



## Clinical trial results:

**A 24-week study to evaluate the effect of fluticasone furoate (GW685698) /vilanterol (GW642444) 100/25 µg Inhalation Powder delivered once-daily via a Novel Dry Powder Inhaler on arterial stiffness compared with placebo and vilanterol in subjects with Chronic Obstructive Pulmonary Disease (COPD).**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2010-023091-10   |
| Trial protocol           | DE NO            |
| Global end of trial date | 04 November 2014 |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 27 April 2016 |
| First version publication date | 01 July 2015  |

### Trial information

#### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | HZC113108 |
|-----------------------|-----------|

#### Additional study identifiers

|                                    |   |
|------------------------------------|---|
| ISRCTN number                      | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN)   | - |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | GlaxoSmithKline  |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact               | GSK Response Center, GlaxoSmithKline, 1 866-435-7343,      |
| Scientific contact           | GSK Response Center, GlaxoSmithKline, 1 866-435-7343,      |

Notes:

### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 29 January 2015  |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 04 November 2014 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the effect of FF/VI Inhalation Powder 100/25 µg administered once daily compared with placebo on arterial stiffness measured as Aortic Pulse Wave Velocity (aPWV) in subjects with COPD and aPWV ≥ 11.0 m/s at baseline.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 04 March 2011 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Germany: 551            |
| Country: Number of subjects enrolled | Norway: 41              |
| Country: Number of subjects enrolled | Korea, Republic of: 211 |
| Country: Number of subjects enrolled | Philippines: 542        |
| Country: Number of subjects enrolled | Thailand: 253           |
| Country: Number of subjects enrolled | United States: 1413     |
| Worldwide total number of subjects   | 3011                    |
| EEA total number of subjects         | 592                     |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |
| Children (2-11 years)                     | 0 |
| Adolescents (12-17 years)                 | 0 |

|                      |      |
|----------------------|------|
| Adults (18-64 years) | 1685 |
| From 65 to 84 years  | 1307 |
| 85 years and over    | 19   |

## Subject disposition

### Recruitment

Recruitment details:

3011 par. were screened, 559 entered Run-in Period (RIP), of whom 444 randomized and received at  $\geq 1$  dose of study medication; 430 included in the Intent-to-Treat (ITT) Population. Par. were considered to have completed the TP if they attended Wk 24 and completed the study if also attended the 1-wk follow-up contact and no early withdrawal.

### Pre-assignment

Screening details:

Eligible participants (par.) at screening entered a 2-week, single-blind placebo RIP to obtain albuterol (salbutamol) use at Baseline, and to ensure that par.'s COPD was stable at randomization. At the end of the RIP, par. meeting the randomization criteria entered the double-blind treatment period (TP) of 24 weeks (Wk).

### Period 1

|                              |                                    |
|------------------------------|------------------------------------|
| Period 1 title               | 2-week, Single-blind Run-In Period |
| Is this the baseline period? | No                                 |
| Allocation method            | Non-randomised - controlled        |
| Blinding used                | Single blind                       |
| Roles blinded                | Subject                            |

### Arms

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Placebo-Run-in |
|------------------|----------------|

Arm description:

Participants received placebo once daily (QD) in the morning for 2 weeks. In addition, participants were provided an inhaled short-acting beta2-receptor agonist (SABA), albuterol (salbutamol) (metered dose inhaler [MDI] or nebulas), to be used as a rescue medication for relief of chronic obstructive pulmonary disease (COPD) symptoms during the Run-in and Treatment Periods.

|  |                   |
|--|-------------------|
| Arm type                               | Placebo           |
| Investigational medicinal product name | Placebo QD        |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Inhalation powder |
| Routes of administration               | Inhalation use    |

Dosage and administration details:

QD in the morning via DPI

| Number of subjects in period 1     | Placebo-Run-in |
|------------------------------------|----------------|
| Started                            | 559            |
| Completed                          | 444            |
| Not completed                      | 115            |
| Did Not Meet Continuation Criteria | 102            |
| Consent withdrawn by subject       | 9              |
| Physician decision                 | 1              |
| Adverse event, non-fatal           | 1              |
| Lost to follow-up                  | 2              |

**Period 2**

|                              |   |
|------------------------------|---|
| Period 2 title               | 24-week, Double-blind Treatment Period                        |
| Is this the baseline period? | Yes <sup>[1]</sup>  |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

**Arms**

|                              |            |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes        |
| <b>Arm title</b>             | Placebo QD |

## Arm description:

Participants received placebo QD in the morning via a dry powder inhaler (DPI) for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

|  |                   |
|--|-------------------|
| Arm type                               | Placebo           |
| Investigational medicinal product name | Placebo QD        |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Inhalation powder |
| Routes of administration               | Inhalation use    |

## Dosage and administration details:

QD in the morning via DPI

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | VI 25 µg QD |
|------------------|-------------|

## Arm description:

Participants received vilanterol (VI) 25 micrograms (µg) inhalation QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | Vilanterol 25 µg QD |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Inhalation powder   |
| Routes of administration               | Inhalation use      |

## Dosage and administration details:

QD in the morning via DPI

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | FF/VI 100/25 µg QD |
|------------------|--------------------|

## Arm description:

Participants received fluticasone furoate (FF)/VI 100/25 µg inhalation QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

|  |   |
|--|---|
| Arm type                               | Experimental                                |
| Investigational medicinal product name | Fluticasone Furoate/Vilanterol 100/25 µg QD |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Inhalation powder                           |
| Routes of administration               | Inhalation use                              |

## Dosage and administration details:

QD in the morning via DPI

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Eligible par. at screening entered a 2-week, single-blind placebo RIP to obtain albuterol (salbutamol) use at Baseline, and to ensure that par.'s COPD was stable at randomization. At the end of the RIP, par. meeting the randomization criteria entered the double-blind treatment period (TP) of 24 weeks (Wk).

| <b>Number of subjects in period 2<sup>[2]</sup>[3]</b> | Placebo QD        | VI 25 µg QD | FF/VI 100/25 µg QD |
|--|-------------------|-------------|--------------------|
| Started  | 141               | 154         | 135                |
| Completed the Treatment Period                         | 96 <sup>[4]</sup> | 124         | 110 <sup>[5]</sup> |
| Completed  | 97                | 124         | 111                |
| Not completed  | 44                | 30          | 24                 |
| Physician decision                                     | 3                 | 1           | 1                  |
| Consent withdrawn by subject                           | 7                 | 4           | 1                  |
| Adverse event, non-fatal                               | 8                 | 6           | 7                  |
| Lack of Efficacy-Sub-Reason Exacerbation               | 13                | 13          | 6                  |
| Protocol-defined Stopping Criteria                     | 4                 | 3           | 6                  |
| Lack of Efficacy-No Sub-Reason                         | 2                 | -           | -                  |
| Lost to follow-up                                      | 3                 | -           | -                  |
| Protocol deviation                                     | 4                 | 3           | 3                  |

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 3011 participants (par.) were screened, 559 entered the Run-in Period (RIP), of whom 444 were randomized and received at least one dose of study medication; 430 of these were included in the Intent-to-Treat (ITT) Population.

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total of 3011 participants (par.) were screened, 559 entered the Run-in Period (RIP), of whom 444 were randomized and received at least one dose of study medication; 430 of these were included in the Intent-to-Treat (ITT) Population.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone reflects the number of participants completing the Treatment Period. Par. were considered to have completed the TP if they attended Wk 24 and completed the study if also attended the 1-wk follow-up contact and no early withdrawal.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone reflects the number of participants completing the Treatment Period. Par. were considered to have completed the TP if they attended Wk 24 and completed the study if also attended the 1-wk follow-up contact and no early withdrawal.

## Baseline characteristics

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Placebo QD |
|-----------------------|------------|

Reporting group description:

Participants received placebo QD in the morning via a dry powder inhaler (DPI) for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

|                       |             |
|-----------------------|-------------|
| Reporting group title | VI 25 µg QD |
|-----------------------|-------------|

Reporting group description:

Participants received vilanterol (VI) 25 micrograms (µg) inhalation QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | FF/VI 100/25 µg QD |
|-----------------------|--------------------|

Reporting group description:

Participants received fluticasone furoate (FF)/VI 100/25 µg inhalation QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

| Reporting group values             | Placebo QD | VI 25 µg QD | FF/VI 100/25 µg QD |
|------------------------------------|------------|-------------|--------------------|
| Number of subjects                 | 141        | 154         | 135                |
| Age categorical<br>Units: Subjects |            |             |                    |

|   |       |        |        |
|---|-------|--------|--------|
| Age continuous<br>Units: years            |       |        |        |
| arithmetic mean                           | 68.2  | 68.7   | 68.5   |
| standard deviation                        | ± 8.1 | ± 7.69 | ± 8.01 |
| Gender categorical<br>Units: Subjects     |       |        |        |
| Female                                    | 22    | 36     | 31     |
| Male                                      | 119   | 118    | 104    |
| Race<br>Units: Subjects                   |       |        |        |
| African American/African Heritage         | 7     | 4      | 6      |
| Asian - Central/South Asian Heritage      | 1     | 0      | 0      |
| Asian - East Asian Heritage               | 21    | 23     | 18     |
| Asian - South East Asian Heritage         | 45    | 51     | 47     |
| Asian - Mixed Race                        | 1     | 0      | 0      |
| White - Arabic/North African Heritage     | 1     | 1      | 0      |
| White - White/Caucasian/European Heritage | 64    | 75     | 64     |
| Mixed Race                                | 1     | 0      | 0      |

| Reporting group values             | Total |  |  |
|------------------------------------|-------|--|--|
| Number of subjects                 | 430   |  |  |
| Age categorical<br>Units: Subjects |       |  |  |

|   |     |  |  |
|---|-----|--|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -   |  |  |
| Gender categorical<br>Units: Subjects                                   |     |  |  |
| Female  | 89  |  |  |
| Male  | 341 |  |  |
| Race<br>Units: Subjects   |     |  |  |
| African American/African Heritage                                       | 17  |  |  |
| Asian - Central/South Asian<br>Heritage                                 | 1   |  |  |
| Asian - East Asian Heritage   | 62  |  |  |
| Asian - South East Asian Heritage                                       | 143 |  |  |
| Asian - Mixed Race  | 1   |  |  |
| White - Arabic/North African<br>Heritage                                | 2   |  |  |
| White - White/Caucasian/European<br>Heritage                            | 203 |  |  |
| Mixed Race  | 1   |  |  |



## End points

### End points reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | Placebo-Run-in     |
| Reporting group description:<br>Participants received placebo once daily (QD) in the morning for 2 weeks. In addition, participants were provided an inhaled short-acting beta2-receptor agonist (SABA), albuterol (salbutamol) (metered dose inhaler [MDI] or nebulas), to be used as a rescue medication for relief of chronic obstructive pulmonary disease (COPD) symptoms during the Run-in and Treatment Periods. |                    |
| Reporting group title   | Placebo QD         |
| Reporting group description:<br>Participants received placebo QD in the morning via a dry powder inhaler (DPI) for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.  |                    |
| Reporting group title   | VI 25 µg QD        |
| Reporting group description:<br>Participants received vilanterol (VI) 25 micrograms (µg) inhalation QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.   |                    |
| Reporting group title   | FF/VI 100/25 µg QD |
| Reporting group description:<br>Participants received fluticasone furoate (FF)/VI 100/25 µg inhalation QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.  |                    |

### Primary: Mean change from Baseline (BL) in Aortic Pulse Wave Velocity (aPWV) at the end of the 24-week Treatment Period (Day 168)

|   |  |
|---|--|
| End point title   | Mean change from Baseline (BL) in Aortic Pulse Wave Velocity (aPWV) at the end of the 24-week Treatment Period (Day 168) |
| End point description:<br>PWV is defined as the speed of travel of the pressure pulse along an arterial segment and can be obtained for any arterial segment accessible to palpation. aPWV is measured with tonometers positioned transcutaneously at the base of the common carotid artery and over the femoral artery. PWV increases with arterial stiffness and is defined by the Moens-Korteweg equation: $PWV = \sqrt{Eh/2\rho R}$ , where E is Young's modulus of the arterial wall, h is the wall thickness, R is the arterial radius at the end of diastole, and ρ is the blood density. Change from BL was calculated as the Day 168 value minus the BL value. The analysis was performed using a repeated measures model with covariates of treatment, visit, age, gender, smoking history, history of exacerbation strata, geographical region, BL aPWV and interaction terms of BL by visit and treatment by visit. ITT Population: all randomized par. who received at least one dose of study medication. |  |
| End point type  | Primary  |
| End point timeframe:<br>BL to Day 168<br>Number of par. presented represent those with data available at the time point being presented; however, all par. in the ITT Population without missing covariate information and with at least one post BL measurement are included.  |  |

| <b>End point values</b>             | Placebo QD      | VI 25 µg QD     | FF/VI 100/25 µg QD |  |
|-------------------------------------|-----------------|-----------------|--------------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group    |  |
| Number of subjects analysed         | 85              | 117             | 103                |  |
| Units: meters per second (m/sec)    |                 |                 |                    |  |
| least squares mean (standard error) | -1.97 (± 0.279) | -1.95 (± 0.241) | -1.75 (± 0.256)    |  |

## Statistical analyses

| <b>Statistical analysis title</b>       | Analysis 1                    |
|---|-------------------------------|
| Comparison groups                       | Placebo QD v VI 25 µg QD      |
| Number of subjects included in analysis | 202                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority                   |
| P-value                                 | = 0.969 <sup>[1]</sup>        |
| Method                                  | Mixed models analysis         |
| Parameter estimate                      | Least Squares Mean Difference |
| Point estimate                          | 0.01                          |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | -0.71                         |
| upper limit                             | 0.74                          |

Notes:

[1] - Restricted maximum likelihood (REML)-based repeated measures approach (MMRM)

| <b>Statistical analysis title</b>       | Analysis 2                      |
|---|---------------------------------|
| Comparison groups                       | Placebo QD v FF/VI 100/25 µg QD |
| Number of subjects included in analysis | 188                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | superiority                     |
| P-value                                 | = 0.568 <sup>[2]</sup>          |
| Method                                  | Mixed models analysis           |
| Parameter estimate                      | Least Squares Mean Difference   |
| Point estimate                          | 0.22                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -0.53                           |
| upper limit                             | 0.96                            |

Notes:

[2] - Restricted maximum likelihood (REML)-based repeated measures approach (MMRM)

| <b>Statistical analysis title</b> | Analysis 3                       |
|-----------------------------------|----------------------------------|
| Comparison groups                 | VI 25 µg QD v FF/VI 100/25 µg QD |

|   |                               |
|---|-------------------------------|
| Number of subjects included in analysis | 220                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority                   |
| P-value                                 | = 0.566 <sup>[3]</sup>        |
| Method                                  | Mixed models analysis         |
| Parameter estimate                      | Least Squares Mean Difference |
| Point estimate                          | 0.2                           |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | -0.49                         |
| upper limit                             | 0.89                          |

Notes:

[3] - Restricted maximum likelihood (REML)-based repeated measures approach (MMRM)

### Secondary: Change from BL in clinic visit trough (pre-bronchodilator and pre-dose) FEV1 at Day 168

|                 |   |
|-----------------|---|
| End point title | Change from BL in clinic visit trough (pre-bronchodilator and pre-dose) FEV1 at Day 168 |
|-----------------|---|

End point description:

Pulmonary function was measured by forced expiratory volume in one second (FEV1), defined as the maximal amount of air that can be forcefully exhaled from the lungs in one second. Trough FEV1 measurements were taken electronically by spirometry at Screening, Days 1, 28, 84, 126, and 168. BL FEV1 was defined as the mean of the assessments made 30 minutes pre-dose and 5 minutes pre-dose on Treatment Day 1. Trough FEV1 was defined as the mean of the FEV1 values obtained 24 hours after previous morning's dosing. Change from BL was calculated as the average at each visit minus the BL value. Analysis was performed using a repeated measures model with covariates of visit, treatment, history of exacerbation strata, geographical region, BL FEV1 and interaction terms of BL by visit and treatment by visit.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

BL to Day 168

Number of par. presented represent those with data available at the time point being presented; however, all par. in the ITT Population without missing covariate information and with at least one post BL measurement are included.

| End point values                    | Placebo QD        | VI 25 µg QD      | FF/VI 100/25 µg QD |  |
|-------------------------------------|-------------------|------------------|--------------------|--|
| Subject group type                  | Reporting group   | Reporting group  | Reporting group    |  |
| Number of subjects analysed         | 96                | 123              | 111                |  |
| Units: Liters (L)                   |                   |                  |                    |  |
| least squares mean (standard error) | -0.049 (± 0.0221) | 0.033 (± 0.0202) | 0.106 (± 0.021)    |  |

### Statistical analyses

|                            |                          |
|----------------------------|--------------------------|
| Statistical analysis title | Analysis 1               |
| Comparison groups          | Placebo QD v VI 25 µg QD |

|   |                               |
|---|-------------------------------|
| Number of subjects included in analysis | 219                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority                   |
| P-value                                 | = 0.007 <sup>[4]</sup>        |
| Method                                  | Mixed models analysis         |
| Parameter estimate                      | Least squares mean difference |
| Point estimate                          | 0.082                         |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 0.023                         |
| upper limit                             | 0.141                         |

Notes:

[4] - Nominal p-value; Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

|   |                                 |
|---|---------------------------------|
| <b>Statistical analysis title</b>       | Analysis 2                      |
| Comparison groups                       | Placebo QD v FF/VI 100/25 µg QD |
| Number of subjects included in analysis | 207                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | superiority                     |
| P-value                                 | < 0.001 <sup>[5]</sup>          |
| Method                                  | Mixed models analysis           |
| Parameter estimate                      | Least squares mean difference   |
| Point estimate                          | 0.155                           |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.095                           |
| upper limit                             | 0.215                           |

Notes:

[5] - Nominal p-value; Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>       | Analysis 3                       |
| Comparison groups                       | VI 25 µg QD v FF/VI 100/25 µg QD |
| Number of subjects included in analysis | 234                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.012 <sup>[6]</sup>           |
| Method                                  | Mixed models analysis            |
| Parameter estimate                      | Least squares mean difference    |
| Point estimate                          | 0.074                            |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 0.016                            |
| upper limit                             | 0.131                            |

Notes:

[6] - Nominal p-value; Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

## Secondary: Mean number of occasions rescue medication [albuterol (salbutamol)]

**used during a 24-hour period averaged over the entire 24-week Treatment Period**

|                 |  |
|-----------------|--|
| End point title | Mean number of occasions rescue medication [albuterol (salbutamol)] used during a 24-hour period averaged over the entire 24-week Treatment Period |
|-----------------|--|

**End point description:**

Participants were given daily record cards for daily completion from BL (Week -1) through Week 24 (Visit 6) each morning and prior to taking study medication (i.e., single-blind and double-blind study medication) supplemental medication (albuterol [salbutamol] if received) and ipratropium bromide (if received). Participants recorded number of occasions supplemental albuterol/salbutamol (MDI and/or nebulas) used over the previous 24 hours and any medical problems that they had experienced and any medication used to treat these medical problems over the previous 24 hours. Analysis was performed using an analysis of covariance (ANCOVA) model with covariates of treatment, BL mean of occasions of rescue medication use (Week -1), history of exacerbation, and geographical region. ITT Population: all randomized participants who received at least one dose of study medication.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

**End point timeframe:**

BL (Week -1), Week 1 to Week 24

Only those participants with at least 1 on treatment rescue medication measurement during the treatment period and without missing covariate information were analyzed.

| <b>End point values</b>             | Placebo QD      | VI 25 µg QD     | FF/VI 100/25 µg QD |  |
|-------------------------------------|-----------------|-----------------|--------------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group    |  |
| Number of subjects analysed         | 139             | 152             | 135                |  |
| Units: Occasions per 24 hours       |                 |                 |                    |  |
| least squares mean (standard error) | 1.97 (± 0.093)  | 1.5 (± 0.089)   | 1.47 (± 0.095)     |  |

**Statistical analyses**

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | Analysis 1                    |
| Comparison groups                       | Placebo QD v VI 25 µg QD      |
| Number of subjects included in analysis | 291                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority                   |
| P-value                                 | < 0.001 <sup>[7]</sup>        |
| Method                                  | ANCOVA                        |
| Parameter estimate                      | Least Squares Mean Difference |
| Point estimate                          | -0.47                         |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | -0.72                         |
| upper limit                             | -0.22                         |

**Notes:**

[7] - Nominal p-value

|                                   |                                 |
|-----------------------------------|---------------------------------|
| <b>Statistical analysis title</b> | Analysis 2                      |
| Comparison groups                 | Placebo QD v FF/VI 100/25 µg QD |

|   |                               |
|---|-------------------------------|
| Number of subjects included in analysis | 274                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority                   |
| P-value                                 | < 0.001 <sup>[8]</sup>        |
| Method                                  | ANCOVA                        |
| Parameter estimate                      | Least Squares Mean Difference |
| Point estimate                          | -0.5                          |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | -0.76                         |
| upper limit                             | -0.24                         |

Notes:

[8] - Nominal p-value

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>       | Analysis 3                       |
| Comparison groups                       | VI 25 µg QD v FF/VI 100/25 µg QD |
| Number of subjects included in analysis | 287                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.803                          |
| Method                                  | ANCOVA                           |
| Parameter estimate                      | Least Squares Mean Difference    |
| Point estimate                          | -0.03                            |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -0.29                            |
| upper limit                             | 0.22                             |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAE) and non-serious AEs were collected from the start of the double-blind (DB) treatment period (Visit 2) through the follow-up contact (7 days after Visit 6 [Week 25]).

Adverse event reporting additional description:

SAEs and non-serious AEs reported for par. of the Safety Population (Pop) comprised of ITT Pop plus par. from the excluded site who qualified for the ITT Pop. On-treatment AE or SAE is defined as an AE with an onset date on or after the start date of DB study medication, but not later than one day after the last dose of DB study medication.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 17.1   |

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Placebo QD |
|-----------------------|------------|

Reporting group description:

Participants received placebo QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

|                       |             |
|-----------------------|-------------|
| Reporting group title | VI 25 µg QD |
|-----------------------|-------------|

Reporting group description:

Participants received VI 25 µg inhalation QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | FF/VI 100/25 µg QD |
|-----------------------|--------------------|

Reporting group description:

Participants received FF/VI 100/25 µg inhalation QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol) to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

| Serious adverse events  | Placebo QD      | VI 25 µg QD      | FF/VI 100/25 µg QD |
|---|-----------------|------------------|--------------------|
| Total subjects affected by serious adverse events                   |                 |                  |                    |
| subjects affected / exposed   | 5 / 145 (3.45%) | 12 / 158 (7.59%) | 9 / 141 (6.38%)    |
| number of deaths (all causes)                                       | 0               | 1                | 1                  |
| number of deaths resulting from adverse events                      |                 |                  |                    |
| Investigations  |                 |                  |                    |
| Hepatic enzyme increased  |                 |                  |                    |
| subjects affected / exposed   | 0 / 145 (0.00%) | 0 / 158 (0.00%)  | 1 / 141 (0.71%)    |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0            | 1 / 1              |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0            | 0 / 0              |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                  |                    |
| Adenocarcinoma of colon   |                 |                  |                    |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 145 (0.00%) | 1 / 158 (0.63%) | 0 / 141 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colorectal cancer                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 145 (0.00%) | 0 / 158 (0.00%) | 1 / 141 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Lung neoplasm malignant                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 145 (0.69%) | 0 / 158 (0.00%) | 0 / 141 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Prostate cancer                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 145 (0.00%) | 0 / 158 (0.00%) | 1 / 141 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Facial bones fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 145 (0.00%) | 1 / 158 (0.63%) | 0 / 141 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fibula fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 145 (0.00%) | 0 / 158 (0.00%) | 1 / 141 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hip fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 145 (0.00%) | 0 / 158 (0.00%) | 1 / 141 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tibia fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 145 (0.00%) | 0 / 158 (0.00%) | 1 / 141 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 145 (0.69%) | 0 / 158 (0.00%) | 0 / 141 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina unstable                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 145 (0.69%) | 0 / 158 (0.00%) | 0 / 141 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardio-respiratory arrest                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 145 (0.00%) | 1 / 158 (0.63%) | 0 / 141 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 145 (0.00%) | 1 / 158 (0.63%) | 0 / 141 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Faecaloma                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 145 (0.00%) | 0 / 158 (0.00%) | 1 / 141 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Inguinal hernia                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 145 (0.69%) | 0 / 158 (0.00%) | 0 / 141 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Benign prostatic hyperplasia                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 145 (0.00%) | 1 / 158 (0.63%) | 0 / 141 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Chronic obstructive pulmonary disease           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                                   | 1 / 145 (0.69%) | 5 / 158 (3.16%) | 2 / 141 (1.42%) |
| occurrences causally related to treatment / all               | 1 / 1           | 0 / 5           | 1 / 2           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                                   |                 |                 |                 |
| Renal failure acute   |                 |                 |                 |
| subjects affected / exposed                                   | 0 / 145 (0.00%) | 1 / 158 (0.63%) | 0 / 141 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                                   |                 |                 |                 |
| Infective exacerbation of chronic obstructive airways disease |                 |                 |                 |
| subjects affected / exposed                                   | 0 / 145 (0.00%) | 1 / 158 (0.63%) | 0 / 141 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia   |                 |                 |                 |
| subjects affected / exposed                                   | 2 / 145 (1.38%) | 1 / 158 (0.63%) | 2 / 141 (1.42%) |
| occurrences causally related to treatment / all               | 1 / 2           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary tuberculosis  |                 |                 |                 |
| subjects affected / exposed                                   | 0 / 145 (0.00%) | 1 / 158 (0.63%) | 0 / 141 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyelonephritis  |                 |                 |                 |
| subjects affected / exposed                                   | 0 / 145 (0.00%) | 0 / 158 (0.00%) | 1 / 141 (0.71%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Septic shock  |                 |                 |                 |
| subjects affected / exposed                                   | 0 / 145 (0.00%) | 1 / 158 (0.63%) | 0 / 141 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders                            |                 |                 |                 |
| Hypokalaemia  |                 |                 |                 |
| subjects affected / exposed                                   | 0 / 145 (0.00%) | 1 / 158 (0.63%) | 0 / 141 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Type 2 diabetes mellitus                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 145 (0.00%) | 1 / 158 (0.63%) | 0 / 141 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

Frequency threshold for reporting non-serious adverse events: 3 %

| <b>Non-serious adverse events</b>                     | Placebo QD        | VI 25 µg QD       | FF/VI 100/25 µg QD |
|---|-------------------|-------------------|--------------------|
| Total subjects affected by non-serious adverse events |                   |                   |                    |
| subjects affected / exposed                           | 24 / 145 (16.55%) | 27 / 158 (17.09%) | 34 / 141 (24.11%)  |
| Nervous system disorders                              |                   |                   |                    |
| Headache  |                   |                   |                    |
| subjects affected / exposed                           | 5 / 145 (3.45%)   | 9 / 158 (5.70%)   | 8 / 141 (5.67%)    |
| occurrences (all)                                     | 6                 | 11                | 13                 |
| Respiratory, thoracic and mediastinal disorders       |                   |                   |                    |
| Oropharyngeal pain                                    |                   |                   |                    |
| subjects affected / exposed                           | 1 / 145 (0.69%)   | 2 / 158 (1.27%)   | 6 / 141 (4.26%)    |
| occurrences (all)                                     | 1                 | 2                 | 6                  |
| Musculoskeletal and connective tissue disorders       |                   |                   |                    |
| Arthralgia  |                   |                   |                    |
| subjects affected / exposed                           | 4 / 145 (2.76%)   | 1 / 158 (0.63%)   | 5 / 141 (3.55%)    |
| occurrences (all)                                     | 4                 | 1                 | 7                  |
| Back pain   |                   |                   |                    |
| subjects affected / exposed                           | 5 / 145 (3.45%)   | 5 / 158 (3.16%)   | 4 / 141 (2.84%)    |
| occurrences (all)                                     | 5                 | 8                 | 8                  |
| Infections and infestations                           |                   |                   |                    |
| Nasopharyngitis                                       |                   |                   |                    |
| subjects affected / exposed                           | 5 / 145 (3.45%)   | 12 / 158 (7.59%)  | 9 / 141 (6.38%)    |
| occurrences (all)                                     | 5                 | 14                | 11                 |
| Oral candidiasis                                      |                   |                   |                    |
| subjects affected / exposed                           | 1 / 145 (0.69%)   | 2 / 158 (1.27%)   | 9 / 141 (6.38%)    |
| occurrences (all)                                     | 1                 | 2                 | 12                 |
| Upper respiratory tract infection                     |                   |                   |                    |
| subjects affected / exposed                           | 6 / 145 (4.14%)   | 4 / 158 (2.53%)   | 2 / 141 (1.42%)    |
| occurrences (all)                                     | 9                 | 4                 | 3                  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment   |
|----------------|---|
| 19 August 2011 | To revise Inclusion Criterion #8: Baseline aortic pulse wave velocity |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported