator Brochure.

3. OBJECTIVE(S) AND ENDPOINT(S)

This open-label randomised clinical study will evaluate the efficacy and safety of fluticasone furoate (FF)/vilanterol (VI) Inhalation Powder (FF 92mcg/VI 22mcg or FF 184mcg/VI 22mcg) compared with existing fixed combinations ICS/LABA (Inhaled Corticosteroids/Long Acting Beta Agonists) inhalation powders, fluticasone propionate/salmeterol (FP/S) and budesonide/formoterol (BUD/F), for asthma maintenance therapy, in a "close to real life" manner in French primary and respiratory specialist care. FF/VI will be administered once-daily (QD) via Ellipta™ and FP/S or BUD/F twice daily (BID) via Diskus™ and Turbuhaler respectively.

Objectives	Endpoints
Primary	
• To compare the efficacy of FF/VI 92mcg/ 22mcg or FF 184mcg/22mcg with usual fixed combinations ICS/LABA for asthma maintenance therapy at Week 12 (Visit 4).	• Change from baseline in the Asthma Control Test (ACT) total score at Week 12 (Visit 4).
Secondary	
• To assess effect of FF/VI on asthma control compared with usual ICS/LABA fixed combination at Week 24 (Visit 6).	• Change from baseline in ACT score at Week 24 (Visit 6).
• To assess ELLIPTA™ inhaler correct use compared with other DPI (Diskus™ and Turbuhaler) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).	• Percentage of subjects making at least 1 critical error and non-critical error at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).
Other	
• To assess effect of FF/VI on pre-dose trough FEV1 compared with usual ICS/LABA fixed combination at Week	• Change from baseline in pre-dose trough FEV1 at Week 12 (Visit 4).

Objectives	Endpoints
12 (Visit 4)	
• To assess the effect of FF/VI on response to treatment at Week 12 (Visit 4) and Week 24 (Visit 6)	• ACT score ≥ 20 or 3 point increase from baseline in ACT at Week 12 (Visit 4) and Week 24 (Visit 6). Note: A 3 point increase in ACT total score was suggested as the Minimal Clinically Important Difference (MCID) in the literature [Schatz, 2009]. • ACT score ≥ 20 at Week 12 (Visit 4) and Week 24 (Visit 6). • Change from baseline in individual question scores for ACT at Weeks 12, 24
• To assess the adherence with study medication at Week 12 (Visit 4) and Week 24 (Visit 6)	• Number of medications dispensed and collected during the study at Week 12 (Visit 4) and Week 24 (Visit 6), • Score of the MARS-A questionnaire (Medication Adherence Report Scale) at the randomisation (Day0), Week12 (Visit 4) and Week24 (Visit 6).
• To assess the effect of FF/VI on severe asthma exacerbation over the study period	• Number of subject with at least 1 severe asthma exacerbation*, number of severe asthma exacerbation and annual severe exacerbation rate over the study period.
• To assess the effect of FF/VI on Health Related Quality of Life at Week 24 (Visit 6)	• Change from baseline in total score and domain scores of AQLQ(S) (Asthma Quality of Life Questionnaire) at Week 24 (Visit 6). • An increase from baseline of ≥ 0.5 in AQLQ(s) total score at Week 24 (Visit 6). • An increase from baseline of ≥ 0.5 in AQLQ(s) environmental stimuli domain score at Week 24 (Visit 6).

Objectives	Endpoints
	• Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) Individual domain scores at Week 24 (Visit 6). • Change from baseline in total score and domain scores of AQLQ(S) at Week 24 (Visit 6). • Health status using the EuroQol Questionnaire (EQ-5D) at Week 24 (Visit 6).
• To assess Patient Satisfaction and Preference assessment with different inhalers at Week 12 (Visit 4)	• Score of PASAP Questionnaire (Patient Satisfaction and Preference) at Week 12 (Visit 4).
• To evaluate the Safety of FF/VI compared with usual ICS/LABA (FP/S and Bud/F).	Serious Adverse Events (SAE) and non-serious Adverse Drug Reactions (ADR): • Frequency and type of serious adverse events, • Frequency and type of non-serious adverse drug reactions related to treatment.

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

Notes defining endpoints:

1. Contacts with a doctor or hospitalisation are defined as exacerbation-related contacts if these contacts were a direct result of an acute worsening of asthma symptoms.
2. A prescription of systemic corticosteroid is defined as exacerbation-related if the reason the drug was given, in whole or in part, was to treat an acute worsening of asthma symptoms.
3. Exacerbation-related hospitalisation includes hospitalisation that is prolonged as a result of an asthma exacerbation.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase IIIb multi-center randomised open label, parallel group study performed in subjects in French primary and respiratory care specialist who have a diagnosis of asthma and a regular treatment for persistent asthma. Subjects with unsatisfactorily controlled asthma (defined as an ACT < 20) and intended to be treated by usual ICS/LABA maintenance therapy to seek a better control of their asthma will be randomised to receive either FF/VI (FF/VI 92mcg/22mcg or FF/VI 184mcg/22mcg) once daily or another usual ICS/LABA combination therapy in inhalation powder twice daily (FP/S or BUD/F) decided by the physician. These medications are recorded in the e-CRF.

Physicians will be allowed during the treatment period to adapt prescription to different doses if necessary as well as to adapt doses of any comparative treatment according to products label. A table (Table 2, Section 6.3) of the indicative dosage equivalence between ICS and the other combination therapies will be provided to the physicians.

For Study Schematic, see Appendix 2.

Investigators

General Practitioners and pulmonologists based in France, all accredited for clinical trials by a CPP (“Comité de Protection des Personnes”) will be approached to participate in the study (approximately 80% General Practitioners, 20% pulmonologists).

Screening, randomisation and follow-up

At the Screening Visit 1, eligible subjects will be consented to participate to the trial and prescribed the necessary examinations. The subjects will be asked to provide responses to the ACT. A screening log will be performed at this visit.

At a further visit (i.e V2, Day 0) occurring within 1 week after the screening visit (V1), subjects who meet all of the Inclusion Criteria, none of the Exclusion Criteria and who accept to give their consent will be randomised in the study. Randomisation at this visit will be on a 1:1 basis, to the FF/VI fixed dose combination delivered by Ellipta™ or to the initiation of the usual ICS/LABA DPI for asthma maintenance therapy chosen by the physician. Visit 1 and Visit 2 can be combined, if the subject did not take his usual asthma medication before coming on site. If Visit 1 and Visit 2 are combined then this visit will be Day 0.

At Visit 2 (Randomisation visit, Day 0) baseline pre-dose FEV1 will be assessed by the Investigator using a spirometer provided by GSK. At least three assessments should be performed with registration of the best value. At least two of the spirometry efforts should be acceptable and repeatable. On the morning of Visit 2 subjects will not take their usual asthma medication. Rescue medication (salbutamol) will be stopped 4 hours before baseline spirometry.

In addition at Visit 2, subjects will be asked to read the written Ellipta™ package insert if randomised into the FF/VI arm, or Diskus™ or Turbuhaler if randomised in the usual ICS/LABA therapy arm and will be instructed by the investigator on the proper use of inhalers. Then the subject will self-administer their first dose of study drug under supervision of the investigator. Any critical error (defined as an error that is most likely to result in no or only minimal medication being inhaled) or non-critical error will be registered by the trained HCP. After completing the procedure, subjects will be instructed in the correct use of the device by the trained physician if needed. Thereafter, each subject randomised into the FF/VI arm will be instructed to self-administer one inhalation with Ellipta™ inhaler each day at the same time of the day, at a time that is convenient for the subject. Subject randomised into usual ICS/LABA therapy arm will be instructed to self-administer the inhalation with Diskus™ or Turbuhaler inhaler twice a day.

Subjects will be recommended to use Salbutamol as needed throughout the study for relief of their asthma symptoms. At Visit 2 (randomisation, Day 0) subject will be asked to provide responses to the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires.

At Week 6 (Visit 3) and at Week 18 (Visit 5), subjects will be telephoned by the Investigator to enquire about whether the subject has experienced any adverse events (only the serious adverse events or non–serious adverse drug reactions will be recorded in eCRF). The Investigator makes the judgment as to whether it is related or not to study treatment. At these telephone calls, subjects will also be asked to complete the ACT questionnaire (paper version) and to send it back to the Investigator.

Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation Visit). Subjects will be asked to withhold from taking study medication on the day of Visit 4. At this visit, subjects will be asked to provide responses to the ACT, MARS-A and PASAP questionnaires and the inhaler use will be assessed by recording critical and non-critical errors following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. Pre-dose trough FEV1 will be assessed at this visit by the Investigator using the spirometer provided by GSK. Rescue medication (salbutamol) will be stopped 4 hours before the spirometry. At least three valid assessments should be performed with registration of the best value. At this visit, subjects will also be interviewed by the Investigator about whether the subject has experienced any adverse events (only the serious adverse events or non–serious adverse drug reactions will be recorded in eCRF). The Investigator makes the judgment as to whether it is related or not to study treatment. Female subjects of child bearing potential will also be reminded about the requirement for contraception throughout their study participation.

The final Visit 6 will occur at Week 24. The ACT, AQLQ(S), EQ-5D and MARS-A questionnaires will be conducted at this visit and the inhaler use will be assessed by recording critical and non-critical errors following the next procedure: self-administration of one dose of study drug by subject; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. Subjects will be interviewed about whether the subject has experienced any serious adverse events or non –serious adverse drug reactions. The Investigator will be asked to make every effort to schedule Visit 6 at the same time of the day as Visit 2.

Although at least 3 formal scheduled visits and 2 phone calls are planned for this study, subjects should continue to visit their physician for any routine (naturalistic) visits as per normal clinical practice, as per the Time and Events Table (Section 7.1). An Early Withdrawal Visit has to be considered in case of early withdrawal of the subject from the study, as per the Time and Events Table (Section 7.1).

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

Outcome description

One of the main challenges of this study performed in so-called 'close to real life setting' is to obtain data on subjects with minimal interference with the actual practice of medicine. Thus, during the 6 months treatment period of the study, all interventions will be recorded as per normal. They will be captured by several means:

1. Physicians participating in the study will be asked to fill in an electronic CRF (eCRF) focused on clinical data at screening visit (Visit 1), at randomisation (Visit2), at Week 12 (Visit 4), at the end of the study at Week 24 (Visit 6) and at two phone calls at Week 6 (Visit 3) and at Week 18 (Visit 5).
2. At Week 6 and at Week 18, subjects will be telephoned to enquire about whether the subject has experienced any adverse events and then the investigator calling the patient must determine whether the event is related to study medication (either arm) and whether the event is serious. At these telephone calls, subjects will also be asked by the Investigator to complete the ACT questionnaire and to send it back to the Investigator.
3. When necessary, information will be obtained from other medical sources: naturalistic visits.

The variables of interest will be documented by a combination of information collected from all these sources.

Collected data

Eligible subjects will complete the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires at Randomisation Visit (Visit 2, Day 0) and at Visit 6 (Week 24), or at the Early Withdrawal visit. ACT questionnaire will be completed also by the subject at Screening visit (Visit 1), Week 6 (phone call 1 or Visit 3), at Week 12 (Visit 4) and Week 18 (phone call 2 or Visit 5). MARS-A questionnaire will be completed also at Week 12 (Visit 4). Inhaler use assessment will be performed at Randomisation Visit (Visit 2, Day 0), at Week 12 (Visit 4) and at Week 24 (Visit 6) / Early Withdrawal visit by recording the

critical and non-critical errors. Patient's satisfaction and preference (PASAP-Q) will be evaluated at Week 12 (Visit 4).

Baseline spirometry will be performed at Randomisation Visit (Visit 2, Day 0) and at Week 12 (Visit 4) by the Investigator using the spirometer provided by GSK, in order to assess pre-dose trough FEV1 at Week 12 (Visit 4).

For the Study Schematic see Appendix 2 and Section 7.1 for the proposed time and events table.

4.2. Treatment arms and duration

Randomisation will be on a 1:1 basis with two treatment arms: one FF/VI arm (FF/VI 92 mcg/22 mcg or FF/VI 184 mcg/22 mcg) once daily, and one arm ICS/LABA combination therapy in inhalation powder twice daily (FP/S 250 mcg/50 mcg or 500 mcg/50mcg, or BUD /F 200 mcg/6mcg or 400 mcg/12mcg) as decided by the physician. The total duration of subject participation will be approximately 6 months (24 weeks). As much as possible, enrolment of subjects should be performed at a constant accrual rate throughout a full year in order to minimize a seasonality bias.

4.3. Type and Number of Subjects

Subjects with documented physician's diagnosis of asthma ≥ 1 year, unsatisfactorily controlled asthma (ACT < 20) treated by ICS alone and intended to be treated by ICS/LABA maintenance therapy. A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.

It is estimated that approximately 70 study centers in France will be required to have a total number of 422 randomised subjects so that at least 382 subjects will be evaluable. Assuming a 10% screen failure rate, approximately 466 subjects will have to be screened in the study with 6 subjects /center.

Subjects withdrawn from the study will not be replaced.

4.4. Design Justification

An open label design is appropriate for such a study because it is a comparison of benefits and risks of FF/VI versus usual ICS/LABA asthma maintenance therapy in close to real life setting.

Previous studies have demonstrated that improvements in ACT score can be seen in periods of 3-6 months making this suitable time frame to assess ACT changes.

The treatment duration of 6 months (24 weeks) in this study is considered sufficient to demonstrate efficacy in the proposed study population.

The primary endpoint is defined as the change from baseline in the ACT total score assessed at Week 12 (Visit 4). The aim will be to prove non-inferiority of FF/VI to any other ICS/LABA comparator. The hypothesis of non-inferiority will be first tested at

Week 12. If (and only if) non-inferiority is significantly achieved at Week 12, non-inferiority will then be tested at Week 24. If (and only if) non-inferiority is achieved at a visit, then superiority of FF/VI to any other comparator will be tested at this visit (Week 12 or Week 24).

4.5. Dose Justification

Two strengths of FF/VI have been approved, 100 mcg/25 mcg (delivered dose of 92 mcg/22 mcg) for moderate persistent asthma and 200 mcg/25 mcg (delivered dose of 184 mcg/22 mcg) for severe persistent asthma. The dose of 92 mcg/ 22 mcg will be preferentially progressed in this study as this dose strength is likely to meet the needs of most subjects. However, physicians will be allowed to change the prescription to higher dose according to subject's response without exceeding the maximum allowed dose.

4.6. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with FF/VI can be found in the Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC). The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Serious Cardiovascular Events	This is a potential class effect of LABAs. In clinical studies, percentages of subjects with fatal events that were cardiovascular in nature were similar across all treatment groups (0 to <1%).	Subjects with historical or current evidence of uncontrolled or clinically significant disease are excluded from the study. Cardiovascular medical history, CV risk factors and exacerbation history will be assessed as described in the time and events table.
Asthma-related intubations and deaths	This is a potential class effect of LABAs. It was not observed in preclinical studies with FF/VI. During the FF/VI studies for the asthma composite endpoint (asthma exacerbations leading to hospitalization, intubation and/or death), there was no significant difference between the FF/VI group and the ICS group or non-LABA group, demonstrating no increased risk when adding a LABA to an ICS.	Subjects with a history of life-threatening asthma are excluded from this study. Subjects are excluded from this study if they have a severe and unstable asthma, with ACT score < 15, history of repeated severe exacerbations (3/year) and/or exacerbation in the previous 6 weeks. Subjects are excluded from this study if they are using LABA without an ICS as asthma maintenance therapy.

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Hypersensitivity	The reported hypersensitivity events in clinical trials, were not generally serious, did not lead to discontinuation in the studies, and were usually confounded, by either the subject's medical condition (such as COPD) or other factors at the time of the event. In spontaneous data, symptoms of hypersensitivity ranged from mild rash and pruritis to severe generalised rash and erythema and severe cases involving angiodema of the face, larynx and pharynx. These events were rare.	Subjects with a history of adverse reaction including immediate or delayed hypersensitivity to any intranasal, inhaled, or systemic corticosteroid and LABA therapy and to components of the inhalation powder (e.g., lactose, magnesium stearate) will be excluded. In addition, subjects with a history of severe milk protein allergy that, in the opinion of the Investigator, contraindicates the subject's participation will also be excluded.
Systemic effects of corticosteroids: adrenal suppression; eye disorders; decreased bone density and associated fractures	Adrenal suppression is a known class effect of corticosteroids. Preclinical studies showed that FF effects are comparable with other corticosteroids. No studies have shown a clinically relevant effect of FF/VI on the hypothalamic pituitary axis (HPA). This includes a formal HPA study (HZA106851), using 24 hour serum cortisol measurements, and multiple studies with COPD and asthma subjects which monitored urinary cortisol. During clinical	The mitigation in this study for all systemic effects of corticosteroids is that chronic users of systemic corticosteroids are excluded from this study: a subject who, in the opinion of the Investigator, is considered to be a chronic user of systemic corticosteroids for respiratory or other indications (if unsure discuss with the medical monitor prior to screening) will be excluded.

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	development, no events of Adrenal Suppression were reported. Eye disorders are a known class effect of corticosteroids. Preclinical studies showed FF at high dose comparable to other high dose corticosteroids. In study HZA106839 (FF/VI , FF and FP in subjects with asthma), formal ophthalmic assessments were conducted (including LOCS III evaluations for ocular opacities) throughout the study. This study showed no apparent effects on lens opacification, compared to baseline. During studies in both subjects with asthma and COPD, no associated affect on ocular disorders was observed. Decreased bone density is a known class effect of corticosteroids. Preclinical data showed that high dose corticosteroid effects of FF were comparable to other corticosteroids. Patients with Asthma In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of fractures with FF/VI was <=1%, and usually associated with trauma.	

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Study Procedures		
Spirometry procedures	Shortness of breath, coughing, light-headedness or fainting, and/or chest tightness	If any of these symptoms should happen to the subject, spirometry will be stopped and he/she will receive medical treatment
Other		
Summaries of findings from both clinical and non-clinical studies conducted with comparators (Seretide Diskus and Symbicort Turbuhaler) can be found in the Summary of Product Characteristics (SmPC).		

4.6.1.1. Benefit Assessment

Combined treatment with ICS and LABA has been shown to be more effective than the individual components in asthma, leading to the development of fixed dose combination inhalers. The use of ICS/LABA combinations is now well established in international treatment guidelines for moderate to severe persistent asthma patients for whom treatment with ICS alone is not sufficient.

Both fluticasone propionate/salmeterol and budesonide/formoterol fumarate are commercially available products for the treatment of persistent asthma and have recognized safety profiles. Both of these products are administered twice-daily.

4.6.2. Overall Benefit: Risk Conclusion

The investigational product (IP) FF/VI has an acceptable safety profile for clinical use and there are no significant associated risks. This conclusion is supported the results of previously performed clinical studies with the products in healthy volunteers and subjects with Asthma and COPD (GlaxoSmithKline Document Number RM2008/00012/06). Adverse effects that could be associated with the use of FF/VI, will be closely monitored. A safety criterion outlining details for subject withdrawal is included in the protocol (Section 5.4, Withdrawal Criteria). A thorough summary and evaluation of the available pre-clinical data can be found in the IB [GlaxoSmithKline Document Number RM2008/00012/06]. Routine safety analysis of this study will be conducted by the company. Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with FF/VI, are justified by the anticipated benefits that may be afforded to patients with asthma.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB/IB supplement(s) (or the SmPC), and other pertinent documents.

5.1. Inclusion Criteria

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. **Informed consent**: Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.
2. **Gender and Age**: Male or female subjects aged ≥18 and ≤ 75years of age at Visit 1.

Female subject: is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin [hCG] test), not lactating, and at least one of the following conditions applies:

a. Non-reproductive potential defined as:

- Pre-menopausal females with one of the following:
    - Documented tubal ligation
    - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
    - Hysterectomy
    - Documented Bilateral Oophorectomy
- Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

b. Reproductive potential and agrees to follow one of the options listed below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) requirements from 30 days prior to the first dose of study medication and until Week 24 (Visit 6).

GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

1. Contraceptive subdermal implant that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label
2. Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007a]
3. Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a]
4. Injectable progestogen [Hatcher, 2007a]
5. Contraceptive vaginal ring [Hatcher, 2007a]
6. Percutaneous contraceptive patches [Hatcher, 2007a]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007a].
8. Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2007b]
9. These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

3. Type of subject:

a. Subjects with documented physician's diagnosis of asthma ≥ 1 year, unsatisfactorily controlled asthma (ACT < 20 at Visit 1 and Visit 2) treated by ICS alone and intended to be treated by ICS/LABA maintenance therapy.

b. A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.

4. Current Asthma Therapy: All subjects must be prescribed maintenance therapy and receiving ICS alone without LABA for at least 4 weeks prior to Visit 2 (Randomisation visit).

Other background asthma medication such as anti-leukotrienes or theophylline is permitted as an alternative to ICS alone, if initiated at least 4 weeks prior to screening visit (Visit 1).

5. Subject questionnaires: Subjects must be able to complete the questionnaires themselves.

5.2. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study.

1. **History of Life-threatening asthma:** Defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnea, respiratory arrest or hypoxic seizures within the last 6 months before Visit 1 and Visit 2.
2. **Subjects having a severe and unstable asthma,** with ACT score < 15 at Visit 1 and at Visit 2, history of repeated severe exacerbations (3/year) and/or a severe exacerbation in the previous 6 weeks before Visit 1 and Visit 2.
3. **COPD Respiratory Disease**: A subject must not have current evidence or diagnosis of chronic obstructive pulmonary disease at Visit 1.
4. **Current or former cigarette smokers with a history of cigarette smoking of ≥ 10 pack-years** at screening (Visit 1) [number of pack years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)].
5. **Other diseases/abnormalities**: Subjects with historical or current evidence of uncontrolled or clinically significant disease at Visit 1 and at Visit 2. 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.
6. **Subjects with a history of adverse reaction** including immediate or delayed hypersensitivity to any intranasal, inhaled, or systemic corticosteroid and LABA therapy and to components of the inhalation powder (e.g., lactose, magnesium stearate) at Visit 1 and at Visit 2. In addition, subjects with a history of severe milk protein allergy that, in the opinion of the Investigator, contraindicates the subject's participation will also be excluded.
7. **Investigational Medications:** A subject must not have used any investigational drug within 30 days prior to Visit 2 or within five half-lives (t½) of the prior investigational study (whichever is longer of the two), (if unsure discuss with the medical monitor prior to screening).
8. **Chronic user of systemic corticosteroids:** A subject who, in the opinion of the Investigator, is considered to be a chronic user of systemic corticosteroids for respiratory or other indications (if unsure discuss with the medical monitor prior to screening) at Visit 1.
9. **Subjects treated by the monoclonal antibody omalizumab (Xolair) at Visit 1.** Treatment with Xolair is not allowed during the study.
10. **Subjects involved in other clinical trials at Visit 1.**
11. **Affiliation with Investigator Site:** Is an investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member of the afore mentioned that is involved in this study.

12. **Subjects who plan to move away from the geographical area where the study is being conducted during the study.**

5.3. Screening/Baseline/Failures

Approximately 466 subjects will be screened as 422 subjects are planned to be randomised and a 10% screen failure rate is expected.

- Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events related to study participation.

5.4. Withdrawal/Stopping Criteria

5.4.1. Subjects Lost to Follow-up

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

5.4.2. Subject Withdrawal by Investigator or Self-withdrawal

Subjects may be withdrawn from study treatment at any time by the Investigator if it is considered to be detrimental for them to continue the study treatment or, may discontinue a subject from the study at his or her discretion. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

The following criteria will cause a subject to be withdrawn from investigational product(IP) but every effort should be made to keep the Subject in the study:

- A subject becomes pregnant.
- A subject meets the Liver Stopping Criteria as defined in Section 5.4.3.

- A subject meets the QTc stopping criteria as defined in Section 5.4.4.

If the subject chooses to withdraw from the study, all study-related medications and other study related materials should be returned to the site by the subject. An Early Withdrawal Visit should be conducted within 24 hours of the subject stopping study medication (Section 7.1 Time and Event Table). In the event a subject withdraws at or during a scheduled visit, an Early Withdrawal Visit is not required; however, all study procedures scheduled at an Early Withdrawal Visit must be performed at this visit instead.

The primary reason for study treatment discontinuation or study withdrawal will be recorded in the electronic Case Report Form (eCRF) and any data collected up until the point of withdrawal will be used in the data analyses.

Specific regard should be given to distinguishing withdrawals due to ADRs, SAEs and protocol deviation, following consultation with the medical monitor. The Investigator will record the primary reason in the eCRF.

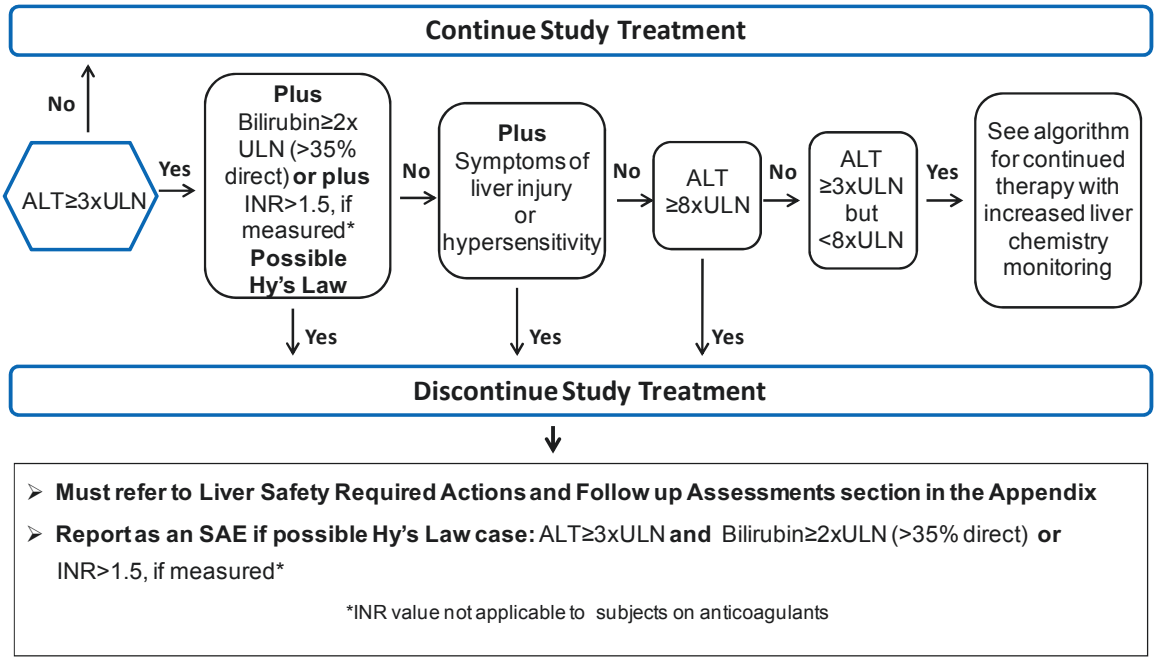
Subjects withdrawn from the study will not be replaced.

Subjects who experience an asthma exacerbation during the Treatment Period can continue in the study, at the discretion of their Investigator.

5.4.3. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

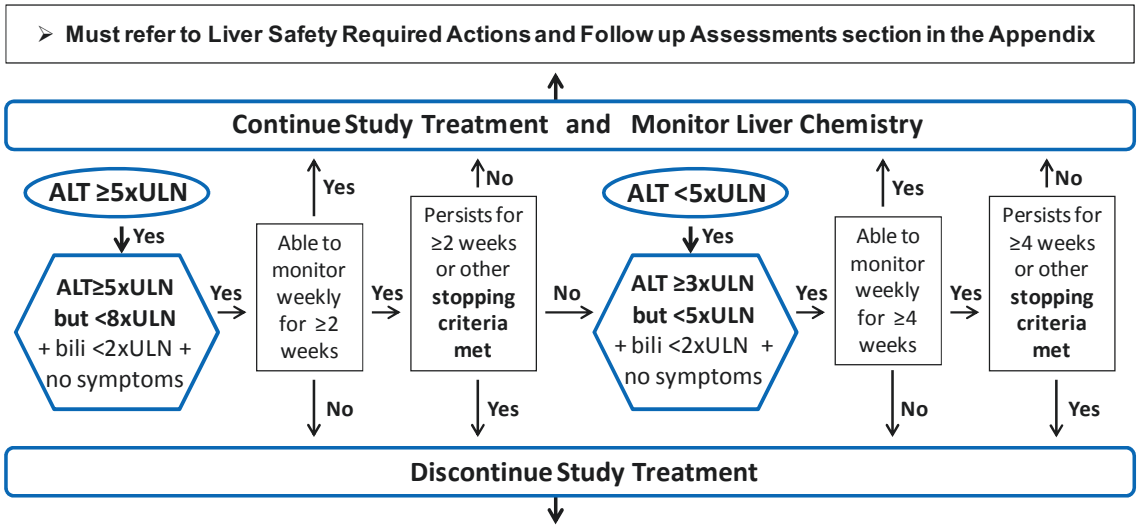
Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



- **Must refer to Liver Safety Required Actions and Follow up Assessments section in the Appendix**
- **Report as an SAE if possible Hy's Law case:** ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) **or** INR>1.5, if measured*

*INR value not applicable to subjects on anticoagulants

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



- **Must refer to Liver Safety Required Actions and Follow up Assessments section in the Appendix**
- **Report as an SAE if possible Hy's Law case:** ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) **or** INR>1.5, if measured*

*INR value not applicable to subjects on anticoagulants

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 4.

5.4.3.1. Study Treatment Restart or Rechallenge

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

5.4.4. QTc Stopping Criteria

An ECG is not required prior to entering this study. There are no other regular ECGs required by this protocol. If, however, while a subject is receiving study medication, an ECG is performed as part of the normal clinical practice and a prolonged QT interval is detected, the following assessments for withdrawal from the study are required, after discussion between Investigator and the medical monitor:

For all subjects:

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

- QTc > 500 msec OR Uncorrected QT > 600 msec
- Increase in QTc >60msec detected compared to a previous ECG

For patients with underlying **bundle branch block**, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	**Discontinuation QTc with Bundle Branch Block**
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec

The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

5.5. Subject and Study Completion

A completed subject is one who has completed all study visits. The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

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.

All subjects will receive the asthma medication to be used during the study from the investigator site.

GlaxoSmithKline Clinical Trials Supplies will provide the investigational products (FF/VI: Relvar™ Ellipta™ and comparative treatments, i.e. Seretide™ Diskus™, Symbicort™ Turbuhaler) as well as rescue medication (Salbutamol) for use in this study.

New ICS/LABA DPI or DPI copies of existing marketed ICS/LABA if any in France at the time of the study will not be considered in this trial.

Each subject randomised to the FF/VI arm will be instructed to administer the study medication once daily (by reading the leaflet and demonstration of it use), at the same time of the day, for the duration of the treatment period. Each subject will be advised to adhere to FF/VI dosing regimen throughout the study. The Investigator may adjust the dose of FF/VI according to the subjects' response, starting by FF/VI 92mcg/22 mcg.

Each subject initiating other ICS/LABA maintenance therapy will be reminded about the techniques of how to use their maintenance medication (by reading the leaflet and demonstration of it use) and the correct dosing. Each subject will be advised to adhere to ICS/LABA dosing regimen throughout the study, starting by FP/S 250mcg/50mcg or by BUD/F 200mcg /6mcg according to the Investigator's decision. The Investigator may adjust the dose of each product according to the subjects' response.

A description of the investigational treatments is provided below:

Table 1 Description of Fluticasone Furoate/Vilanterol Inhalation Powder Dry Powder Inhaler and comparative treatments

Compound Formulation	**Fluticasone Furoate/ Vilanterol** First strip: FF 92 mcg or 184 mcg blended with lactose Second strip: Vilanterol 22 mcg blended with lactose and magnesium stearate[1]
Dosage Form	DPI Ellipta™ – 30 doses per device
Unit Dose Strength	92 mcg/22 mcg or 184 mcg/22 mcg per actuation
Route of Administration	Inhaled
Compound Formulation	**Fluticasone propionate/ Salmeterol** FP 250 mcg or 500 mcg blended with lactose Salmeterol 50 mcg blended with lactose
Dosage Form	DPI Diskus™ – 60 doses per device
Unit Dose Strength	250 mcg/50 mcg or 500 mcg/50 mcg per actuation
Route of Administration	Inhaled
Compound Formulation	**Budesonide/Formoterol Fumarate** Budesonide 200 mcg or 400 mcg blended with lactose Formoterol Furoate 6 mcg or 12 mcg blended with lactose
Dosage Form	DPI Turbuhaler 60 or 120 doses (200 mcg/6 mcg or 400 mcg/12 mcg) per device
Unit Dose Strength	200 mcg/6mcg or 400 mcg/12 mcg per actuation
Route of Administration	Inhaled

1. matgnesium stearate 1% w/w of total drug product

The subject's use of short/rapid acting beta$_2$-agonist bronchodilator will be assessed as it would be in routine care and if required, rescue medication will be prescribed to subjects to use as needed throughout the study for relief of asthma symptoms as per usual practice.

6.2. Medical Devices

Medical devices (spirometers) will be provided by GSK for use in this study. However, none of the devices provided are manufactured by, or on behalf of GSK.

6.3. Treatment Assignment

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

Subjects will be randomized (1:1) to one of the following treatment groups:

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

Dose Guidance:

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

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

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

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

Information extracted from GINA, 2012, refer to GINA for further guidance.

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

6.4. Planned Dose Adjustments

Subjects randomised to the usual ICS/LABA asthma maintenance therapy arm can have their treatment adjusted as would be normal clinical practice at the Investigator's discretion. This will not require the subject to be withdrawn from the study. These subjects should not receive FF/VI, if the medication is marketed during the study period.

Subjects randomized to the FF/VI arm and for whom it is considered appropriate/ necessary to adjust treatment, can have their regimen changed as required as per normal clinical practice at any point in the study and the subject could remain in the study. Subjects on FF/VI arm can also change between the two FF/VI doses as appropriate and at the Investigator's discretion.

6.5. Blinding

This study is an open label randomised study.

6.6. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.7. Preparation/Handling/Storage/Accountability

All FF/VI and comparative ICS/LABA maintenance therapy prescribed throughout the study will be dispensed at, and collected from the investigator site.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. All DPIs containing FF/VI must be stored at a temperature of up to 25°C. Budesonide/Formoterol DPIs must be stored at a temperature of up to 30°C and Fluticasone Propionate/Salmeterol DPIs stored at 2-25°C.

Access to and administration of the investigational product will be limited to the investigator and authorised site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

All used and unused study medication inhalers (FF/VI or usual ICS/LABA asthma maintenance therapy) should be returned to the investigator site when the subjects collect prescriptions of study medication.

At the end of the study, all study supplied study medication (used and unused) will be destroyed following local standard operating procedures, except where it is suspected that Ellipta™ or GSK DPI packaging is defective. The device and packaging should be returned to GSK.

Details for both return and destruction and of study medication are found in the Study Procedure Manual (SPM).

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

In accordance with local regulatory requirements, the Investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

6.8. Investigational Product Malfunction

Any investigational product inhaler that fails to function properly must be identified to GSK personnel . Details of the failure will be documented in the eCRF. Ellipta inhalers will be returned to GSK for testing. The subject should return the inhaler to the clinic as soon as possible to avoid missing any doses. The site will then contact GSK's internal IWRS (also known as the Registration and Medication Ordering System [RAMOS] NG) and obtain a new treatment pack number for this subject and dispense a new study medication kit from the site's investigational product supply, as instructed per the IWRS.

6.9. Compliance with Study Treatment Administration

When the subjects attend the investigator site, they will be instructed to administer the study medication once daily at the same time of the day for the duration of the treatment, when randomised to FF/VI via Ellipta™ and twice daily (on the morning and evening) when randomised to ICS/LABA DPI (Diskus™ or Turbuhaler). All used and unused study medication inhalers (FF/VI or usual asthma maintenance therapy) should be returned to the investigator site when the subjects collect prescriptions of study medication.

Treatment adherence with study medication will be assessed based on analysis of medications (dispensed and collected) during the study and on Medication Adherence Report Scale for Asthma (MARS-A) questionnaire at randomisation Day 0, at Week 12 and at Week 24.

6.10. Treatment of Study Treatment Overdose

An overdose will be defined as the subject receiving any amount of IP greater than the maximum dose permitted by the protocol, which results in clinical signs or symptoms.

In the event of an overdose of study medication, the Investigator should use clinical judgment in treating the overdose and contact the study medical monitor.

GlaxoSmithKline (GSK) is not recommending specific treatment guidelines for overdose and toxicity management. The Investigator should 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(s) or equivalent document provided by GSK for study medications.

6.11. Treatment after the End of the Study

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

6.12. Concomitant Medications and Non-Drug Therapies

All respiratory-related prescribed and dispensed concomitant medications taken during the study will be recorded. The minimum requirement is that drug trade name and the dates of prescribing, dispensing and collection will be recorded.

6.12.1. Permitted Medications and Non-Drug Therapies

All medications for asthma and other disorders that are not contraindicated in asthma, or listed as a prohibited medication (see Section 6.12.2), may be continued throughout the study.

At clinical doses, low plasma concentrations of FF and VI are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and/or liver, any clinically significant drug interactions mediated by FF or VI are unlikely.

A CYP3A4 drug interaction study was performed in healthy subjects with the FF/VI combination (200/25) and Ketoconazole. Co-administration increased mean FF AUC(0-24) and Cmax by 36% and 33%, respectively. The increase in FF exposure was associated with a 27% reduction in 0-24 h weighted mean serum cortisol. Co-administration increased mean VI AUC(0-t') and Cmax 65% and 22%, respectively. The increase in VI exposure was not associated with an increase in beta-agonist related systemic effects on heart rate, blood potassium or QTcF interval.

Care is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for an increased systemic exposure to both FF and VI. Consideration should be given to the clinical situation and the duration of treatment with such concurrent medications.

6.12.2. Prohibited Medications and Non-Drug Therapies

- **Systemic corticosteroids**, except in case of a severe asthma exacerbation.
- **Monoclonal antibody omalizumab (Xolair).**

7. STUDY ASSESSMENTS AND PROCEDURES

The Time and Events Table is provided in Section 7.1. All study assessments should be conducted by the Investigator or his/her qualified designee unless otherwise specified in the protocol or SPM. Please refer to the SPM for the suggested order of assessments.

7.1. Time and Events Table

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

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

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

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

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

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

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

¥ Only for childbearing women.

Note: All adverse events will be recorded in the source documents but only information regarding non-serious adverse drug reactions (ADRs) and serious adverse events (SAEs) will be documented and reported in the eCRF.

7.2. Screening and Critical Baseline Assessments

The following demographic parameters will be captured: year of birth, sex, and ethnicity. Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5 and as indicated in the time and event table.

Cardiovascular medical history, CV risk factors and exacerbation history will be assessed as indicated in the time and event table.

Smoking status will be also captured as follows: non smoker, current or former cigarette smokers. Former smokers will be defined as those who have stopped smoking for at least 6 months prior to Visit 1 (or Visit 2 if the visit 1 and 2 are combined). Number of pack-years should be assessed at screening (Visit 1): number of pack years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years).

Procedures conducted as part of the subject's routine clinical management [e.g. blood count] and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

ACT will be assessed at screening (Visit 1) and randomisation (Visit 2). AQLQ(S), EQ-5D and MARS-A will be assessed at Visit 2 (Randomisation). These Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit, in the order specified. The correct use of inhaler will be assessed also at randomization visit (Visit 2):

1. after reading the package insert of product by the patient and
2. after demonstration of it use by the investigator. Any critical errors will be registered by the Investigator when using each device.

Baseline pre-dose FEV1 will be assessed at this visit by the Investigator using a spirometer provided by GSK. Rescue medication (salbutamol) will be stopped 4 hours before baseline spirometry and usual asthma medication will be not be taken by the patient before coming on site.

No study related procedures may be performed until the informed consent form document has been reviewed with and signed by the subject.

7.3. Efficacy

See Section 3 for the efficacy endpoints and Section 7.1 for the proposed time and events table.

7.3.1. Inhaler Correct Use Assessment

Correct use of the inhaler will be assessed as outlined in the Time and Events Table (Section 7.1).

Table 3 Critical and Non-critical errors for Ellipta™

Instructions: Critical Errors are identified in **bold text** in the list below. A critical error is defined as an error that is most likely to result in no or only minimalmedication being inhaled. Check only one box.					
Did the subject make an error while using the device? [ ] No [ ]Yes *if yes, tick appropriate options below*					
Critical Errors for Ellipta™	**yes**	**no**	**Non-critical Errors for Ellipta™**	**yes**	**no**
Failed to open cover			No exhalation before an inhalation		
Shook the device upside down after dose preparation			Inhalation manoeuvre was not: - long - steady - deep		
Exhaled directly into mouthpiece			Blocked air inlet during inhalation manoeuvre -		
No seal by the lips around the mouthpiece during the inhalation			Did not hold breath		
			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
Any other comments: [free text box]					

Table 4 Critical and Non-critical errors for Diskus™

Instructions: Critical Errors are identified in **bold text** in the list below. A critical error is defined as an error that is most likely to result in no or only minimal medication being inhaled. Check only one box.					
Did the subject make an error while using the device? [ ] No [ ]Yes *if yes, tick appropriate options below*					
Critical Errors for Diskus™	**yes**	**no**	**Non-critical Errors for Diskus™**	**yes**	**no**
Failed to open cover			No exhalation before an inhalation		
Lever is not pushed back			Inhalation manoeuvre was not: - steady - deep		
Shook the device after dose preparation			Did not hold breath		
Exhaled directly into mouthpiece			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
No seal by the lips round the mouthpiece during the inhalation					
Any other comments: [free text box]					

Table 5 Critical and Non-critical errors for Turbuhaler

Instructions: Critical Errors are identified in **bold text** in the list below. A critical error is defined as an error that is most likely to result in no or only minimal medication being inhaled. Check only one box.					
Did the subject make an error while using the device? [ ] No [ ]Yes *if yes, tick appropriate options below*					
Critical Errors for Turbuhaler	**yes**	**no**	**Non-critical Errors for Turbuhaler**	**yes**	**no**
Failed to remove cap			Device tipped downwards after dose preparation		
Did not hold device upright (±45% OK) during dose preparation			No exhalation before an inhalation		
Base not twisted fully backwards and forwards, no click heard			Inhalation manoeuvre was not: - forceful - deep Note to *HCP: it is important that the inhalation is forceful and deep from the start for this inhaler*		
Shook the device after dose preparation			Blocked air inlet during inhalation manoeuvre		
Exhaled directly into mouthpiece			Did not hold breath		
No seal by the lips round the mouthpiece during the inhalation			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
Any other comments: [free text box]					

7.3.2. Trough (pre-dose) FEV1 assessment

FEV1 will be measured to assess lung function at Visit 2 (Randomisation) and Visit 4 (Week 12), as outlined in the Time and Events Table. Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation visit). Measurements should be taken pre-dose and subjects should be instructed not to take their asthma medication/study drug prior to coming into the clinic at these visits. Subjects should also

withhold from using their rescue medication for at least 4 hours prior to Visit 2 (Randomisation) and Visit 4 (Week 12).

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

The Investigator will be asked to make every effort to perform the spirometry at the same time of the day at Visit 2 and at Visit 4.

7.3.3. Questionnaires

7.3.3.1. Asthma Control Test (ACT)

The ACT is a validated self-administered questionnaire utilising 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5). Subjects will complete the ACT at Screening (Visit 1), at Randomisation (Visit 2), at Week 6 (Phone Call 1 or Visit 3), at Week 12 (Visit 4), at Week 18 (Phone Call 2 or Visit 5) and at Week 24 (Visit 6) / Early Withdrawal visit.

An ACT score of 5 to 19 suggests that the subject's asthma is unlikely to be well controlled. A score of 20 to 25 suggests that the subject's asthma is likely to be well controlled.

Please refer to Appendix 3 and the Study Procedures Manual for further details.

7.3.3.2. Asthma Quality of Life Questionnaire (AQLQ-S)

The AQLQ is a disease-specific, self-administered quality of life questionnaire developed to evaluate the impact of asthma treatments on the quality of life of asthma sufferers, over the last 2 weeks [Juniper, 1993]. AQLQ(S) will be measured at Randomisation (Visit 2), at Week 24 (Visit 6) / Early Withdrawal visit. Please refer to Appendix 3 and the Study Procedures Manual for further details.

7.3.3.3. EuroQol Questionnaire (EQ-5D)-5 Level

General health status will be assessed with the EuroQol (EQ-5D)-5 Level Questionnaire at Randomisation (Visit 2) and at Week 24 (Visit 6) / Early Withdrawal visit.

Please refer to Appendix 3 and the Study Procedures Manual for further details.

7.3.3.4. Medication Adherence Report Scale for Asthma (MARS-A)

Reported adherence to medication will be assessed with the Medication Adherence Report Scale for Asthma (MARS-A) questionnaire at Visit 2, Week 12 (Visit 4) and Week 24 (Visit 6) / Early Withdrawal visit.

The MARS-A is a 10-item questionnaire where medication use is rated on a 5-point Likert scale (1 indicating 'always' to 5 indicating 'never'). It has been validated as a self-

reported measure of adherence with ICS for subjects with asthma and includes generic ("I use it regularly every day") and lung condition-specific questions about medication use ("I only use it when I feel breathless") [Cohen, 2009]. There is no specified timeframe on which responses should be based.

The Investigator should ensure the subject completes the MARS-A at the same time at the specified visits and before any study procedures. The MARS-A have no specified timeframe on which responses should be based.

7.3.3.5. Patients Satisfaction and Preference with the device (PASAP Questionnaire)

The Patient Satisfaction and Preference Questionnaire (PASAPQ) [C.M. Kozma, 2005], is a multi-item measure of respiratory inhalation device satisfaction and preference designed to be easily understood and administered to patients with asthma and COPD. Patient satisfaction with each device and device preference will be assessed at Week 12 (Visit 4) / Early Withdrawal visit if subject is withdrawn before Week 12 (Visit 4).

The Investigator should ensure the subject completes the PASAP-Q at the same time at the specified visits and before any study procedures. The PASAP-Q has no specified timeframe on which responses should be based.

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (see Section 7.1).

Serious Adverse Events (SAE) and non-serious Adverse Drug Reactions (ADR) will be collected in this study.

Safety endpoints will include:

- Frequency and type of serious adverse events,
- Frequency and type of non serious adverse drug reactions related to treatment.

7.4.1. Adverse Events (AE), Adverse Drug Reactions (ADRs) and Serious Adverse Events (SAEs)

The definitions of an AE, ADR or SAE can be found in Appendix 5.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. All adverse events will be recorded in the source documents but only information regarding non-serious adverse drug reactions (ADRs) and serious adverse events (SAEs) will be documented and reported in the eCRF.

7.4.1.1. Time period and Frequency for collecting non serious ADRs and SAE information

- All non-serious ADRs and SAEs will be collected from the start of Study Treatment until the end of the study (see Section 7.4.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- 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 SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 5.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 5.

7.4.1.2. Method of Detecting non serious ADRs and SAEs

The Investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of a non-serious adverse drug reaction (ADR) or serious adverse events (SAE).

The method of detecting, recording, evaluating and follow-up of SAEs and non-serious ADRs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study SAEs/non-serious ADRs are provided in the SPM.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

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

Potential SAEs and non serious ADRs may be identified by hospitalisation alerts through the medical record. The Investigator will have the ultimate responsibility for determining causality and seriousness.

7.4.1.3. Follow-up of non serious ADRs and SAEs

After the initial non serious ADRs/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious ADRs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 5.

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 5 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.

7.4.1.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Any clinically significant safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition, are **not** to be reported as non-serious ADRs or SAEs.

7.4.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the Investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met. This will also include potential SAEs identified by hospitalisation alerts through the medical record.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority/Independent Ethics Committee (IEC) and Investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An Investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IEC, if appropriate according to local requirements.

The method of detecting, recording, evaluating and follow-up of SAEs and non-serious ADRs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study SAEs/non-serious ADRs are provided in the SPM.

Procedures for documenting, transmitting and follow-up of medical device incidents along with the regulatory reporting requirements for medical devices are provided in the SPM.

7.4.2. Pregnancy

- Details of all pregnancies in female subjects will be collected from the time the informed consent is signed (Visit 1) and until the end of the study (Visit 6).
- Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 7.
- Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

7.4.3. Medical Device Incidents (Including Malfunctions)

Medical devices (spirometers) will be provided by GSK for use in this study. However, none of the devices provided are manufactured by, or on behalf of GSK.

7.4.4. Physical Exams

A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.4.5. Vital Signs

Vital sign measurements will include height, weight, pulse rate, systolic and diastolic blood pressure.

Vital signs will be measured and recorded in the eCRF at Screening visit (Visit 1), at the Randomisation Visit 2 (Day 0), at Week 12 (Visit 4), at Week 24 (Visit 6) and at Early Withdrawal Visit except for height and weight that will be collected at Visit 1 only.

7.4.6. Electrocardiogram (ECG)

An ECG is not required prior to entering this study. There are no other regular ECGs required by this protocol.

7.4.7. Clinical Safety Laboratory Assessments

There are no clinical safety laboratory assessment requirements for this study.

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) recorded during a routine clinic visit, including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the Investigator are to be recorded as non-serious ADRs or SAEs as appropriate.

7.5. Genetics

Information regarding genetic research is included in Appendix 6.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary (GSKDrug).
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The objective of the study is to compare the efficacy of fluticasone furoate (FF)/vilanterol (VI) Inhalation Powder (FF/VI 92 mcg/22mcg or FF/VI 184 mcg/22mcg) with usual ICS/LABA inhalation dry powder for asthma maintenance therapy over six months in a large French primary and respiratory specialist care population of subjects with asthma.

The primary endpoint is defined as the change from baseline in the ACT total score assessed at Week 12 (Visit 4). Regarding the primary efficacy endpoint (i.e. the change from baseline in the ACT total score assessed at Week 12 [Visit 4]), the primary analysis will show that the fixed combination FF/VI (92mcg/22mcg or 184mcg/22mcg) is non-inferior to any other ICS/LABA combinations in inhalation powder assuming a non-inferiority margin of 1.5. Non-inferiority will be claimed if the 95% two-sided confidence interval on the difference in mean primary efficacy endpoints (FF/VI minus Comparator) precludes the non-inferiority margin of -1.5.

If (and only if) non-inferiority is significantly achieved at Week 12 (Visit 4) with regard to the primary endpoint, then non-inferiority of the fixed combination FF/VI (92mcg/22mcg or 184mcg/22mcg) to any other ICS/LABA combinations will be tested at Week 24 (Visit 6) considering the same non-inferiority margin of 1.5. Non-inferiority will be claimed if the 95% two-sided confidence interval on the difference in mean primary efficacy endpoints (FF/VI minus Comparator) at Week 24 (Visit 6) precludes the non-inferiority margin of -1.5.

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

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

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

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

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

9.2.2. Sample Size Sensitivity

To demonstrate the sensitivity of the sample size calculation for this study, the following table presents the power of the study under different circumstances in terms of the standard deviation.

The assumption used is shaded.

Standard deviation	Power for the subjects evaluable (N = 382)
3.8	97.0%
4.2	93.6%
4.5	90.1%
4.7	87.5%
4.9	84.7%

9.2.3. Sample Size Re-estimation or Adjustment

Not planned

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Populations considered for analysis are as follows:

Intent to treat (ITT) population: All randomized subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy). The ITT population will be used to analyze the primary efficacy endpoint analysis, the secondary efficacy endpoint and other efficacy endpoints. Subjects will be assigned to the treatment group as randomized for the ITT population.

Per-protocol (PP) population: all ITT subjects without any major violations of study procedures. Major protocol violations will be identified prior to database lock. Protocol deviations will be reviewed and classified as minor or major during a data review meeting that will be held before database lock. The exclusion of subjects from the PP population will be specified and documented in the RAP.

Safety population: All enrolled subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy) and considered as-treated. The Safety population will be the basis for safety analyses. Subjects will be assigned to the treatment group as treated for the Safety population.

Details of the analysis datasets to be created will be specified in the Report Analysis Plan (RAP).

9.3.2. Interim Analysis

Not applicable

9.4. Key Elements of Analysis Plan

The primary comparison of interest is the comparison of the change from baseline (Visit 2) in the total ACT score assessed at Week 12 (Visit 4) between FF/VI (92mcg/22mcg or 184mcg/22mcg) and usual ICS/LABA inhalation powder for asthma maintenance therapy.

The primary set for analysis will be performed on the intent to treat population. A sensitivity analysis will be performed in the PP population.

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

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

Of note, this step-down testing procedure still strongly controls the overall type I error at the 0.05 two-sided level.

Definition of the treatment failure will be as follow:

- Treatment withdrawal,
- Change of treatment,
- Dose increase beyond the maximum allowed daily dose in the EU license (for FF/VI > 184mcg/22mcg, for FP/S > 500mcg twice daily, for BUD/F > 800 mcg twice daily.

Other Comparisons of Interest: Other efficacy endpoints and safety endpoints will be described. Estimated differences between groups with 95% confidence intervals will be provided when applicable.

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the Reporting Analysis Plan (RAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report Descriptive summaries will be provided by treatment group.

Demographic and baseline characteristics will be summarized.

Continuous variables will be summarized using descriptive statistics (number of observed and missing data, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum).

Categorical variables will be summarized as numbers of observed and missing data, counts and percentage for each category (reported to the number of non-missing values). For binary variables, 95% confidence intervals for proportions will be estimated based on the Clopper-Pearson method.

The contrast between FF/VI and usual ICS/LABA asthma maintenance therapy in inhalation powder will be of primary interest for all efficacy endpoints.

Non-inferiority of FF/VI versus usual ICS/LABA asthma therapy will be first tested at Week 12 (Visit 4). If and only if significance is achieved at Week 12 (Visit 4), then non-inferiority will be tested at Week 24 (Visit 6) at the two-sided 0.05 level of significance. This step-down testing procedure strongly controls the overall type I error at the 0.05 two-sided level.

If non-inferiority is achieved at Week 12 (Visit 4), then superiority of FF/VI versus usual ICS/LABA asthma therapy will be tested at the same two-sided nominal significance level of 0.05. If non-inferiority is achieved at Week 24 (Visit 6), then superiority of FF/VI versus usual ICS/LABA asthma therapy will be tested at the same two-sided nominal significance level of 0.05.

Baseline ACT score will be included in the primary efficacy analyses. Gender, age, study site and potentially season at randomization will be further investigated in sensitivity analyses when appropriate. Other covariates may be considered and if so it will be detailed in the RAP.

Treatment by prognostic factors interactions will be specifically investigated in secondary models.

Handling of treatment withdrawal: treatment withdrawal will be considered as a failure and the primary endpoint at the treatment withdrawal time will be assessed based on the last available ACT post randomization score before withdrawal. Of note, a change in the dose regimen will not be considered as a treatment failure.

Handling of missing data: as a general rule, missing data will not be replaced. Nevertheless sensitivity analyses regarding the primary and key secondary endpoint will replace missing ACT assessments by the last available post randomization ACT value (i.e. based on the last observation carried forward method).

The study is adequately powered for the primary and the key secondary endpoint, i.e. to show non-inferiority of FF/VI to current ICS/LABA at Week 12 (Visit 4) and at Week 24 (Visit 6) considering a non-inferiority margin of 1.5. Other secondary endpoints are not necessarily adequately powered and a descriptive analysis will only be proposed for these endpoints.

The primary efficacy analysis population set is defined as all subjects belonging to the Intent-to-Treat population (ITT), which include all subjects who have been randomised and received at least one prescription of study medication (e.g. FF/VI or usual ICS/LABA inhalation powder for asthma maintenance therapy).

Each subject will complete the ACT at Visit 2 (Randomisation), Week 12 (Visit 4) and Week 24 (Visit 6). ACT scores will also be assessed at Week 6 (Visit 3) and at Week 18 (Visit 5) and at the withdrawal time, if any.

9.4.1. Primary Analyses

The primary endpoint is defined as the change from baseline (Visit 2) in the ACT total score assessed at Week 12 (Visit 4).

The primary population of analysis will be the ITT population.

If treatment is withdrawn, then the missing ACT score at the nearest visit after treatment withdrawal will be replaced by the ACT score assessed at withdrawal time. If no ACT

score is assessed at withdrawal time, then the ACT missing score at the nearest visit after treatment withdrawal will not be replaced.

1) Non-inferiority testing.

The non-inferiority of FF/VI versus any other ICS/LABA DPI comparator will be primarily tested in a mixed model repeated measures (MMRM) approach. The model will include factors and covariates as follow: treatment, scheduled visit time point (Week 6 and Week 12), baseline ACT, treatment by visit interaction, baseline ACT by visit interaction, gender, age and patient will be fitted as a random factor. The Restricted Maximum Likelihood (REML) estimation approach will be used, and the default covariance structure will be unstructured. Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point will be performed. The 95% confidence interval on the treatment effect (FF/VI vs ICS/LABA comparator) will be estimated at Week 12 (Visit 4) in this model. Non-inferiority will be achieved if the non-inferiority margin of -1.5 is lower than the lower bound of the confidence interval on the difference between FF/VI and any other comparator (positive values of the difference favour FF/VI).

Sensitivity analyses:

a) Handling missing data

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

1. Missing values at Week 12 (Visit 4) will be replaced by the post-randomization last available value (either the week 6-based ACT score or the ACT score at treatment withdrawal time, if any), i.e. based on the Last Observation Carried Forward method. The change from baseline in ACT at Week 12 (Visit 4) will be analyzed in an ANCOVA model adjusting for treatment and baseline ACT score. The treatment effect (FF/VI versus any other ICS/LABA comparator) and its corresponding 95% confidence interval will be estimated in this model to test the non-inferiority hypothesis.

2. Multiple imputation (MI) analyses utilizing covariates known to be predictive of response: season at randomization, observed value of ACT at Week 6, observed value of ACT at Week 12 (Visit 4). Other covariates may be considered and if so it will be detailed in the RAP.

Step 1: For each treatment group separately, missing measurements are imputed for subjects with a baseline measurement where there are missing observations (at either Week 6 or Week 12) using the above covariates and regression-based imputation method. The Markov Chain Monte Carlo (MCMC) method for MI will be used and ten such sets

of imputed data will be created each with the observed values or imputed values for subjects with missing observations.

Step 2: Each imputed data set will be analyzed using the primary MMRM model. The treatment effect from these 10 analyses will then be pooled using standard MI theory to make an overall inference. The difference in the least squares means between the two groups at Week 12 (Visit 4) and the corresponding 95% confidence interval for the difference will be presented.

b) A sensitivity analysis based on the semi parametric Hodges-Lehmann (HL) approach will be proposed to assess the robustness of the MMRM Model-based non-inferiority results. The HL difference between groups with the corresponding 95% confidence interval will be provided.

c) Sensitivity analyses for handling treatment withdrawal: when treatment withdrawal occurs, an alternative method for imputing the missing value at the nearest visit after withdrawal time will be proposed: the primary endpoint missing value will be estimated by the worst ACT score observed between baseline visit (included) and withdrawal time (included).

d) The primary analysis (i.e. based on the MMRM approach) and the same sensitivity analyses presented here above will be performed on the Per Protocol population.

Model assumptions checking:

a) Assumptions underlying the MMRM (resp. ANCOVA for the sensitivity analysis) model (residual normality, linear relationship between response and baseline ACT, etc) will be checked with graphical methods (plots of studentized residuals, etc)

b) Baseline ACT will be categorized according the distribution quartiles and the same MMRM model (resp. ANCOVA for the sensitivity analysis) adjusting for categorized Baseline ACT will be fitted again.

c) Possible treatment by covariates (baseline ACT, baseline Asthma therapy, season at randomisation) interaction will be investigated MMRM (resp. ANCOVA for the sensitivity analysis) adjusting for these additional interaction terms

d) The influence of the covariates and potential additional covariates on the outcome will be investigated.

2) Superiority testing.

If non-inferiority is statistically achieved at Week 12 (Visit 4), then superiority of FF/VI to any other comparator will be tested at the usual 0.05 two-sided nominal level of significance.

The same models and analyses mentioned above will be used to assess the superiority hypothesis.

9.4.2. Secondary Analyses

Key secondary analysis

The key secondary endpoint is defined as the change from baseline (Visit 2) in the ACT total score assessed at Week 24 (Visit 6).

1) Non-inferiority testing

If non-inferiority is statistically achieved at Week 12 (Visit 4), then non-inferiority will be tested at Week 24 at the 0.05 two-sided nominal level. If non-inferiority is not accepted at Week 12 (Visit 4), non-inferiority will not be tested at Week 24 (Visit 6) and assessed on a descriptive basis only

More precisely, the key secondary endpoint assessed at Week 24 (Visit 6) will also be analyzed using a mixed model repeated measures (MMRM) approach where data up to and including Week 24 (Visit 6) will be used in the model. The model will include factors and covariates as follow: treatment, scheduled visit time point (Week 6, Week 12, Week 18 and Week 24), baseline ACT, treatment by visit interaction, baseline ACT by visit interaction, gender, age and patient will be fitted as a random factor. The Restricted Maximum Likelihood (REML) estimation approach will be used, and the default covariance structure will be unstructured. Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point will be performed. The 95% confidence interval on the treatment effect (FF/VI vs ICS/LABA comparator) will be estimated at Week 24 in this model. Non-inferiority will be achieved if the non-inferiority margin of -1.5 is lower than the lower bound of the confidence interval on the difference between FF/VI and any other comparator (positive values of the difference favour FF/VI).

Sensitivity analyses: the same sensitivity analyses as those described above for the primary endpoint will be performed for the key secondary efficacy endpoint.

Model assumptions checking: the analyses proposed to check model assumptions for the analysis of the key secondary efficacy endpoint will be the same as those described above for the primary endpoint.

2) Superiority testing.

If non-inferiority is statistically achieved at Week 24 (Visit 6), then superiority of FF/VI versus any other comparator will be tested at the usual 0.05 two-sided nominal level of significance.

The same models and analyses mentioned above will be used to assess the superiority hypothesis.

Other secondary analyses

Proper use of the medical device

The other key secondary endpoint will be the correct use of the inhaler device assessed at randomisation (Visit 2), at Week 12 (Visit 4) and at Week 24 (Visit 6). The device will be considered as adequately used if the patient didn't make any critical error at the corresponding visits (randomisation [Visit 2], week 12 [Visit 4] and week 24 [Visit 6]). Proportions of subjects correctly using the device will be estimated within each group. A corresponding 95% confidence interval of the difference in proportions will also be provided. Additional exploratory analyses could be performed and will be detailed in the RAP. Even if tests will be performed, no causal association will be inferred from these analyses.

9.4.3. Other Analyses

Other Analyses

The analysis of the other endpoints defined in this section will be provided for exploratory purposes only. Additional exploratory analyses could be performed and will be detailed in the RAP. Even if tests will be performed and 95% confidence intervals will be provided, no causal association will be inferred from these analyses.

Change from baseline in pre-dose trough FEV1

Results will be summarized for each group at Week 12 (Visit 4). More detail will be provided in the RAP.

Response to treatment

- Binary response defined as an ACT score ≥ 20 at a given visit OR a 3 point increase from baseline in ACT change.

The responder analyses will be conducted using a logistic regression model at a given Visit or Phone Call adjusting for treatment and stratification factors (baseline ACT score categorized into two classes, baseline asthma therapy, and potentially season at randomization). Treatment by stratification factors interaction effects will be further investigated in additional logistic models adjusting for these specific effects.

- Binary response defined as an ACT score ≥ 20 at a given visit.

The frequency and the percentage of subjects with ACT score ≥ 20 at a given visit will be described by treatment group. More detail will be provided in the RAP.

- Change from baseline in individual question scores for ACT at a given visit

For each question the statistical parameters of the changes will be summarized by treatment group. More detail will be provided in the RAP.

Adherence with study medication

- Number of percentage of medications (dispensed and collected) during the study will be tabulated for each visit and by treatment group.
- The score for Medication Adherence Report Scale for Asthma (MARS-A) at Day0, Week 12 and Week 24 will be described by treatment group.

Severe asthma exacerbations

- Number of subjects with at least one severe exacerbation, number of severe asthma exacerbation and annual exacerbation rate over the study period.

A severe asthma exacerbation is defined as deterioration of asthma requiring the use of systemic corticosteroids[2] (tablets, suspension, or injection) with or without antibiotics prescribed or an inpatient hospitalisation or emergency department visit due to asthma that required systemic corticosteroids or antibiotics[1,2,3] .

The number and percentage of subjects experiencing an asthma exacerbation during the study period will be summarized for each treatment group. Listing will be provided to include the primary causes of the exacerbation.

If feasible (i.e. if the number of exacerbation events is high enough), mean annual rate of asthma exacerbation will be analysed using a generalised linear model, assuming the negative binomial distribution, with the logarithm of time on treatment as an offset

variable. The adjusted mean rates per year, treatment ratio and associated p-value and 95% confidence interval will be presented.

Health Related Quality of Life and Health status

- An increase from baseline of ≥ 0.5 in AQLQ(s) total score at Week 24 (Visit 6).
- An increase from baseline of ≥ 0.5 in AQLQ(s) environmental stimuli domain score at Week 24 (Visit 6).
- Change from baseline in total score and domain scores of AQLQ(S) at Week 24 (Visit 6).
- Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) Individual domain scores at Week 24 (Visit 6).
- Health status using the EuroQol Questionnaire (EQ-5D) at Week 24 (Visit 6).

Patients Satisfaction and Preference with the inhaler (PASAP Questionnaire) (see Appendix 3)

The overall inhaler satisfaction and preference will be measured at Week 12 (Visit 4). The PASAP score will be summarised by treatment group.

Further analyses will be specified in the Report Analysis Plan.

Subgroup Analyses

Subgroup summaries and/or analyses will also be provided, when appropriate, for efficacy and safety endpoints based on baseline disease characteristics.

Additional analyses could be carried out using appropriate methods to account for changes in treatment during the course of the study. Further details will be provided in the analysis plan.

The details will be provided in the RAP.

Safety Analyses

Safety data will be summarized and/or listed by treatment group and by visit for the Safety population.

Extent of Exposure

Extent of exposure to study treatment (i.e., number of days on randomised treatment) will be summarised by treatment group using mean, standard deviation, median, minimum, and maximum. In addition, duration of subject exposed to study drug will be summarised across treatment groups.

Adverse Drug Reactions

Adverse drug reactions during the treatment period and during the post treatment period will be summarised and displayed by treatment group. Adverse drug reactions during the treatment period include those with a date of onset on the date of study treatment initiation to one day after study treatment termination.

The adverse drug reactions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and will be reported using the primary System Organ Class (SOC) and Preferred Term. Preferred Terms will be summarised within the primary SOC. The relationship of primary SOC, preferred terms, and verbatim text will be listed.

The number of subjects with one or more events of any type will be calculated. Results will be displayed in the order of decreasing frequency, both across primary SOC and within primary SOC.

Adverse drug reactions during the study period will also be listed. The demographic details (e.g., age, sex) and the details on individual adverse events will be included in these listings. Listings will be sorted within subject by the adverse drug reaction date of onset.

Similar summaries and listings will be provided for adverse events leading to withdrawal from study.

Deaths and Serious Adverse Events

Deaths and serious adverse events during the study period will be listed. Serious adverse events during the study period will also be summarised by treatment group.

Any pregnancies, serious adverse events and deaths reported during this study will also be summarised in case narratives written by GSK GCSP personnel.

Other safety parameters

All others safety parameters will be listed and summarized.
More specifically the vital signs (BMI, pulse rate, systolic blood pressure and diastolic blood pressure) will be summarized by visit and treatment group.

Genetic research

Information regarding genetic research is included in Appendix 6.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2013 including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review, CPP in France ("Comité de Protection des Personnes") and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which medical records will serve as the source document.

GSK will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The Investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

Upon completion or termination of the study, the GSK monitor will conduct site closure activities with the Investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the Investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all Investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the Investigator or head of the medical institution must inform the IEC promptly and provide the reason(s) for the suspension/termination.

10.6. Records Retention

Following closure of the study, the Investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The Investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The Investigator and GSK must also

ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the Investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The GP/Investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the Investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator signatory will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 8 months after the last subject's last visit (LSLV) [this applies to each data analysis phase for studies with multiple phases, e.g., primary analysis, follow up analysis etc]. In addition, the aim is to submit a manuscript to a peer-reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11. REFERENCES

British Guideline on the Management of Asthma. British Thoracic Society: A national clinical guideline. 2008 63: iv1-iv121

Cohen JL, Mann DM, Wisnivesky JP, Horne R, Leventhal H, Musumeci-SzaboTJ, Halm EA. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. Ann Allergy Asthma Immunol. 2009: 103: 325-31

Dolan P. Modeling valuations for EuroQol health states. Med Care 1997; 35(11):1095-1108.

Fanta CH. Drug Therapy: Asthma. *New Engl J Med.* 2009;360(1):1002-1014.

GINA 2012, http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf

GlaxoSmithKline Document Number RM2008/00012/06. Fluticasone Furoate + Vilanterol Investigator's Brochure. 25-Jun-2014

Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention.* GINA, www.ginasthma.org; 2009.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. *Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(a): 24. Table 3-2.*

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. *Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(b): 28*

James LP et al. Pharmacokinetics of Acetaminophen-Protein Adducts in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37(8): 1779-1784.

Juniper EF et al. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol. 1994 Jan;47(1):81-7.

Juniper EF et al. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax. 1992 Feb;47(2):76-83

Juniper EF, Guyatt GH, Williams A, Griffith LE. Measuring quality of life in asthma. *Am Rev Respir Dis.* 1993;147:832-838.

Juniper EF. Asthma quality of life questionnaires (AQLQ, AQLQ(S) and MiniAQLQ): Background information and interviewing tips. QOL Technologies Inc. 1998.

Kozma CM et al. Development and Validation of a Patient Satisfaction and Preference Questionnaire for Inhalation Devices (PASAPQ). Treat Respir Med 2005

Le Gal F et al. 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.

Nathan RA, Sorkness CA, Kosinski M et al, Development of the Asthma Control Test: A survey for assessing asthma control, J Allergy Clin Immunol January 2004.

NIH, 2007, Asthma Guidelines Summary, http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.pdf

Pedersen S, O'Byrne P. A comparison of efficacy and safety of inhaled corticosteroids in asthma. *Allergy.* 1997;52(39):1-34.

Schatz M et al. The minimally important difference of the Asthma Control Test, The Journal of allergy and clinical immunology (2009)

The EuroQol Group, 1990. The EuroQol Group. EuroQol- a new facility for the measurement of health-related quality of life. Health Policy 1990; 199-208

12. APPENDICES

12.1. Appendix 1: Abbreviation and Trademarks

ACT	Asthma Control Test
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Co-variance
AQLQ(S)	Asthma Quality of Life Questionnaire
AST	Aspartate Aminotransferase
BID	Twice daily
BUD	Budesonide
°C	Celsius
CRF	Case Record Form
eCRF	Electronic Case Record Form
CV	Cardiovascular
DNA	Deoxyribonucleic acid
DPI	Dry Powder Inhaler
FP	Fluticasone Propionate
ECG	Electrocardiogram
EPI	Epidemiology
EQ-5D	EuroQol 5D
F	Formoterol
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in one second
FF	Fluticasone Furoate
FP	Fluticasone Propionate
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GINA	Global Initiative for Asthma
GP	General Practitioner
GSK	GlaxoSmithKline
HPA	Hypothalamic pituitary axis
HL	Hodges-Lehmann
IB	Investigators Brochure
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IgG	Immunoglobulin G
INR	International Normalised Ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IVD	In Vitro Diagnostic
IRT	Interactive Response Technology
LABA	Long Acting Beta Agonist

LDH	Lactate Dehydrogenase
LSLV	Last Subject Last Visit
MARS-A	Medication Adherence Report Scale in Asthma questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
Mcg	Microgram
MI	Multiple imputation
MID	Minimally Important Difference
MDI	Metered Dose Inhaler
MCID	Minimally Clinically Important Difference
ml	Millilitre
MSDS	Material Safety Data Sheet
MMRM	Mixed effects model with repeated measures
NDPI	Novel Dry Powder Inhaler
PASAP-Q	Patients Satisfaction and Preference Questionnaire
PK	Pharmacokinetics
PP	Per-protocol
PRO	Patient Reported Outcomes
pg	Picogram
pmol	Picomoles
QD	Once Daily
QoL	Quality of Life
QTc	Corrected QT interval
RAP	Reporting Analysis Plan
REML	Restricted maximum likelihood
RNA	Ribonucleic Acid
S	Salmeterol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
S&P	Statistics and Programming
SPM	Study Procedures Manual
ULN	Upper Limit of Normal
VI	Vilanterol
WHO	World Health Organisation

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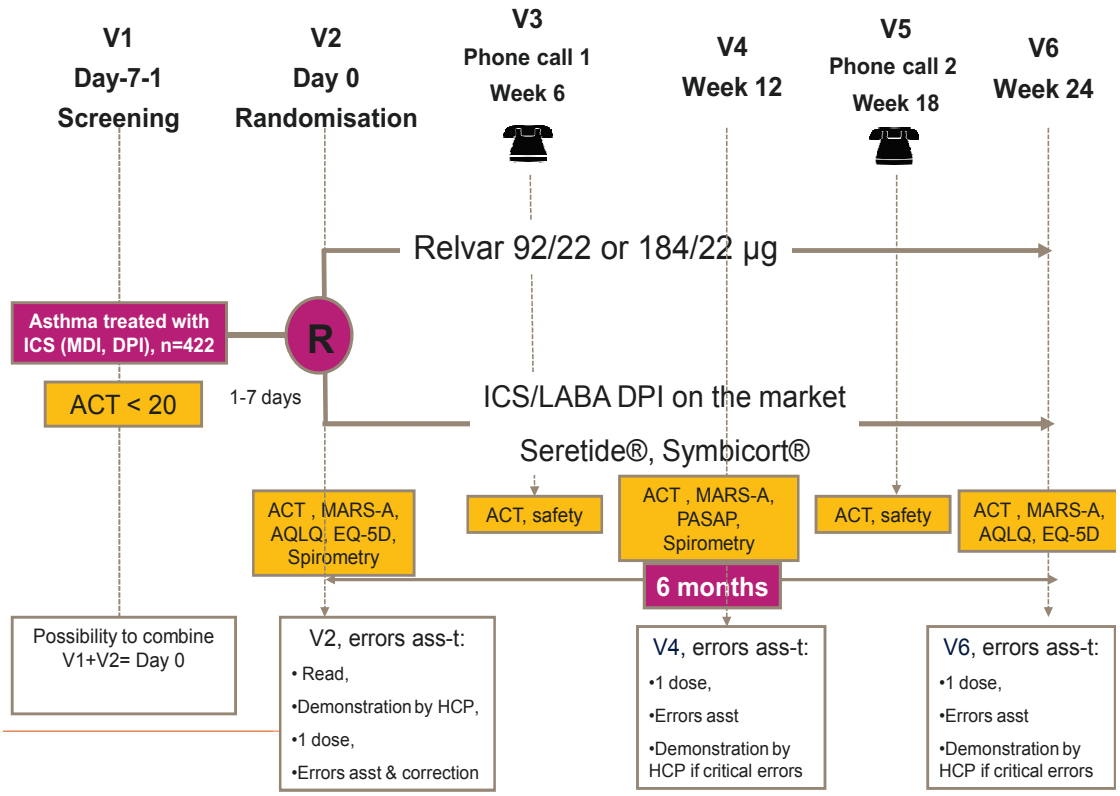
ACT
Asthma Quality of Life Questionnaire - AQLQ(S)
EQ-5D
MARS-A questionnaire
PASAP Questionnaire
Symbicort Turbuhaler
XOLAIR

12.2. Appendix 2: Study Schematic

FF/VI open- label or usual asthma maintenance treatment

HZA 116492: study design



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

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

12.3. Appendix 3: Questionnaires

Asthma Control Test (ACT)

The ACT is a validated self-administered questionnaire utilising 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5). By answering all 5 questions a subject with asthma can obtain a score that may range between 5 and 25, with higher scores indicating better control. An ACT score of 5 to 19 suggests that the subject's asthma is unlikely to be well controlled. A score of 20 to 25 suggests that the subject's asthma is likely to be well controlled. The total score is calculated as the sum of the scores from all 5 questions. [Nathan R, 2004]. The minimally important difference (MID) for ACT is 3 [Schatz, 2009].

Subjects will complete the ACT at Screening (Visit 1), at Randomisation (Visit 2), at Week 12 (Visit 4) and at Week 24 (Visit 6) on site. Two telephone calls are provided at Week 6 and 18 and subjects will be asked to provide responses to the ACT questionnaire and to send it back to the Investigator.

The ACT has been developed as a measure of subjects' asthma control that can be quickly and easily completed in clinical practice. The questions are designed to be self-completed by the subject. It is recommended that the ACT be administered at the same time during each visit. The ACT should be completed before any procedures are performed on the subject to avoid influencing the subject's response. Adequate time should be allowed to complete all items on the ACT.

The subject should complete the questionnaire in a quiet area.

The Investigator should ask the subject to complete the questions as accurately as possible. If the subject requests help or clarification with any of the questions, he/she will be asked to re-read the instructions and give the answer that best reflects how he/she felt over the previous 4 weeks. The subject should be reassured that there are no right or wrong answers. The Investigator should not provide the subject with any answer or attempt to interpret any portion of a question.

Please refer to the Study Procedures Manual for further details.

Asthma Quality of Life Questionnaire (AQLQ-S)

The AQLQ (S) is a modified version of the original AQLQ in which all the activity questions are generic and it has been validated for use in asthma subjects between the ages of 17 and 70. The AQLQ is a disease-specific, self-administered quality of life questionnaire developed to evaluate the impact of asthma treatments on the quality of life of asthma sufferers, over the last 2 weeks [Juniper, 1993]. AQLQ(S) will be measured at Randomisation and at Week 24 / Early Withdrawal visit.

The AQLQ, which is available in numerous languages, has a demonstrated validity, reliability and reproducibility [Juniper, 1992; Juniper, 1998]. The AQLQ contains 32 items in four domains: activity limitation (11 items), symptoms (12 items), emotional function (5 items), and environmental stimuli (4 items). In addition, the 32 items of the

questionnaire are also averaged to produce an overall quality of life score. The response format consists of a seven-point scale where a value of 1 indicates “total impairment” and 7 indicates “no impairment”. Assuming a statistically significant result ($p < 0.05$), the minimal clinically meaningful change in overall quality of life, or in quality of life for any of the individual domains, is 0.5 points [Juniper, 1994].

It is recommended that the AQLQ (S) be administered at the same time during each visit. The AQLQ (S) must be administered before inquiring about AEs and any study assessments. Adequate time should be allowed to complete all items on the AQLQ (S). No stated or implied time for completing the AQLQ (S) will be given, though the survey typically takes 10 to 20 minutes to complete.

Subjects should complete all the questions from the AQLQ (S). The Investigator will ask the subject to complete all questions as accurately as possible. If the subject requests help or clarification of any question in the AQLQ (S) he or she should be asked to reread the instructions and give the answer that best reflects how he/she feels over the previous two weeks. The subject should be reassured that there are no right or wrong answers. The Investigator will not provide the subject with any answer or attempt to interpret any portion of a question. Please refer to the Study Procedures Manual for further details.

EuroQol Questionnaire (EQ-5D)-5 Level

General health status will be assessed with the EuroQol (EQ-5D)-5 Level Questionnaire at Randomisation and Week 24 / Early Withdrawal visit.

The EQ-5D is a standardised instrument for use as a measure of health status that asks subjects questions about their health status “today” [The EuroQol Group, 1990]. It is designed for self-completion and is cognitively simple. The EQ-5D is a two-part self-assessment questionnaire. The first part consists of five items covering five dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a three-point Likert scale (1-no problem, 2-some/moderate problem[s], and 3-unable/extreme problem[s]).

Respondents are asked to choose one level that reflects their "own health state today" for each of the five dimensions. Respondents can then be classified into one of 243 distinct health states. EQ-5D health states can be converted to a single summary index by applying a formula that attaches weights to each of the levels in each dimension. The formula is based on the valuation of EQ-5D health states from general population samples [Dolan, 1997].

The second part of the questionnaire consists of a vertical visual analogue scale (EQ-5D VAS) that has endpoints of "The best health you can imagine" (anchored at 100) and "The worst health you can imagine" (anchored at 0). Respondents are asked to indicate how they rate their current health state by drawing a line from the box marked “your health status today” to the appropriate point on the EQ-5D VAS scale.

The Investigator should ensure the subject completes the EQ-5D at the same time at the specified visits and before any study procedures. The EQ-5D will be administered at Randomisation (Visit 2) and Week 24 (Visit 6) / Early Withdrawal visit.

Medication Adherence Report Scale for Asthma (MARS-A)

Reported adherence to medication will be assessed with the Medication Adherence Report Scale for Asthma (MARS-A) questionnaire at Visit 2, Visit 4 and Visit 6/Early Withdrawal visit.

The MARS-A is a 10-item questionnaire where medication use is rated on a 5-point Likert scale (1 indicating 'always' to 5 indicating 'never'). It has been validated as a self-reported measure of adherence with ICS for subjects with asthma and includes generic ("I use it regularly every day") and lung condition-specific questions about medication use ("I only use it when I feel breathless") [Cohen, 2009]. There is no specified timeframe on which responses should be based.

The Investigator should ensure the subject completes the MARS-A at the same time at the specified visits and before any study procedures. The MARS have no specified timeframe on which responses should be based.

Patient Satisfaction and Preference Questionnaire (PASAP-Q)

The Patient Satisfaction and Preference Questionnaire (PASAP-Q) [C.M. Kozma, 2005], is a multi-item measure of respiratory inhalation device satisfaction and preference designed to be easily understood and administered to patients with asthma and COPD. Patient satisfaction with each device and device preference will be assessed at Visit 4/ Early Withdrawal visit.

The Investigator should ensure the subject completes the PASAP-Q at the same time at the specified visits and before any study procedures. The PASAP-Q has no specified timeframe on which responses should be based.

12.4. Appendix 4: Liver Chemistry Stopping and Follow-up Criteria

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase III-IV liver chemistry stopping criteria and required follow up assessments

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 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 • Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is**	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for pharmacokinetic (PK) analysis, obtained within after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN

granted (refer to Appendix 4) • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Obtain complete blood count with differential 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 **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • 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 subject 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 subjects 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
5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].

6. PK sample may not be required for subjects 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 subject'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 subject safety. • Subject can continue study treatment • Subject 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 subject 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 subjects twice monthly until liver chemistries normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

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.

12.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.5.1. Definition of Adverse Events and ADRs

Adverse Event and ADRs Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • The definition of an ADR is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, for which there is a reasonable possibility that the untoward occurrence is causally related to the medicinal product. ADRs are a subset of AEs for a given medicinal product. • 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 medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • 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 prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected 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 this is an intentional overdose taken with possible suicidal/self-harming intent. This 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. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events NOT meeting definition of an AE include:
• 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 subject'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 subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where 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.

12.5.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 hospitalization or prolongation of existing hospitalization NOTE: • In general, hospitalization signifies that the subject 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 out-patient setting. Complications that occur during hospitalization are AEs. 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 disability/incapacity NOTE: • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere 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 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are 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
g) Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.
• Refer to Appendix 4 for the required liver chemistry follow-up instructions

12.5.3. 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

12.5.4. Recording of AEs (ADRs) and SAEs

AEs and SAE Recording:

- When an AE (ADRs) /SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE (ADRs) /SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE (ADRs) /SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE (ADRs) /SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE (ADRs) data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE (ADRs) is inappropriate.

12.5.5. Evaluating AEs (ADRs) and SAEs

Assessment of Intensity
The investigator will make an assessment of intensity for each AE (ADRs) and SAE reported during the study and will assign it to one of the following categories: • Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities • Severe: An event that prevents normal everyday activities. - an AE (ADRs) that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs (ADRs) and SAEs can be assessed as severe. • An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. • A "reasonable possibility" is meant to convey that there are facts/evidence 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 natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. • The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of 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 when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.** • The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. • The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. • If a subject 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 the designated reporting time frames.

12.5.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the SAE coordinator • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) 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 subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the SAE coordinator by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.6. Appendix 6: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;
- Asthma susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 2 ml saliva sample will be taken for Deoxyribonucleic acid (DNA) extraction. A saliva sample is collected at the baseline visit (Visit 2), after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the saliva sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The saliva sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or “coded”) with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the

subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any saliva being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample

reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.7. Appendix 7: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of foetal 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 5. 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 subject who becomes pregnant while participating

- will be withdrawn from the study
- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner’s pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.

Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

12.8. Appendix 8: Protocol Changes

This protocol amendment has been created to correct mistakes in the wording of the inhaler errors questionnaires for the ELLIPTA™, DISKUS™ and Turbuhaler inhalers, which are included in Section 7.3.1 of the protocol. All references to 'Type A errors' and 'overall errors' within the protocol, have been changed to 'critical' and 'non-critical' errors, respectively for consistency with the inhaler errors questionnaire worksheets.

Storage condition instructions for Seretide (fluticasone propionate/salmeterol) in Section 6.7 have been amended. Section 6.7 of the protocol states that the storage conditions of Seretide (fluticasone propionate/salmeterol) must be stored at temperatures up to 30°C. At the point at which the protocol was approved it was intended that Seretide commercial stock would be provided for use in this study. However, due to labelling requirements this was not possible and the clinical trial image needed to be used instead. All Seretide (fluticasone propionate/salmeterol) DPIs should be stored at temperatures between 2-25°C.

The wording for the recommended number of spirometry efforts has been revised.

New text has been included with regards to investigational product malfunction in Section 6.8.

The secondary medical monitor contact information has been revised to include a new study physician.

Other minor corrections and edits have been made.

Method of Amendment

Original and amended texts are specified as follows:

Original text: as written in the original protocol

Revised text: as written in Amendment No. 01 with revisions in bold font.

Protocol synopsis for study HZA116492 and Section 3: Secondary Objectives and Endpoints

Original table:

Secondary	
• To assess effect of FF/VI on asthma control compared with usual ICS/LABA fixed combination at Week 24 (Visit 6).	• Change from baseline in ACT score at Week 24 (Visit 6).
• To assess ELLIPTA™ inhaler correct use compared with other DPI (Diskus™ and	• Percentage of subjects making at least 1 Type A error (likely to be critical) and

Turbuhaler) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).	overall errors at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).
Other	
• To assess effect of FF/VI on trough (pre-dose) FEV1 compared with usual ICS/LABA fixed combination at Week 12 (Visit 4)	• Change from baseline in trough (pre-dose) FEV1 at Week 12 (Visit 4).
• To assess the effect of FF/VI on response to treatment at Week 12 (Visit 4) and Week 24 (Visit 6)	• ACT score ≥ 20 or 3 point increase from baseline in ACT at Week 12 (Visit 4) and Week 24 (Visit 6). Note: A 3 point increase in ACT total score was suggested as the Minimal Clinically Important Difference (MCID) in the literature [Schatz, 2009].
• To assess the adherence with study medication at Week 12 (Visit 4) and Week 24 (Visit 6)	• Number of medications dispensed and collected during the study at Week12 (Visit 4) and Week 24 (Visit 6), • Score of the MARS-A questionnaire (Medication Adherence Report Scale) at the randomisation (Day0), Week12 (Visit 4) and Week24 (Visit 6).
• To assess the effect of FF/VI on severe asthma exacerbation over the study period	• Number of subject with at least 1 severe asthma exacerbation*, number of severe asthma exacerbation and annual severe exacerbation rate over the study period.
• To assess the effect of FF/VI on Health Related Quality of Life at Week 24 (Visit 6)	• Change from baseline in total score and domain scores of AQLQ(S) (Asthma Quality of Life Questionnaire) at Week 24 (Visit 6). • An increase from baseline of ≥ 0.5 in AQLQ(s) total score at Week 24 (Visit 6). • An increase from baseline of ≥ 0.5 in

	AQLQ(s) environmental stimuli domain score at Week 24 (Visit 6). • Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) Individual domain scores at Week 24 (Visit 6). • Change from baseline in total score and domain scores of AQLQ(S) at Week 24 (Visit 6). • Health status using the EuroQol Questionnaire (EQ-5D) at Week 24 (Visit 6).
• To assess Patient Satisfaction and Preference assessment with different inhalers at Week 12 (Visit 4)	• Score of PASAP Questionnaire (Patient Satisfaction and Preference) at Week 12 (Visit 4).
• To evaluate the Safety of FF/VI compared with usual ICS/LABA (FP/S and Bud/F).	Serious Adverse Events (SAE) and non-serious Adverse Drug Reactions (ADR): • Frequency and type of serious adverse events, • Frequency and type of non-serious adverse drug reactions related to treatment.

Revised table:

Secondary	
• To assess effect of FF/VI on asthma control compared with usual ICS/LABA fixed combination at Week 24 (Visit 6). • To assess ELLIPTA™ inhaler correct use compared with other DPI (Diskus™ and Turbuhaler) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).	• Change from baseline in ACT score at Week 24 (Visit 6). • Percentage of subjects making at least 1 **critical error and non-critical error** at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).
Other	
• To assess effect of FF/VI on trough (pre-	• Change from baseline in trough (pre-

dose) FEV1 compared with usual ICS/LABA fixed combination at Week 12 (Visit 4)	dose) FEV1 at Week 12 (Visit 4).
• To assess the effect of FF/VI on response to treatment at Week 12 (Visit 4) and Week 24 (Visit 6)	• ACT score ≥ 20 or 3 point increase from baseline in ACT at Week 12 (Visit 4) and Week 24 (Visit 6). Note: A 3 point increase in ACT total score was suggested as the Minimal Clinically Important Difference (MCID) in the literature [Schatz, 2009]. • **ACT score ≥ 20 at Week 12 (Visit 4) and Week 24 (Visit 6).** • **Change from baseline in individual question scores for ACT at Weeks 12, 24**
• To assess the adherence with study medication at Week 12 (Visit 4) and Week 24 (Visit 6)	• Number of medications dispensed and collected during the study at Week12 (Visit 4) and Week 24 (Visit 6), • Score of the MARS-A questionnaire (Medication Adherence Report Scale) at the randomisation (Day0), Week12 (Visit 4) and Week24 (Visit 6).
• To assess the effect of FF/VI on severe asthma exacerbation over the study period	• Number of subject with at least 1 severe asthma exacerbation*, number of severe asthma exacerbation and annual severe exacerbation rate over the study period.
• To assess the effect of FF/VI on Health Related Quality of Life at Week 24 (Visit 6)	• Change from baseline in total score and domain scores of AQLQ(S) (Asthma Quality of Life Questionnaire) at Week 24 (Visit 6). • An increase from baseline of ≥ 0.5 in AQLQ(s) total score at Week 24 (Visit 6).

	• An increase from baseline of ≥ 0.5 in AQLQ(s) environmental stimuli domain score at Week 24 (Visit 6). • Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) Individual domain scores at Week 24 (Visit 6). • Change from baseline in total score and domain scores of AQLQ(S) at Week 24 (Visit 6). • Health status using the EuroQol Questionnaire (EQ-5D) at Week 24 (Visit 6).
• To assess Patient Satisfaction and Preference assessment with different inhalers at Week 12 (Visit 4)	• Score of PASAP Questionnaire (Patient Satisfaction and Preference) at Week 12 (Visit 4).
• To evaluate the Safety of FF/VI compared with usual ICS/LABA (FP/S and Bud/F).	Serious Adverse Events (SAE) and non-serious Adverse Drug Reactions (ADR): • Frequency and type of serious adverse events, • Frequency and type of non-serious adverse drug reactions related to treatment.

Protocol synopsis for study HZA116492: Overall Design

Original text:

In addition, each subject whose FF/VI (Ellipta™) for asthma maintenance therapy is initiated at Visit 2 will be asked to read the information leaflet and will be instructed by the investigator on the proper use of Ellipta™. Each subject whose usual ICS/LABA DPI (Diskus™ or Turbuhaler) for asthma maintenance therapy is initiated at Visit 2 will follow the same procedure: reading of the information leaflet, demonstration of the proper use of the inhalers by the Investigator, and the correct dosing. This will be followed by an inhalation demonstration by the patient. Any mistakes (Type A errors, corresponding to critical errors) and overall errors will be registered by the Investigator. For the definition of Type A errors and overall errors see Section 7.3.1

Randomisation at this visit will be performed on a 1:1 basis; to the FF/VI fixed dose combination delivered via Ellipta™ or the initiation with usual ICS/LABA inhalation powder for asthma maintenance therapy.

At Week 6 (Visit 3) and at Week 18 (Visit 5) subjects will be telephoned to enquire about whether the subject has experienced any serious adverse events or non serious adverse drug reactions. At these telephone calls subjects will also be asked to complete the ACT questionnaire (paper version) and to send it back to the Investigator.

Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation Visit). Subjects will be asked to withhold from taking study medication on the day of Visit 4. At this visit, subjects will be asked to provide responses to the ACT, MARS-A and PASAP questionnaires and the inhaler use will be assessed by recording Type A errors and overall errors following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. At this visit, a trough (pre-dose) FEV1 will be assessed by the Investigator using a spirometer provided by GSK and subjects will also be interviewed about whether the subject has experienced any serious adverse events or non –serious adverse drug reactions. Female subjects of child bearing potential will also be reminded about the requirement for contraception throughout their study participation.

The final Visit 6 will occur at Week 24. The ACT, AQLQ(S), EQ-5D and MARS-A questionnaires will be conducted at this visit and Type A errors and overall errors with inhaler will be recorded following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. At this visit, subjects will also be interviewed about whether they had experienced any serious adverse events or non –serious adverse drug reactions. The Investigator will be asked to make every effort to schedule Visit 6 at the same time of the day as Visit 2.

Revised text:

In addition, each subject whose FF/VI (Ellipta™) for asthma maintenance therapy is initiated at Visit 2 will be asked to read the information leaflet and will be instructed by the investigator on the proper use of Ellipta™. Each subject whose usual ICS/LABA DPI (Diskus™ or Turbuhaler) for asthma maintenance therapy is initiated at Visit 2 will follow the same procedure: reading of the information leaflet, demonstration of the proper use of the inhalers by the Investigator, and the correct dosing. This will be followed by an inhalation demonstration by the patient. **Any critical error (defined as an error that is most likely to result in no or only minimal medication being inhaled) and/or non-critical error** will be registered by the Investigator.

Randomisation at this visit will be performed on a 1:1 basis; to the FF/VI fixed dose combination delivered via Ellipta™ or the initiation with usual ICS/LABA inhalation powder for asthma maintenance therapy.

At Week 6 (Visit 3) and at Week 18 (Visit 5) subjects will be telephoned to enquire about whether the subject has experienced any serious adverse events or non serious adverse

drug reactions. At these telephone calls subjects will also be asked to complete the ACT questionnaire (paper version) and to send it back to the Investigator.

Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation Visit). Subjects will be asked to withhold from taking study medication on the day of Visit 4. At this visit, subjects will be asked to provide responses to the ACT, MARS-A and PASAP questionnaires and the inhaler use will be assessed by recording **critical and non-critical** errors following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. At this visit, a trough (pre-dose) FEV1 will be assessed by the Investigator using a spirometer provided by GSK and subjects will also be interviewed about whether the subject has experienced any serious adverse events or non –serious adverse drug reactions. Female subjects of child bearing potential will also be reminded about the requirement for contraception throughout their study participation.

The final Visit 6 will occur at Week 24. The ACT, AQLQ(S), EQ-5D and MARS-A questionnaires will be conducted at this visit and **critical and non-critical errors** with inhaler will be recorded following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. At this visit, subjects will also be interviewed about whether they had experienced any serious adverse events or non –serious adverse drug reactions. The Investigator will be asked to make every effort to schedule Visit 6 at the same time of the day as Visit 2.

Protocol synopsis for study HZA116492: Analysis

Original text:

The primary endpoint is defined as the change from baseline in the ACT total score assessed at Week 12 (Visit 4). The primary set of analysis is the ITT set.

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

Revised text:

The primary endpoint is defined as the change from baseline in the ACT total score assessed at Week 12 (Visit 4). The primary set of analysis is the ITT set.

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

Even though this study is open-label, the team will explore ways to ensure study blind is maintained during reviews of the data and pre-programming, prior to database lock. More information will be provided in the RAP.

Section 4.1 – Overall Design: Screening, randomisation and follow-up

Original text:

At the Screening Visit 1, eligible subjects will be consented to participate to the trial and prescribed the necessary examinations. The subjects will be asked to provide responses to the ACT. A screening log will be performed at this visit.

At a further visit (i.e V2, Day 0) occurring within 1 week after the screening visit (V1), subjects who meet all of the Inclusion Criteria, none of the Exclusion Criteria and who accept to give their consent will be randomised in the study. Randomisation at this visit will be on a 1:1 basis, to the FF/VI fixed dose combination delivered by Ellipta™ or to the initiation of any usual ICS/LABA DPI for asthma maintenance therapy chosen by the physician. Visit 1 and Visit 2 can be combined, if the subject did not take his usual asthma medication before coming on site. If Visit 1 and Visit 2 are combined then this visit will be Day 0.

At Visit 2 (Randomisation visit, Day 0) baseline pre-dose FEV1 will be assessed by the Investigator using a spirometer provided by GSK. At least three valid assessments should be performed with registration of the best value. On the morning of Visit 2 subjects will not take their usual asthma medication. Rescue medication (salbutamol) will be stopped 4 hours before baseline spirometry.

In addition at Visit 2, subjects will be asked to read the written Ellipta™ package insert if randomised into the FF/VI arm, or Diskus™ or Turbuhaler if randomised in the usual ICS/LABA therapy arm and will be instructed by the investigator on the proper use of inhalers. Then the subject will self-administer their first dose of study drug under supervision of the investigator. Any mistakes (Type A errors, likely to be critical and overall errors) will be registered by the trained HCP. After completing the procedure, subjects will be instructed in the correct use of the device by the trained physician if needed. Thereafter, each subject randomised into the FF/VI arm will be instructed to self-administer one inhalation with Ellipta™ inhaler each day at the same time of the day, at a time that is convenient for the subject. Subject randomised into usual ICS/LABA therapy arm will be instructed to self-administer the inhalation with Diskus™ or Turbuhaler inhaler twice a day.

Subjects will be recommended to use Salbutamol as needed throughout the study for relief of their asthma symptoms. At Visit 2 (randomisation, Day 0) subject will be asked to provide responses to the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires.

At Week 6 (Visit 3) and at Week 18 (Visit 5), subjects will be telephoned by the Investigator to enquire about whether the subject has experienced any adverse events (only the serious adverse events or non–serious adverse drug reactions will be recorded in eCRF). The Investigator makes the judgment as to whether it is related or not to study treatment. At these telephone calls, subjects will also be asked to complete the ACT questionnaire (paper version) and to send it back to the Investigator.

Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation Visit). Subjects will be asked to withhold from taking study medication on the day of Visit 4. At this visit, subjects will be asked to provide responses to the ACT, MARS-A

and PASAP questionnaires and the inhaler use will be assessed by recording Type A errors and overall errors following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. Pre-dose trough FEV1 will be assessed at this visit by the Investigator using the spirometer provided by GSK. Rescue medication (salbutamol) will be stopped 4 hours before the spirometry. At least three valid assessments should be performed with registration of the best value. At this visit, subjects will also be interviewed by the Investigator about whether the subject has experienced any adverse events (only the serious adverse events or non–serious adverse drug reactions will be recorded in eCRF). The Investigator makes the judgment as to whether it is related or not to study treatment. Female subjects of child bearing potential will also be reminded about the requirement for contraception throughout their study participation.

The final Visit 6 will occur at Week 24. The ACT, AQLQ(S), EQ-5D and MARS-A questionnaires will be conducted at this visit and the inhaler use will be assessed by recording Type A errors and overall errors following the next procedure: self-administration of one dose of study drug by subject; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. Subjects will be interviewed about whether the subject has experienced any serious adverse events or non –serious adverse drug reactions. The Investigator will be asked to make every effort to schedule Visit 6 at the same time of the day as Visit 2.

Revised text:

At the Screening Visit 1, eligible subjects will be consented to participate to the trial and prescribed the necessary examinations. The subjects will be asked to provide responses to the ACT. A screening log will be performed at this visit.

At a further visit (i.e V2, Day 0) occurring within 1 week after the screening visit (V1), subjects who meet all of the Inclusion Criteria, none of the Exclusion Criteria and who accept to give their consent will be randomised in the study. Randomisation at this visit will be on a 1:1 basis, to the FF/VI fixed dose combination delivered by Ellipta™ or to the initiation of **the** usual ICS/LABA DPI for asthma maintenance therapy chosen by the physician. Visit 1 and Visit 2 can be combined, if the subject did not take his usual asthma medication before coming on site. If Visit 1 and Visit 2 are combined then this visit will be Day 0.

At Visit 2 (Randomisation visit, Day 0) baseline pre-dose FEV1 will be assessed by the Investigator using a spirometer provided by GSK. At least three assessments should be performed with registration of the best value. **At least two of the spirometry efforts should be acceptable and repeatable.** On the morning of Visit 2 subjects will not take their usual asthma medication. Rescue medication (salbutamol) will be stopped 4 hours before baseline spirometry.

In addition at Visit 2, subjects will be asked to read the written Ellipta™ package insert if randomised into the FF/VI arm, or Diskus™ or Turbuhaler if randomised in the usual ICS/LABA therapy arm and will be instructed by the investigator on the proper use of inhalers. Then the subject will self-administer their first dose of study drug under

supervision of the investigator. Any **critical error (defined as an error that is most likely to result in no or only minimal medication being inhaled) or non-critical error** will be registered by the trained HCP. After completing the procedure, subjects will be instructed in the correct use of the device by the trained physician if needed. Thereafter, each subject randomised into the FF/VI arm will be instructed to self-administer one inhalation with Ellipta™ inhaler each day at the same time of the day, at a time that is convenient for the subject. Subject randomised into usual ICS/LABA therapy arm will be instructed to self-administer the inhalation with Diskus™ or Turbuhaler inhaler twice a day.

Subjects will be recommended to use Salbutamol as needed throughout the study for relief of their asthma symptoms. At Visit 2 (randomisation, Day 0) subject will be asked to provide responses to the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires.

At Week 6 (Visit 3) and at Week 18 (Visit 5), subjects will be telephoned by the Investigator to enquire about whether the subject has experienced any adverse events (only the serious adverse events or non–serious adverse drug reactions will be recorded in eCRF). The Investigator makes the judgment as to whether it is related or not to study treatment. At these telephone calls, subjects will also be asked to complete the ACT questionnaire (paper version) and to send it back to the Investigator.

Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation Visit). Subjects will be asked to withhold from taking study medication on the day of Visit 4. At this visit, subjects will be asked to provide responses to the ACT, MARS-A and PASAP questionnaires and the inhaler use will be assessed by recording **critical and non-critical** errors following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. Pre-dose trough FEV1 will be assessed at this visit by the Investigator using the spirometer provided by GSK. Rescue medication (salbutamol) will be stopped 4 hours before the spirometry. At least three valid assessments should be performed with registration of the best value. At this visit, subjects will also be interviewed by the Investigator about whether the subject has experienced any adverse events (only the serious adverse events or non–serious adverse drug reactions will be recorded in eCRF). The Investigator makes the judgment as to whether it is related or not to study treatment. Female subjects of child bearing potential will also be reminded about the requirement for contraception throughout their study participation.

The final Visit 6 will occur at Week 24. The ACT, AQLQ(S), EQ-5D and MARS-A questionnaires will be conducted at this visit and the inhaler use will be assessed by recording **critical and non-critical** errors following the next procedure: self-administration of one dose of study drug by subject; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. Subjects will be interviewed about whether the subject has experienced any serious adverse events or non –serious adverse drug reactions. The Investigator will be asked to make every effort to schedule Visit 6 at the same time of the day as Visit 2.

Section 4.1 – Overall Design: Collected data

Original text:

Eligible subjects will complete the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires at Randomisation Visit (Visit 2, Day 0) and at Visit 6 (Week 24), or at the Early Withdrawal visit. ACT questionnaire will be completed also by the subject at Screening visit (Visit 1), Week 6 (phone call 1 or Visit 3), at Week 12 (Visit 4) and Week 18 (phone call 2 or Visit 5). MARS-A questionnaire will be completed also at Week 12 (Visit 4). Inhaler use assessment will be performed at Randomisation Visit (Visit 2, Day 0), at Week 12 (Visit 4) and at Week 24 (Visit 6) / Early Withdrawal visit by recording the Type A errors and the overall errors. Patient's satisfaction and preference (PASAP-Q) will be evaluated at Week 12 (Visit 4).

Revised text:

Eligible subjects will complete the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires at Randomisation Visit (Visit 2, Day 0) and at Visit 6 (Week 24), or at the Early Withdrawal visit. ACT questionnaire will be completed also by the subject at Screening visit (Visit 1), Week 6 (phone call 1 or Visit 3), at Week 12 (Visit 4) and Week 18 (phone call 2 or Visit 5). MARS-A questionnaire will be completed also at Week 12 (Visit 4). Inhaler use assessment will be performed at Randomisation Visit (Visit 2, Day 0), at Week 12 (Visit 4) and at Week 24 (Visit 6) / Early Withdrawal visit by recording the **critical and non-critical** errors. Patient's satisfaction and preference (PASAP-Q) will be evaluated at Week 12 (Visit 4).

Section 4.3 – Type and Number of Subjects

Original text:

Subjects with documented physician's diagnosis of asthma ≥ 1 year, unsatisfactorily controlled asthma (ACT < 20) treated by ICS alone and intended to be treated by ICS/LABA maintenance therapy. A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.

It is estimated that approximately 70 study centers in France will be required to have a total number of 422 randomised subjects so that at least 382 subjects will be evaluable. Assuming a 10% of screen failure, 466 subjects will have to be screened in the study with 6 subjects /center.

Revised text:

Subjects with documented physician's diagnosis of asthma ≥ 1 year, unsatisfactorily controlled asthma (ACT < 20) treated by ICS alone and intended to be treated by ICS/LABA maintenance therapy. A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.

It is estimated that approximately 70 study centers in France will be required to have a total number of 422 randomised subjects so that at least 382 subjects will be evaluable. Assuming a 10% screen failure **rate**, **approximately** 466 subjects will have to be screened in the study with 6 subjects /center.

Section 4.6.1 – Risk Assessment

Original text:

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Hypersensitivity	The reported hypersensitivity events in clinical trials, were not generally serious, did not lead to discontinuation in the studies, and were usually confounded, by either the subject's medical condition (such as COPD) or other factors at the time of the event. In spontaneous data, symptoms of hypersensitivity ranged from mild rash and pruritis to severe generalised rash and erythema and severe cases involving angiodema of the face, larynx and pharynx. These events were rare.	Subjects with a history of adverse reaction including immediate or delayed hypersensitivity to any intranasal, inhaled, or systemic corticosteroid and LABA therapy and to components of the inhalation powder (e.g., lactose, magnesium stearate). In addition, subjects with a history of severe milk protein allergy that, in the opinion of the Investigator, contraindicates the subject's participation will also be excluded.

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Systemic effects of corticosteroids: adrenal suppression; eye disorders; decreased bone density and associated fractures	Adrenal suppression is a known class effect of corticosteroids. Preclinical studies showed that FF effects are comparable with other corticosteroids. No studies have shown a clinically relevant effect of FF/VI on the hypothalamic pituitary axis (HPA). This includes a formal HPA study (HZA106851), using 24 hour serum cortisol measurements, and multiple studies with COPD and asthma subjects which monitored urinary cortisol. During clinical development, no events of Adrenal Suppression were reported. Eye disorders are a known class effect of corticosteroids. Preclinical studies showed FF at high dose comparable to other high dose corticosteroids. In study HZA106839 (FF/VI , FF and FP in subjects with asthma), formal ophthalmic assessments were conducted (including LOCS III evaluations for ocular opacities) throughout the study. This study showed no apparent effects on lens opacification, compared to baseline. During studies in both subjects with asthma and COPD, no associated affect on ocular disorders	The mitigation in this study for all systemic effects of corticosteroids is that chronic users of systemic corticosteroids are excluded from this study: a subject who, in the opinion of the Investigator, is considered to be a chronic user of systemic corticosteroids for respiratory or other indications (if unsure discuss with the medical monitor prior to screening).

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	was observed. Decreased bone density is a down class effect of corticosteroids. Preclinical data showed that high dose corticosteroid effects of FF were comparable to other conrticosteroids. Patients with Asthma In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of fractures with FF/VI was <=1%, and usually associated with trauma.	

Revised text:

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Hypersensitivity	The reported hypersensitivity events in clinical trials, were not generally serious, did not lead to discontinuation in the studies, and were usually confounded, by either the subject's medical condition (such as COPD) or other factors at the time of the event. In spontaneous data, symptoms of hypersensitivity ranged from mild rash and pruritis	Subjects with a history of adverse reaction including immediate or delayed hypersensitivity to any intranasal, inhaled, or systemic corticosteroid and LABA therapy and to components of the inhalation powder (e.g., lactose, magnesium stearate) **will be excluded**. In addition, subjects with a history of severe milk protein allergy that, in the opinion of the Investigator, contraindicates the subject's

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	to severe generalised rash and erythema and severe cases involving angiodema of the face, larynx and pharynx. These events were rare.	participation will also be excluded.
Systemic effects of corticosteroids: adrenal suppression; eye disorders; decreased bone density and associated fractures	Adrenal suppression is a known class effect of corticosteroids. Preclinical studies showed that FF effects are comparable with other corticosteroids. No studies have shown a clinically relevant effect of FF/VI on the hypothalamic pituitary axis (HPA). This includes a formal HPA study (HZA106851), using 24 hour serum cortisol measurements, and multiple studies with COPD and asthma subjects which monitored urinary cortisol. During clinical development, no events of Adrenal Suppression were reported. Eye disorders are a known class effect of corticosteroids. Preclinical studies showed FF at high dose comparable to other high dose corticosteroids. In study HZA106839 (FF/VI , FF and FP in subjects with asthma), formal ophthalmic assessments were conducted (including LOCS III evaluations for ocular	The mitigation in this study for all systemic effects of corticosteroids is that chronic users of systemic corticosteroids are excluded from this study: a subject who, in the opinion of the Investigator, is considered to be a chronic user of systemic corticosteroids for respiratory or other indications (if unsure discuss with the medical monitor prior to screening) **will be excluded**.

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	opacities) throughout the study. This study showed no apparent effects on lens opacification, compared to baseline. During studies in both subjects with asthma and COPD, no associated affect on ocular disorders was observed. Decreased bone density is a **known** class effect of corticosteroids. Preclinical data showed that high dose corticosteroid effects of FF were comparable to other conrticosteroids. Patients with Asthma In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of fractures with FF/VI was <=1%, and usually associated with trauma.	

Section 5.3 – Screening/Baseline/Failures

Original text:

A total of 466 subjects will be screened as 422 subjects are planned to be randomised and 10% of screen failure is expected.

Revised text:

Approximately 466 subjects will be screened as 422 subjects are planned to be randomised and **a** 10% of screen failure **rate** is expected.

Section 6.7 – Preparation/Handling/Storage/Accountability

Original text:

All FF/VI and comparative ICS/LABA maintenance therapy prescribed throughout the study will be dispensed at, and collected from the investigator site.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. All DPIs containing FF/VI must be stored at a temperature of up to 25°C. Budesonide/Formoterol and Fluticasone Propionate/Salmeterol DPIs must be stored at a temperature of up to 30°C.

Revised text:

All FF/VI and comparative ICS/LABA maintenance therapy prescribed throughout the study will be dispensed at, and collected from the investigator site.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. All DPIs containing FF/VI must be stored at a temperature of up to 25°C. Budesonide/Formoterol DPIs must be stored at a temperature of up to 30°C **and Fluticasone Propionate/Salmeterol DPIs stored at 2-25°C**.

Section 6.7 – Investigational Product Malfunction

New Text:

Any investigational product inhaler that fails to function properly must be identified to GSK personnel. Details of the failure will be documented in the eCRF. Ellipta inhalers will be returned to GSK for testing. The subject should return the inhaler to the clinic as soon as possible to avoid missing any doses. The site will then contact GSK's internal IWRS (also known as the Registration and Medication Ordering System [RAMOS] NG) and obtain a new treatment pack number for this subject and dispense a new study medication kit from the site's investigational product supply, as instructed per the IWRS.

Section 7.1 – Time and Events Table

Original table:

Study Visits	Visit 1* Screening	Visit 2* Randomisation	Visit 3 Phone call 1	Visit 4**	Visit 5 Phone call 2	Visit 6	Early Withdrawal
Study week (± specified no. of days)	Day -7 to -1	Day 0	Week 6 (±3 days)	Week 12 (±7 days)	Week 18 (±3 days)	Week 24 (±14 days)	Early Withdrawal
Visit	x	x		x		x	x
Phone interview			x		x		
Assessments							

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

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

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

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

***PGx saliva sample collected at Visit 2 (Randomisation) or any scheduled clinic visit thereafter.
**** Only if early withdrawal occurs before Week 12.
¥ Only for childbearing women.

Revised table:

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

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

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

* Visit 1 and Visit 2 can be combined if the subject did not take his usual asthma medication before coming on site. Then this visit will be Day 0 and all baseline characteristics will be collected at this visit. Written Informed Consent must be obtained prior to initiation of study procedures or initiating changes in medications.
** Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation visit).
***PGx saliva sample collected at Visit 2 (Randomisation) or any scheduled clinic visit thereafter.
**** Only if early withdrawal occurs before Week 12.
¥ Only for childbearing women.
Note: All adverse events will be recorded in the source documents but only information regarding non-serious adverse drug reactions (ADRs) and serious adverse events (SAEs) will be documented and reported in the eCRF.

Section 7.3.1: Inhaler Correct Use Assessment

Original text:

Correct use of the inhaler will be assessed as outlined in the Time and Events Table (Section 7.1).

Table 6 List of Type A (likely to be critical) and overall errors for Ellipta™

Type A errors for Ellipta™	**yes**	**no**	**Overall errors for Ellipta™**	**yes**	**no**
Failed to open cover			No exhalation before an inhaling		
Exhaled directly into mouthpiece			Blocked air inlet during inhalation manoeuvre		
Shook the device upside down after dose preparation			Inhalation manoeuvre: - long - steady - deep		
Inhalation from mouthpiece (kept between lips)			Blocked air inlet during inhalation manoeuvre		
			Did not hold breath		

			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
			Any other comments: [free text box]		

Table 7 List Type A (likely to be critical) and overall errors for Diskus™

Type A errors for Diskus™	**yes**	**no**	**Overall errors for Diskus™**	**yes**	**no**
Failed to open cover			No exhalation before an inhalation		
Lever is not pushed back			Inhalation manoeuvre: - steady - deep		
Exhaled directly into mouthpiece			Did not hold breath		
No seal by the lips round the mouthpiece during the inhalation			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
			Any other comments: [free text box]		

Table 8 List of Type A (likely to be critical) errors and overall errors for Turbuhaler

Type A errors for Turbuhaler	**yes**	**no**	**Overall errors for Turbuhaler**	**yes**	**no**
Failed to remove cap			No exhalation before an inhalation		
Did not hold device upright (±45% OK) during dose preparation			Inhalation manoeuvre: - forceful - deep Note to *HCP: it is important that the inhalation is forceful and deep from the start for this inhaler*		
Base not twisted fully backwards and forwards, no click heard			Blocked air inlet during inhalation manoeuvre		
Shook the device after dose preparation			Did not hold breath		

Exhaled directly into mouthpiece			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
No seal by the lips round the mouthpiece during the inhalation			Any other comments: [free text box]		

Revised text:

Correct use of the inhaler will be assessed as outlined in the Time and Events Table (Section 7.1).

Table 9 Critical and Non-critical errors for Ellipta™

Instructions: Critical Errors are identified in bold text in the list below. A critical error is defined as an error that is most likely to result in no or only minimal medication being inhaled. Check only one box.					
Did the subject make an error while using the device? [ ] No [ ]Yes if yes, tick appropriate options below					
Critical Errors for Ellipta™	**yes**	**no**	**Non-critical Errors for Ellipta™**	**yes**	**no**
Failed to open cover			No exhalation before an inhalation		
Shook the device upside down after dose preparation			Inhalation manoeuvre was not: - long - steady - deep		
Exhaled directly into mouthpiece			Blocked air inlet during inhalation manoeuvre -		
No seal by the lips around the mouthpiece during the inhalation			Did not hold breath		
			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
Any other comments: [free text box]					

Table 10 Critical and Non-critical errors for Diskus™

Instructions: Critical Errors are identified in bold text in the list below. A critical error is defined as an error that is most likely to result in no or only minimal medication being inhaled. Check only one box.					
Did the subject make an error while using the device? [ ] No [ ]Yes if yes, tick appropriate options below					
Critical Errors for Diskus™	**yes**	**no**	**Non-critical Errors for Diskus™**	**yes**	**no**
Failed to open cover			No exhalation before an inhalation		
Lever is not pushed back			Inhalation manoeuvre was not: - steady - deep		
Shook the device after dose preparation			Did not hold breath		
Exhaled directly into mouthpiece			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
No seal by the lips round the mouthpiece during the inhalation					
Any other comments: [free text box]					

Table 11 Critical and Non-critical errors for Turbuhaler

Instructions: Critical Errors are identified in **bold text** in the list below. A critical error is defined as an error that is most likely to result in no or only minimal medication being inhaled. Check only one box.					
Did the subject make an error while using the device? [ ] No [ ]Yes *if yes, tick appropriate options below*					
Critical Errors for Turbuhaler	**yes**	**no**	**Non-critical Errors for Turbuhaler**	**yes**	**no**
Failed to remove cap			Device tipped downwards after dose preparation		
Did not hold device upright (±45% OK) during dose preparation			No exhalation before an inhalation		

Base not twisted fully backwards and forwards, no click heard			Inhalation manoeuvre was not: - forceful - deep Note to *HCP: it is important that the inhalation is forceful and deep from the start for this inhaler*		
Shook the device after dose preparation			Blocked air inlet during inhalation manoeuvre		
Exhaled directly into mouthpiece			Did not hold breath		
No seal by the lips round the mouthpiece during the inhalation			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
Any other comments: [free text box]					

Section 7.3.2: Trough (pre-dose) FEV1 assessment

Original text:

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

Revised text:

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

Section 7.4.7: Clinical Safety Laboratory Assessment

Original text:

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the Investigator are to be recorded as non-serious ADRs or SAEs as appropriate.

Revised text:

There are no clinical safety laboratory assessment requirements for this study.

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) **recorded during a routine clinic visit**, including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the Investigator are to be recorded as non-serious ADRs or SAEs as appropriate.

Section 9.3.1 – Analysis Population

Original text:

Populations considered for analysis are as follows:

Intent to treat (ITT) set: All randomized subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy). The ITT set will be used to analyze the primary efficacy endpoint analysis, the secondary efficacy endpoint and other efficacy endpoints. Subjects will be assigned to the treatment group as randomized for the ITT set.

Per-protocol (PP) set: all ITT subjects without any major violations of study procedures. Major protocol violations will be identified prior to database lock. Protocol deviations will be reviewed and classified as minor or major during a data review meeting that will be held before database lock. The exclusion of subjects from the PP set will be specified and documented in the RAP.

Safety set: All enrolled subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy) and considered as-treated. The Safety set will be the basis for safety analyses. Subjects will be assigned to the treatment group as treated for the Safety set.

Revised text:

Populations considered for analysis are as follows:

Intent to treat (ITT) population: All randomized subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy). The ITT **population** will be used to analyze the primary efficacy endpoint analysis, the secondary efficacy endpoint and other efficacy endpoints. Subjects will be assigned to the treatment group as randomized for the ITT **population**.

Per-protocol (PP) population: all ITT subjects without any major violations of study procedures. Major protocol violations will be identified prior to database lock. Protocol deviations will be reviewed and classified as minor or major during a data

review meeting that will be held before database lock. The exclusion of subjects from the PP **population** will be specified and documented in the RAP.

Safety population: All enrolled subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy) and considered as-treated. The Safety **population** will be the basis for safety analyses. Subjects will be assigned to the treatment group as treated for the Safety **population**.

Section 9.4 – Key Elements of Analysis Plan

Original text:

The primary comparison of interest is the comparison of the change from baseline (Visit 2) in the total ACT score assessed at Week 12 (Visit 4) between FF/VI (92mcg/22mcg or 184mcg/22mcg) and usual ICS/LABA inhalation powder for asthma maintenance therapy.

The primary set for analysis is the intent to treat set. A sensitivity analysis will be performed in the PP set.

Revised text:

The primary comparison of interest is the comparison of the change from baseline (Visit 2) in the total ACT score assessed at Week 12 (Visit 4) between FF/VI (92mcg/22mcg or 184mcg/22mcg) and usual ICS/LABA inhalation powder for asthma maintenance therapy.

The primary set for analysis **will be performed on** the intent to treat **population**. A sensitivity analysis will be performed in the PP **population**.

Section 9.4.1 – Primary Analysis

Original text:

The primary endpoint is defined as the change from baseline (Visit 2) in the ACT total score assessed at Week 12 (Visit 4).

The primary set of analysis is the ITT set.

1) **Non-inferiority testing.**

The non-inferiority of FF/VI versus any other ICS/LABA DPI comparator will be primarily tested in a mixed model repeated measures (MMRM) approach. The model will include factors and covariates as follow: treatment, scheduled visit time point (Week 6 and Week 12), baseline ACT, treatment by visit interaction, baseline ACT by visit interaction, gender, age and patient will be fitted as a random factor. The Restricted Maximum Likelihood (REML) estimation approach will be used, and the default

covariance structure will be unstructured. Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point will be performed. The 95% confidence interval on the treatment effect (FF/VI vs ICS/LABA comparator) will be estimated at Week 12 (Visit 4) in this model. Non-inferiority will be achieved if the non-inferiority margin of -1.5 is lower than the lower bound of the confidence interval on the difference between FF/VI and any other comparator (positive values of the difference favour FF/VI).

Sensitivity analyses:

e) Handling missing data

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

1. Missing values at Week 12 (Visit 4) will be replaced by the post-randomization last available value (either the week 6-based ACT score or the ACT score at treatment withdrawal time, if any), i.e. based on the Last Observation Carried Forward method. The change from baseline in ACT at Week 12 (Visit 4) will be analyzed in an ANCOVA model adjusting for treatment and baseline ACT score. The treatment effect (FF/VI versus any other ICS/LABA comparator) and its corresponding 95% confidence interval will be estimated in this model to test the non-inferiority hypothesis.

2. Multiple imputation (MI) analyses utilizing covariates known to be predictive of response: season at randomization, observed value of ACT at Week 6, observed value of ACT at Week 12 (Visit 4). Other covariates may be considered and if so it will be detailed in the RAP.

   Step 1: For each treatment group separately, missing measurements are imputed for subjects with a baseline measurement where there are missing observations (at either Week 6 or Week 12) using the above covariates and regression-based imputation method. The Markov Chain Monte Carlo (MCMC) method for MI will be used and ten such sets of imputed data will be created each with the observed values or imputed values for subjects with missing observations.

   Step 2: Each imputed data set will be analyzed using the primary MMRM model. The treatment effect from these 10 analyses will then be pooled using standard MI theory to make an overall inference. The difference in the least squares means between the two groups at Week 12 (Visit 4) and the corresponding 95% confidence interval for the difference will be presented.

f) A sensitivity analysis based on the semi parametric Hodges-Lehmann (HL) approach will be proposed to assess the robustness of the MMRM Model-based

non-inferiority results. The HL difference between groups with the corresponding 95% confidence interval will be provided.

g) Sensitivity analyses for handling treatment withdrawal: when treatment withdrawal occurs, an alternative method for imputing the missing value at the nearest visit after withdrawal time will be proposed: the primary endpoint missing value will be estimated by the worst ACT score observed between baseline visit (included) and withdrawal time (included).

h) The primary analysis (i.e. based on the MMRM approach) and the same sensitivity analyses presented here above will be performed in the Per Protocol set.

Revised text:

The primary endpoint is defined as the change from baseline (Visit 2) in the ACT total score assessed at Week 12 (Visit 4).

The primary **population** of analysis **will be** the ITT **population**.

1) Non-inferiority testing.

The non-inferiority of FF/VI versus any other ICS/LABA DPI comparator will be primarily tested in a mixed model repeated measures (MMRM) approach. The model will include factors and covariates as follow: treatment, scheduled visit time point (Week 6 and Week 12), baseline ACT, treatment by visit interaction, baseline ACT by visit interaction, gender, age and patient will be fitted as a random factor. The Restricted Maximum Likelihood (REML) estimation approach will be used, and the default covariance structure will be unstructured. Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point will be performed. The 95% confidence interval on the treatment effect (FF/VI vs ICS/LABA comparator) will be estimated at Week 12 (Visit 4) in this model. Non-inferiority will be achieved if the non-inferiority margin of -1.5 is lower than the lower bound of the confidence interval on the difference between FF/VI and any other comparator (positive values of the difference favour FF/VI).

Sensitivity analyses:

i) Handling missing data

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

3. Missing values at Week 12 (Visit 4) will be replaced by the post-randomization last available value (either the week 6-based ACT score or the ACT score at treatment withdrawal time, if any), i.e. based on the Last

Observation Carried Forward method. The change from baseline in ACT at Week 12 (Visit 4) will be analyzed in an ANCOVA model adjusting for treatment and baseline ACT score. The treatment effect (FF/VI versus any other ICS/LABA comparator) and its corresponding 95% confidence interval will be estimated in this model to test the non-inferiority hypothesis.

4. Multiple imputation (MI) analyses utilizing covariates known to be predictive of response: season at randomization, observed value of ACT at Week 6, observed value of ACT at Week 12 (Visit 4). Other covariates may be considered and if so it will be detailed in the RAP.

   Step 1: For each treatment group separately, missing measurements are imputed for subjects with a baseline measurement where there are missing observations (at either Week 6 or Week 12) using the above covariates and regression-based imputation method. The Markov Chain Monte Carlo (MCMC) method for MI will be used and ten such sets of imputed data will be created each with the observed values or imputed values for subjects with missing observations.

   Step 2: Each imputed data set will be analyzed using the primary MMRM model. The treatment effect from these 10 analyses will then be pooled using standard MI theory to make an overall inference. The difference in the least squares means between the two groups at Week 12 (Visit 4) and the corresponding 95% confidence interval for the difference will be presented.

j) A sensitivity analysis based on the semi parametric Hodges-Lehmann (HL) approach will be proposed to assess the robustness of the MMRM Model-based non-inferiority results. The HL difference between groups with the corresponding 95% confidence interval will be provided.

k) Sensitivity analyses for handling treatment withdrawal: when treatment withdrawal occurs, an alternative method for imputing the missing value at the nearest visit after withdrawal time will be proposed: the primary endpoint missing value will be estimated by the worst ACT score observed between baseline visit (included) and withdrawal time (included).

l) The primary analysis (i.e. based on the MMRM approach) and the same sensitivity analyses presented here above will be performed **on** the Per Protocol **population**.

Section 9.4.2 – Secondary Analyses: Other Secondary Analyses

Original text:

Proper use of the medical device

The other key secondary endpoint will be the correct use of the inhaler device assessed at randomisation (Visit 2), at Week 12 (Visit 4) and at Week 24 (Visit 6). The device will be considered as adequately used if the patient didn't make any Type A error (all critical items correct) at the corresponding visits (randomisation [Visit 2], week 12 [Visit 4] and

week 24 [Visit 6]). Proportions of subjects correctly using the device will be estimated within each group. A corresponding 95% confidence interval of the difference in proportions will also be provided. Additional exploratory analyses could be performed and will be detailed in the RAP. Even if tests will be performed, no causal association will be inferred from these analyses.

Revised text:

Proper use of the medical device

The other key secondary endpoint will be the correct use of the inhaler device assessed at randomisation (Visit 2), at Week 12 (Visit 4) and at Week 24 (Visit 6). The device will be considered as adequately used if the patient didn't make any **critical error** at the corresponding visits (randomisation [Visit 2], week 12 [Visit 4] and week 24 [Visit 6]). Proportions of subjects correctly using the device will be estimated within each group. A corresponding 95% confidence interval of the difference in proportions will also be provided. Additional exploratory analyses could be performed and will be detailed in the RAP. Even if tests will be performed, no causal association will be inferred from these analyses.

Section 9.4.3 – Other Analyses: Change from baseline in pre-dose trough FEV1

Original text:

The analysis of the other endpoints defined in this section will be provided for exploratory purposes only. Additional exploratory analyses could be performed and will be detailed in the RAP. Even if tests will be performed and 95% confidence intervals will be provided, no causal association will be inferred from these analyses.

Change from baseline in pre-dose trough FEV1

Results will be summarized for each group and the results of the difference between groups will be presented with the corresponding 95% confidence interval at Week 12 (Visit 4).

Response to treatment

- Binary response defined as an ACT score ≥ 20 at a given visit OR a 3 point increase from baseline in ACT change.

The responder analyses will be conducted using a logistic regression model at a given Visit or Phone Call adjusting for treatment and stratification factors (baseline ACT score categorized into two classes, baseline asthma therapy, and potentially season at randomization). Treatment by stratification factors interaction effects will be further investigated in additional logistic models adjusting for these specific effects.

Revised text:

The analysis of the other endpoints defined in this section will be provided for exploratory purposes only. Additional exploratory analyses could be performed and will be detailed in the RAP. Even if tests will be performed and 95% confidence intervals will be provided, no causal association will be inferred from these analyses.

Change from baseline in pre-dose trough FEV1

Results will be summarized for each group at Week 12 (Visit 4). **More detail will be provided in the RAP.**

Response to treatment

- Binary response defined as an ACT score ≥ 20 at a given visit OR a 3 point increase from baseline in ACT change.

The responder analyses will be conducted using a logistic regression model at a given Visit or Phone Call adjusting for treatment and stratification factors (baseline ACT score categorized into two classes, baseline asthma therapy, and potentially season at randomization). Treatment by stratification factors interaction effects will be further investigated in additional logistic models adjusting for these specific effects.

- **Binary response defined as an ACT score ≥ 20 at a given visit.**

The frequency and the percentage of subjects with ACT score ≥ 20 at a given visit will be described by treatment group. More detail will be provided in the RAP.

- **Change from baseline in individual question scores for ACT at a given visit**

For each question the statistical parameters of the changes will be summarized by treatment group. More detail will be provided in the RAP.

TITLE PAGE

Division: Worldwide Development
Information Type: Clinical Protocol

Title:	A 6-month, open label, randomised, efficacy study to evaluate fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) Inhalation Powder delivered once daily via the Dry Powder Inhaler Ellipta™ compared with usual ICS/LABA maintenance therapy delivered by Dry Powder Inhaler in subjects with Persistent Asthma

Compound Number: GW685698+GW642444

Development Phase IIIb

Effective Date: 27-FEB-2015

Subject: Fluticasone Furoate, Vilanterol, Dry Powder Inhaler, Efficacy, Safety, Quality of Life, Asthma

Author(s): Dr PPD (Medical Project Leader France), Dr PPD (Respiratory Medical Director France), PPD (Statistical Coordinator France), PPD (Operations and Science Leader France), PPD (Clinical Development Director, MDC Global Clinical Develop-UK, RD Respiratory R&D), PPD PPD (Director SERM, GCSP SERM - Development UK, RD Chief Medical Office).

SPONSOR SIGNATORY

Sponsor Signatory: Medicines Development Center, VP or designee	**Signature:**	**Date:**
David Leather, MD **Medical VP, Global Medical Affairs Leader - Relvar** Global Respiratory Franchise GlaxoSmithKline 1-3 Ironbridge Road, Stockley Park West, Uxbridge, Middlesex, UB11 1BT, UK	PPD	27th Feb 2015.
Soizic Courcier, MD **Medical and Regulatory Affairs Director, VP** Laboratoire GlaxoSmithKline 100 route de Versailles 78163 Marly-le-Roi cedex, France	PPD	27.02.2015

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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Regulatory Agency Identifying Number(s): EudraCT No: 2014-000551-81

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

Investigator Signature	Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY HZA116492

Rationale

The pivotal phase III studies were key to demonstrate the safety and efficacy of Fluticasone Furoate/ Vilanterol in asthma. However, it is increasingly acknowledged that randomised clinical trials by definition tend to be highly controlled and enrol a more highly selected patient population than is expected to be prescribed the medication post-approval. The need for data in a more representative population in a close to 'real world' setting is increasingly being recognised as important to complement pivotal phase III safety and efficacy studies in order to establish the benefits and therefore the value of a medication in the context of clinical practice.

Moreover, double-blind comparison of once daily to twice daily medicines, while important for assessing efficacy, removes a potential source of difference in effectiveness derived from patient behaviour and experience. GlaxoSmithKline (GSK) has observed an increasing demand from payers who make reimbursement and policy decisions for data that enables the evaluation of a drug's effectiveness and impact on the health care system at launch, e.g. effectiveness data from a setting close to 'real world' in addition to traditional randomised clinical studies.

This open-label randomised clinical study will evaluate the efficacy and safety of FF/VI Inhalation Powder (FF 92mcg/VI 22mcg or FF 184mcg/VI 22mcg) compared with two fixed combinations ICS/LABA (Inhaled Corticosteroids/Long Acting Beta Agonists) inhalation powders, fluticasone propionate/salmeterol (FP/S) and budesonide/formoterol (BUD/F), for asthma maintenance therapy, in a "close to real life" manner in French primary and respiratory specialist care. FF/VI will be administered once-daily (QD) via Ellipta™ and FP/S or BUD/F twice daily (BID) via Diskus™ and Turbuhaler respectively.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To compare the efficacy of FF/VI 92mcg/ 22mcg or FF 184mcg/22mcg with usual fixed combinations ICS/LABA for asthma maintenance therapy at Week 12 (Visit 4).	• Change from baseline in the Asthma Control Test (ACT) total score at Week 12 (Visit 4).
Secondary	
• To assess effect of FF/VI on asthma control compared with usual ICS/LABA fixed combination at Week 24 (Visit 6).	• Change from baseline in ACT score at Week 24 (Visit 6).
• To assess ELLIPTA™ inhaler correct use compared with other DPI (Diskus™ and Turbuhaler) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the	• Percentage of subjects making at least 1 Type A error (likely to be critical) and overall errors at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of

Objectives	Endpoints
use at Week 12 (Visit 4).	the use at Week 12 (Visit 4).
Other	
• To assess effect of FF/VI on trough (pre-dose) FEV1 compared with usual ICS/LABA fixed combination at Week 12 (Visit 4)	• Change from baseline in trough (pre-dose) FEV1 at Week 12 (Visit 4).
• To assess the effect of FF/VI on response to treatment at Week 12 (Visit 4) and Week 24 (Visit 6)	• ACT score ≥ 20 or 3 point increase from baseline in ACT at Week 12 (Visit 4) and Week 24 (Visit 6). Note: A 3 point increase in ACT total score was suggested as the Minimal Clinically Important Difference (MCID) in the literature [Schatz, 2009].
• To assess the adherence with study medication at Week 12 (Visit 4) and Week 24 (Visit 6)	• Number of medications dispensed and collected during the study at Week12 (Visit 4) and Week 24 (Visit 6), • Score of the MARS-A questionnaire (Medication Adherence Report Scale) at the randomisation (Day0), Week12 (Visit 4) and Week24 (Visit 6).
• To assess the effect of FF/VI on severe asthma exacerbation over the study period	• Number of subject with at least 1 severe asthma exacerbation*, number of severe asthma exacerbation and annual severe exacerbation rate over the study period.
• To assess the effect of FF/VI on Health Related Quality of Life at Week 24 (Visit 6)	• Change from baseline in total score and domain scores of AQLQ(S) (Asthma Quality of Life Questionnaire) at Week 24 (Visit 6). • An increase from baseline of ≥ 0.5 in AQLQ(s) total score at Week 24 (Visit 6). • An increase from baseline of ≥ 0.5 in AQLQ(s) environmental stimuli domain score at Week 24 (Visit 6).

Objectives	Endpoints
• To assess Patient Satisfaction and Preference assessment with different inhalers at Week 12 (Visit 4) • To evaluate the Safety of FF/VI compared with usual ICS/LABA (FP/S and Bud/F).	• Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) Individual domain scores at Week 24 (Visit 6). • Change from baseline in total score and domain scores of AQLQ(S) at Week 24 (Visit 6). • Health status using the EuroQol Questionnaire (EQ-5D) at Week 24 (Visit 6). • Score of PASAP Questionnaire (Patient Satisfaction and Preference) at Week 12 (Visit 4). Serious Adverse Events (SAE) and non-serious Adverse Drug Reactions (ADR): • Frequency and type of serious adverse events, • Frequency and type of non-serious adverse drug reactions related to treatment.

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

Notes defining endpoints:

1. Contacts with a doctor or hospitalisation are defined as exacerbation-related contacts if these contacts were a direct result of an acute worsening of asthma symptoms.
2. A prescription of systemic corticosteroid is defined as exacerbation-related if the reason the drug was given, in whole or in part, was to treat an acute worsening of asthma symptoms.
3. Exacerbation-related hospitalisation includes hospitalisation that is prolonged as a result of an asthma exacerbation.

Overall Design

This is a Phase IIIb multi-centre, randomised open label, parallel group study performed in subjects in primary and respiratory specialist care who have a diagnosis of asthma and regular treatment for asthma in France.

Approximately 422 asthmatic subjects who are taking an inhaled corticosteroid (ICS) alone without any other controller treatment will be randomised in a 1:1 ratio to receive either FF/VI (FF/VI 92mcg/22mcg or FF/VI 184mcg/22mcg) once daily or one ICS/LABA inhalation powder twice daily for asthma maintenance therapy.

As much as possible enrolment of subjects should be performed at a constant accrual rate throughout a full year in order to minimize a seasonality bias.

Subjects will visit the HCP (general practitioner or pulmonologist) a minimum of 3 times as per protocol over a 6 month period while participating in the study. The first visit will be Visit 1 Screening Visit, which can take place between Day -7 and Day -1. At Visit 1, suitable subjects will be consented. The second visit will be Visit 2 (Day 0, Randomisation Visit) where subjects who meet all of the Inclusion Criteria and none of the Exclusion Criteria will be randomised. Visit 1 and Visit 2 can be combined, if the subject did not take his usual asthma medication before coming on site. If Visit 1 and Visit 2 are combined then this visit will be Day 0 and all baseline characteristics will be collected at this visit.

At Visit 2 (Day 0) subject will be asked to provide responses to the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires. Baseline pre-dose FEV1 will be assessed at this visit by the Investigator using a spirometer provided by GSK. At least three valid assessments should be performed with registration of the best value. On the morning of Visit 2 subjects will not take their usual asthma medication. Rescue medication (salbutamol) will be stopped 4 hours before baseline spirometry.

Subjects will self-administer their first dose of study drug in the clinic at Visit 2 (or the combined Visit 1 and Visit 2 if appropriate) under supervision of the site staff.

Thereafter, each subject randomised into the FF/VI arm will be instructed to self-administer one inhalation with Ellipta™ inhaler each day at the same time of the day, at a time that is convenient for the subject. Each subject will be advised to adhere to FF/VI dosing regimen throughout the study. The investigator may adjust the dose of FF/VI according to the subject's response. Dose adjustment is allowed and is not considered as a treatment failure in accordance with treatment failure definition.

In addition, each subject whose FF/VI (Ellipta™) for asthma maintenance therapy is initiated at Visit 2 will be asked to read the information leaflet and will be instructed by the investigator on the proper use of Ellipta™. Each subject whose usual ICS/LABA DPI (Diskus™ or Turbuhaler) for asthma maintenance therapy is initiated at Visit 2 will follow the same procedure: reading of the information leaflet, demonstration of the proper use of the inhalers by the Investigator, and the correct dosing. This will be followed by an inhalation demonstration by the patient. Any mistakes (Type A errors, corresponding to

critical errors) and overall errors will be registered by the Investigator. For the definition of Type A errors and overall errors see Section 7.3.1

Randomisation at this visit will be performed on a 1:1 basis; to the FF/VI fixed dose combination delivered via Ellipta™ or the initiation with usual ICS/LABA inhalation powder for asthma maintenance therapy.

At Week 6 (Visit 3) and at Week 18 (Visit 5) subjects will be telephoned to enquire about whether the subject has experienced any serious adverse events or non serious adverse drug reactions. At these telephone calls subjects will also be asked to complete the ACT questionnaire (paper version) and to send it back to the Investigator.

Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation Visit). Subjects will be asked to withhold from taking study medication on the day of Visit 4. At this visit, subjects will be asked to provide responses to the ACT, MARS-A and PASAP questionnaires and the inhaler use will be assessed by recording Type A errors and overall errors following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. At this visit, a trough (pre-dose) FEV1 will be assessed by the Investigator using a spirometer provided by GSK and subjects will also be interviewed about whether the subject has experienced any serious adverse events or non –serious adverse drug reactions. Female subjects of child bearing potential will also be reminded about the requirement for contraception throughout their study participation.

The final Visit 6 will occur at Week 24. The ACT, AQLQ(S), EQ-5D and MARS-A questionnaires will be conducted at this visit and Type A errors and overall errors with inhaler will be recorded following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. At this visit, subjects will also be interviewed about whether they had experienced any serious adverse events or non –serious adverse drug reactions. The Investigator will be asked to make every effort to schedule Visit 6 at the same time of the day as Visit 2.

Although at least 3 formal scheduled visits and 2 phone calls are planned for this study, subjects should continue to visit their physician for any routine (naturalistic) visits as per normal clinical practice, as per the Time and Events Table (Section 7.1). An Early Withdrawal Visit has to be considered in case of early withdrawal of the subject from the study, as per the Time and Events Table (Section 7.1).

Treatment Arms and Duration

Two treatment arms: one FF/VI arm (FF/VI 92 mcg/22 mcg or FF/VI 184 mcg/22 mcg) once daily, and one arm ICS/LABA combination therapy in inhalation powder twice daily (FP/S 250 mcg/50 mcg or 500 mcg/50mcg, or BUD/F 200 mcg/6mcg or 400 mcg/12mcg) as decided by the physician. The total duration of subject participation will be approximately 6 months (24 weeks).

Type and Number of Subjects

Subjects with documented physician's diagnosis of asthma ≥ 1 year, unsatisfactorily controlled asthma (ACT < 20) treated by ICS alone and intended to be treated by ICS/LABA maintenance therapy. A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.

It is estimated that approximately 70 study centers in France will be required to have a total number of 422 randomised subjects so that at least 382 subjects will be evaluable. Assuming a 10% of screen failure, 466 subjects will have to be screened in the study with 6 subjects /center.

Analysis

The primary endpoint is defined as the change from baseline in the ACT total score assessed at Week 12 (Visit 4). The primary set of analysis is the ITT set.

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

2. INTRODUCTION

2.1. Study Rationale

Inhaled corticosteroids (ICS) are considered the most effective anti-inflammatory treatments for all severities of persistent asthma. This open-label randomised clinical study will evaluate the efficacy and safety of fluticasone furoate (FF)/vilanterol (VI) Inhalation Powder compared with existing fixed combinations ICS/LABA (Inhaled Corticosteroids/Long Acting Beta Agonists) inhalation powders.

Fluticasone furoate (FF) is a glucocorticoid developed for use as a once daily inhaled treatment for asthma. Vilanterol is an orally inhaled long-acting agonist of the $beta_2$-adrenoceptor (LABA) and has been also developed for use in combination with ICS as a once-daily maintenance treatment of asthma.

The pivotal phase III studies demonstrated the safety and efficacy of FF/ VI. However, it is increasingly acknowledged that randomised clinical trials by definition tend to be highly controlled and enrol a more highly selected patient population than is expected to be prescribed the medication post-approval. The need for data in a more representative population in close to a 'real world' setting is increasingly being recognised as important to complement pivotal phase III safety and efficacy studies in order to establish the benefits and therefore the value of a medication in the context of clinical practice. Indeed, in the close to 'real life' conditions, physicians have the ability to choose the best treatment in their view for any individual patient and adapt treatments to subjects' characteristics and response. Thus, double-blind comparison of once daily to twice daily medicines, while important for assessing efficacy, removes a potential source of difference in effectiveness derived from patient behaviour and experience. Moreover, a head-to-head study comparing Relvar 92mcg/22mcg Ellipta™ (FF/VI) once a day vs

Seretide 250mcg/50mcg Diskus™ (Fluticasone propionate/salmeterol) twice a day failed to demonstrate superiority on 24 hours weighted mean FEV1 after 6 months of treatment. However, 50% of subjects in both arms were uncontrolled (ACT score ≤ 19) at randomisation, after 4 weeks of Fluticasone propionate 250 mcg twice a day. For this sub-group of subjects, at the end of the 6 month-treatment period, 63% of subjects were controlled in the FF/VI arm vs 55% in the Seretide Diskus ™ arm. The study was not powered on this criterion nor designed to include uncontrolled subjects only. Anyway, this trend justifies exploring if this difference would disappear or increase in a close to real life setting.

Subjects recruited into the study will be those currently taking an ICS alone without any other controller treatment with evidence of sub-optimal asthma control, corresponding to European Marketing Authorisation of FF/VI. These subjects will be randomised to receive FF/VI via Ellipta™ inhaler once daily or to receive usual ICS/LABA fixed combination in DPI (fluticasone propionate/salmeterol (FP/S) via Diskus™ inhaler and budesonide/formoterol (BUD/F) via Turbuhaler twice daily for asthma maintenance therapy as per normal clinical practice. Ellipta™ is a new powder inhaler designed to be easy to use. Current powder inhalers have been associated with handling errors some of which may impact the ability of drug to reach the lung and hence impact clinical efficacy. Such errors deemed as critical will be evaluated in this study between different inhalers as well as overall inhaler preference and satisfaction.

2.2. Brief Background

Asthma is a chronic disease of the lungs characterised by airway inflammation, bronchoconstriction and increased airway responsiveness. Inhaled corticosteroids (ICS) are considered the most effective anti-inflammatory treatments for all severities of persistent asthma [GINA, 2009; NIH, 2007; British Thoracic Society, 2008]. The benefits of ICS include control of asthma symptoms, improvement in lung function, decrease in airway hyper-responsiveness and possibly, prevention of airway wall remodelling [Pedersen, 1997; Fanta, 2009].

Fluticasone furoate is a novel glucocorticoid developed for use as a once daily inhaled treatment for asthma. The drug consists of FF formulated in lactose for oral inhalation via the DPI Ellipta™. Pre-clinical data and early phase clinical studies indicate that FF has a longer duration of action than fluticasone propionate (FP) and is therefore suitable for development for once daily administration.

Vilanterol is an orally inhaled long-acting agonist of the $beta_2$-adrenoceptor (LABA) and has been developed for use in combination with ICS as a once-daily maintenance treatment of asthma. The drug consists of vilanterol formulated in lactose and magnesium stearate for oral inhalation via Ellipta™.

The combination of these two agents has been developed as a once-daily combination therapy for the long-term maintenance treatment of asthma in adults and children ≥ 12 years of age. The availability of a once-daily ICS combined with a LABA would be expected to help to improve compliance and therefore improve asthma control.

Information on the physical, chemical and pharmaceutical properties of fluticasone furoate, vilanterol, and fluticasone furoate/vilanterol may be found in SmPC or Investigator Brochure.

3. OBJECTIVE(S) AND ENDPOINT(S)

This open-label randomised clinical study will evaluate the efficacy and safety of fluticasone furoate (FF)/vilanterol (VI) Inhalation Powder (FF 92mcg/VI 22mcg or FF 184mcg/VI 22mcg) compared with existing fixed combinations ICS/LABA (Inhaled Corticosteroids/Long Acting Beta Agonists) inhalation powders, fluticasone propionate/salmeterol (FP/S) and budesonide/formoterol (BUD/F), for asthma maintenance therapy, in a "close to real life" manner in French primary and respiratory specialist care. FF/VI will be administered once-daily (QD) via Ellipta™ and FP/S or BUD/F twice daily (BID) via Diskus™ and Turbuhaler respectively.

Objectives	Endpoints
Primary	
• To compare the efficacy of FF/VI 92mcg/ 22mcg or FF 184mcg/22mcg with usual fixed combinations ICS/LABA for asthma maintenance therapy at Week 12 (Visit 4).	• Change from baseline in the Asthma Control Test (ACT) total score at Week 12 (Visit 4).
Secondary	
• To assess effect of FF/VI on asthma control compared with usual ICS/LABA fixed combination at Week 24 (Visit 6).	• Change from baseline in ACT score at Week 24 (Visit 6).
• To assess ELLIPTA™ inhaler correct use compared with other DPI (Diskus™ and Turbuhaler) at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).	• Percentage of subjects making at least 1 Type A error (likely to be critical) and overall errors at Week 12 (Visit 4) and at Week 24 (Visit 6) independently of the use at Week 12 (Visit 4).
Other	
• To assess effect of FF/VI on pre-dose trough FEV1 compared with usual ICS/LABA fixed combination at Week 12 (Visit 4)	• Change from baseline in pre-dose trough FEV1 at Week 12 (Visit 4).
• To assess the effect of FF/VI on response to treatment at Week 12 (Visit 4) and Week 24 (Visit 6)	• ACT score ≥ 20 or 3 point increase from baseline in ACT at Week 12 (Visit 4) and Week 24 (Visit 6). Note:

Objectives	Endpoints
	A 3 point increase in ACT total score was suggested as the Minimal Clinically Important Difference (MCID) in the literature [Schatz, 2009].
• To assess the adherence with study medication at Week 12 (Visit 4) and Week 24 (Visit 6)	• Number of medications dispensed and collected during the study at Week 12 (Visit 4) and Week 24 (Visit 6), • Score of the MARS-A questionnaire (Medication Adherence Report Scale) at the randomisation (Day0), Week12 (Visit 4) and Week24 (Visit 6).
• To assess the effect of FF/VI on severe asthma exacerbation over the study period	• Number of subject with at least 1 severe asthma exacerbation*, number of severe asthma exacerbation and annual severe exacerbation rate over the study period.
• To assess the effect of FF/VI on Health Related Quality of Life at Week 24 (Visit 6)	• Change from baseline in total score and domain scores of AQLQ(S) (Asthma Quality of Life Questionnaire) at Week 24 (Visit 6). • An increase from baseline of ≥ 0.5 in AQLQ(s) total score at Week 24 (Visit 6). • An increase from baseline of ≥ 0.5 in AQLQ(s) environmental stimuli domain score at Week 24 (Visit 6). • Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) Individual domain scores at Week 24 (Visit 6). • Change from baseline in total score and domain scores of AQLQ(S) at Week 24 (Visit 6). • Health status using the EuroQol Questionnaire (EQ-5D) at Week 24 (Visit 6).
	• Score of PASAP Questionnaire (Patient

Objectives	Endpoints
• To assess Patient Satisfaction and Preference assessment with different inhalers at Week 12 (Visit 4)	Satisfaction and Preference) at Week 12 (Visit 4).
• To evaluate the Safety of FF/VI compared with usual ICS/LABA (FP/S and Bud/F).	Serious Adverse Events (SAE) and non-serious Adverse Drug Reactions (ADR): • Frequency and type of serious adverse events, • Frequency and type of non-serious adverse drug reactions related to treatment.

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

Notes defining endpoints:

1. Contacts with a doctor or hospitalisation are defined as exacerbation-related contacts if these contacts were a direct result of an acute worsening of asthma symptoms.
2. A prescription of systemic corticosteroid is defined as exacerbation-related if the reason the drug was given, in whole or in part, was to treat an acute worsening of asthma symptoms.
3. Exacerbation-related hospitalisation includes hospitalisation that is prolonged as a result of an asthma exacerbation.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase IIIb multi-center randomised open label, parallel group study performed in subjects in French primary and respiratory care specialist who have a diagnosis of asthma and a regular treatment for persistent asthma. Subjects with unsatisfactorily controlled asthma (defined as an ACT < 20) and intended to be treated by usual ICS/LABA maintenance therapy to seek a better control of their asthma will be randomised to receive either FF/VI (FF/VI 92mcg/22mcg or FF/VI 184mcg/22mcg) once daily or another usual ICS/LABA combination therapy in inhalation powder twice daily (FP/S or BUD/F) decided by the physician. These medications are recorded in the e-CRF.

Physicians will be allowed during the treatment period to adapt prescription to different doses if necessary as well as to adapt doses of any comparative treatment according to products label. A table (Table 2 Section 6.3) of the indicative dosage equivalence between ICS and the other combination therapies will be provided to the physicians.

For Study Schematic, see Appendix 2.

Investigators

General Practitioners and pulmonologists based in France, all accredited for clinical trials by a CPP ("Comité de Protection des Personnes") will be approached to participate in the study (approximately 80% General Practitioners, 20% pulmonologists).

Screening, randomisation and follow-up

At the Screening Visit 1, eligible subjects will be consented to participate to the trial and prescribed the necessary examinations. The subjects will be asked to provide responses to the ACT. A screening log will be performed at this visit.

At a further visit (i.e V2, Day 0) occurring within 1 week after the screening visit (V1), subjects who meet all of the Inclusion Criteria, none of the Exclusion Criteria and who accept to give their consent will be randomised in the study. Randomisation at this visit will be on a 1:1 basis, to the FF/VI fixed dose combination delivered by Ellipta™ or to the initiation of any usual ICS/LABA DPI for asthma maintenance therapy chosen by the physician. Visit 1 and Visit 2 can be combined, if the subject did not take his usual asthma medication before coming on site. If Visit 1 and Visit 2 are combined then this visit will be Day 0.

At Visit 2 (Randomisation visit, Day 0) baseline pre-dose FEV1 will be assessed by the Investigator using a spirometer provided by GSK. At least three valid assessments should be performed with registration of the best value. On the morning of Visit 2 subjects will not take their usual asthma medication. Rescue medication (salbutamol) will be stopped 4 hours before baseline spirometry.

In addition at Visit 2, subjects will be asked to read the written Ellipta™ package insert if randomised into the FF/VI arm, or Diskus™ or Turbuhaler if randomised in the usual ICS/LABA therapy arm and will be instructed by the investigator on the proper use of inhalers. Then the subject will self-administer their first dose of study drug under supervision of the investigator. Any mistakes (Type A errors, likely to be critical and overall errors) will be registered by the trained HCP. After completing the procedure, subjects will be instructed in the correct use of the device by the trained physician if needed. Thereafter, each subject randomised into the FF/VI arm will be instructed to self-administer one inhalation with Ellipta™ inhaler each day at the same time of the day, at a time that is convenient for the subject. Subject randomised into usual ICS/LABA therapy arm will be instructed to self-administer the inhalation with Diskus™ or Turbuhaler inhaler twice a day.

Subjects will be recommended to use Salbutamol as needed throughout the study for relief of their asthma symptoms. At Visit 2 (randomisation, Day 0) subject will be asked to provide responses to the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires.

At Week 6 (Visit 3) and at Week 18 (Visit 5), subjects will be telephoned by the Investigator to enquire about whether the subject has experienced any adverse events (only the serious adverse events or non–serious adverse drug reactions will be recorded in

eCRF). The Investigator makes the judgment as to whether it is related or not to study treatment. At these telephone calls, subjects will also be asked to complete the ACT questionnaire (paper version) and to send it back to the Investigator.

Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation Visit). Subjects will be asked to withhold from taking study medication on the day of Visit 4. At this visit, subjects will be asked to provide responses to the ACT, MARS-A and PASAP questionnaires and the inhaler use will be assessed by recording Type A errors and overall errors following the next procedure: self-administration of one dose of study drug; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. Pre-dose trough FEV1 will be assessed at this visit by the Investigator using the spirometer provided by GSK. Rescue medication (salbutamol) will be stopped 4 hours before the spirometry. At least three valid assessments should be performed with registration of the best value. At this visit, subjects will also be interviewed by the Investigator about whether the subject has experienced any adverse events (only the serious adverse events or non–serious adverse drug reactions will be recorded in eCRF). The Investigator makes the judgment as to whether it is related or not to study treatment. Female subjects of child bearing potential will also be reminded about the requirement for contraception throughout their study participation.

The final Visit 6 will occur at Week 24. The ACT, AQLQ(S), EQ-5D and MARS-A questionnaires will be conducted at this visit and the inhaler use will be assessed by recording Type A errors and overall errors following the next procedure: self-administration of one dose of study drug by subject; errors assessment by the investigator; demonstration of correct use of inhaler in case of multiple errors detection. Subjects will be interviewed about whether the subject has experienced any serious adverse events or non –serious adverse drug reactions. The Investigator will be asked to make every effort to schedule Visit 6 at the same time of the day as Visit 2.

Although at least 3 formal scheduled visits and 2 phone calls are planned for this study, subjects should continue to visit their physician for any routine (naturalistic) visits as per normal clinical practice, as per the Time and Events Table (Section 7.1). An Early Withdrawal Visit has to be considered in case of early withdrawal of the subject from the study, as per the Time and Events Table (Section 7.1).

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

Outcome description

One of the main challenges of this study performed in so-called 'close to real life setting' is to obtain data on subjects with minimal interference with the actual practice of medicine. Thus, during the 6 months treatment period of the study, all interventions will be recorded as per normal. They will be captured by several means:

1) Physicians participating in the study will be asked to fill in an electronic CRF (eCRF) focused on clinical data at screening visit (Visit 1), at randomisation (Visit2), at Week 12 (Visit 4), at the end of the study at Week 24 (Visit 6) and at two phone calls at Week 6 (Visit 3) and at Week 18 (Visit 5).

2) At Week 6 and at Week 18, subjects will be telephoned to enquire about whether the subject has experienced any adverse events and then the investigator calling the patient must determine whether the event is related to study medication (either arm) and whether the event is serious. At these telephone calls, subjects will also be asked by the Investigator to complete the ACT questionnaire and to send it back to the Investigator.

3) When necessary, information will be obtained from other medical sources: naturalistic visits.

The variables of interest will be documented by a combination of information collected from all these sources.

Collected data

Eligible subjects will complete the ACT, AQLQ(S), EQ-5D and MARS-A questionnaires at Randomisation Visit (Visit 2, Day 0) and at Visit 6 (Week 24), or at the Early Withdrawal visit. ACT questionnaire will be completed also by the subject at Screening visit (Visit 1), Week 6 (phone call 1 or Visit 3), at Week 12 (Visit 4) and Week 18 (phone call 2 or Visit 5). MARS-A questionnaire will be completed also at Week 12 (Visit 4). Inhaler use assessment will be performed at Randomisation Visit (Visit 2, Day 0), at Week 12 (Visit 4) and at Week 24 (Visit 6) / Early Withdrawal visit by recording the Type A errors and the overall errors. Patient's satisfaction and preference (PASAP-Q) will be evaluated at Week 12 (Visit 4).

Baseline spirometry will be performed at Randomisation Visit (Visit 2, Day 0) and at Week 12 (Visit 4) by the Investigator using the spirometer provided by GSK, in order to assess pre-dose trough FEV1 at Week 12 (Visit 4).

For the Study Schematic see Appendix 2 and Section 7.1 for the proposed time and events table.

4.2. Treatment arms and duration

Randomisation will be on a 1:1 basis with two treatment arms: one FF/VI arm (FF/VI 92 mcg/22 mcg or FF/VI 184 mcg/22 mcg) once daily, and one arm ICS/LABA combination therapy in inhalation powder twice daily (FP/S 250 mcg/50 mcg or 500

mcg/50mcg, or BUD /F 200 mcg/6mcg or 400 mcg/12mcg) as decided by the physician. The total duration of subject participation will be approximately 6 months (24 weeks). As much as possible, enrolment of subjects should be performed at a constant accrual rate throughout a full year in order to minimize a seasonality bias.

4.3. Type and Number of Subjects

Subjects with documented physician's diagnosis of asthma ≥ 1 year, unsatisfactorily controlled asthma (ACT < 20) treated by ICS alone and intended to be treated by ICS/LABA maintenance therapy. A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.

It is estimated that approximately 70 study centers in France will be required to have a total number of 422 randomised subjects so that at least 382 subjects will be evaluable. Assuming a 10% of screen failure, 466 subjects will have to be screened in the study with 6 subjects /center.

Subjects withdrawn from the study will not be replaced.

4.4. Design Justification

An open label design is appropriate for such a study because it is a comparison of benefits and risks of FF/VI versus usual ICS/LABA asthma maintenance therapy in close to real life setting.

Previous studies have demonstrated that improvements in ACT score can be seen in periods of 3-6 months making this suitable time frame to assess ACT changes.

The treatment duration of 6 months (24 weeks) in this study is considered sufficient to demonstrate efficacy in the proposed study population.

The primary endpoint is defined as the change from baseline in the ACT total score assessed at Week 12 (Visit 4). The aim will be to prove non-inferiority of FF/VI to any other ICS/LABA comparator. The hypothesis of non-inferiority will be first tested at Week 12. If (and only if) non-inferiority is significantly achieved at Week 12, non-inferiority will then be tested at Week 24. If (and only if) non-inferiority is achieved at a visit, then superiority of FF/VI to any other comparator will be tested at this visit (Week 12 or Week 24).

4.5. Dose Justification

Two strengths of FF/VI have been approved, 100 mcg/25 mcg (delivered dose of 92 mcg/22 mcg) for moderate persistent asthma and 200 mcg/25 mcg (delivered dose of 184 mcg/22 mcg) for severe persistent asthma. The dose of 92 mcg/ 22 mcg will be preferentially progressed in this study as this dose strength is likely to meet the needs of most subjects. However, physicians will be allowed to change the prescription to higher dose according to subject's response without exceeding the maximum allowed dose.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with FF/VI can be found in the Investigator's Brochure (IB) or Summary of Product Characteristics (SPC). The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Serious Cardiovascular Events	This is a potential class effect of LABAs. In clinical studies, percentages of subjects with fatal events that were cardiovascular in nature were similar across all treatment groups (0 to <1%).	Subjects with historical or current evidence of uncontrolled or clinically significant disease are excluded from the study. Cardiovascular medical history, CV risk factors and exacerbation history will be assessed as described in the time and events table.
Asthma-related intubations and deaths	This is a potential class effect of LABAs. It was not observed in preclinical studies with FF/VI. During the FF/VI studies for the asthma composite endpoint (asthma exacerbations leading to hospitalization, intubation and/or death), there was no significant difference between the FF/VI group and the ICS group or non-LABA group, demonstrating no increased risk when adding a LABA to an ICS.	Subjects with a history of life-threatening asthma are excluded from this study. Subjects are excluded from this study if they have a severe and unstable asthma, with ACT score < 15, history of repeated severe exacerbations (3/year) and/or exacerbation in the previous 6 weeks. Subjects are excluded from this study if they are using LABA without an ICS as asthma maintenance therapy.

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Hypersensitivity	The reported hypersensitivity events in clinical trials, were not generally serious, did not lead to discontinuation in the studies, and were usually confounded, by either the subject's medical condition (such as COPD) or other factors at the time of the event. In spontaneous data, symptoms of hypersensitivity ranged from mild rash and pruritis to severe generalised rash and erythema and severe cases involving angiodema of the face, larynx and pharynx. These events were rare.	Subjects with a history of adverse reaction including immediate or delayed hypersensitivity to any intranasal, inhaled, or systemic corticosteroid and LABA therapy and to components of the inhalation powder (e.g., lactose, magnesium stearate). In addition, subjects with a history of severe milk protein allergy that, in the opinion of the Investigator, contraindicates the subject's participation will also be excluded.
Systemic effects of corticosteroids: adrenal suppression; eye disorders; decreased bone density and associated fractures	Adrenal suppression is a known class effect of corticosteroids. Preclinical studies showed that FF effects are comparable with other corticosteroids. No studies have shown a clinically relevant effect of FF/VI on the hypothalamic pituitary axis (HPA). This includes a formal HPA study (HZA106851), using 24 hour serum cortisol measurements, and multiple studies with COPD and asthma subjects which monitored urinary cortisol. During clinical	The mitigation in this study for all systemic effects of corticosteroids is that chronic users of systemic corticosteroids are excluded from this study: a subject who, in the opinion of the Investigator, is considered to be a chronic user of systemic corticosteroids for respiratory or other indications (if unsure discuss with the medical monitor prior to screening).

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	development, no events of Adrenal Suppression were reported. Eye disorders are a known class effect of corticosteroids. Preclinical studies showed FF at high dose comparable to other high dose corticosteroids. In study HZA106839 (FF/VI , FF and FP in subjects with asthma), formal ophthalmic assessments were conducted (including LOCS III evaluations for ocular opacities) throughout the study. This study showed no apparent effects on lens opacification, compared to baseline. During studies in both subjects with asthma and COPD, no associated affect on ocular disorders was observed. Decreased bone density is a down class effect of corticosteroids. Preclinical data showed that high dose corticosteroid effects of FF were comparable to other conrticosteroids. Patients with Asthma In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of fractures with FF/VI was <=1%, and usually associated with trauma.	

Investigational Product (IP) [FF/VI]		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Study Procedures		
Spirometry procedures	Shortness of breath, coughing, light-headedness or fainting, and/or chest tightness	If any of these symptoms should happen to the subject, spirometry will be stopped and he/she will receive medical treatment
Other		
Summaries of findings from both clinical and non-clinical studies conducted with comparators (Seretide Diskus and Symbicort Turbuhaler) can be found in the Summary of Product Characteristics (SPC).		

4.6.1.1. Benefit Assessment

Combined treatment with ICS and LABA has been shown to be more effective than the individual components in asthma, leading to the development of fixed dose combination inhalers. The use of ICS/LABA combinations is now well established in international treatment guidelines for moderate to severe persistent asthma patients for whom treatment with ICS alone is not sufficient.

Both fluticasone propionate/salmeterol and budesonide/formoterol fumarate are commercially available products for the treatment of persistent asthma and have recognized safety profiles. Both of these products are administered twice-daily.

4.6.2. Overall Benefit: Risk Conclusion

The investigational product (IP) FF/VI has an acceptable safety profile for clinical use and there are no significant associated risks. This conclusion is supported the results of previously performed clinical studies with the products in healthy volunteers and subjects with Asthma and COPD (GlaxoSmithKline Document Number RM2008/00012/06). Adverse effects that could be associated with the use of FF/VI, will be closely monitored. A safety criterion outlining details for subject withdrawal is included in the protocol (Section 5.4, Withdrawal Criteria). A thorough summary and evaluation of the available pre-clinical data can be found in the IB [GlaxoSmithKline Document Number RM2008/00012/06]. Routine safety analysis of this study will be conducted by the company. Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with FF/VI, are justified by the anticipated benefits that may be afforded to patients with asthma.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB/IB supplement(s) (or the SPC), and other pertinent documents.

5.1. Inclusion Criteria

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. **Informed consent**: Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.
2. **Gender and Age**: Male or female subjects aged ≥18 and ≤ 75years of age at Visit 1.

   Female subject: is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin (hCG) test), not lactating, and at least one of the following conditions applies:

   a. Non-reproductive potential defined as:

   - Pre-menopausal females with one of the following:
     - Documented tubal ligation
     - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
     - Hysterectomy
     - Documented Bilateral Oophorectomy
   - Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

   b. Reproductive potential and agrees to follow one of the options listed below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) requirements from 30 days prior to the first dose of study medication and until Week 24 (Visit 6).

GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

1. Contraceptive subdermal implant that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label
2. Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007a]
3. Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a]
4. Injectable progestogen [Hatcher, 2007a]
5. Contraceptive vaginal ring [Hatcher, 2007a]
6. Percutaneous contraceptive patches [Hatcher, 2007a]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007a].
8. Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2007b]
9. These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

3. **Type of subject:**
   a. Subjects with documented physician's diagnosis of asthma ≥ 1 year, unsatisfactorily controlled asthma (ACT < 20 at Visit 1 and Visit 2) treated by ICS alone and intended to be treated by ICS/LABA maintenance therapy.
   b. A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a Social Security category.
4. **Current Asthma Therapy:** All subjects must be prescribed maintenance therapy and receiving ICS alone without LABA for at least 4 weeks prior to Visit 2 (Randomisation visit).

   Other background asthma medication such as anti-leukotrienes or theophylline is permitted as an alternative to ICS alone, if initiated at least 4 weeks prior to screening visit (Visit 1).
5. **Subject questionnaires:** Subjects must be able to complete the questionnaires themselves.

5.2. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study.

1. **History of Life-threatening asthma:** Defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnea, respiratory arrest or hypoxic seizures within the last 6 months before Visit 1 and Visit 2.
2. **Subjects having a severe and unstable asthma,** with ACT score < 15 at Visit 1 and at Visit 2, history of repeated severe exacerbations (3/year) and/or a severe exacerbation in the previous 6 weeks before Visit 1 and Visit 2.
3. **COPD Respiratory Disease**: A subject must not have current evidence or diagnosis of chronic obstructive pulmonary disease at Visit 1.
4. **Current or former cigarette smokers with a history of cigarette smoking of ≥ 10 pack-years** at screening (Visit 1) [number of pack years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)].
5. **Other diseases/abnormalities**: Subjects with historical or current evidence of uncontrolled or clinically significant disease at Visit 1 and at Visit 2. 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.
6. **Subjects with a history of adverse reaction** including immediate or delayed hypersensitivity to any intranasal, inhaled, or systemic corticosteroid and LABA therapy and to components of the inhalation powder (e.g., lactose, magnesium stearate) at Visit 1 and at Visit 2. In addition, subjects with a history of severe milk protein allergy that, in the opinion of the Investigator, contraindicates the subject's participation will also be excluded.
7. **Investigational Medications:** A subject must not have used any investigational drug within 30 days prior to Visit 2 or within five half-lives (t½) of the prior investigational study (whichever is longer of the two), (if unsure discuss with the medical monitor prior to screening).
8. **Chronic user of systemic corticosteroids:** A subject who, in the opinion of the Investigator, is considered to be a chronic user of systemic corticosteroids for respiratory or other indications (if unsure discuss with the medical monitor prior to screening) at Visit 1.
9. **Subjects treated by the monoclonal antibody omalizumab (Xolair) at Visit 1.** Treatment with Xolair is not allowed during the study.
10. **Subjects involved in other clinical trials at Visit 1.**
11. **Affiliation with Investigator Site:** Is an investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member of the aforementioned that is involved in this study.

12. **Subjects who plan to move away from the geographical area where the study is being conducted during the study.**

5.3. Screening/Baseline/Failures

A total of 466 subjects will be screened as 422 subjects are planned to be randomised and 10% of screen failure is expected.

- Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events related to study participation.

5.4. Withdrawal/Stopping Criteria

5.4.1. Subjects Lost to Follow-up

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

5.4.2. Subject Withdrawal by Investigator or Self-withdrawal

Subjects may be withdrawn from study treatment at any time by the Investigator if it is considered to be detrimental for them to continue the study treatment or, may discontinue a subject from the study at his or her discretion. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

The following criteria will cause a subject to be withdrawn from investigational product (IP) but every effort should be made to keep the Subject in the study:

- A subject becomes pregnant.
- A subject meets the Liver Stopping Criteria as defined in Section 5.4.3.
- A subject meets the QTc stopping criteria as defined in Section 5.4.4.

If the subject chooses to withdraw from the study, all study-related medications and other study related materials should be returned to the site by the subject. An Early Withdrawal Visit should be conducted within 24 hours of the subject stopping study medication (Section 7.1 Time and Event Table). In the event a subject withdraws at or during a scheduled visit, an Early Withdrawal Visit is not required; however, all study procedures scheduled at an Early Withdrawal Visit must be performed at this visit instead.

The primary reason for study treatment discontinuation or study withdrawal will be recorded in the electronic Case Report Form (eCRF) and any data collected up until the point of withdrawal will be used in the data analyses.

Specific regard should be given to distinguishing withdrawals due to ADRs, SAEs and protocol deviation, following consultation with the medical monitor. The Investigator will record the primary reason in the eCRF.

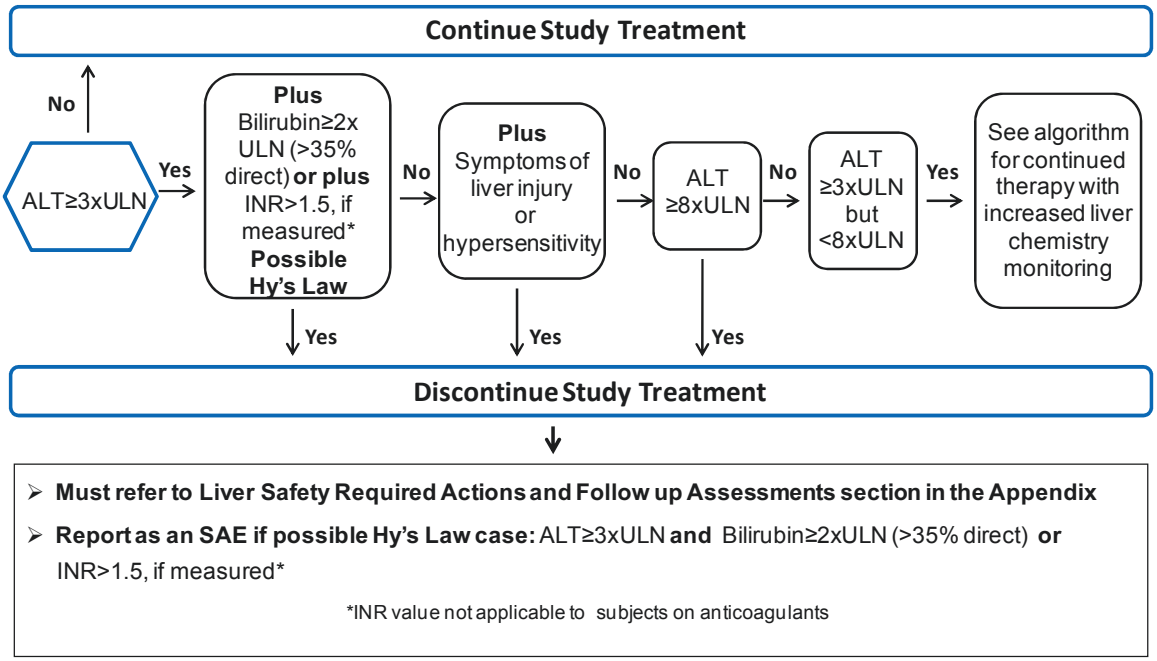
Subjects withdrawn from the study will not be replaced.

Subjects who experience an asthma exacerbation during the Treatment Period can continue in the study, at the discretion of their Investigator.

5.4.3. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

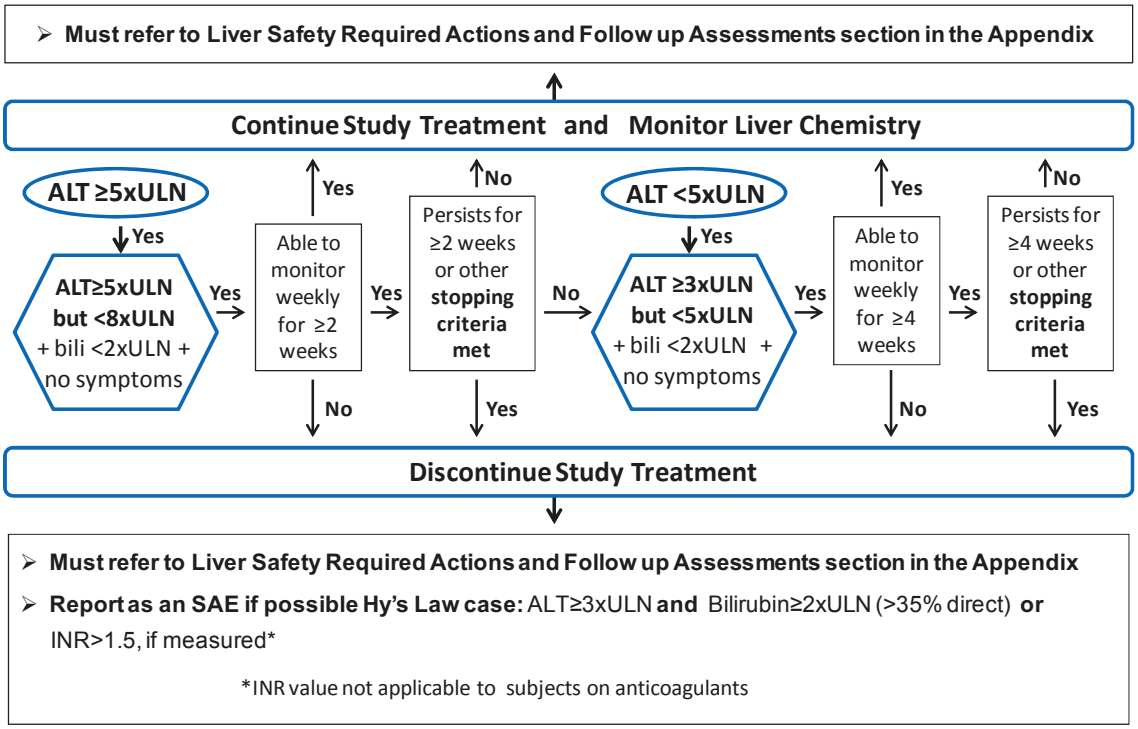
Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



- **Must refer to Liver Safety Required Actions and Follow up Assessments section in the Appendix**
- **Report as an SAE if possible Hy's Law case:** ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) **or** INR>1.5, if measured*

*INR value not applicable to subjects on anticoagulants

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 4.

5.4.3.1. Study Treatment Restart or Rechallenge

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

5.4.4. QTc Stopping Criteria

An ECG is not required prior to entering this study. There are no other regular ECGs required by this protocol. If, however, while a subject is receiving study medication, an ECG is performed as part of the normal clinical practice and a prolonged QT interval is detected, the following assessments for withdrawal from the study are required, after discussion between Investigator and the medical monitor:

For all subjects:

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

- QTc > 500 msec OR Uncorrected QT > 600 msec
- Increase in QTc >60msec detected compared to a previous ECG

For patients with underlying **bundle branch block**, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	**Discontinuation QTc with Bundle Branch Block**
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec

The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

5.5. Subject and Study Completion

A completed subject is one who has completed all study visits. The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

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.

All subjects will receive the asthma medication to be used during the study from the investigator site.

GlaxoSmithKline Clinical Trials Supplies will provide the investigational products (FF/VI: Relvar™ Ellipta™ and comparative treatments, i.e. Seretide™ Diskus™, Symbicort™ Turbuhaler) as well as rescue medication (Salbutamol) for use in this study.

New ICS/LABA DPI or DPI copies of existing marketed ICS/LABA if any in France at the time of the study will not be considered in this trial.

Each subject randomised to the FF/VI arm will be instructed to administer the study medication once daily (by reading the leaflet and demonstration of it use), at the same time of the day, for the duration of the treatment period. Each subject will be advised to adhere to FF/VI dosing regimen throughout the study. The Investigator may adjust the dose of FF/VI according to the subjects' response, starting by FF/VI 92mcg/22 mcg.

Each subject initiating other ICS/LABA maintenance therapy will be reminded about the techniques of how to use their maintenance medication (by reading the leaflet and demonstration of it use) and the correct dosing. Each subject will be advised to adhere to ICS/LABA dosing regimen throughout the study, starting by FP/S 250mcg/50mcg or by BUD/F 200mcg /6mcg according to the Investigator's decision. The Investigator may adjust the dose of each product according to the subjects' response.

A description of the investigational treatments is provided below:

Table 1 Description of Fluticasone Furoate/Vilanterol Inhalation Powder Dry Powder Inhaler and comparative treatments

Compound Formulation	**Fluticasone Furoate/ Vilanterol** First strip: FF 92 mcg or 184 mcg blended with lactose Second strip: Vilanterol 22 mcg blended with lactose and magnesium stearate[1]
Dosage Form	DPI Ellipta™ – 30 doses per device
Unit Dose Strength	92 mcg/22 mcg or 184 mcg/22 mcg per actuation
Route of Administration	Inhaled

1. magnesium stearate 1%mw/w of total drug product

Compound Formulation	**Fluticasone propionate/ Salmeterol** FP 250 mcg or 500 mcg blended with lactose Salmeterol 50 mcg blended with lactose
Dosage Form	DPI Diskus™ – 60 doses per device
Unit Dose Strength	250 mcg/50 mcg or 500 mcg/50 mcg per actuation
Route of Administration	Inhaled

Compound Formulation	**Budesonide/Formoterol Fumarate** Budesonide 200 mcg or 400 mcg blended with lactose Formoterol Furoate 6 mcg or 12 mcg blended with lactose
Dosage Form	DPI Turbuhaler 60 or 120 doses (200 mcg/6 mcg or 400 mcg/12 mcg) per device
Unit Dose Strength	200 mcg/6mcg or 400 mcg/12 mcg per actuation
Route of Administration	Inhaled

The subject's use of short/rapid acting beta$_2$-agonist bronchodilator will be assessed as it would be in routine care and if required, rescue medication will be prescribed to subjects to use as needed throughout the study for relief of asthma symptoms as per usual practice.

6.2. Medical Devices

Medical devices (spirometers) will be provided by GSK for use in this study. However, none of the devices provided are manufactured by, or on behalf of GSK.

6.3. Treatment Assignment

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

Subjects will be randomized (1:1) to one of the following treatment groups:

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

Dose Guidance:

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

- FF/VI 92 mcg/22mcg dose once a day is approximately equivalent to fluticasone propionate/salmeterol (FP/S) medium dose (250 mcg/50mcg) and to budesonide/formoterol (BUD/F) medium dose (200 mcg/6 mcg) twice a day. See Table 2 for further guidance for doses conversion for other corticosteroids.

- FF/VI 184 mcg/22 mcg dose once a day is approximately equivalent to fluticasone propionate/salmeterol high dose (500 mcg/50 mcg) and to budesonide/formoterol high dose (400 mcg/12 mcg) twice a day. See Table 2 for guidance for dose conversion for other corticosteroids.

- Starting doses are: 92 mcg/22 mcg once daily for FF/VI; 250 mcg/50 mcg twice daily for FP/S and 200 mcg/6 mcg twice daily for BUD/F.

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

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

Information extracted from GINA, 2012, refer to GINA for further guidance.

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

6.4. Planned Dose Adjustments

Subjects randomised to the usual ICS/LABA asthma maintenance therapy arm can have their treatment adjusted as would be normal clinical practice at the Investigator's discretion. This will not require the subject to be withdrawn from the study. These subjects should not receive FF/VI, if the medication is marketed during the study period.

Subjects randomized to the FF/VI arm and for whom it is considered appropriate/ necessary to adjust treatment, can have their regimen changed as required as per normal clinical practice at any point in the study and the subject could remain in the study.

Subjects on FF/VI arm can also change between the two FF/VI doses as appropriate and at the Investigator's discretion.

6.5. Blinding

This study is an open label randomised study.

6.6. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.7. Preparation/Handling/Storage/Accountability

All FF/VI and comparative ICS/LABA maintenance therapy prescribed throughout the study will be dispensed at, and collected from the investigator site.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. All DPIs containing FF/VI must be stored at a temperature of up to 25°C. Budesonide/Formoterol and Fluticasone Propionate/Salmeterol DPIs must be stored at a temperature of up to 30°C.

Access to and administration of the investigational product will be limited to the investigator and authorised site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

All used and unused study medication inhalers (FF/VI or usual ICS/LABA asthma maintenance therapy) should be returned to the investigator site when the subjects collect prescriptions of study medication.

At the end of the study, all study supplied study medication (used and unused) will be destroyed following local standard operating procedures, except where it is suspected that Ellipta™ or GSK DPI packaging is defective. The device and packaging should be returned to GSK.

Details for both return and destruction and of study medication are found in the Study Procedure Manual (SPM).

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

In accordance with local regulatory requirements, the Investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount

returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

6.8. Compliance with Study Treatment Administration

When the subjects attend the investigator site, they will be instructed to administer the study medication once daily at the same time of the day for the duration of the treatment, when randomised to FF/VI via Ellipta™ and twice daily (on the morning and evening) when randomised to ICS/LABA DPI (Diskus™ or Turbuhaler). All used and unused study medication inhalers (FF/VI or usual asthma maintenance therapy) should be returned to the investigator site when the subjects collect prescriptions of study medication.

Treatment adherence with study medication will be assessed based on analysis of medications (dispensed and collected) during the study and on Medication Adherence Report Scale for Asthma (MARS-A) questionnaire at randomisation Day 0, at Week 12 and at Week 24.

6.9. Treatment of Study Treatment Overdose

An overdose will be defined as the subject receiving any amount of IP greater than the maximum dose permitted by the protocol, which results in clinical signs or symptoms.

In the event of an overdose of study medication, the Investigator should use clinical judgment in treating the overdose and contact the study medical monitor.

GlaxoSmithKline (GSK) is not recommending specific treatment guidelines for overdose and toxicity management. The Investigator should 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(s) or equivalent document provided by GSK for study medications.

6.10. Treatment after the End of the Study

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

6.11. Concomitant Medications and Non-Drug Therapies

All respiratory-related prescribed and dispensed concomitant medications taken during the study will be recorded. The minimum requirement is that drug trade name and the dates of prescribing, dispensing and collection will be recorded.

6.11.1. Permitted Medications and Non-Drug Therapies

All medications for asthma and other disorders that are not contra indicated in asthma, or listed as a prohibited medication (see Section 6.11.2), may be continued throughout the study.

At clinical doses, low plasma concentrations of FF and VI are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and/or liver, any clinically significant drug interactions mediated by FF or VI are unlikely.

A CYP3A4 drug interaction study was performed in healthy subjects with the FF/VI combination (200/25) and Ketoconazole. Co-administration increased mean FF AUC(0-24) and Cmax by 36% and 33%, respectively. The increase in FF exposure was associated with a 27% reduction in 0-24 h weighted mean serum cortisol. Co-administration increased mean VI AUC(0-t') and Cmax 65% and 22%, respectively. The increase in VI exposure was not associated with an increase in beta-agonist related systemic effects on heart rate, blood potassium or QTcF interval.

Care is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for an increased systemic exposure to both FF and VI. Consideration should be given to the clinical situation and the duration of treatment with such concurrent medications.

6.11.2. Prohibited Medications and Non-Drug Therapies

- **Systemic corticosteroids**, except in case of a severe asthma exacerbation.
- **Monoclonal antibody omalizumab (Xolair).**

7. STUDY ASSESSMENTS AND PROCEDURES

The Time and Events Table is provided in Section 7.1. All study assessments should be conducted by the Investigator or his/her qualified designee unless otherwise specified in the protocol or SPM. Please refer to the SPM for the suggested order of assessments.

7.1. Time and Events Table

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

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

* Visit 1 and Visit 2 can be combined if the subject did not take his usual asthma medication before coming on site. Then this visit will be Day 0 and all baseline characteristics will be collected at this visit. Written Informed Consent must be obtained prior to initiation of study procedures or initiating changes in medications.
** Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation visit).
***PGx saliva sample collected at Visit 2 (Randomisation) or any scheduled clinic visit thereafter.
**** Only if early withdrawal occurs before Week 12.
¥ Only for childbearing women.

7.2. Screening and Critical Baseline Assessments

The following demographic parameters will be captured: year of birth, sex, and ethnicity. Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5 and as indicated in the time and event table.

Cardiovascular medical history, CV risk factors and exacerbation history will be assessed as indicated in the time and event table.

Smoking status will be also captured as follow: non smoker, current or former cigarette smokers. Former smokers will be defined as those who have stopped smoking for at least 6 months prior to Visit 1 (or Visit 2 if the visit 1 and 2 are combined). Number of pack-years should be assessed at screening (Visit 1): number of pack years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years).

Procedures conducted as part of the subject's routine clinical management [e.g. blood count] and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

ACT will be assessed at screening (Visit 1) and randomisation (Visit 2). AQLQ(S), EQ-5D and MARS-A will be assessed at Visit 2 (Randomisation). These Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit, in the order specified. The correct use of inhaler will be assessed also at randomization visit (Visit 2):

1. after reading the package insert of product by the patient and

2. after demonstration of it use by the investigator. Any critical errors will be registered by the Investigator when using each device.

Baseline pre-dose FEV1 will be assessed at this visit by the Investigator using a spirometer provided by GSK. Rescue medication (salbutamol) will be stopped 4 hours before baseline spirometry and usual asthma medication will be not be taken by the patient before coming on site.

No study related procedures may be performed until the informed consent form document has been reviewed with and signed by the subject.

7.3. Efficacy

See Section 3 for the efficacy endpoints and Section 7.1 for the proposed time and events table.

7.3.1. Inhaler Correct Use Assessment

Correct use of the inhaler will be assessed as outlined in the Time and Events Table (Section 7.1).

Table 3 List of Type A (likely to be critical) and overall errors for Ellipta™

Type A errors for Ellipta™	**yes**	**no**	**Overall errors for Ellipta™**	**yes**	**no**
Failed to open cover			No exhalation before an inhaling		
Exhaled directly into mouthpiece			Blocked air inlet during inhalation manoeuvre		
Shook the device upside down after dose preparation			Inhalation manoeuvre: - long - steady - deep		
Inhalation from mouthpiece (kept between lips)			Blocked air inlet during inhalation manoeuvre		
			Did not hold breath		
			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
			Any other comments: [free text box]		

Table 4 List Type A (likely to be critical) and overall errors for Diskus™

Type A errors for Diskus™	**yes**	**no**	**Overall errors for Diskus™**	**yes**	**no**
Failed to open cover			No exhalation before an inhalation		
Lever is not pushed back			Inhalation manoeuvre: - steady - deep		
Exhaled directly into mouthpiece			Did not hold breath		
No seal by the lips round the mouthpiece during the inhalation			Did not close the device (*Note: this is an error but one which does not affect the*		

Type A errors for Diskus™	**yes**	**no**	**Overall errors for Diskus™**	**yes**	**no**
			medication that is inhaled)		
			Any other comments: [free text box]		

Table 5 List of Type A (likely to be critical) errors and overall errors for Turbuhaler

Type A errors for Turbuhaler	**yes**	**no**	**Overall errors for Turbuhaler**	**yes**	**no**
Failed to remove cap			No exhalation before an inhalation		
Did not hold device upright (±45% OK) during dose preparation			Inhalation manoeuvre: - forceful - deep Note to *HCP: it is important that the inhalation is forceful and deep from the start for this inhaler*		
Base not twisted fully backwards and forwards, no click heard			Blocked air inlet during inhalation manoeuvre		
Shook the device after dose preparation			Did not hold breath		
Exhaled directly into mouthpiece			Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*		
No seal by the lips round the mouthpiece during the inhalation			Any other comments: [free text box]		

7.3.2. Trough (pre-dose) FEV1 assessment

FEV_1 will be measured to assess lung function at Visit 2 (Randomisation) and Visit 4 (Week 12), as outlined in the Time and Events Table. Visit 4 (Week 12) should be scheduled at the same time of day as Visit 2 (Randomisation visit). Measurements should be taken pre-dose and subjects should be instructed not to take their asthma medication/study drug prior to coming into the clinic at these visits. Subjects should also withhold from using their rescue medication for at least 4 hours prior to Visit 2 (Randomisation) and Visit 4 (Week 12).

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

The Investigator will be asked to make every effort to perform the spirometry at the same time of the day at Visit 2 and at Visit 4.

7.3.3. Questionnaires

7.3.3.1. Asthma Control Test (ACT)

The ACT is a validated self-administered questionnaire utilising 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5). Subjects will complete the ACT at Screening (Visit 1), at Randomisation (Visit 2), at Week 6 (Phone Call 1 or Visit 3), at Week 12 (Visit 4), at Week 18 (Phone Call 2 or Visit 5) and at Week 24 (Visit 6) / Early Withdrawal visit.

An ACT score of 5 to 19 suggests that the subject's asthma is unlikely to be well controlled. A score of 20 to 25 suggests that the subject's asthma is likely to be well controlled.

Please refer to Appendix 3 and the Study Procedures Manual for further details.

7.3.3.2. Asthma Quality of Life Questionnaire (AQLQ-S)

The AQLQ is a disease-specific, self-administered quality of life questionnaire developed to evaluate the impact of asthma treatments on the quality of life of asthma sufferers, over the last 2 weeks [Juniper, 1993]. AQLQ(S) will be measured at Randomisation (Visit 2), at Week 24 (Visit 6) / Early Withdrawal visit. Please refer to Appendix 3 and the Study Procedures Manual for further details.

7.3.3.3. EuroQol Questionnaire (EQ-5D)-5 Level

General health status will be assessed with the EuroQol (EQ-5D)-5 Level Questionnaire at Randomisation (Visit 2) and at Week 24 (Visit 6) / Early Withdrawal visit.

Please refer to Appendix 3 and the Study Procedures Manual for further details.

7.3.3.4. Medication Adherence Report Scale for Asthma (MARS-A)

Reported adherence to medication will be assessed with the Medication Adherence Report Scale for Asthma (MARS-A) questionnaire at Visit 2, Week 12 (Visit 4) and Week 24 (Visit 6) / Early Withdrawal visit.

The MARS-A is a 10-item questionnaire where medication use is rated on a 5-point Likert scale (1 indicating 'always' to 5 indicating 'never'). It has been validated as a self-reported measure of adherence with ICS for subjects with asthma and includes generic ("I use it regularly every day") and lung condition-specific questions about medication use ("I only use it when I feel breathless") [Cohen, 2009]. There is no specified timeframe on which responses should be based.

The Investigator should ensure the subject completes the MARS-A at the same time at the specified visits and before any study procedures. The MARS-A have no specified timeframe on which responses should be based.

7.3.3.5. Patients Satisfaction and Preference with the device (PASAP Questionnaire)

The Patient Satisfaction and Preference Questionnaire (PASAPQ) [C.M. Kozma, 2005], is a multi-item measure of respiratory inhalation device satisfaction and preference designed to be easily understood and administered to patients with asthma and COPD. Patient satisfaction with each device and device preference will be assessed at Week 12 (Visit 4) / Early Withdrawal visit if subject is withdrawn before Week 12 (Visit 4).
The Investigator should ensure the subject completes the PASAP-Q at the same time at the specified visits and before any study procedures. The PASAP-Q has no specified timeframe on which responses should be based.

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (see Section 7.1).

Serious Adverse Events (SAE) and non-serious Adverse Drug Reactions (ADR) will be collected in this study.

Safety endpoints will include:

- Frequency and type of serious adverse events,
- Frequency and type of non serious adverse drug reactions related to treatment.

7.4.1. Adverse Events (AE), Adverse Drug Reactions (ADRs) and Serious Adverse Events (SAEs)

The definitions of an AE, ADR or SAE can be found in Appendix 5.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. All adverse events will be recorded in the source documents but only information regarding non-serious adverse drug reactions (ADRs) and serious adverse events (SAEs) will be documented and reported in the eCRF.

7.4.1.1. Time period and Frequency for collecting non serious ADRs and SAE information

- All non-serious ADRs and SAEs will be collected from the start of Study Treatment until the end of the study (see Section 7.4.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.

- 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 SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 5.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 5.

7.4.1.2. Method of Detecting non serious ADRs and SAEs

The Investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of a non-serious adverse drug reaction (ADR) or serious adverse events (SAE).

The method of detecting, recording, evaluating and follow-up of SAEs and non-serious ADRs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study SAEs/non-serious ADRs are provided in the SPM.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

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

Potential SAEs and non serious ADRs may be identified by hospitalisation alerts through the medical record. The Investigator will have the ultimate responsibility for determining causality and seriousness.

7.4.1.3. Follow-up of non serious ADRs and SAEs

After the initial non serious ADRs/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious ADRs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 5.

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 5 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.

7.4.1.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Any clinically significant safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition, are **not** to be reported as non-serious ADRs or SAEs.

7.4.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the Investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met. This will also include potential SAEs identified by hospitalisation alerts through the medical record.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority/Independent Ethics Committee (IEC) and Investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An Investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IEC, if appropriate according to local requirements.

The method of detecting, recording, evaluating and follow-up of SAEs and non-serious ADRs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study SAEs/non-serious ADRs are provided in the SPM.

Procedures for documenting, transmitting and follow-up of medical device incidents along with the regulatory reporting requirements for medical devices are provided in the SPM.

7.4.2. Pregnancy

- Details of all pregnancies in female subjects will be collected from the time the informed consent is signed (Visit 1) and until the end of the study (Visit 6).
- Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 7.
- Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

7.4.3. Medical Device Incidents (Including Malfunctions)

Medical devices (spirometers) will be provided by GSK for use in this study. However, none of the devices provided are manufactured by, or on behalf of GSK.

7.4.4. Physical Exams

A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.4.5. Vital Signs

Vital sign measurements will include height, weight, pulse rate, systolic and diastolic blood pressure.
Vital signs will be measured and recorded in the eCRF at Screening visit (Visit 1), at the Randomisation Visit 2 (Day 0), at Week 12 (Visit 4), at Week 24 (Visit 6) and at Early Withdrawal Visit except for height and weight that will be collected at Visit 1 only.

7.4.6. Electrocardiogram (ECG)

An ECG is not required prior to entering this study. There are no other regular ECGs required by this protocol.

7.4.7. Clinical Safety Laboratory Assessments

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the Investigator are to be recorded as non-serious ADRs or SAEs as appropriate.

7.5. Genetics

Information regarding genetic research is included in Appendix 6.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary (GSKDrug).
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The objective of the study is to compare the efficacy of fluticasone furoate (FF)/vilanterol (VI) Inhalation Powder (FF/VI 92 mcg/22mcg or FF/VI 184 mcg/22mcg) with usual ICS/LABA inhalation dry powder for asthma maintenance therapy over six months in a large French primary an respiratory specialist care population of subjects with asthma.

The primary endpoint is defined as the change from baseline in the ACT total score assessed at Week 12 (Visit 4). Regarding the primary efficacy endpoint (i.e. the change

from baseline in the ACT total score assessed at Week 12 [Visit 4]), the primary analysis will show that the fixed combination FF/VI (92mcg/22mcg or 184mcg/22mcg) is non-inferior to any other ICS/LABA combinations in inhalation powder assuming a non-inferiority margin of 1.5. Non-inferiority will be claimed if the 95% two-sided confidence interval on the difference in mean primary efficacy endpoints (FF/VI minus Comparator) precludes the non-inferiority margin of -1.5.

If (and only if) non-inferiority is significantly achieved at Week 12 (Visit 4) with regard to the primary endpoint, then non-inferiority of the fixed combination FF/VI (92mcg/22mcg or 184mcg/22mcg) to any other ICS/LABA combinations will be tested at Week 24 (Visit 6) considering the same non-inferiority margin of 1.5. Non-inferiority will be claimed if the 95% two-sided confidence interval on the difference in mean primary efficacy endpoints (FF/VI minus Comparator) at Week 24 (Visit 6) precludes the non-inferiority margin of -1.5.

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

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

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

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

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

9.2.2. Sample Size Sensitivity

To demonstrate the sensitivity of the sample size calculation for this study, the following table presents the power of the study under different circumstances in terms of the standard deviation.

The assumption used is shaded.

Standard deviation	Power for the subjects evaluable (N = 382)
3.8	97.0%
4.2	93.6%
4.5	90.1%
4.7	87.5%
4.9	84.7%

9.2.3. Sample Size Re-estimation or Adjustment

Not planned

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Populations considered for analysis are as follows:

Intent to treat (ITT) set: All randomized subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy). The ITT set will be used to analyze the primary efficacy endpoint analysis, the secondary efficacy endpoint and other efficacy endpoints. Subjects will be assigned to the treatment group as randomized for the ITT set.

Per-protocol (PP) set: all ITT subjects without any major violations of study procedures. Major protocol violations will be identified prior to database lock. Protocol deviations will be reviewed and classified as minor or major during a data review meeting that will be held before database lock. The exclusion of subjects from the PP set will be specified and documented in the RAP.

Safety set: All enrolled subjects having received at least one dose of the prescription of study medication (either FF/VI or usual ICS/LABA asthma maintenance therapy) and considered as-treated. The Safety set will be the basis for safety analyses. Subjects will be assigned to the treatment group as treated for the Safety set.

Details of the analysis datasets to be created will be specified in the Report Analysis Plan (RAP).

9.3.2. Interim Analysis

Not applicable

9.4. Key Elements of Analysis Plan

The primary comparison of interest is the comparison of the change from baseline (Visit 2) in the total ACT score assessed at Week 12 (Visit 4) between FF/VI (92mcg/22mcg or 184mcg/22mcg) and usual ICS/LABA inhalation powder for asthma maintenance therapy.

The primary set for analysis is the intent to treat set. A sensitivity analysis will be performed in the PP set.

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

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

Of note, this step-down testing procedure still strongly controls the overall type I error at the 0.05 two-sided level.

Definition of the treatment failure will be as follow:

- Treatment withdrawal,
- Change of treatment,
- Dose increase beyond the maximum allowed daily dose in the EU license (for FF/VI > 184mcg/22mcg, for FP/S > 500mcg twice daily, for BUD/F > 800 mcg twice daily.

Other Comparisons of Interest: Other efficacy endpoints and safety endpoints will be described. Estimated differences between groups with 95% confidence intervals will be provided when applicable.

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the Reporting Analysis Plan (RAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report Descriptive summaries will be provided by treatment group.

Demographic and baseline characteristics will be summarized.

Continuous variables will be summarized using descriptive statistics (number of observed and missing data, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum).

Categorical variables will be summarized as numbers of observed and missing data, counts and percentage for each category (reported to the number of non-missing values). For binary variables, 95% confidence intervals for proportions will be estimated based on the Clopper-Pearson method.

The contrast between FF/VI and usual ICS/LABA asthma maintenance therapy in inhalation powder will be of primary interest for all efficacy endpoints.

Non-inferiority of FF/VI versus usual ICS/LABA asthma therapy will be first tested at Week 12 (Visit 4). If and only if significance is achieved at Week 12 (Visit 4), then non-inferiority will be tested at Week 24 (Visit 6) at the two-sided 0.05 level of significance. This step-down testing procedure strongly controls the overall type I error at the 0.05 two-sided level.

If non-inferiority is achieved at Week 12 (Visit 4), then superiority of FF/VI versus usual ICS/LABA asthma therapy will be tested at the same two-sided nominal significance level of 0.05. If non-inferiority is achieved at Week 24 (Visit 6), then superiority of FF/VI versus usual ICS/LABA asthma therapy will be tested at the same two-sided nominal significance level of 0.05.

Baseline ACT score will be included in the primary efficacy analyses. Gender, age, study site and potentially season at randomization will be further investigated in sensitivity analyses when appropriate. Other covariates may be considered and if so it will be detailed in the RAP.

Treatment by prognostic factors interactions will be specifically investigated in secondary models.

Handling of treatment withdrawal: treatment withdrawal will be considered as a failure and the primary endpoint at the treatment withdrawal time will be assessed based on the last available ACT post randomization score before withdrawal. Of note, a change in the dose regimen will not be considered as a treatment failure.

Handling of missing data: as a general rule, missing data will not be replaced. Nevertheless sensitivity analyses regarding the primary and key secondary endpoint will replace missing ACT assessments by the last available post randomization ACT value (i.e. based on the last observation carried forward method).

The study is adequately powered for the primary and the key secondary endpoint, i.e. to show non-inferiority of FF/VI to current ICS/LABA at Week 12 (Visit 4) and at Week 24 (Visit 6) considering a non-inferiority margin of 1.5. Other secondary endpoints are not necessarily adequately powered and a descriptive analysis will only be proposed for these endpoints.

The primary efficacy analysis population set is defined as all subjects belonging to the Intent-to-Treat population (ITT), which include all subjects who have been randomised and received at least one prescription of study medication (e.g. FF/VI or usual ICS/LABA inhalation powder for asthma maintenance therapy).

Each subject will complete the ACT at Visit 2 (Randomisation), Week 12 (Visit 4) and Week 24 (Visit 6). ACT scores will also be assessed at Week 6 (Visit 3) and at Week 18 (Visit 5) and at the withdrawal time, if any.

9.4.1. Primary Analyses

The primary endpoint is defined as the change from baseline (Visit 2) in the ACT total score assessed at Week 12 (Visit 4).

The primary set of analysis is the ITT set.

If treatment is withdrawn, then the missing ACT score at the nearest visit after treatment withdrawal will be replaced by the ACT score assessed at withdrawal time. If no ACT score is assessed at withdrawal time, then the ACT missing score at the nearest visit after treatment withdrawal will not be replaced.

1) **Non-inferiority testing.**

The non-inferiority of FF/VI versus any other ICS/LABA DPI comparator will be primarily tested in a mixed model repeated measures (MMRM) approach. The model will include factors and covariates as follow: treatment, scheduled visit time point (Week 6 and Week 12), baseline ACT, treatment by visit interaction, baseline ACT by visit interaction, gender, age and patient will be fitted as a random factor. The Restricted Maximum Likelihood (REML) estimation approach will be used, and the default covariance structure will be unstructured. Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point will be performed. The 95% confidence interval on the treatment effect (FF/VI vs ICS/LABA comparator) will be estimated at Week 12 (Visit 4) in this model. Non-inferiority will be achieved if the non-inferiority margin of -1.5 is lower than the lower bound of the confidence interval on the difference between FF/VI and any other comparator (positive values of the difference favour FF/VI).

Sensitivity analyses:

a) Handling missing data

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

1. Missing values at Week 12 (Visit 4) will be replaced by the post-randomization last available value (either the week 6-based ACT score or the ACT score at treatment withdrawal time, if any), i.e. based on the Last Observation Carried Forward method. The change from baseline in ACT at

Week 12 (Visit 4) will be analyzed in an ANCOVA model adjusting for treatment and baseline ACT score. The treatment effect (FF/VI versus any other ICS/LABA comparator) and its corresponding 95% confidence interval will be estimated in this model to test the non-inferiority hypothesis.

2. Multiple imputation (MI) analyses utilizing covariates known to be predictive of response: season at randomization, observed value of ACT at Week 6, observed value of ACT at Week 12 (Visit 4). Other covariates may be considered and if so it will be detailed in the RAP.

   Step 1: For each treatment group separately, missing measurements are imputed for subjects with a baseline measurement where there are missing observations (at either Week 6 or Week 12) using the above covariates and regression-based imputation method. The Markov Chain Monte Carlo (MCMC) method for MI will be used and ten such sets of imputed data will be created each with the observed values or imputed values for subjects with missing observations.

   Step 2: Each imputed data set will be analyzed using the primary MMRM model. The treatment effect from these 10 analyses will then be pooled using standard MI theory to make an overall inference. The difference in the least squares means between the two groups at Week 12 (Visit 4) and the corresponding 95% confidence interval for the difference will be presented.

b) A sensitivity analysis based on the semi parametric Hodges-Lehmann (HL) approach will be proposed to assess the robustness of the MMRM Model-based non-inferiority results. The HL difference between groups with the corresponding 95% confidence interval will be provided.

c) Sensitivity analyses for handling treatment withdrawal: when treatment withdrawal occurs, an alternative method for imputing the missing value at the nearest visit after withdrawal time will be proposed: the primary endpoint missing value will be estimated by the worst ACT score observed between baseline visit (included) and withdrawal time (included).

d) The primary analysis (i.e. based on the MMRM approach) and the same sensitivity analyses presented here above will be performed in the Per Protocol set.

Model assumptions checking:

a) Assumptions underlying the MMRM (resp. ANCOVA for the sensitivity analysis) model (residual normality, linear relationship between response and baseline ACT, etc) will be checked with graphical methods (plots of studentized residuals, etc)

b) Baseline ACT will be categorized according the distribution quartiles and the same MMRM model (resp. ANCOVA for the sensitivity analysis) adjusting for categorized Baseline ACT will be fitted again.

c) Possible treatment by covariates (baseline ACT, baseline Asthma therapy, season at randomisation) interaction will be investigated MMRM (resp. ANCOVA for the sensitivity analysis) adjusting for these additional interaction terms

d) The influence of the covariates and potential additional covariates on the outcome will be investigated.

2) Superiority testing.

If non-inferiority is statistically achieved at Week 12 (Visit 4), then superiority of FF/VI to any other comparator will be tested at the usual 0.05 two-sided nominal level of significance.

The same models and analyses mentioned above will be used to assess the superiority hypothesis.

9.4.2. Secondary Analyses

Key secondary analysis

The key secondary endpoint is defined as the change from baseline (Visit 2) in the ACT total score assessed at Week 24 (Visit 6).

1) Non-inferiority testing

If non-inferiority is statistically achieved at Week 12 (Visit 4), then non-inferiority will be tested at Week 24 at the 0.05 two-sided nominal level. If non-inferiority is not accepted at Week 12 (Visit 4), non-inferiority will not be tested at Week 24 (Visit 6) and assessed on a descriptive basis only.

More precisely, the key secondary endpoint assessed at Week 24 (Visit 6) will also be analyzed using a mixed model repeated measures (MMRM) approach where data up to and including Week 24 (Visit 6) will be used in the model. The model will include factors and ~~as~~ covariates as follow: treatment, scheduled visit time point (Week 6, Week 12, Week 18 and Week 24), baseline ACT, treatment by visit interaction, baseline ACT by visit interaction, gender, age and patient will be fitted as a random factor. The Restricted Maximum Likelihood (REML) estimation approach will be used, and the default covariance structure will be unstructured. Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point will be performed. The 95% confidence interval on the treatment effect (FF/VI vs ICS/LABA comparator) will be estimated at Week 24 in this model. Non-inferiority will be achieved if the non-inferiority margin of -1.5 is lower than the lower bound of the confidence interval on the difference between FF/VI and any other comparator (positive values of the difference favour FF/VI).

Sensitivity analyses: the same sensitivity analyses as those described above for the primary endpoint will be performed for the key secondary efficacy endpoint.

Model assumptions checking: the analyses proposed to check model assumptions for the analysis of the key secondary efficacy endpoint will be the same as those described above for the primary endpoint.

2) **Superiority testing.**

If non-inferiority is statistically achieved at Week 24 (Visit 6), then superiority of FF/VI versus any other comparator will be tested at the usual 0.05 two-sided nominal level of significance.

The same models and analyses mentioned above will be used to assess the superiority hypothesis.

Other secondary analyses

Proper use of the medical device

The other key secondary endpoint will be the correct use of the inhaler device assessed at randomisation (Visit 2), at Week 12 (Visit 4) and at Week 24 (Visit 6). The device will be considered as adequately used if the patient didn't make any Type A error (all critical items correct) at the corresponding visits (randomisation [Visit 2], week 12 [Visit 4] and week 24 [Visit 6]). Proportions of subjects correctly using the device will be estimated within each group. A corresponding 95% confidence interval of the difference in proportions will also be provided. Additional exploratory analyses could be performed and will be detailed in the RAP. Even if tests will be performed, no causal association will be inferred from these analyses.

9.4.3. Other Analyses

Other Analyses

The analysis of the other endpoints defined in this section will be provided for exploratory purposes only. Additional exploratory analyses could be performed and will be detailed in the RAP. Even if tests will be performed and 95% confidence intervals will be provided, no causal association will be inferred from these analyses.

Change from baseline in pre-dose trough FEV1

Results will be summarized for each group and the results of the difference between groups will be presented with the corresponding 95% confidence interval at Week 12 (Visit 4).

Response to treatment

- Binary response defined as an ACT score ≥ 20 at a given visit OR a 3 point increase from baseline in ACT change.

The responder analyses will be conducted using a logistic regression model at a given Visit or Phone Call adjusting for treatment and stratification factors (baseline ACT score categorized into two classes, baseline asthma therapy, and potentially season at randomization). Treatment by stratification factors interaction effects will be further investigated in additional logistic models adjusting for these specific effects.

Adherence with study medication

- Number of percentage of medications (dispensed and collected) during the study will be tabulated for each visit and by treatment group.
- The score for Medication Adherence Report Scale for Asthma (MARS-A) at Day0, Week 12 and Week 24 will be described by treatment group.

Severe asthma exacerbations

- Number of subjects with at least one severe exacerbation, number of severe asthma exacerbation and annual exacerbation rate over the study period.

A severe asthma exacerbation is defined as deterioration of asthma requiring the use of systemic corticosteroids[2] (tablets, suspension, or injection) with or without antibiotics prescribed or an inpatient hospitalisation or emergency department visit due to asthma that required systemic corticosteroids or antibiotics[1,2,3] .

The number and percentage of subjects experiencing an asthma exacerbation during the study period will be summarized for each treatment group. Listing will be provided to include the primary causes of the exacerbation.

If feasible (i.e. if the number of exacerbation events is high enough), mean annual rate of asthma exacerbation will be analysed using a generalised linear model, assuming the negative binomial distribution, with the logarithm of time on treatment as an offset variable. The adjusted mean rates per year, treatment ratio and associated p-value and 95% confidence interval will be presented.

Health Related Quality of Life and Health status

- An increase from baseline of ≥ 0.5 in AQLQ(s) total score at Week 24 (Visit 6).
- An increase from baseline of ≥ 0.5 in AQLQ(s) environmental stimuli domain score at Week 24 (Visit 6).

- Change from baseline in total score and domain scores of AQLQ(S) at Week 24 (Visit 6).
- Percentage of subjects who have an increase from baseline of ≥ 0.5 in AQLQ(S) Individual domain scores at Week 24 (Visit 6).
- Health status using the EuroQol Questionnaire (EQ-5D) at Week 24 (Visit 6).

Patients Satisfaction and Preference with the inhaler (PASAP Questionnaire) (see Appendix 3)

The overall inhaler satisfaction and preference will be measured at Week 12 (Visit 4). The PASAP score will be ~~described~~ summarised by treatment group.

Further analyses will be specified in the Report Analysis Plan.

Subgroup Analyses

Subgroup summaries and/or analyses will also be provided, when appropriate, for efficacy and safety endpoints based on baseline disease characteristics.

Additional analyses could be carried out using appropriate methods to account for changes in treatment during the course of the study. Further details will be provided in the analysis plan.

The details will be provided in the RAP.

Safety Analyses

Safety data will be summarized and/or listed by treatment group and by visit for the Safety population.

Extent of Exposure

Extent of exposure to study treatment (i.e., number of days on randomised treatment) will be summarised by treatment group using mean, standard deviation, median, minimum, and maximum. In addition, duration of subject exposed to study drug will be summarised across treatment groups.

Adverse Drug Reactions

Adverse drug reactions during the treatment period and during the post treatment period will be summarised and displayed by treatment group. Adverse drug reactions during the treatment period include those with a date of onset on the date of study treatment initiation to one day after study treatment termination.

The adverse drug reactions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and will be reported using the primary System Organ Class (SOC)

and Preferred Term. Preferred Terms will be summarised within the primary SOC. The relationship of primary SOC, preferred terms, and verbatim text will be listed.

The number of subjects with one or more events of any type will be calculated. Results will be displayed in the order of decreasing frequency, both across primary SOC and within primary SOC.

Adverse drug reactions during the study period will also be listed. The demographic details (e.g., age, sex) and the details on individual adverse events will be included in these listings. Listings will be sorted within subject by the adverse drug reaction date of onset.

Similar summaries and listings will be provided for adverse events leading to withdrawal from study.

Deaths and Serious Adverse Events

Deaths and serious adverse events during the study period will be listed. Serious adverse events during the study period will also be summarised by treatment group.

Any pregnancies, serious adverse events and deaths reported during this study will also be summarised in case narratives written by GSK GCSP personnel.

Other safety parameters

All others safety parameters will be listed and summarized.
More specifically the vital signs (BMI, pulse rate, systolic blood pressure and diastolic blood pressure) will be summarized by visit and treatment group.

Genetic research

Information regarding genetic research is included in Appendix 6.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2013 including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review, CPP in France ("Comité de Protection des Personnes") and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which medical records will serve as the source document.
GSK will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The Investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

Upon completion or termination of the study, the GSK monitor will conduct site closure activities with the Investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the Investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all Investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the Investigator or head of the medical institution must inform the IEC promptly and provide the reason(s) for the suspension/termination.

10.6. Records Retention

Following closure of the study, the Investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The Investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The Investigator and GSK must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the Investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The GP/Investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the Investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator signatory will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 8 months after the last subject's last visit (LSLV) [this applies to each data analysis phase for studies with multiple phases, e.g., primary analysis, follow up analysis etc]. In addition, the aim is to submit a manuscript to a peer-reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11. REFERENCES

British Guideline on the Management of Asthma. British Thoracic Society: A national clinical guideline. 2008 63: iv1-iv121

Cohen JL, Mann DM, Wisnivesky JP, Horne R, Leventhal H, Musumeci-SzaboTJ, Halm EA. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. Ann Allergy Asthma Immunol. 2009: 103: 325-31

Dolan P. Modeling valuations for EuroQol health states. Med Care 1997; 35(11):1095-1108.

Fanta CH. Drug Therapy: Asthma. *New Engl J Med.* 2009;360(1):1002-1014.

GINA 2012, http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf

GlaxoSmithKline Document Number RM2008/00012/06. Fluticasone Furoate + Vilanterol Investigator's Brochure. 25-Jun-2014

Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention.* GINA, www.ginasthma.org; 2009.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. *Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(a): 24. Table 3-2.*

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. *Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(b): 28*

James LP et al. Pharmacokinetics of Acetaminophen-Protein Adducts in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37(8): 1779-1784.

Juniper EF et al. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol. 1994 Jan;47(1):81-7.

Juniper EF et al. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax. 1992 Feb;47(2):76-83

Juniper EF, Guyatt GH, Williams A, Griffith LE. Measuring quality of life in asthma. *Am Rev Respir Dis.* 1993;147:832-838.

Juniper EF. Asthma quality of life questionnaires (AQLQ, AQLQ(S) and MiniAQLQ): Background information and interviewing tips. QOL Technologies Inc. 1998.

Kozma CM et al. Development and Validation of a Patient Satisfaction and Preference Questionnaire for Inhalation Devices (PASAPQ). Treat Respir Med 2005

Le Gal F et al. 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.

Nathan RA, Sorkness CA, Kosinski M et al, Development of the Asthma Control Test: A survey for assessing asthma control, J Allergy Clin Immunol January 2004.

NIH, 2007, Asthma Guidelines Summary, http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.pdf

Pedersen S, O'Byrne P. A comparison of efficacy and safety of inhaled corticosteroids in asthma. *Allergy.* 1997;52(39):1-34.

Schatz M et al. The minimally important difference of the Asthma Control Test, The Journal of allergy and clinical immunology (2009)

The EuroQol Group, 1990. The EuroQol Group. EuroQol- a new facility for the measurement of health-related quality of life. Health Policy 1990; 199-208

EQ-5D-5L user guide. Basic information on how to use the EQ-5D-5L instrument. Version 2.0. October 2013. Mandy Oerman, Bas Janssen

WHO/CONRAD Technical Consultation on nonoxynol-9. WHO, Geneva, 9–10 October 2001. Summary report. Geneva, World Health Organization, 2003.

12. APPENDICES

12.1. Appendix 1: Abbreviation and Trademarks

ACT	Asthma Control Test
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Co-variance
AQLQ(S)	Asthma Quality of Life Questionnaire
AST	Aspartate Aminotransferase
BID	Twice daily
BUD	Budesonide
°C	Celsius
CRF	Case Record Form
eCRF	Electronic Case Record Form
CV	Cardiovascular
DPI	Dry Powder Inhaler
FP	Fluticasone Propionate
EPI	Epidemiology
EQ-5D	EuroQol 5D
F	Formoterol
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in one second
FF	Fluticasone Furoate
FP	Fluticasone Propionate
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GP	General Practitioner
GSK	GlaxoSmithKline
IB	Investigators Brochure
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
INR	International Normalised Ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IVD	In Vitro Diagnostic
IRT	Interactive Response Technology
LABA	Long Acting Beta Agonist
LDH	Lactate Dehydrogenase
LSLV	Last Subject Last Visit
MARS-A	Medication Adherence Report Scale in Asthma questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
Mcg	Microgram

MID	Minimally Important Difference
MDI	Metered Dose Inhaler
MCID	Minimally Clinically Important Difference
ml	Millilitre
MSDS	Material Safety Data Sheet
MMRM	Mixed effects model with repeated measures
NDPI	Novel Dry Powder Inhaler
PASAP-Q	Patients Satisfaction and Preference Questionnaire
PK	Pharmacokinetics
PP	Per-protocol
PRO	Patient Reported Outcomes
pg	Picogram
pmol	Picomoles
QD	Once Daily
QoL	Quality of Life
QTc	Corrected QT interval
RAP	Reporting Analysis Plan
REML	Restricted maximum likelihood
RNA	Ribonucleic Acid
S	Salmeterol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
SOP	Standard Operating Procedure
S&P	Statistics and Programming
SPM	Study Procedures Manual
ULN	Upper Limit of Normal
VI	Vilanterol
WHO	World Health Organisation

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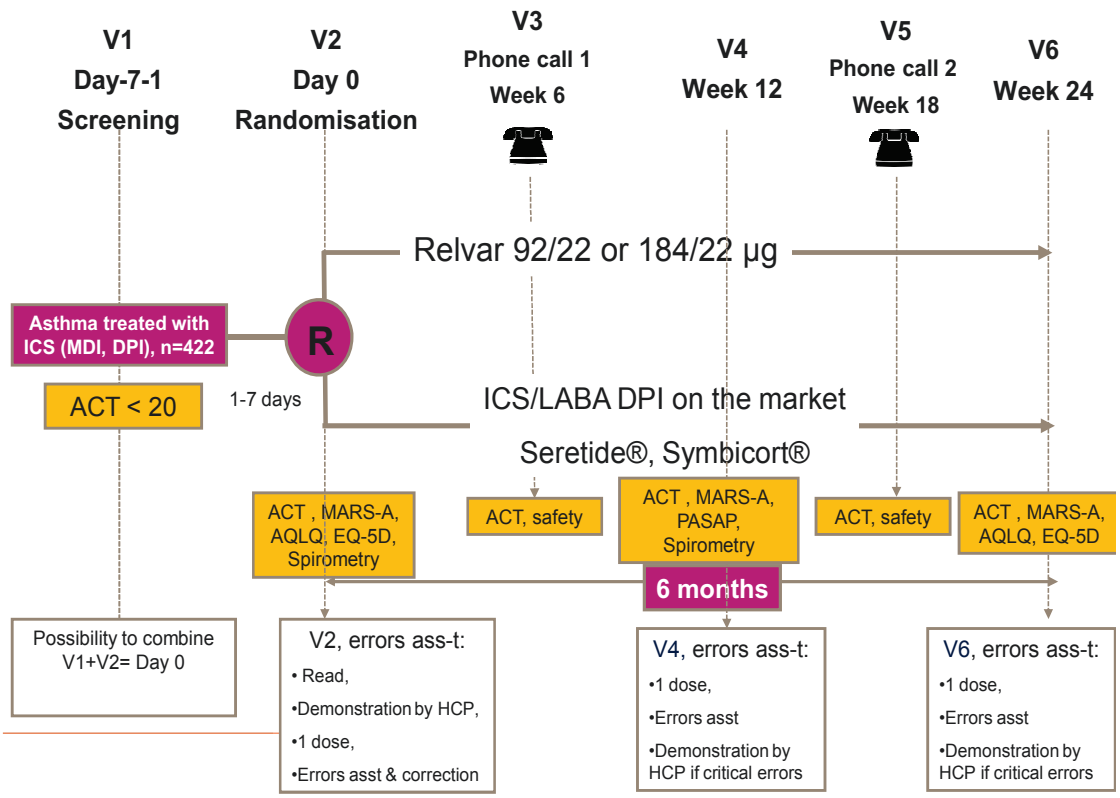
ACT
Asthma Quality of Life Questionnaire - AQLQ(S)
EQ-5D
MARS-A questionnaire
PASAP Questionnaire
Symbicort Turbuhaler
XOLAIR

12.2. Appendix 2: Study Schematic

FF/VI open- label or usual asthma maintenance treatment

HZA 116492: study design



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

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

12.3. Appendix 3: Questionnaires

Asthma Control Test (ACT)

The ACT is a validated self-administered questionnaire utilising 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5). By answering all 5 questions a subject with asthma can obtain a score that may range between 5 and 25, with higher scores indicating better control. An ACT score of 5 to 19 suggests that the subject's asthma is unlikely to be well controlled. A score of 20 to 25 suggests that the subject's asthma is likely to be well controlled. The total score is calculated as the sum of the scores from all 5 questions. [Nathan R, 2004]. The minimally important difference (MID) for ACT is 3 [Schatz, 2009].

Subjects will complete the ACT at Screening (Visit 1), at Randomisation (Visit 2), at Week 12 (Visit 4) and at Week 24 (Visit 6) on site. Two telephone calls are provided at Week 6 and 18 and subjects will be asked to provide responses to the ACT questionnaire and to send it back to the Investigator.
The ACT has been developed as a measure of subjects' asthma control that can be quickly and easily completed in clinical practice. The questions are designed to be self-completed by the subject. It is recommended that the ACT be administered at the same time during each visit. The ACT should be completed before any procedures are performed on the subject to avoid influencing the subject's response. Adequate time should be allowed to complete all items on the ACT.

The subject should complete the questionnaire in a quiet area.

The Investigator should ask the subject to complete the questions as accurately as possible. If the subject requests help or clarification with any of the questions, he/she will be asked to re-read the instructions and give the answer that best reflects how he/she felt over the previous 4 weeks. The subject should be reassured that there are no right or wrong answers. The Investigator should not provide the subject with any answer or attempt to interpret any portion of a question.

Please refer to the Study Procedures Manual for further details.

Asthma Quality of Life Questionnaire (AQLQ-S)

The AQLQ (S) is a modified version of the original AQLQ in which all the activity questions are generic and it has been validated for use in asthma subjects between the ages of 17 and 70. The AQLQ is a disease-specific, self-administered quality of life questionnaire developed to evaluate the impact of asthma treatments on the quality of life of asthma sufferers, over the last 2 weeks [Juniper, 1993]. AQLQ(S) will be measured at Randomisation and at Week 24 / Early Withdrawal visit.

The AQLQ, which is available in numerous languages, has a demonstrated validity, reliability and reproducibility [Juniper, 1992; Juniper, 1998]. The AQLQ contains 32 items in four domains: activity limitation (11 items), symptoms (12 items), emotional function (5 items), and environmental stimuli (4 items). In addition, the 32 items of the

questionnaire are also averaged to produce an overall quality of life score. The response format consists of a seven-point scale where a value of 1 indicates “total impairment” and 7 indicates “no impairment”. Assuming a statistically significant result ($p < 0.05$), the minimal clinically meaningful change in overall quality of life, or in quality of life for any of the individual domains, is 0.5 points [Juniper, 1994].

It is recommended that the AQLQ (S) be administered at the same time during each visit. The AQLQ (S) must be administered before inquiring about AEs and any study assessments. Adequate time should be allowed to complete all items on the AQLQ (S). No stated or implied time for completing the AQLQ (S) will be given, though the survey typically takes 10 to 20 minutes to complete.

Subjects should complete all the questions from the AQLQ (S). The Investigator will ask the subject to complete all questions as accurately as possible. If the subject requests help or clarification of any question in the AQLQ (S) he or she should be asked to reread the instructions and give the answer that best reflects how he/she feels over the previous two weeks. The subject should be reassured that there are no right or wrong answers. The Investigator will not provide the subject with any answer or attempt to interpret any portion of a question. Please refer to the Study Procedures Manual for further details.

EuroQol Questionnaire (EQ-5D)-5 Level

General health status will be assessed with the EuroQol (EQ-5D)-5 Level Questionnaire at Randomisation and Week 24 / Early Withdrawal visit.

The EQ-5D is a standardised instrument for use as a measure of health status that asks subjects questions about their health status “today” [The EuroQol Group, 1990]. It is designed for self-completion and is cognitively simple. The EQ-5D is a two-part self-assessment questionnaire. The first part consists of five items covering five dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a three-point Likert scale (1-no problem, 2-some/moderate problem(s), and 3-unable/extreme problem(s)).

Respondents are asked to choose one level that reflects their "own health state today" for each of the five dimensions. Respondents can then be classified into one of 243 distinct health states. EQ-5D health states can be converted to a single summary index by applying a formula that attaches weights to each of the levels in each dimension. The formula is based on the valuation of EQ-5D health states from general population samples [Dolan, 1997].

The second part of the questionnaire consists of a vertical visual analogue scale (EQ-5D VAS) that has endpoints of "The best health you can imagine" (anchored at 100) and "The worst health you can imagine" (anchored at 0). Respondents are asked to indicate how they rate their current health state by drawing a line from the box marked “your health status today” to the appropriate point on the EQ-5D VAS scale.

The Investigator should ensure the subject completes the EQ-5D at the same time at the specified visits and before any study procedures. The EQ-5D will be administered at Randomisation (Visit 2) and Week 24 (Visit 6) / Early Withdrawal visit.

Medication Adherence Report Scale for Asthma (MARS-A)

Reported adherence to medication will be assessed with the Medication Adherence Report Scale for Asthma (MARS-A) questionnaire at Visit 2, Visit 4 and Visit 6/Early Withdrawal visit.

The MARS-A is a 10-item questionnaire where medication use is rated on a 5-point Likert scale (1 indicating 'always' to 5 indicating 'never'). It has been validated as a self-reported measure of adherence with ICS for subjects with asthma and includes generic ("I use it regularly every day") and lung condition-specific questions about medication use ("I only use it when I feel breathless") [Cohen, 2009]. There is no specified timeframe on which responses should be based.

The Investigator should ensure the subject completes the MARS-A at the same time at the specified visits and before any study procedures. The MARS have no specified timeframe on which responses should be based.

Patient Satisfaction and Preference Questionnaire (PASAP-Q)

The Patient Satisfaction and Preference Questionnaire (PASAP-Q) [C.M. Kozma, 2005], is a multi-item measure of respiratory inhalation device satisfaction and preference designed to be easily understood and administered to patients with asthma and COPD. Patient satisfaction with each device and device preference will be assessed at Visit 4/ Early Withdrawal visit.
The Investigator should ensure the subject completes the PASAP-Q at the same time at the specified visits and before any study procedures. The PASAP-Q has no specified timeframe on which responses should be based.

12.4. Appendix 4: Liver Chemistry Stopping and Follow-up Criteria

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase III-IV liver chemistry stopping criteria and required follow up assessments

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
Bilirubin1, 2	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR2	ALT ≥ 3xULN **and** INR>1.5, if INR 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
Symptomatic3	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 • Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is**	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for pharmacokinetic (PK) analysis, obtained within after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN

granted (refer to Appendix 4) • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Obtain complete blood count with differential 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 **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • 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 subject 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 subjects 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
5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005]. PK sample may not be required for subjects 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 subject'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 subject safety. • Subject can continue study treatment • Subject 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 subject 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 subjects twice monthly until liver chemistries normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

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.

12.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.5.1. Definition of Adverse Events and ADRs

Adverse Event and ADRs Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • The definition of an ADR is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, for which there is a reasonable possibility that the untoward occurrence is causally related to the medicinal product. ADRs are a subset of AEs for a given medicinal product. • 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 medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • 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 prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected 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 this is an intentional overdose taken with possible suicidal/self-harming intent. This 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. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events NOT meeting definition of an AE include:
• 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 subject'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 subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where 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.

12.5.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 hospitalization or prolongation of existing hospitalization NOTE: • In general, hospitalization signifies that the subject 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 out-patient setting. Complications that occur during hospitalization are AEs. 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 disability/incapacity NOTE: • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere 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 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are 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
g) Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.
• Refer to Appendix 4 for the required liver chemistry follow-up instructions

12.5.3. 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

12.5.4. Recording of AEs (ADRs) and SAEs

AEs and SAE Recording:

- When an AE (ADRs) /SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE (ADRs) /SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE (ADRs) /SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE (ADRs) /SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE (ADRs) data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE (ADRs) is inappropriate.

12.5.5. Evaluating AEs (ADRs) and SAEs

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE (ADRs) that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs (ADRs) and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence 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 natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of 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 when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. • The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. • If a subject 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 the designated reporting time frames.

12.5.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the SAE coordinator • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) 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 subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the SAE coordinator by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.6. Appendix 6: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;
- Asthma susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 2 ml saliva sample will be taken for Deoxyribonucleic acid (DNA) extraction. A saliva sample is collected at the baseline visit (Visit 2), after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the saliva sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The saliva sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or “coded”) with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the

subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any saliva being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample

reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.7. Appendix 7: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of foetal 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 5. 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 subject who becomes pregnant while participating

- will be withdrawn from the study
- This will only be included if either of the following apply:
- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner’s pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.

Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure. Additional references supporting the rationale for genetic research on the study treatment can be inserted if available.