# TITLE PAGE

**Division:** Worldwide Development

**Information Type:** Clinical Protocol

| | |
|---|---|
| **Title:** | A randomised, placebo-controlled, double-blind, two period crossover study to characterise the exhaled nitric oxide time profile as a biomarker of airway inflammation in adult asthma patients following repeat administration of inhaled Fluticasone Furoate (FF)/ Vilanterol (VI) 100/25 mcg |

**Compound Number:** GW685698+GW642444

**Development Phase** IIA

**Effective Date:** 12-JAN-2016

**Author(s):**

PPD (Respiratory TAU); PPD (Respiratory TAU); PPD (CPEMT); PPD (Respiratory Medical Franchise); PPD PPD (Clinical Statistics).

**SPONSOR SIGNATORY:**

PPD

12 Jan 2016

Cur PPD n, MD
Direc piratory HUP

**Date**

PPD

# MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): Not applicable

# 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 |

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# 1. PROTOCOL SYNOPSIS FOR STUDY 201499

## Rationale

This study will determine the duration of action of FF by monitoring the return of the fraction of exhaled nitric oxide (FeNO) levels to baseline following the cessation of repeat dose treatment with FF/VI. The study will use a clinical strength of FF/VI (Relvar ELLIPTA 100/25 mcg OD) administered for a two week treatment period. FeNO will continue to be monitored up to 21 days after treatment with FF/VI together with $FEV_1$ (up to 7 days).

## Objective(s)/Endpoint(s)

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To characterise the fraction of exhaled nitric oxide (FeNO) time profile following repeat administration of fluticasone furoate/vilanterol (FF/VI) 100/25mcg combination in comparison with placebo in subjects with asthma. | • Change from baseline FeNO over time following the cessation of repeat dose treatment with FF/VI. |
| **Secondary** | |
| • Change in FeNO over the treatment period following repeat administration of FF/VI 100/25mcg combination in comparison with placebo in subjects with asthma. | • Change from baseline FeNO over the FF/VI treatment period. |
| • To determine the Peak Expiratory Flow (PEF) during and following repeat administration of FF/VI 100/25mcg combination in comparison with placebo in subjects with asthma. | • Measurement of PEF during treatment and following cessation of repeat dose treatment with FF/VI. |
| • To determine forced expiratory volume in 1 second ($FEV_1$) following repeat administration of FF/VI 100/25mcg combination in comparison with placebo in subjects with asthma | • Measurement of $FEV_1$ pre-treatment and for up to 7 days after cessation of repeat dose treatment with FF/VI. |
| **Exploratory** | |
| • To investigate the effect of repeat administration of FF/VI 100/25mcg combination on exploratory biomarkers, including but not limited to, blood eosinophil levels and serum periostin levels, in comparison with placebo in subjects with asthma. | • Measurement of exploratory biomarkers, including but not limited to, blood eosinophil and serum periostin levels at baseline, and at various time points after cessation of repeat dose treatment with FF/VI. |

## Overall Design

This study will be a randomised, double blind, placebo-controlled, two-period, crossover repeat dose study in adult subjects with asthma.

Following screening, subjects will provide AM and PM FeNO and PEF data from Day -7 of Treatment Period 1. The Day -7 AM FeNO readings will be used to confirm eligibility (FeNO >40ppb). On Day 1, pre-treatment (AM) FeNO, $FEV_1$ and PEF readings will be used as baseline for Treatment Period 1. Subjects will then receive FF/VI 100/25 or placebo once daily (AM) for 14 (± 2) days. All treatments will be taken at the same time of day (within ± 2 hours of the treatment on Day 1).

FeNO will be measured by the subjects AM (pre-dose) and PM for 14 days during each treatment period. On Day 14, $FEV_1$ and FeNO will be recorded before the final dose of FF/VI or placebo.

FeNO (AM and PM) will be measured for 21 days after the end of treatment (up to Day 35 for each of the two treatment periods). This will be as an in-patient on Days 14 to 19. All FeNO (out-patient and in clinic) measurements will be obtained using the same FeNO meter for each subject.

$FEV_1$ will be recorded AM and PM (i.e. every 12 hours) as an in-patient on Days 14 to 19. Subjects will then be discharged before returning 2 days later (on Day 21) for a further measurement of $FEV_1$ (168 hours post-treatment). An $FEV_1$ measurement will also be performed on Day 35.

Up to 4 weeks after the final assessment is collected on Day 35 of Treatment Period 1, subjects will then be crossed over to the alternative treatment. Baseline $FEV_1$, PEF and FeNO values will be collected pre-treatment in the morning on Day 1: these will be the baseline values for Treatment Period 2. Subjects will then receive FF/VI 100/25 or placebo once daily (AM) for 14 (± 2) days. The second treatment period procedures will be identical to the first treatment period.

A single measurement of FeNO will be collected according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines at each time point, using a NIOX Vero device with electronic data capture. Appropriate dietary and/or lifestyle restrictions will be applied. The order of assessments collected in the clinic will be: FeNO, $FEV_1$, and then PEF. When the subjects are at home, FeNO will be collected before the PEF measurements. $FEV_1$ measurements taken within 6 hours of short acting beta2-receptor agonist (SABA) use will not be analysed.

PEF measurements (best of 3 recordings) will be recorded AM and PM (i.e. every 12 hours) from Day-7 through to Day 35 of Treatment Period 1, and then from Day 1 of Treatment Period 2 through to the follow-up visit. Subjects will be provided with a PEF meter and these measurements will be captured electronically whilst they are at home and in the clinic.

## Treatment Arms and Duration

Each subject will participate in two treatment periods of 14 (± 2 days). FF/VI 100/25 mcg will be received once daily (AM dosing) in one period and placebo (AM dosing) will be administered in the other period. At the end of each treatment period, there will be a monitoring period of 21 days.

Total duration for each subject (from screening to follow-up) will be a minimum of 76 days, with a maximum of up to 21 weeks, depending on the screening period and the time period between Treatment Periods 1 and 2.

A complete subject is one who has completed both treatment periods, all assessments up to Day 35 of both treatment periods, and all of the follow-up assessments.

## Type and Number of Subjects

Approximately 28 adult subjects with asthma will be enrolled into this study to ensure that 24 subjects complete dosing and critical assessments for both treatment periods.

## Analysis

Following $\log_e$-transformation, primary endpoint of FeNO change from baseline ratio following cessation of treatment will be analyzed using a mixed effects repeated measures model with fixed effect terms for period, treatment, day, time, (period-level baseline)*day*time interaction term, treatment*day*time interaction term, period-level baseline and subject-level baseline. Day*time interaction term will be fitted as repeated measure.

Secondary endpoints of FeNO change from baseline ratio during treatment and $FEV_1$ will be analysed similarly to the primary FeNO endpoint. $FEV_1$ will not be log-transformed.

PEF and safety data will be listed and summarised. Exploratory biomarker data (including blood eosinophil and serum periostin data) will be summarized descriptively, if available.

# 2. INTRODUCTION

## 2.1. Study Rationale/Brief Background

Treatment with an inhaled corticosteroid (ICS) is recommended for asthma patients who are symptomatic while taking as-needed short acting bronchodilators. In patients who remain symptomatic on low to medium doses of ICS, treatment with a combination of a long-acting $\beta_2$ agonists (LABA) and an ICS is recommended. The combination of the ICS fluticasone furoate (FF) and the LABA vilanterol (VI) is approved for the once daily treatment of asthma (RELVAR ELLIPTA or BREO ELLIPTA; 100/25 and 200/25 mcg).

The FF/VI asthma clinical development program demonstrated efficacy over the 24 hour dosing interval resulting in regulatory approvals for once-daily administration. The duration of bronchodilation produced by a single dose of FF/VI 100/25 mcg beyond the

24 hour dosing interval was assessed [GlaxoSmithKline Document Number 2014N194756_00] and showed clinically significant bronchodilation over 48 hours with effects still apparent up to 72 hours post-dose. This effect was predominantly attributed to the LABA (VI) component. The persistence of the anti-inflammatory effect of the ICS (FF) component of FF/VI following cessation of dosing has not been determined.

In subjects with asthma the fraction of exhaled nitric oxide (FeNO) is a non-invasive marker of airway inflammation. In symptomatic subjects high FeNO levels (>50ppb) indicate significant airway eosinophilia which is likely to respond to ICS (Taylor, 2006; Smith, 2005). The onset of action for ICS in reducing FeNO occurs within one week and is maintained with chronic dosing (Kharitonov, 2002; Nolte, 2013). Dose-related reductions in FeNO have been shown with low dose ICS (Kharitonov, 2002; Silkoff, 2001), while fluticasone propionate (FP) produced comparable near-maximal reductions in FeNO across a wide dose range (50-2,000 mcg/5 days) with a maximum possible effect for the agonist (Emax) of 63% reduction and an effective dose for 50% of people receiving the drug (ED50) of 18 mcg which is below the minimal approved clinical dose [GSK Document Number GM2005/00525/00]. A limited investigation (3 days treatment) of the effects of high doses of FF (250 mcg and 1000 mcg) in comparison with FP (1000 mcg) on FeNO was conducted during the early clinical development of FF [GSK Document Number GM2003/00418/00]. Both FF and FP reduced FeNO with a greater effect seen with FF 1000 mcg compared with either FF 250 mcg or FP 1000mcg. However, the overall response to FP was approximately half that produced by the same dose administered for 5 days [GSK Document Number GM2005/00525/00] indicating that the 3 day treatment duration may have been insufficient to produce maximal reductions in FeNO. In a study with mometasone furoate (Nolte, 2013) a greater effect on FeNO was seen after 14 days compared with the response at 7 days across all doses (100, 200 and 400 mcg), although the difference was minimal (approximately 90% of the Day 14 response was apparent by Day 7). This indicates a treatment with ICS for at least 14 days is necessary for the optimal effect on airway inflammation as measured by FeNO.

Following the cessation of ICS treatment FeNO levels progressively return to pre-treatment baseline levels, suggesting a return of inflammation. FeNO levels returned to baseline 7 days after cessation of treatment with budesonide (Kharitonov, 2002) and two weeks after administration of FP 1000 mcg/day for one month, although earlier time-points were not assessed (Van Rensen, 1999). Following short term FF treatment (3 days) FeNO levels remained lowered for 72 hours after the last dose [GSK Document Number GM2003/00418/00]; later time-points were not investigated.

FF demonstrates a number of characteristics that could result in a prolonged anti-inflammatory action including a greater glucocorticoid receptor binding and higher tissue uptake and retention than other ICS molecules (Salter, 2007; Valotis, 2007) together with a longer lung retention than FP in man (Allen, 2013). The duration of anti-inflammatory activity of the FF component of FF/VI beyond the 24 hour dosing interval is not known. This study will determine the duration of action of FF by monitoring the return of FeNO levels to baseline following the cessation of repeat dose treatment with FF/VI. The study will use a clinical strength of FF/VI (RELVAR ELLIPTA 100/25 mcg Once Daily (OD)) administered for a two week treatment period. FeNO will continue to be monitored up to

21 days after treatment with FF/VI together with forced expiratory volume in 1 second ($FEV_1$) (up to 7 days).

Information on the physical, chemical and pharmaceutical properties of FF/VI is available in the Investigator Brochure (IB) [GlaxoSmithKline Document Number RM2008/00012/07] and also in the BREO ELLIPTA datasheet on the New Zealand Medsafe website: http://www.medsafe.govt.nz/profs/datasheet/b/breoelliptainhalation.pdf.

# 3. OBJECTIVE(S) AND ENDPOINT(S)

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To characterise the fraction of exhaled nitric oxide (FeNO) time profile following repeat administration of fluticasone furoate/vilanterol (FF/VI) 100/25mcg combination in comparison with placebo in subjects with asthma. | • Change from baseline FeNO over time following the cessation of repeat dose treatment with FF/VI. |
| **Secondary** | |
| • Change in FeNO over the treatment period following repeat administration of FF/VI 100/25mcg combination in comparison with placebo in subjects with asthma. | • Change from baseline FeNO over the FF/VI treatment period. |
| • To determine the Peak Expiratory Flow (PEF) during and following repeat administration of FF/VI 100/25mcg combination in comparison with placebo in subjects with asthma. | • Measurement of PEF during treatment and following cessation of repeat dose treatment with FF/VI. |
| • To determine $FEV_1$ following repeat administration of FF/VI 100/25mcg combination in comparison with placebo in subjects with asthma | • Measurement of $FEV_1$ pre-treatment and for up to 7 days after cessation of repeat dose treatment with FF/VI. |
| **Exploratory** | |
| • To investigate the effect of repeat administration of FF/VI 100/25mcg combination on exploratory biomarkers, including but not limited to, blood eosinophil levels and serum periostin levels, in comparison with placebo in subjects with asthma. | • Measurement of exploratory biomarkers, including but not limited to, blood eosinophil and serum periostin levels at baseline, and at various time points after cessation of repeat dose treatment with FF/VI. |

# 4. STUDY DESIGN

## 4.1. Overall Design

This study will be a randomised, double blind, placebo-controlled, two-period, crossover repeat dose study in adult subjects with asthma.

Following screening, subjects will provide AM and PM FeNO and PEF data from Day -7 of Treatment Period 1. The Day -7 AM FeNO readings will be used to confirm eligibility (FeNO >40ppb). On Day 1, pre-treatment (AM) FeNO, $FEV_1$ and PEF readings will be used as baseline for Treatment Period 1. Subjects will then receive FF/VI 100/25 or placebo once daily (AM) for 14 (± 2) days. All treatments will be taken at the same time of day (within ± 2 hours of the treatment on Day 1).

FeNO will be measured by the subjects AM (pre-dose) and PM for 14 days during each treatment period. On Day 14, $FEV_1$ and FeNO will be recorded before the final dose of FF/VI or placebo.

FeNO (AM and PM) will be measured for 21 days after the end of treatment (up to Day 35 for each of the two treatment periods). This will be as an in-patient on Days 14 to 19. All FeNO (out-patient and in clinic) measurements will be obtained using the same FeNO meter for each subject.

$FEV_1$ will be recorded AM and PM (i.e. every 12 hours) as an in-patient on Days 14 to 19. Subjects will then be discharged before returning 2 days later (on Day 21) for a further measurement of $FEV_1$ (168 hours post-treatment). An $FEV_1$ measurement will also be performed on Day 35.

Up to 4 weeks after the final assessment is collected on Day 35 of Treatment Period 1, subjects will then be crossed over to the alternative treatment. Baseline $FEV_1$, PEF and FeNO values will be collected pre-treatment in the morning on Day 1: these will be the baseline values for Treatment Period 2. Subjects will then receive FF/VI 100/25 or placebo once daily (AM) for 14 (± 2) days. The second treatment period procedures will be identical to the first treatment period.

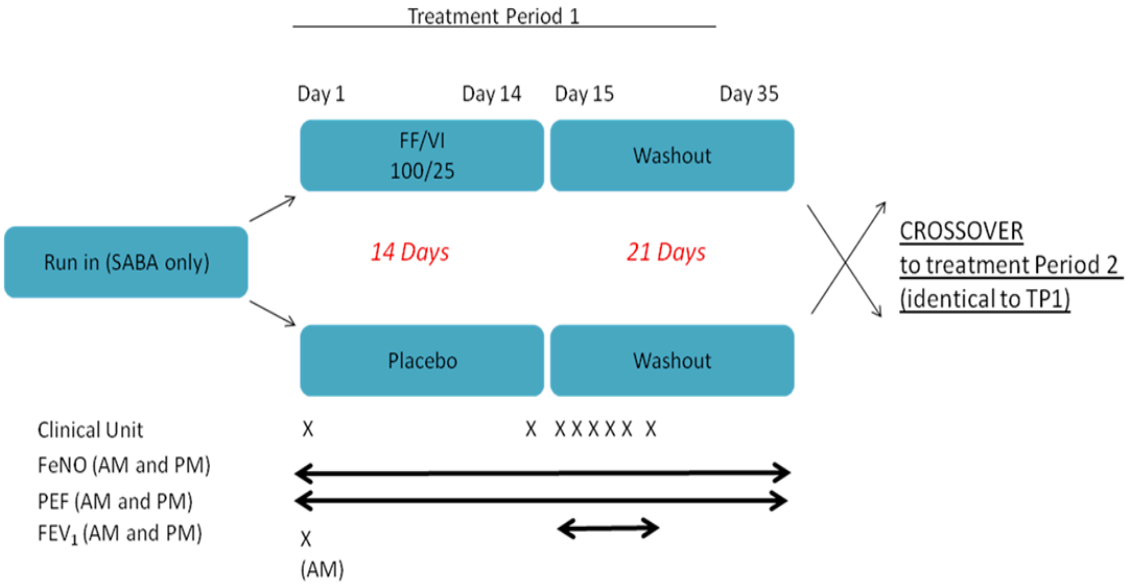
A single measurement of FeNO will be collected according to ATS/ERS guidelines at each time point, using a NIOX Vero device with electronic data capture. Appropriate dietary and/or lifestyle restrictions will be applied. The order of assessments collected in the clinic will be: FeNO, $FEV_1$, and then PEF. When the subjects are at home, FeNO will be collected before the PEF measurements. $FEV_1$ measurements taken within 6 hours of SABA use will not be analysed.

PEF measurements (best of 3 recordings) will be recorded AM and PM (i.e. every 12 hours) from Day-7 through to Day 35 of Treatment Period 1, and then from Day 1 of Treatment Period 2 through to the follow-up visit. Subjects will be provided with a PEF meter and these measurements will be captured electronically whilst they are at home and in the clinic.

## 4.2. Treatment Arms and Duration

Each subject will participate in two treatment periods of 14 (± 2 days). FF/VI 100/25 mcg will be received once daily (AM dosing) in one period and placebo (AM dosing) will be administered in the other period. At the end of each treatment period, there will be a monitoring period of 21 days. At the end of this monitoring period following Treatment Period 1, there may be a period of up to a further 4 weeks before the subjects start Treatment Period 2.

A schematic is shown below:




Total duration for each subject (from screening to follow-up) will be a minimum of 76 days, with a maximum of up to 21 weeks, depending on the screening period and the time period between Treatment Periods 1 and 2. The screening visit can be combined with the Day -7 visit if convenient. Likewise, if no gap is required between Treatment Period 1 and Treatment Period 2, the Day 35 visit for Treatment Period 1 can be combined with the Day 1 visit of Treatment Period 2.

A complete subject is one who has completed both treatment periods, all assessments up to Day 35 of both treatment periods, and all of the follow-up assessments.

## 4.3. Type and Number of Subjects

Approximately 28 adult subjects with asthma will be enrolled into this study to ensure that 24 subjects complete dosing and critical assessments for both treatment periods.

If more than 4 subjects prematurely discontinue the study, these subjects may be replaced at the discretion of the sponsor, in consultation with the investigator. A replacement subject would be assigned to the same treatment sequence as the original withdrawn subject.

## 4.4. Design Justification

**Treatment period.** The characterisation of the FeNO time profile following administration of FF is not known and its determination is the primary objective of this study. The onset of action of ICS on FeNO occurs within a few days with significant and near maximal effects seen after one week. In subjects with asthma and elevated FeNO (mean baseline eNO >65ppb) treatment with FP for 5 days reduced FeNO by 47-60% with a similar effect produced across a 40-fold dose range (50-2,000 mcg twice daily (BD); GSK Document Number GM2005/00525/00). A lesser reduction of approximately 33% from baseline was seen with FP 1,000 mcg BD for 3 days [GSK Document Number GM2003/00418/00] suggesting that this treatment duration may have been sub-optimal. Approximately 90% of the maximal effect of mometasone furoate on FeNO was seen after 7 days treatment compared with 14 days treatment (Nolte, 2013) These data suggest that the selected treatment period of 14 days should be associated with a near maximal effect of FF on eNO and that a longer treatment duration would be unlikely to result in further substantial effects.

**Washout.** As the duration of action of FF on eNO is not known, the washout period of at least 21 days represents a pragmatic balance between a likely duration of action and successful and timely study completion. A washout period of 14-28 days was successfully used in a previous study with repeat dose FP [GSK Document Number GM2005/00525/00]. There is a minimum of a 21 day washout period from the end of Treatment Period 1 to the start of Treatment Period 2. This is expected to be a sufficient washout for FeNO levels to return to baseline. However, to provide flexible scheduling for Treatment Period 2, there may be a further period of up to 4 weeks after the end of this initial 21 day washout period has finished before the subject commences Treatment Period 2.

**Design Rationale.** A placebo-controlled double-blind crossover study is preferred to a parallel group as this will require fewer subjects. Screening failure rates in a similar study [GSK Document Number 2014N194756_00] at the same site were in the order of 90% and a parallel group study is not considered to be feasible. The drop-out rate predicted for this study is considered to be low (based on the previous study HZA116592 conducted at the same site) [GSK Document Number 2014N194756_00].

**Baseline FeNO (for eligibility).** Based on the ATS FeNO 2011 guidelines [ATS, 2011], the lower limit of 40ppb to be used in this study is classified as 'intermediate' (range 25-50ppb). Patients with intermediate FeNO values respond to ICS treatment and clinical cut-offs between 35 and 50ppb have been linked with a high likelihood of asthma diagnosis as well as an increased risk of worsening symptoms and exacerbations (Bjermer, 2014). FeNO >40ppb is considered to be elevated and this lower limit has previously been successfully used by the study site. In a previous study with repeat dose FP in AMP sensitive asthmatics receiving SABA only [GSK Document Number GM2005/00525/00], mean baseline FeNO across the treatments ranged between 66 and 85ppb.

**Dietary and smoking restrictions.** In healthy subjects, eNO increased by 60% two hours after a nitrate-rich meal and was still 22% higher than baseline after 15 hours before

returning to baseline at 20 hours [Vints, 2005]. Therefore, avoidance of nitrate-rich foods is a restriction in this study.

Smoking can reduce FeNO by 30-60%, dependent on daily cigarette consumption (Bjermer, 2014). Consequently, all subjects will be non-smokers.

## 4.5. Dose Justification

FF/VI 100/25 mcg represents the lower approved dose for asthma (RELVAR ELLIPTA and BREO ELLIPTA) and is likely to be the most frequently prescribed strength. The predicted effects of FF/VI 200/25 on FeNO would either be of comparable or of longer duration and therefore the 100/25 mcg dose represent the 'worst case' in terms of duration. The dose response for FF reduction in eNO is not known. However, repeat dose FP for 5 days [GSK Document Number GM2005/00525/00] produced similar reductions in FeNO (ranging from 47% [50 mcg BD] to 60% [2,000 mcg BD] with an ED50 of 18 mcg and an Emax of 63%). Given the greater potency, higher glucocorticoid receptor selectivity, greater tissue uptake and longer intracellular and lung retention of FF compared with FP it is considered to be reasonable to assume that FF 100 mcg for 14 days will produce a maximal or near maximal reduction of eNO.

## 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) [GlaxoSmithKline Document Number RM2008/00012/07] and also in the BREO ELLIPTA datasheet on the New Zealand Medsafe website:
http://www.medsafe.govt.nz/profs/datasheet/b/breoelliptainhalation.pdf.

The study is considered low risk. The dose of FF/VI to be used in this study (100/25mcg) is an approved dose world-wide and has been administered on an out-patient basis in phase III studies in both asthma and chronic obstructive pulmonary disease (COPD) and was well tolerated. The asthma patients to be included in this study are comparable to those in the asthma phase III studies. There are some low risks associated with the study design and procedures and these are summarised below:

### 4.6.1. Risk Assessment

| Potential Risk of Clinical Significance | Mitigation Strategy | Monitoring implemented |
|---|---|---|
| **Investigational Product (IP)** | | |
| There is a potential risk of worsening asthma as subjects will receive placebo in one treatment arm and no treatments during the washout periods (however access to SABA rescue medication will be available throughout the entire study). | Stopping criteria will be applied for both $FEV_1$ (during the clinic stays/visits) and PEF (out-patient and in-clinic) which will be monitored throughout the study treatment and washout periods. | Stopping criteria will be applied for both $FEV_1$ (during the clinic stays) and PEF (out-patient and in-clinic) which will be monitored throughout the study treatment and washout periods. |
| As with any inhaled medication paradoxical bronchospasm may occur with an immediate wheeze after dosing. | If bronchospasm occurs following dosing, immediate administration of a short-acting (i.e., quick relief) inhaled bronchodilator (e.g., albuterol) is recommended. If this treatment fails to provide relief, a physician should be contacted immediately and/or emergency treatment should be sought. | First dose of the study medication in each treatment period will be administered in the clinic under the supervision of a physician. |
| FF/VI is contraindicated in subjects with severe milk protein allergy or known hypersensitivity or any ingredient of the preparation. | These subjects will be excluded from the study. | Not applicable. |
| Cardiovascular effects, such as cardiac arrhythmias e.g. supraventricular tachycardia and extrasystoles may be seen with sympathomimetic drugs, including fluticasone furoate/vilanterol. Therefore fluticasone furoate/vilanterol should be used with caution in patients with severe cardiovascular disease. | Caution is needed in patients with pre-existing cardiovascular (CV) disease, especially severe CV disease. Patients with severe CV disease will be excluded. | Not applicable |

| Potential Risk of Clinical Significance | Mitigation Strategy | Monitoring implemented |
|---|---|---|
| **Investigational Product (IP)** | | |
| There is limited experience of inhaled FF/VI, FF, and VI exposure during pregnancy in clinical studies. The use of FF/VI is not recommended during pregnancy or lactation | Pregnant/ lactating females will be excluded from the study. | Highly effective methods of contraception are required by the protocol in females of childbearing potential |

### 4.6.2. Benefit Assessment

Benefit considerations for each individual subject may include:

- Potential benefit of receiving FF/VI combined inhaled therapy during the study
- Contributing to the process of developing new asthma therapies
- Medical evaluations/assessments associated with study procedures e.g. PEF, $FEV_1$, physical examinations and vital signs.

### 4.6.3. Overall Benefit:Risk Conclusion

The study is considered low risk. The dose of FF/VI to be used in this study (100/25mcg) is an approved dose world-wide and has been administered on an out-patient basis in phase III studies in both asthma and COPD and was well tolerated. The asthma patients to be included in this study are comparable to those in the asthma phase III studies. Taking into account the measures taken to minimise risk to patients participating in this study, the potential low risks identified in association with inhaled FF/VI are justified by the anticipated benefits that will be afforded to subjects with asthma.

# 5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events (AEs), and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the BREO ELLIPTA datasheet on the New Zealand Medsafe website: http://www.medsafe.govt.nz/profs/datasheet/b/breoelliptainhalation.pdf.

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

## 5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

| AGE |
|---|
| 1. **Age of subject**: Between 18 and 65 years of age inclusive, at the time of signing the informed consent. |

| TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY |
|---|
| 2. **Asthma**: A doctor diagnosis of asthma for at least 6 months prior to the start of the study.<br>3. **Severity of disease**: A screening pre-bronchodilator $FEV_1 \geq 60\%$ of predicted |

NOTE: Predicted values will be based upon NHANES III [Hankinson, 1999]

4. **Reversibility of disease**:

Demonstrated presence of reversible airway disease at screening (repeat testing of eligibility can be undertaken following the screening visit up to Day -7).

OR

The presence of reversible airways disease can have been demonstrated historically within 6 months of the screening visit.

NOTE: Reversible airway disease is defined as increase in $FEV_1$ of ≥ 12% over baseline and an absolute change of ≥ 200 mL within 30 minutes following 4 inhalations of albuterol/salbutamol inhalation aerosol/spacer (or equivalent nebulised treatment with albuterol/salbutamol solution).

5. **Current Therapy:**

- Short-Acting Beta2-Agonists (SABA): prescribed SABA for at least 12 weeks prior to screening.

No ICS, LABA, long acting muscarinic anatagonist (LAMA), leukotriene receptor antagonist (LTRA) therapy for three months prior to the start of the study.

6. Non-smoker or ex-smoker (no smoking in previous 12 weeks, ≤10 pack years).
7. Screening and Day -7 AM FeNO values > 40ppb.

   NOTE: Both screening and Day -7 AM FeNO values for Treatment Period 1 need to be > 40ppb for the subject to be eligible.

| WEIGHT |
|---|
| 8. **Bodyweight and BMI:** Bodyweight ≥ 50 kg and Body Mass Index (BMI) within the range 18.0-40.0 $kg/m^2$ (inclusive) |

| SEX |
|---|
| 9. Male OR Female<br>**Females**:<br>A 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:Non-reproductive potential defined as:<br>• Pre-menopausal females reporting one of the following:<br>• Tubal ligation<br>• Hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion<br>• Hysterectomy |

- 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 in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 3) from 30 days prior to the first dose of study medication and until after the last dose of study medication and completion of the follow-up visit.

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

| INFORMED CONSENT |
|---|
| 10. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol. |

## 5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

| CONCURRENT CONDITIONS/MEDICAL HISTORY |
|---|
| **1. A history of life-threatening asthma**.<br>NOTE**:** Life-threatening asthma is defined as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within the last 5 years<br>**2. Other significant pulmonary diseases to include (but not limited to):** pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, bronchopulmonary dysplasia, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, or other respiratory abnormalities other than asthma.<br>**3. Respiratory Infection:** Culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear that is not resolved within 4 weeks of screening that:<br>• led to a change in asthma management<br>OR<br>• in the opinion of the Investigator, is expected to affect the subject's asthma status OR |

the subject's ability to participate in the study.

However, subjects can be rescreened to allow for an adequate time period (of at least 4 weeks) between resolution of the infection and the date of randomisation.

4. **Asthma Exacerbation:** Any asthma exacerbation requiring oral corticosteroids within 12 weeks of screening or that resulted in overnight hospitalization requiring additional treatment for asthma within 6 months prior to screening.

CONCOMITANT MEDICATIONS

5. **Concomitant Medications:** These are listed in detail in Section 6.9 of the protocol. Restrictions of nitrate-rich foods are listed in detail in Section 6.9.1.1 of the protocol.

RELEVANT HABITS

6. **Tobacco Use:** Current smokers or a smoking history of ≥ 10 pack years. A subject may not have used any inhaled tobacco products in 12 weeks preceding the screening visit.

CONTRAINDICATIONS

7. **Previous Participation:** Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

8. **Other concurrent Diseases/Abnormalities:** A subject has any clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the subject at risk through study participation or would confound the interpretation of the study results if the condition/disease exacerbated during the study.

The list of additional excluded conditions/diseases includes, but is not limited to the following:

| | |
|---|---|
| Congestive heart failure | Known aortic aneurysm |
| Clinically significant coronary heart disease | Clinically significant cardiac arrhythmia |
| Stroke within 3 months of Visit 1 | Uncontrolled hypertension* |
| Recent or poorly controlled peptic ulcer | Haematologic, hepatic**, or renal disease |
| Immunologic compromise | Current malignancy*** |
| Tuberculosis (current or untreated)**** | Cushing's disease |
| Addison's disease | Uncontrolled diabetes mellitus |
| Liver cirrhosis | Systemic Lupus Erythematosus |
| Uncontrolled thyroid disorder | Recent history of drug or alcohol abuse |

*Two or more measurements with systolic BP>160mmHg, or diastolic BP >100mmHg
**Subjects with chronic stable hepatitis B and C are acceptable provided their screening ALT is < 2x upper limit of normal (ULN) and the subject otherwise meets the entry criteria. Subjects who have chronic co-infection with both hepatitis B and hepatitis C are not eligible.
***history of malignancy is acceptable only if subject has been in remission for one year prior to Visit 1 (remission = no current evidence of malignancy and no treatment for the malignancy in the 12 months prior to Visit 1)
****Subjects with a history of tuberculosis infection who have completed an appropriate course of antituberculous treatment may be suitable for study entry provided that there is no clinical suspicion of active or recurrent disease.

9. **Oropharyngeal examination**: A subject will not be eligible if he/she has clinical visual evidence of oral candidiasis at screening.
10. **Pregnancy and Lactating Females**:
    - Pregnant females as determined by positive serum hCG test at screening or by positive urine hCG test prior to dosing.
    - Lactating females
11. **Allergies:**
    - **Milk Protein Allergy:** History of severe milk protein allergy.
    - **Drug Allergy:** Any adverse reaction including immediate or delayed hypersensitivity to any beta$_2$-agonist, sympathomimetic drug, or any intranasal, inhaled, or systemic corticosteroid therapy. Known or suspected sensitivity to the constituents of the Dry Powder Inhaler (DPI) (i.e., lactose or magnesium stearate).
    - **Historical Allergy:** History of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation.

## 5.3. Screening Failures

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 Serious Adverse Events (SAEs) (see Section 7.4.1.6).

Subjects who initially fail screening based on not meeting one of the inclusion/exclusion criteria may be rescreened subsequently. A limited rescreen checking this parameter against the inclusion/exclusion criteria may be performed, and if the subject then meets all the eligibility criteria, they would be allowed to be enrolled onto the study. However, repeat Day -7 visits cannot be performed.

## 5.4. Withdrawal/Stopping Criteria

**Worsening asthma**: The following criteria will be used to aid the Investigator in determining asthma stability. A randomised subject who meets any of the following stopping criteria will be withdrawn from the study:

- Clinic PEF and $FEV_1$ below the stability limit values calculated at pre-treatment Day 1, Treatment Period 1. Subjects must have completed a minimum of at least 10 out of 14 peak flow measurements during the one week prior to randomisation (Day -7 to Day 1).
- During the study, the subject experienced:
    1. At least 4 consecutive days in which the PEF (either AM, PM or both) has fallen below the PEF Stability Limit calculated at pre-treatment Day 1, Treatment Period 1 OR
    2. At least 3 days in which ≥12 inhalations/day of albuterol/salbutamol were used.
- Subjects who experience a protocol-defined severe exacerbation, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.
- Clinical asthma worsening which in the opinion of the investigator requires additional asthma treatment other than study medication or study supplied albuterol/ salbutamol.

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".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. 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.

## 5.5. Subject and Study Completion

A complete subject is one who has completed both treatment periods, all assessments up to Day 35 of both treatment periods, and all of the follow-up assessments.

The end of the study is defined as the last subject's last visit.

# 6. STUDY TREATMENT

## 6.1. Investigational Product

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.

| | **Study Treatment** | |
|---|---|---|
| **Product name:** | FF/Vilanterol Inhalation Powder , 100/25 mcg per blister | Placebo To Match FF/Vilanterol Inhalation Powder |
| **Formulation description:** | First strip: FF blended with lactose, 100 mcg per blister<br>Second strip: Vilanterol blended with lactose and magnesium stearate[1], 25 mcg per blister[2] | First strip: lactose<br>Second strip: lactose and magnesium stearate[1] |
| **Dosage form:** | Dry Powder Inhaler | Dry Powder Inhaler |
| **Unit dose strength(s)/Dosage level(s):** | FF/Vilanterol 100/25 mcg[2] | N/A |
| **Route of Administration/ Duration:** | Inhaled/ Taken once a day for 14 ± 2 days | Inhaled/Taken once a day for 14 ± 2 days |
| **Dosing instructions:** | 1 inhalation | 1 inhalation |
| **Physical description:** | Dry powder Inhaler | |
| **Manufacturer/ source of procurement:** | GSK | GSK |

1. Magnesium stearate 1% w/w of total drug product
2. 40 mcg of Vilanterol trifenatate (triphenylacetate salt) is equivalent to 25 mcg of Vilanterol (free base).

## 6.2. Treatment Assignment

Subjects will be assigned to one of two treatment sequences (AB or BA, where A is placebo and B is FF/VI 100/25 mcg) in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

If more than 4 subjects prematurely discontinue the study, these subjects may be replaced at the discretion of the Sponsor, in consultation with the investigator. A replacement subject would be assigned to the same treatment sequence as the original withdrawn subject.

## 6.3. Blinding

This will be a double-blind study and the following will apply.

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR **in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator**.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF.

The patients, site staff and GSK will remain blinded for the duration of the study.

A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

Sealed code break envelopes will be provided to the site, in case of unblinding.

## 6.4. Packaging and Labeling

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

## 6.5. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

## 6.6. Compliance with Study Treatment Administration

When subjects are dosed at the site (on Day 1 and Day 14 of each treatment period), they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

When subjects self-administer study treatment at home (on Days 2 to 13 of each treatment period), dosing details will be completed by the subjects in individual paper diaries, and then later transcribed by the site into the CRF. Dosing compliance will be assessed through querying the subject during the subsequent site visits and this will be documented in the source documents and CRF. A dosing record for each subject must be maintained and reconciled with study treatment and compliance records.

Subject compliance with study treatment administered at home will be reinforced by the site using various methods including the use of daily text reminders and weekly telephone contact. More details will be given in the SRM.

## 6.7. Treatment of Study Treatment Overdose

An overdose for this study will be considered as any dose of study drug more than the planned dose on each dosing occasion. In the event of an overdose, there are no recommended medications or non-drug therapies for treatment. GSK is not recommending specific treatment guidelines for overdose and toxicity management. The investigator should contact the GSK Medical Monitor, and is advised to refer to the relevant documents for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug(s) being used in this study. Such documents may include, but not limited to, the Investigator's Brochure (IB) or equivalent document provided by GSK, the approved product label if applicable, or both. Clinical judgment should be used in treating the

overdose. Management should be supportive and the investigator should use his/her clinical judgement in treating any overdose situation. Subjects experiencing such adverse events will be followed up clinically until the event has resolved.

## 6.8. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because the indication being studied is not life threatening or seriously debilitating and/or other treatment options are available.

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

## 6.9. Lifestyle and/or Dietary Restrictions

### 6.9.1. Meals and Dietary Restrictions

#### 6.9.1.1. Nitrate-rich foods

Nitrate-rich foods should be avoided as much as possible from Day -7 throughout the duration of the study until completion of the follow-up visit. Details of nitrate-rich foods are given in the table below:

| **Nitrate-rich Food*** |
|---|
| Beetroot |
| Celery |
| Cabbage |
| Aubergine |
| Spinach |
| Radish |
| Broccoli |
| Cauliflower |
| Carrot |
| Lettuce |
| Radish |
| Turnip/swede |

*Vegetables such as beetroot, celery, lettuce, radishes and spinach contribute about 85 to 90% of an adult's dietary intake of nitrate, with nitrate levels ranging from 1700 to 2400 mg/kg food [Vints, 2005]. This food should be avoided as much as possible for the duration of the study. Specially prepared food will be given to the subjects whilst in-clinic and subjects will be reminded about this restriction for all other periods.

#### 6.9.1.2. Caffeine and Alcohol

- From the screening visit until the follow up visit, subjects must not drink more than the equivalent of 4 standard cups of coffee/tea per day (e.g. 4 single shot cups or 2

double shot cups) and they must not drink more than 2 standard alcoholic drinks per day (e.g. 2 standard glasses of wine, where a standard glass = 175 mL).

- Subjects must abstain completely from coffee, tea, and alcohol within 2 hours of any of the lung function measurements.

### 6.9.2. Activity

Patients should avoid rigorous exercise for at least 2 hours before each FeNO and lung function measurement.

## 6.10. Concomitant Medications and Non-Drug Therapies

### 6.10.1. Permitted Medications and Non-Drug Therapies

#### 6.10.1.1. Permitted asthma medications

The current asthma therapy for the patients enrolled in this study will be Short-Acting Beta2-Agonists (SABA), and patients must have been prescribed SABA for at least 12 weeks prior to screening.

#### 6.10.1.2. Other permitted medications

Regarding subjects with any upper respiratory disorders including allergic rhinitis (both seasonal and perennial) and chronic rhinosinusitis (with or without nasal polyps), any subject who is on chronic maintenance therapies for these conditions will continue on their current standard of care medications (i.e. intranasal corticosteroids, antihistamines, cromones) throughout the entire duration of the study.

### 6.10.2. Prohibited Medications and Non-Drug Therapies

#### 6.10.2.1. Prohibited asthma medications

Inhaled corticosteroids (ICS), long acting beta agonists (LABA), leukotriene receptor antagonists (LTRA), long acting muscarinic anatagonists (LAMA), oral steroids, omalizumab (Xolair) and mepolizumab (Nucala) are prohibited from 3 months prior to the start of the study until after the study follow-up visit.

#### 6.10.2.2. Prohibited non-asthma medications

The following medications may not be used during the study from first dosing to the end of Treatment Period 2 inclusive:

- Anticonvulsants (barbiturates, hydantoins, and carbamazepine)
- Polycyclic antidepressants
- β-adrenergic blocking agents
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Phenothiazines

- Monoamine oxidase (MAO) inhibitors

# 7. STUDY ASSESSMENTS AND PROCEDURES

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.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1.

Additional detailed procedures for obtaining each assessment are provided in the Study Reference Manual (SRM) where specified.

The timing and number of planned study assessments, including safety and spirometry assessments may be altered during the course of the study to ensure appropriate monitoring. The change in timing or addition of time points for any planned study assessments must be approved and documented by GSK, but this will not constitute a protocol amendment. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme.

A subject may attend an unscheduled visit at any time if the investigator deems necessary for safety reasons.

## 7.1. Time and Events Table

| Procedure | Screening (up to 42 days prior to Day 1) | Study Day (each treatment period) | | | | | | Follow-up (Days 35-42)[13] | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | | Day -7 (start of run-in)[1] | Day 1 | Days 2-13 | Days 14-19 | Day 21 | Day 35 | | |
| Out-patient visit to the unit | X | X | X | | | X | X | X | [1] Day -7 is the start of the one week run-in period and therefore this visit and the assessments on this day only apply to Treatment Period 1 |
| Admission to the unit | | | | | X | | | | |
| Informed consent | X | | | | | | | | |
| Inhaler, PEF meter and FeNO device practice | X | | | | | | | | |
| Inclusion and exclusion criteria/eligibility review | X | X | X[2] | | | | | | [2] Treatment Period 1 only |
| Demography | X | | | | | | | | |
| Full physical exam including height and weight | X | | | | | | | | |
| Medical history (includes substance usage [and family history of premature CV disease]) | X | | | | | | | | Substances: [Drugs, Alcohol, tobacco and caffeine] |
| Past and current medical conditions [including cardiovascular medical history] | X | | | | | | | | |
| Urine pregnancy test (WCBP) | X | | X[3] | | | X | | X | [3] Collected pre-dose |
| Vital signs | X | | | | | | | | |
| Set up PEF and FeNO monitoring | | X | | | | | | | |
| Study Treatment | | | X[4] | | X[5] | | | | [4] Dosing every morning; dosing in the unit on Days 1 and 14 and at home on Days 2-13<br>[5] Dosing on the morning of Day 14 only |

| Procedure | Screening (up to 42 days prior to Day 1) | Study Day (each treatment period) | | | | | | Follow-up (Days 35-42)[13] | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | | Day -7 (start of run-in)[1] | Day 1 | Days 2-13 | Days 14-19 | Day 21 | Day 35 | | |
| Exploratory biomarker sampling[6] | | | X | | X | X | X | | [6] These measurements are taken at baseline (Day 1 pre-dose), at the end of treatment (Day 15), on Day 21 and on Day 35. |
| $FEV_1$ readings[7] | X | | X[8] | | X[9] | X[10] | X[10] | | [7] Measured in the unit only<br>[8] Taken pre-dose<br>[9] Collected AM (pre-dose on Day 14) and PM<br>[10] Collected AM only |
| FeNO assessment[11] | X | ←==========→ | | | | | | | [11] Start of collection 7 days before Day 1 (Day -7), then collected every day AM and PM through to Day 35 of each treatment period. |
| PEF[12] | | ←==========→ | | | | | | | [12] Collected AM and PM every day from Day -7 through to Day 35 for Treatment Period 1, and from Day 1 through to follow up for Treatment Period 2. |
| AE/SAE review | | ←==========→ | | | | | | | |
| Concomitant medication review | | ←==========→ | | | | | | | [13] Follow up visit only after Treatment period 2. The follow-up visit can be combined with the Day 35 visit for Treatment Period 2. |
| Issue of diary card | X | | | | | X[14] | | | [14] Second diary card given out on Day 21 of Treatment Period 1, to capture data for Treatment Period 2 |

## 7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

## 7.3. Pharmacodynamics

### 7.3.1. FeNO measurements

Fractionated exhaled nitric oxide (FeNO) measurements will be collected from 7 days before Day 1 (start of treatment) (Day -7), and then every morning and evening all the way through to Day 35 of each treatment period (see Time and Events Table in Section 7.1). Additional time points may be added during the course of the study based on newly available information.

Single FeNO measurements will be collected at each time-point in accordance with ATS/ERS guidelines. These measurements will be recorded using a NIOX Vero device which will be supplied to the patient on Day -7 by the site. Measurements will be captured electronically and regularly downloaded by the site at each clinic visit.

Training and practice with these devices will be given to each patient at the screening visit.

More details will be given in the SRM.

### 7.3.2. Spirometry

Three technically acceptable $FEV_1$ measurements will be made at the time points outlined in the Time and Events table (Section 7.1) and the highest values will be recorded.

Spirometry assessments must be performed in accordance with ATS/ERS guidelines [ATS/ERS Task Force, 2005]. The Forced Expiratory Volume during the first 6 seconds (FVC6), rather than the full Forced Vital Capacity (FVC) will be measured.

**Screening $FEV_1$** must be measured between 7am-10am.

#### 7.3.2.1. Reversibility testing

The presence of reversible airways disease can have been demonstrated historically within 6 months of the screening visit.

OR

It must be demonstrated at the screening visit.

Following the spirometry assessment at screening, administer a single dose of 400 μg inhaled albuterol / salbutamol using a metered dose inhaler (MDI) and spacer device. The bronchodilator will be withheld for 6 hours prior to the screening visit. At any time point between 15 and 30 minutes post administration of albuterol / salbutamol, take triplicate $FEV_1$ measurements and record the highest.

Reversibility is shown if there is an increase in $FEV_1$ of ≥ 12.0% over baseline **and** an absolute change of ≥ 200 mL between the highest pre and post salbutamol $FEV_1$.

#### 7.3.2.2. $FEV_1$ Stability Limit

Calculate a $FEV_1$ Stability Limit as follows:

**Best pre-dose $FEV_1$ x 80%**

The $FEV_1$ Stability Limit value will be calculated at the pre-dose time point of treatment period 1 and used as reference until the pre-dose time point of treatment period 2. The stability limit will be re-calculated at the pre-dose time point of treatment period 2 and used for the remainder of the study.

### 7.3.3. PEF

Each subject will be given a PEF meter by the site on Day -7. Data will be captured electronically.

Subjects must measure morning and evening PEF as indicated in the time and events table. Three technically acceptable PEF measurements will be collected at each time point and the highest values will be recorded.

#### 7.3.3.1. PEF Stability Limit

Subjects must have completed a minimum of at least 10 out of 14 peak flow measurements during the one week prior to randomisation (Day -7 to Day 1).

Calculate a PEF Stability Limit as follows:

**Mean AM PEF from the available 7 days preceding Day 1 dose x 80%**

The AM PEF from the morning of Day 1 will be included in the calculation of the PEF stability limit.

The PEF Stability Limit value will be used for the remainder of the study.

PEF devices will be set to alert the subject if their PEF drops below this limit.

#### 7.3.3.2. PEF below Stability Limit

Should the PEF fall below the PEF stability limit, the subject should contact the site. The investigator must monitor the subject and withdraw the subject is he/she meets any of the criteria in Section 5.4.

## 7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs and physical examinations) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

### 7.4.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 2.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

#### 7.4.1.1. Time period and Frequency for collecting AE and SAE information

- 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.
- AEs will be collected from the start of the run-in period (Day -7) until the follow-up contact (see Section 7.4.1.3), at the time-points 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.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 2.
- 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 2.

#### 7.4.1.2. Method of Detecting AEs and SAEs

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?"

#### 7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) 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 2.

#### 7.4.1.4. Cardiovascular and Death Events

Investigators will be required to fill out event specific data collection tools 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 thrombosis
- Deep Venous Thrombosis
- Revascularization

For these cardiovascular events detailed above and for 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 Medical Dictionary for Regulatory Activities (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

The following disease related events (DREs) are common in subjects with asthma and can be serious/life threatening:

1. Wheezing
2. Chest tightness or chest heaviness
3. Coughing

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of a SAE). These events will be recorded on the DRE page in the subject's CRF within 5 working days.

*NOTE: However, if either of the following conditions apply, then the event must be recorded and reported as an SAE (instead of a DRE):*

- *The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject, or*
- *The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product*

#### 7.4.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) 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.

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, Institutional Review Board (IRB)/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 IRB/IEC, if appropriate according to local requirements.

### 7.4.2. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until the follow-up visit.
- 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 3.

### 7.4.3. Physical Exams

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

### 7.4.4. Vital Signs

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure (BP) and pulse rate.

### 7.4.5. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments as detailed in Table 1 must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Parameters to be tested are listed in Table 1.

**Table 1 Protocol Required Safety Laboratory Assessments**

| Laboratory Assessments | Parameters |
|---|---|
| Other Screening Tests | • FSH and estradiol (as needed in women of non-child bearing potential only)<br>• Urine hCG Pregnancy test (as needed for women of child bearing potential)[1] |
| NOTES :<br><br>1. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee. | |

## 7.5. Biomarker(s)/Pharmacodynamic Markers

### 7.5.1. Exploratory Biomarkers

With the subject's consent, blood samples will be collected during this study and used for the purposes of measuring exploratory biomarkers, including but not limited to, blood eosinophil and serum periostin levels on Day 1 pre-dose (baseline) and following inhaled administration of FF/VI.

Samples will be collected at the time-points indicated in the Time and Events Table in Section 7.1. The timing of the collections may be adjusted on the basis of emerging data from this study or other new information in order to ensure optimal evaluation of the PD endpoints. Analyses of these biomarker data may be reported separately. Further details will be provided in the SRM.

# 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.
- Subject paper diaries will also be used for when the subjects are at home, for collection of dosing information, details of any AEs/SAEs and concomitant medications. These will then be transcribed into the CRF by clinic staff.
- 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

No formal hypothesis will be tested, an estimation approach will be adopted to address the primary objective. A point estimate and corresponding 95% CI will be constructed for the treatment ratio of test treatment, μ(test) and reference treatment(reference), where FF/VI 100/25mcg is the test treatment and placebo the reference treatment.

## 9.2. Sample Size Considerations

### 9.2.1. Sample Size Assumptions

Approximately 28 subjects will be recruited to ensure 24 evaluable subjects. An evaluable subject is defined as a subject who completes dosing and critical assessments in both treatment periods.

A re-analysis of FeNO data from the FFA10028 study [GlaxoSmithKline Document Number GM2003/00418/00] was carried out to estimate the within-subject coefficient of variation (CVw) from a repeated measures analysis using the treatments and time-points most relevant to this study (i.e. FF and placebo treatments and all pre-dose, 12 hour and 24 hour time-points on all days assessed (Days 1-5). A mixed effects repeated measures model was fitted with fixed effect terms for period, treatment, day, time, period-level baseline, subject-level baseline, (period-level baseline)*day*time interaction term and the treatment*day*time interaction term. Day*time interaction term was fitted as a repeated measure. FeNO was loge-transformed prior to deriving subject-level baseline and period-level baseline. The CVw from the re-analysis was 21.6%.

Based upon a CVw of 21.6% and a sample size of 24 subjects, it is estimated that the lower and upper bounds of the 95% confidence interval for the treatment ratio (FF/VI vs Placebo) for FeNO will be approximately 14% of the point estimate.

### 9.2.2. Sample Size Sensitivity

A sensitivity analysis was conducted in the event that the variability deviates from that estimated from the FFA10028 study [GlaxoSmithKline Document Number GM2003/00418/00]. The table below shows precision estimates for varying within subject coefficient of variability keeping all other variables constant.

| Confidence Level | Sample Size (N) | CVw% | Half Width (%) |
|---|---|---|---|
| 0.95 | 24 | 15% | 10% |
| | | 20% | 13% |
| | | 25% | 16% |
| | | 30% | 20% |

The precision estimates are deemed acceptable to assess the study objectives.

### 9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation or adjustment will be performed.

## 9.3. Data Analysis Considerations

### 9.3.1. Analysis Populations

Statistical analyses of the pharmacodynamic parameter data will be the responsibility of Clinical Statistics, GlaxoSmithKline.

Subjects excluded from any analyses will be fully documented and justified within the clinical study report. All analyses will be based on the actual treatment that each subject received. Any departures from the planned treatment according to the randomisation schedule will be documented in the clinical study report.

The 'All Subjects' population will consist of all subjects randomised to treatment who received at least one dose of study treatment.

The 'Pharmacodynamic' (PD) population will consist of all subjects from the 'All Subjects' population who had at least one PD assessment.

### 9.3.2. Interim Analysis

No interim analysis is planned.

## 9.4. Key Elements of Analysis Plan

### 9.4.1. Primary Analyses

Following $\log_e$-transformation, primary endpoint of FeNO change from baseline ratio following cessation of treatment will be analyzed using a mixed effects repeated measures model with fixed effect terms for period, treatment, day, time, (period-level baseline)*day*time interaction term, treatment*day*time interaction term, period-level baseline and subject-level baseline. Day*time interaction term will be fitted as repeated measure. FeNO will be $\log_e$-transformed prior to deriving subject-level baseline and period-level baseline. Point estimates and their associated 95% confidence intervals will be constructed for the difference [FF/VI 100/25mcg] – [Placebo] at each timepoint (AM/PM i.e. pre-dose & 12 hours) on each day. The point estimates and their associated 95% confidence intervals will then be back-transformed to provide point estimates and 95% confidence intervals for the ratios, [FF/VI 100/25mcg]/[Placebo] for each day and AM/PM timepoint. Further details will be provided in the Reporting and Analysis Plan (RAP) regarding the model to be fitted and model checking.

### 9.4.2. Secondary Analyses

Secondary endpoints of FeNO change from baseline ratio during treatment and $FEV_1$ will be analysed similarly to the primary FeNO endpoint. $FEV_1$ will not be log-transformed.

PEF data will be listed and summarised.

Further details will be provided in the RAP.

### 9.4.3. Other Analyses

Safety data will be listed and summarised. Exploratory biomarker data (including blood eosinophil and serum periostin data) will be summarized descriptively, if available.

# 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 enrollment of subjects begins.

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

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.

## 10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including 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 also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify 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 premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

## 10.6. Records Retention

- Following closure of the study, the investigator or the 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 maintained to allow easy and timely retrieval, 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 these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to 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 and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event 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 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 will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

# 11. REFERENCES

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# 12. APPENDICES

## 12.1. Appendix 1 – Abbreviations and Trademarks

### Abbreviations

| | |
|---|---|
| µg | Microgram |
| AE | Adverse Event |
| ATS | American Thoracic Society |
| BD | Twice daily |
| BMI | Body mass index |
| BP | Blood pressure |
| COPD | Chronic obstructive pulmonary disease |
| CPEMT | Clinical Pharmacology Experimental Medicine and Technologies |
| CRF | Case Report Form |
| CV | Cardiovascular |
| DPI | Dry powder Inhaler |
| ED50 | Effective dose for 50% of people receiving the drug |
| Emax | Maximum possible effect for the agonist |
| eNO | Exhaled Nitric Oxide |
| ERS | European Respiratory Society |
| FeNO | Fraction of exhaled nitric oxide |
| FEV1 | Forced expiratory volume in 1 second |
| FF | Fluticasone furoate |
| FP | Fluticasone proprionate |
| FRP | Females of Reproductive Potential |
| FSH | Follicle Stimulating Hormone |
| FVC | Forced Vital Capacity |
| FVC6 | Forced Vital Capacity in 6 seconds |
| GCP | Good Clinical Practice |
| GCSP | Global Clinical Safety and Pharmacovigilence |
| GSK | GlaxoSmithKline |
| hCG | Human chorionic gonadotropin |
| HIV | Human Immunodeficiency Virus |
| HRT | Hormone Replacement Therapy |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICS | Inhaled Corticosteriods |
| IEC | Independent Ethics Committee |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| Kg | Kilogram |
| L | Liter |
| LABA | Long-acting, beta2-receptor agonist |
| LAMA | long acting muscarinic anatagonist |

| | |
|---|---|
| LTRA | leukotriene receptor antagonist |
| MAO | Monoamine oxidase |
| mcg | Micrograms |
| MDI | Metered dose inhaler |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mL | Milliliter |
| mmHg | Millimeter of mercury |
| MSDS | Material Safety Data Sheet |
| N | Number |
| OD | Once daily |
| PEF | Peak Expiratory Flow |
| ppb | Parts per billion |
| RAP | Reporting and Analysis Plan |
| SABA | Short acting beta2-receptor agonist |
| SAE | Serious adverse event(s) |
| SRM | Study Reference Manual |
| TAU | Therapeutic Area Unit |
| UK | United Kingdom |
| ULN | Upper limit of normal |
| VI | Vilanterol |

## Trademark Information

| Trademarks of the GlaxoSmithKline group of companies |
|---|
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## 12.2. Appendix 2: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

### 12.2.1. Definition of Adverse Events

| **Adverse Event 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.<br>• 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.<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected interaction.<br>• 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). |

| **Events <u>NOT</u> 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.<br>• 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.<br>• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.<br>• 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.

### 12.2.2. 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:**<br>• 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.<br>• 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:**<br>• ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**<br>• ALT ≥ 3xULN and INR** > 1.5.<br>* 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.<br>** 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. |

### 12.2.3. 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:<br>• Myocardial infarction/unstable angina<br>• Congestive heart failure<br>• Arrhythmias<br>• Valvulopathy<br>• Pulmonary hypertension<br>• Cerebrovascular events/stroke and transient ischemic attack<br>• Peripheral arterial thromboembolism<br>• Deep venous thrombosis/pulmonary embolism |

- Revascularization

### 12.2.4. Recording of AEs and SAEs

**AEs and SAE Recording:**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/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/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/SAE and not the individual signs/symptoms.

### 12.2.5. Evaluating AEs and SAEs

**Assessment of Intensity**

The investigator will make an assessment of intensity for each AE 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 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 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.

### 12.2.6. 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<br>• 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 Medical Monitor and the GSK Study Manager<br>• Site will enter the serious adverse event data into the electronic system as soon as it becomes available.<br>• 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.<br>• 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<br>• 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 Medical Monitor or the GSK Study Manager by telephone.<br>• Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page. |

## 12.3. Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

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

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011])
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
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, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

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.

### 12.3.2. 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 fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 2. 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 discontinue study medication or 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.

### 12.3.3. References

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.