# Clinical trial results:
# A Phase III, randomized, double-blind, active controlled, parallel group study, comparing the efficacy, safety and tolerability of the fixed dose combination FF/UMEC/VI with the fixed dose dual combination of FF/VI, administered once-daily via a dry powder inhaler in subjects with inadequately controlled asthma

## Summary

| | |
|---|---|
| EudraCT number | 2016-001304-37 |
| Trial protocol | DE NL ES PL GB IT |
| Global end of trial date | 22 February 2019 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 20 February 2020 |
| First version publication date | 20 February 2020 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 205715 |

**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 8664357343, GSKClinicalSupportHD@gsk.com |
| Scientific contact | GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com |

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 May 2019 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 22 February 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effects of FF/UMEC/VI on lung function compared with FF/VI after 24 weeks of treatment

Protection of trial subjects:

The AM3 electronic diary (eDiary) was used to provide alerts to participants and investigators. These alerts highlighted unfavorable changes in one or more measures of asthma control (e.g. nocturnal awakening requiring rescue medication; increase in daytime asthma symptom score; increase in daily rescue medication use; worsening pulmonary function) which may have warranted investigator intervention to address a participant's worsening condition.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 13 October 2016 |
| 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 | Argentina: 195 |
| Country: Number of subjects enrolled | Australia: 17 |
| Country: Number of subjects enrolled | Canada: 72 |
| Country: Number of subjects enrolled | Germany: 127 |
| Country: Number of subjects enrolled | Italy: 37 |
| Country: Number of subjects enrolled | Japan: 229 |
| Country: Number of subjects enrolled | Korea, Republic of: 58 |
| Country: Number of subjects enrolled | Netherlands: 26 |
| Country: Number of subjects enrolled | Poland: 238 |
| Country: Number of subjects enrolled | Romania: 267 |
| Country: Number of subjects enrolled | Russian Federation: 640 |
| Country: Number of subjects enrolled | South Africa: 60 |
| Country: Number of subjects enrolled | Spain: 58 |
| Country: Number of subjects enrolled | United Kingdom: 13 |
| Country: Number of subjects enrolled | United States: 399 |
| Worldwide total number of subjects | 2436 |
| EEA total number of subjects | 766 |

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) | 1927 |
| From 65 to 84 years | 507 |
| 85 years and over | 2 |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled from 322 centers across 15 countries.

### Pre-assignment

Screening details:

Total 5185 participants were screened and 2436 participants were enrolled into the study and received the study treatment.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | FF/VI 100/25 mcg |

Arm description:

Participants received Fluticasone Furoate/ Vilanterol (FF/VI) 100/25 micrograms (mcg) inhalation powder via dry powder inhaler (DPI), once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | FF/VI 100/25 mcg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Participants received Fluticasone Furoate/ Vilanterol (FF/VI) 100/25 micrograms (mcg) inhalation powder via DPI, once daily in the morning for up to 52 weeks.

| | |
|---|---|
| Investigational medicinal product name | Albuterol/ Salbutamol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Albuterol/ Salbutamol were provided as a rescue inhaler to be used on an as needed basis.

| | |
|---|---|
| **Arm title** | FF/UMEC/VI 100/ 31.25/25 mcg |

Arm description:

Participants received Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) 100/31.25/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | FF/UMEC/VI 100/ 31.25/25 mcg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Participants received FF/UMEC/VI 100/ 31.25/25 mcg inhalation powder via dry powder inhaler (DPI), once daily in the morning for up to 52 weeks.

| | |
|---|---|
| Investigational medicinal product name | Albuterol/ Salbutamol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Albuterol/ Salbutamol were provided as a rescue inhaler to be used on an as needed basis.

| | |
|---|---|
| **Arm title** | FF/UMEC/VI 100/62.5/25 mcg |

Arm description:

Participants received FF/UMEC/VI 100/62.5/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | FF/UMEC/VI 100/62.5/25 mcg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Participants received FF/UMEC/VI 100/62.5/25 mcg inhalation powder via DPI, once daily in the morning for up to 52 weeks.

| | |
|---|---|
| Investigational medicinal product name | Albuterol/ Salbutamol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Albuterol/ Salbutamol were provided as a rescue inhaler to be used on an as needed basis.

| | |
|---|---|
| **Arm title** | FF/VI 200/25 mcg |

Arm description:

Participants received FF/VI 200/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | FF/VI 200/25 mcg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Participants received FF/VI 200/25 mcg inhalation powder via DPI, once daily in the morning for up to 52 weeks.

| | |
|---|---|
| Investigational medicinal product name | Albuterol/ Salbutamol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Albuterol/ Salbutamol were provided as a rescue inhaler to be used on an as needed basis.

| | |
|---|---|
| **Arm title** | FF/UMEC/VI 200/ 31.25/25 mcg |

Arm description:

Participants received FF/UMEC/VI 200/31.25/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | FF/UMEC/VI 200/ 31.25/25 mcg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Participants received FF/UMEC/VI 200/ 31.25/25 mcg inhalation powder via DPI, once daily in the morning for up to 52 weeks.

| | |
|---|---|
| Investigational medicinal product name | Albuterol/ Salbutamol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Albuterol/ Salbutamol were provided as a rescue inhaler to be used on an as needed basis.

| | |
|---|---|
| **Arm title** | FF/UMEC/VI 200/62.5/25 mcg |

Arm description:

Participants received FF/UMEC/VI 200/62.5/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | FF/UMEC/VI 200/62.5/25 mcg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Participants received FF/UMEC/VI 200/62.5/25 mcg inhalation powder via DPI, once daily in the morning for up to 52 weeks.

| | |
|---|---|
| Investigational medicinal product name | Albuterol/ Salbutamol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Albuterol/ Salbutamol were provided as a rescue inhaler to be used on an as needed basis.

| **Number of subjects in period 1** | FF/VI 100/25 mcg | FF/UMEC/VI 100/ 31.25/25 mcg | FF/UMEC/VI 100/62.5/25 mcg |
|---|---|---|---|
| Started | 407 | 405 | 406 |
| Completed | 374 | 374 | 383 |
| Not completed | 33 | 31 | 23 |
| Adverse event, serious fatal | - | 2 | - |
| Physician decision | 2 | 1 | - |

| | | | |
|---|---|---|---|
| Consent withdrawn by subject | 14 | 13 | 9 |
| Adverse event, non-fatal | 9 | 1 | 2 |
| Protocol defined withdrawal criteria met | 1 | - | 1 |
| Lost to follow-up | 2 | 4 | 2 |
| Lack of efficacy | 2 | 3 | 4 |
| Protocol deviation | 3 | 7 | 5 |

| **Number of subjects in period 1** | FF/VI 200/25 mcg | FF/UMEC/VI 200/ 31.25/25 mcg | FF/UMEC/VI 200/62.5/25 mcg |
|---|---|---|---|
| Started | 406 | 404 | 408 |
| Completed | 378 | 381 | 384 |
| Not completed | 28 | 23 | 24 |
| Adverse event, serious fatal | 1 | - | - |
| Physician decision | 1 | 1 | 1 |
| Consent withdrawn by subject | 12 | 13 | 14 |
| Adverse event, non-fatal | 1 | 3 | 2 |
| Protocol defined withdrawal criteria met | 1 | 1 | - |
| Lost to follow-up | 4 | 2 | 4 |
| Lack of efficacy | 2 | 1 | 1 |
| Protocol deviation | 6 | 2 | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | FF/VI 100/25 mcg |
| Reporting group description: | |
| Participants received Fluticasone Furoate/ Vilanterol (FF/VI) 100/25 micrograms (mcg) inhalation powder via dry powder inhaler (DPI), once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period. | |
| Reporting group title | FF/UMEC/VI 100/ 31.25/25 mcg |
| Reporting group description: | |
| Participants received Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) 100/31.25/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period. | |
| Reporting group title | FF/UMEC/VI 100/62.5/25 mcg |
| Reporting group description: | |
| Participants received FF/UMEC/VI 100/62.5/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period. | |
| Reporting group title | FF/VI 200/25 mcg |
| Reporting group description: | |
| Participants received FF/VI 200/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period. | |
| Reporting group title | FF/UMEC/VI 200/ 31.25/25 mcg |
| Reporting group description: | |
| Participants received FF/UMEC/VI 200/31.25/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period. | |
| Reporting group title | FF/UMEC/VI 200/62.5/25 mcg |
| Reporting group description: | |
| Participants received FF/UMEC/VI 200/62.5/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period. | |

| Reporting group values | FF/VI 100/25 mcg | FF/UMEC/VI 100/ 31.25/25 mcg | FF/UMEC/VI 100/62.5/25 mcg |
|---|---|---|---|
| Number of subjects | 407 | 405 | 406 |
| Age categorical<br>Units: Subjects | | | |
| All Participants | 407 | 405 | 406 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 53.3 | 51.7 | 52.9 |
| standard deviation | ± 13.03 | ± 13.27 | ± 13.39 |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 254 | 262 | 248 |
| Male | 153 | 143 | 158 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Black or African American (AA) | 20 | 21 | 17 |
| American Indian or Alaska Native | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Asian-Central/South Asian Heritage (H.) | 5 | 4 | 1 |
| Asian-Japanese H./East Asian H. /SouthEast Asian H. | 54 | 55 | 50 |
| Mixed Asian Race | 0 | 0 | 0 |
| Native Hawaiian or other Pacific Islander | 0 | 1 | 0 |
| White | 326 | 319 | 338 |
| American Indian or Alaska Native and Black or AA | 0 | 1 | 0 |
| American Indian or Alaska Native and White | 1 | 0 | 0 |
| Asian and Black or African American and White | 0 | 1 | 0 |
| Asian and White | 0 | 1 | 0 |
| Black or African American and White | 1 | 2 | 0 |
| Missing | 0 | 0 | 0 |

| **Reporting group values** | FF/VI 200/25 mcg | FF/UMEC/VI 200/ 31.25/25 mcg | FF/UMEC/VI 200/62.5/25 mcg |
|---|---|---|---|
| Number of subjects | 406 | 404 | 408 |
| Age categorical<br>Units: Subjects | | | |
| All Participants | 406 | 404 | 408 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 53.9 | 53.5 | 53.7 |
| standard deviation | ± 13.30 | ± 13.12 | ± 12.50 |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 252 | 240 | 258 |
| Male | 154 | 164 | 150 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Black or African American (AA) | 26 | 11 | 24 |
| American Indian or Alaska Native | 0 | 2 | 2 |
| Asian-Central/South Asian Heritage (H.) | 5 | 9 | 0 |
| Asian-Japanese H./East Asian H. /SouthEast Asian H. | 53 | 55 | 52 |
| Mixed Asian Race | 0 | 1 | 0 |
| Native Hawaiian or other Pacific Islander | 0 | 1 | 1 |
| White | 316 | 325 | 326 |
| American Indian or Alaska Native and Black or AA | 0 | 0 | 0 |
| American Indian or Alaska Native and White | 0 | 0 | 2 |
| Asian and Black or African American and White | 2 | 0 | 0 |
| Asian and White | 0 | 0 | 0 |
| Black or African American and White | 3 | 0 | 1 |
| Missing | 1 | 0 | 0 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 2436 | | |
| Age categorical<br>Units: Subjects | | | |
| All Participants | 2436 | | |
| Age Continuous<br>Units: Years<br>arithmetic mean<br>standard deviation | <br><br><br>- | | |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 1514 | | |
| Male | 922 | | |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Black or African American (AA) | 119 | | |
| American Indian or Alaska Native | 4 | | |
| Asian-Central/South Asian Heritage (H.) | 24 | | |
| Asian-Japanese H./East Asian H. /SouthEast Asian H. | 319 | | |
| Mixed Asian Race | 1 | | |
| Native Hawaiian or other Pacific Islander | 3 | | |
| White | 1950 | | |
| American Indian or Alaska Native and Black or AA | 1 | | |
| American Indian or Alaska Native and White | 3 | | |
| Asian and Black or African American and White | 3 | | |
| Asian and White | 1 | | |
| Black or African American and White | 7 | | |
| Missing | 1 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | FF/VI 100/25 mcg |
| Reporting group description: | |
| Participants received Fluticasone Furoate/ Vilanterol (FF/VI) 100/25 micrograms (mcg) inhalation powder via dry powder inhaler (DPI), once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period. | |
| Reporting group title | FF/UMEC/VI 100/ 31.25/25 mcg |
| Reporting group description: | |
| Participants received Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) 100/31.25/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period. | |
| Reporting group title | FF/UMEC/VI 100/62.5/25 mcg |
| Reporting group description: | |
| Participants received FF/UMEC/VI 100/62.5/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period. | |
| Reporting group title | FF/VI 200/25 mcg |
| Reporting group description: | |
| Participants received FF/VI 200/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period. | |
| Reporting group title | FF/UMEC/VI 200/ 31.25/25 mcg |
| Reporting group description: | |
| Participants received FF/UMEC/VI 200/31.25/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period. | |
| Reporting group title | FF/UMEC/VI 200/62.5/25 mcg |
| Reporting group description: | |
| Participants received FF/UMEC/VI 200/62.5/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period. | |
| Subject analysis set title | FF/VI |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants received FF/VI 100/25 mcg or 200/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period. | |
| Subject analysis set title | FF/UMEC/VI (UMEC 31.25 mcg) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants received FF/UMEC/VI 100/31.25/25 mcg or 200/31.25/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period. | |
| Subject analysis set title | FF/UMEC/VI (UMEC 62.5 mcg) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants received FF/UMEC/VI 100/62.5/25 mcg or 200/62.5/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period. | |
| Subject analysis set title | FF/VI |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Participants received FF/VI 100/25 mcg or 200/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication | |

when needed during the treatment period.

| | |
|---|---|
| Subject analysis set title | FF/UMEC/VI (UMEC 31.25 mcg) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants received FF/UMEC/VI 100/31.25/25 mcg or 200/31.25/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Subject analysis set title | FF/UMEC/VI (UMEC 62.5 mcg) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants received FF/UMEC/VI 100/62.5/25 mcg or 200/62.5/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Subject analysis set title | FF/UMEC/VI (UMEC 31.25 mcg) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants received FF/UMEC/VI 100/31.25/25 mcg or 200/31.25/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Subject analysis set title | FF/UMEC/VI (UMEC 62.5 mcg) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants received FF/UMEC/VI 100/62.5/25 mcg or 200/62.5/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Subject analysis set title | FF/VI |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants received FF/VI 100/25 mcg or 200/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Subject analysis set title | FF/UMEC/VI (UMEC 31.25 mcg) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants received FF/UMEC/VI 100/31.25/25 mcg or 200/31.25/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Subject analysis set title | FF/UMEC/VI (UMEC 62.5 mcg) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants received FF/UMEC/VI 100/62.5/25 mcg or 200/62.5/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

## Primary: Mean change from Baseline in trough Forced Expiratory Volume in 1 second (FEV1) at Week 24

| | |
|---|---|
| End point title | Mean change from Baseline in trough Forced Expiratory Volume in 1 second (FEV1) at Week 24 |

End point description:

FEV1 is a measure of lung function and is defined as the maximal volume of air that can be forcefully exhaled in one second. Trough FEV1 on treatment is defined as the highest FEV1 value obtained prior to the morning dose of investigational product. Baseline value is the last acceptable/borderline acceptable pre-dose FEV1 prior to randomized treatment start date (pre-dose at Day 1). Change from Baseline value is the value at Week 24 minus the Baseline value. Intent-to-Treat(ITT) Population comprised of all randomized participants, excluding those who were randomized in error, who did not receive the study drug. Treatment policy estimand was assessed, including all on- and post-treatment data. Different participants may have been analyzed at different time points; thus, overall number of participants analyzed reflects everyone in ITT Population without missing covariate information, with Baseline and at least one post-baseline measurement. Mixed Model Repeated Measures(MMRM) was used.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline (pre-dose at Day 1) and Week 24

| **End point values** | FF/VI 100/25 mcg | FF/UMEC/VI 100/ 31.25/25 mcg | FF/UMEC/VI 100/62.5/25 mcg | FF/VI 200/25 mcg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 400[1] | 399[2] | 404[3] | 403 |
| Units: Liters | | | | |
| least squares mean (standard error) | 0.024 (± 0.0157) | 0.120 (± 0.0157) | 0.134 (± 0.0155) | 0.076 (± 0.0156) |

Notes:

[1] - ITT Population

[2] - Only those participants with data available at the specified data point were analyzed.

[3] - Participants with Baseline value and at least one post-baseline measurement were analyzed.

| **End point values** | FF/UMEC/VI 200/ 31.25/25 mcg | FF/UMEC/VI 200/62.5/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 399 | 405 | | |
| Units: Liters | | | | |
| least squares mean (standard error) | 0.157 (± 0.0156) | 0.168 (± 0.0155) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | FF/VI 100/25 mcg v FF/UMEC/VI 100/ 31.25/25 mcg |
| Number of subjects included in analysis | 799 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [4] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 0.096 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.052 |
| upper limit | 0.139 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0222 |

Notes:

[4] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study inhaled corticosteroids (ICS) dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | FF/VI 100/25 mcg v FF/UMEC/VI 100/62.5/25 mcg |
| Number of subjects included in analysis | 804 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [5] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.066 |
| upper limit | 0.153 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0221 |

Notes:

[5] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

| **Statistical analysis title** | Statistical Analysis 3 |
|---|---|
| Comparison groups | FF/VI 200/25 mcg v FF/UMEC/VI 200/ 31.25/25 mcg |
| Number of subjects included in analysis | 802 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [6] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 0.082 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.039 |
| upper limit | 0.125 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0221 |

Notes:

[6] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

| **Statistical analysis title** | Statistical Analysis 4 |
|---|---|
| Comparison groups | FF/VI 200/25 mcg v FF/UMEC/VI 200/62.5/25 mcg |
| Number of subjects included in analysis | 808 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [7] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 0.092 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.049 |
| upper limit | 0.135 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.022 |

Notes:

[7] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

## Secondary: Annualized rate of moderate and severe asthma exacerbations

| | |
|---|---|
| End point title | Annualized rate of moderate and severe asthma exacerbations |

End point description:

A moderate asthma exacerbation is considered to be a deterioration in asthma symptoms or in lung function, or increased rescue bronchodilator use lasting for at least 2 days or more, but not be severe enough to warrant systemic corticosteroid use (or a doubling or more of the maintenance systemic corticosteroid dose, if applicable) for 3 days or more and/or hospitalization. It is an event that, when recognized, should result in a temporary change in treatment, to prevent it from becoming severe. A severe asthma exacerbation is defined as the deterioration of asthma requiring the use of systemic corticosteroids (tablets,suspension or injection), or an increase from a stable maintenance dose (For participants receiving maintenance systemic corticosteroids, at least double the maintenance systemic corticosteroid dose for at least 3 days is required), for at least 3 days or an inpatient hospitalization or emergency department visit because of asthma, requiring systemic corticosteroids.

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

End point timeframe:

Up to Week 52

| **End point values** | FF/VI | FF/UMEC/VI (UMEC 31.25 mcg) | FF/UMEC/VI (UMEC 62.5 mcg) | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 813[8] | 809[9] | 814[10] | |
| Units: Exacerbations per year | | | | |
| arithmetic mean (confidence interval 95%) | 0.70 (0.61 to 0.80) | 0.68 (0.60 to 0.78) | 0.61 (0.53 to 0.70) | |

Notes:

[8] - ITT Population. Participants with at least one day on study post-randomization were analyzed.

[9] - Primary analysis used pooleddata from 2 FF/UMEC/VI arms for fixed UMEC dose compared to 2 FF/VI arms

[10] - Arms were pooled to provide more precise estimate for treatment effect of addition of UMEC to FF/VI

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Treatment policy estimand was assessed, including all on- and post-treatment data.

| | |
|---|---|
| Comparison groups | FF/VI v FF/UMEC/VI (UMEC 31.25 mcg) |

| | |
|---|---|
| Number of subjects included in analysis | 1622 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.778 [11] |
| Method | Negative Binomial Model |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.17 |

Notes:

[11] - p-value was calculated using Generalized linear model with covariates for age, sex, region, treatment group, stratification by pre-study ICS dosage at screening, and severe asthma exacerbations in the previous year (0, 1, >=2).

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Treatment policy estimand was assessed, including all on- and post-treatment data.

| | |
|---|---|
| Comparison groups | FF/VI v FF/UMEC/VI (UMEC 62.5 mcg) |
| Number of subjects included in analysis | 1627 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.151 [12] |
| Method | Negative Binomial Model |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 1.05 |

Notes:

[12] - p-value was calculated using Generalized linear model with covariates for age, sex, region, treatment group, stratification by pre-study ICS dosage at screening, and severe asthma exacerbations in the previous year (0, 1, >=2).

## Secondary: Mean change from Baseline in clinic FEV1 at 3 hours post study treatment at Week 24

| End point title | Mean change from Baseline in clinic FEV1 at 3 hours post study treatment at Week 24 |
|---|---|

End point description:

FEV1 is a measure of lung function and is defined as the maximal volume of air that can be forcefully exhaled in one second. Baseline value is the last acceptable/borderline acceptable pre-dose FEV1 prior to randomized treatment start date (pre-dose at Day 1). Change from Baseline value is the value at Week 24 (recorded at 3 hours post dose) minus the Baseline value. Only those participants with available Baseline and on-treatment data at Week 24 were analyzed

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

End point timeframe:

Baseline (pre-dose at Day 1) and 3 hours post dose at Week 24

| End point values | FF/VI 100/25 mcg | FF/UMEC/VI 100/ 31.25/25 mcg | FF/UMEC/VI 100/62.5/25 mcg | FF/VI 200/25 mcg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 369[13] | 375 | 379 | 377 |
| Units: Liters | | | | |
| least squares mean (standard error) | 0.132 (± 0.0160) | 0.220 (± 0.0159) | 0.243 (± 0.0158) | 0.168 (± 0.0159) |

Notes:

[13] - ITT Population

| End point values | FF/UMEC/VI 200/ 31.25/25 mcg | FF/UMEC/VI 200/62.5/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 371 | 378 | | |
| Units: Liters | | | | |
| least squares mean (standard error) | 0.256 (± 0.0160) | 0.286 (± 0.0158) | | |

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | FF/VI 100/25 mcg v FF/UMEC/VI 100/ 31.25/25 mcg |
| Number of subjects included in analysis | 744 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [14] |
| Method | ANCOVA |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 0.088 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.044 |
| upper limit | 0.132 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0226 |

Notes:

[14] - p-value was calculated using Analysis of Covariance (ANCOVA) with covariates of treatment, age, sex, region, Baseline value, and pre-study ICS dosage at screening.

| Statistical analysis title | Statistical Analysis 2 |
|---|---|
| Comparison groups | FF/VI 100/25 mcg v FF/UMEC/VI 100/62.5/25 mcg |
| Number of subjects included in analysis | 748 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [15] |
| Method | ANCOVA |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 0.111 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.067 |
| upper limit | 0.155 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0225 |

Notes:

[15] - p-value was calculated using ANCOVA with covariates of treatment, age, sex, region, Baseline value, and pre-study ICS dosage at screening.

| **Statistical analysis title** | Statistical Analysis 3 |
|---|---|
| Comparison groups | FF/VI 200/25 mcg v FF/UMEC/VI 200/ 31.25/25 mcg |
| Number of subjects included in analysis | 748 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [16] |
| Method | ANCOVA |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 0.088 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.044 |
| upper limit | 0.132 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0225 |

Notes:

[16] - p-value was calculated using ANCOVA with covariates of treatment, age, sex, region, Baseline value, and pre-study ICS dosage at screening.

| **Statistical analysis title** | Statistical Analysis 4 |
|---|---|
| Comparison groups | FF/VI 200/25 mcg v FF/UMEC/VI 200/62.5/25 mcg |
| Number of subjects included in analysis | 755 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [17] |
| Method | ANCOVA |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 0.118 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.074 |
| upper limit | 0.162 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0224 |

Notes:

[17] - p-value was calculated using ANCOVA with covariates of treatment, age, sex, region, Baseline value, and pre-study ICS dosage at screening.

## Secondary: Mean change from Baseline in Asthma Control Questionnaire-7 (ACQ-7) total score at Week 24

| End point title | Mean change from Baseline in Asthma Control Questionnaire-7 (ACQ-7) total score at Week 24 |
|---|---|

End point description:

The ACQ-7 consists of 7 attributes of asthma control, of which 6 to be self-completed by participant in a 6-item questionnaire, enquire about frequency and/or severity of symptoms over the previous week on: nocturnal awakening, symptoms on waking in the morning, activity limitation, shortness of breath, wheeze,and rescue medication use. The seventh attribute measures the lung function, which was included via pre-bronchodilator FEV1 % predicted value. All 7 items of ACQ have response on 0-6 ordinal scale (0=no impairment/limitation, 6=total impairment/limitation). The total score is calculated as the average of all non-missing item responses, ranges from 0 to 6. Higher score indicates worst symptoms. Treatment policy estimand was assessed, including all on- and post-treatment data. Baseline value was at randomization visit (pre-dose,Day 1). Change from Baseline was defined as value at Week 24 minus Baseline value.

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

End point timeframe:

Baseline (pre-dose at Day 1) and Week 24

| **End point values** | FF/VI | FF/UMEC/VI (UMEC 31.25 mcg) | FF/UMEC/VI (UMEC 62.5 mcg) | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 784[18] | 784[19] | 790[20] | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | -0.678 (± 0.0240) | -0.734 (± 0.0240) | -0.767 (± 0.0238) | |

Notes:

[18] - ITT Population. Participants with Baseline and at least one post-baseline measurement were analyzed.
[19] - Primary analysis used pooleddata from 2 FF/UMEC/VI arms for fixed UMEC dose compared to 2 FF/VI arms
[20] - Arms were pooled to provide more precise estimate for treatment effect of addition of UMEC to FF/VI

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | FF/VI v FF/UMEC/VI (UMEC 31.25 mcg) |
| Number of subjects included in analysis | 1568 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.094 [21] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | -0.057 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.124 |
| upper limit | 0.01 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.034 |

Notes:

[21] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | FF/VI v FF/UMEC/VI (UMEC 62.5 mcg) |
| Number of subjects included in analysis | 1574 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.008 [22] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | -0.089 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.156 |
| upper limit | -0.023 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0338 |

Notes:

[22] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

## Secondary: Mean change from Baseline in Saint George's Respiratory Questionnaire (SGRQ) total score at Week 24

| End point title | Mean change from Baseline in Saint George's Respiratory Questionnaire (SGRQ) total score at Week 24 |
|---|---|

End point description:

The SGRQ had 50 questions (scored from 0 to 100 where 0 indicates best and 100 indicates worst health) designed to measure quality of life (QoL) of participants with airway obstruction, measuring symptoms, impact, and activity. The questions are designed to be self-completed by the participant with a recall over the past 3 months. SGRQ total score was calculated by summing the pre-assigned weights of answers, dividing by the sum of the maximum weights for items in SGRQ and multiplying by 100. SGRQ total score ranges from 0 to 100 where 0 indicates best and 100 indicates worst health. A change of 4 points is considered a clinically relevant change. Treatment policy estimand was assessed, including all on- and post-treatment data. Baseline value was at randomization visit (pre-dose at Day 1). Change from Baseline value is the value at Week 24 minus the Baseline value.

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

End point timeframe:

Baseline (pre-dose at Day 1) and Week 24

| **End point values** | FF/VI | FF/UMEC/VI (UMEC 31.25 mcg) | FF/UMEC/VI (UMEC 62.5 mcg) | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 784[23] | 782[24] | 795[25] | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | -11.39 (± 0.491) | -10.29 (± 0.494) | -11.69 (± 0.487) | |

Notes:

[23] - ITT Population. Participants with Baseline and at least one post-baseline measurement were analyzed.
[24] - Primary analysis used pooleddata from 2 FF/UMEC/VI arms for fixed UMEC dose compared to 2 FF/VI arms
[25] - Arms were pooled to provide more precise estimate for treatment effect of addition of UMEC to FF/VI

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | FF/VI v FF/UMEC/VI (UMEC 31.25 mcg) |
| Number of subjects included in analysis | 1566 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.115 [26] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.27 |
| upper limit | 2.47 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.697 |

Notes:

[26] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | FF/VI v FF/UMEC/VI (UMEC 62.5 mcg) |
| Number of subjects included in analysis | 1579 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.662 [27] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.66 |
| upper limit | 1.05 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.692 |

Notes:

[27] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

## Secondary: Mean change from Baseline in Evaluating Respiratory Symptoms (E-RS) total score over Weeks 21 to 24 (inclusive) of the treatment period

| End point title | Mean change from Baseline in Evaluating Respiratory |
|---|---|

| | |
|---|---|
| | Symptoms (E-RS) total score over Weeks 21 to 24 (inclusive) of the treatment period |

End point description:

The E-RS in Chronic Obstructive Pulmonary Disease (COPD) consists of 11 items. E-RS captures information related to respiratory symptoms, i.e. breathlessness, cough, sputum production, chest congestion and chest tightness. The E-RS was completed daily and data was derived by 4-weekly intervals, requiring at least 50% of data to be present during a period. 7 items are scored from 0 (not at all) to 4 (extreme) and 4 items are scored from 0 (not at all) to 3 (extreme). The E-RS total score was calculated by taking sum of all the items. The E-RS total score has a scoring range of 0 to 40, with higher scores indicating more severe respiratory symptoms. Treatment policy estimand was assessed, including all on- and post-treatment data. Baseline value was the mean value of 14 days prior to randomization. Change from Baseline was calculated as post-baseline value (mean of daily E-RS total scores during Week 21 to 24) minus Baseline value.

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

End point timeframe:

Baseline (14 days prior to randomization) and Weeks 21 to 24

| **End point values** | FF/VI | FF/UMEC/VI (UMEC 31.25 mcg) | FF/UMEC/VI (UMEC 62.5 mcg) | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 787[28] | 796[29] | 802[30] | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | -2.47 (± 0.131) | -2.60 (± 0.130) | -2.89 (± 0.130) | |

Notes:

[28] - ITT Population. Participants with Baseline and at least one post-baseline measurement were analyzed.
[29] - Primary analysis used pooleddata from 2 FF/UMEC/VI arms for fixed UMEC dose compared to 2 FF/VI arms
[30] - Arms were pooled to provide more precise estimate for treatment effect of addition of UMEC to FF/VI

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | FF/VI v FF/UMEC/VI (UMEC 31.25 mcg) |
| Number of subjects included in analysis | 1583 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.479 [31] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | -0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.49 |
| upper limit | 0.23 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.185 |

Notes:

[31] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and 4-weekly period, interaction terms for Baseline value by 4-weekly period and treatment by 4-weekly period.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | FF/VI v FF/UMEC/VI (UMEC 62.5 mcg) |
| Number of subjects included in analysis | 1589 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.023 [32] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | -0.42 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.78 |
| upper limit | -0.06 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.184 |

Notes:

[32] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and 4-weekly period, interaction terms for Baseline value by 4-weekly period and treatment by 4-weekly period.

## Secondary: Number of participants with any serious adverse event (SAE) and common (>=3%) non-SAE

| End point title | Number of participants with any serious adverse event (SAE) and common (>=3%) non-SAE |
|---|---|

End point description:

Adverse event (AE) is any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Any untoward event resulting in death, life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, congenital anomaly/birth defect, events associated with liver injury and impaired liver function, or any other situation according to medical or scientific judgment were categorized as SAE. Number of participants with any SAE and common (>=3%) non-SAEs are presented.

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

End point timeframe:

Up to Week 52

| **End point values** | FF/VI 100/25 mcg | FF/UMEC/VI 100/ 31.25/25 mcg | FF/UMEC/VI 100/62.5/25 mcg | FF/VI 200/25 mcg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 407[33] | 405 | 406 | 406 |
| Units: Participants | | | | |
| Common non-SAE | 136 | 150 | 135 | 122 |
| SAE | 25 | 18 | 23 | 21 |

Notes:

[33] - ITT Population

| End point values | FF/UMEC/VI 200/ 31.25/25 mcg | FF/UMEC/VI 200/62.5/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 404 | 408 | | |
| Units: Participants | | | | |
| Common non-SAE | 127 | 122 | | |
| SAE | 23 | 21 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Abnormal Electrocardiogram (ECG) Findings

| End point title | Number of Participants With Abnormal Electrocardiogram (ECG) Findings |
|---|---|

End point description:

Twelve-lead ECGs were performed during the study using an automated ECG machine. All ECG measurements were made with the participant in a supine position having rested in this position for approximately 5 minutes before each reading. The number of participants with worst case post-Baseline abnormal ECG findings were reported. Only those participants with data available at the specified time point were analyzed.

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

End point timeframe:

Up to Week 52

| End point values | FF/VI 100/25 mcg | FF/UMEC/VI 100/ 31.25/25 mcg | FF/UMEC/VI 100/62.5/25 mcg | FF/VI 200/25 mcg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 401[34] | 398 | 398 | 397 |
| Units: Participants | 115 | 118 | 109 | 109 |

Notes:

[34] - ITT Population

| End point values | FF/UMEC/VI 200/ 31.25/25 mcg | FF/UMEC/VI 200/62.5/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 399 | 404 | | |
| Units: Participants | 106 | 108 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Change from Baseline in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) at Week 24

| End point title | Mean Change from Baseline in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) at Week 24 |
|---|---|

End point description:

Blood pressure (systolic and diastolic) was measured in the sitting position after approximately 5 minutes rest. Baseline value is the last acceptable/borderline acceptable value prior to randomized treatment start date (pre-dose at Day 1). Change from Baseline value is the value at the clinic visit minus the Baseline value. Different participants may have been analyzed at different time points; thus, overall number of participants analyzed reflects everyone in ITT Population without missing covariate information, with Baseline and at least one post-baseline measurement. Only those participants with data available at the specified data point were analyzed. Participants with a Baseline value and at least one post-baseline measurement were analyzed.

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

End point timeframe:

Baseline (pre-dose at Day 1) and Week 24

| **End point values** | FF/VI 100/25 mcg | FF/UMEC/VI 100/ 31.25/25 mcg | FF/UMEC/VI 100/62.5/25 mcg | FF/VI 200/25 mcg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 401[35] | 398 | 399 | 397 |
| Units: Millimeter of mercury | | | | |
| least squares mean (standard error) | | | | |
| SBP | 1.6 (± 0.53) | 0.6 (± 0.53) | 1.1 (± 0.52) | 0.2 (± 0.53) |
| DBP | 0.4 (± 0.39) | 0.1 (± 0.39) | 1.3 (± 0.39) | 0.4 (± 0.39) |

Notes:

[35] - ITT Population

| **End point values** | FF/UMEC/VI 200/ 31.25/25 mcg | FF/UMEC/VI 200/62.5/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 399 | 402 | | |
| Units: Millimeter of mercury | | | | |
| least squares mean (standard error) | | | | |
| SBP | 0.8 (± 0.53) | 0.9 (± 0.52) | | |
| DBP | 0.2 (± 0.40) | 0.8 (± 0.39) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Comparison for SBP

| Comparison groups | FF/VI 100/25 mcg v FF/UMEC/VI 100/ 31.25/25 mcg |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.172 [36] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.5 |
| upper limit | 0.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.75 |

Notes:

[36] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Statistical analysis description: | |
| Comparison for SBP | |
| Comparison groups | FF/VI 100/25 mcg v FF/UMEC/VI 100/62.5/25 mcg |
| Number of subjects included in analysis | 800 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.436 [37] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2 |
| upper limit | 0.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.74 |

Notes:

[37] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

| **Statistical analysis title** | Statistical Analysis 3 |
|---|---|
| Statistical analysis description: | |
| Comparison for SBP | |
| Comparison groups | FF/VI 200/25 mcg v FF/UMEC/VI 200/ 31.25/25 mcg |
| Number of subjects included in analysis | 796 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.426 [38] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 0.6 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 2.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.75 |

Notes:

[38] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

| **Statistical analysis title** | Statistical Analysis 4 |
|---|---|
| Statistical analysis description: | |
| Comparison for SBP | |
| Comparison groups | FF/VI 200/25 mcg v FF/UMEC/VI 200/62.5/25 mcg |
| Number of subjects included in analysis | 799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.349 [39] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 2.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.74 |

Notes:

[39] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

| **Statistical analysis title** | Statistical Analysis 5 |
|---|---|
| Statistical analysis description: | |
| Comparison for DBP | |
| Comparison groups | FF/VI 100/25 mcg v FF/UMEC/VI 100/ 31.25/25 mcg |
| Number of subjects included in analysis | 799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.482 [40] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.5 |
| upper limit | 0.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.56 |

Notes:

[40] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

| **Statistical analysis title** | Statistical Analysis 6 |
|---|---|
| Statistical analysis description: | |
| Comparison for DBP | |
| Comparison groups | FF/VI 100/25 mcg v FF/UMEC/VI 100/62.5/25 mcg |
| Number of subjects included in analysis | 800 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.142 [41] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 1.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.56 |

Notes:

[41] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

| **Statistical analysis title** | Statistical Analysis 7 |
|---|---|
| Statistical analysis description: | |
| Comparison for DBP | |
| Comparison groups | FF/VI 200/25 mcg v FF/UMEC/VI 200/ 31.25/25 mcg |
| Number of subjects included in analysis | 796 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.806 [42] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.56 |

Notes:

[42] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

| **Statistical analysis title** | Statistical Analysis 8 |
|---|---|
| Statistical analysis description: | |
| Comparison for DBP | |

| | |
|---|---|
| Comparison groups | FF/VI 200/25 mcg v FF/UMEC/VI 200/62.5/25 mcg |
| Number of subjects included in analysis | 799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.447 [43] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 1.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.55 |

Notes:

[43] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

## Secondary: Mean Change from Baseline in Pulse Rate at Week 24

| | |
|---|---|
| End point title | Mean Change from Baseline in Pulse Rate at Week 24 |

End point description:

Pulse Rate was measured in the sitting position after approximately 5 minutes rest. Baseline value is the last acceptable/borderline acceptable value prior to randomized treatment start date (pre-dose at Day 1). Change from Baseline value is the value at the clinic visit minus the Baseline value. Different participants may have been analyzed at different time points; thus, overall number of participants analyzed reflects everyone in ITT Population without missing covariate information, with Baseline and at least one post-baseline measurement. Only those participants with data available at the specified data point were analyzed. Participants with a Baseline value and at least one post-baseline measurement were analyzed.

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

End point timeframe:

Baseline (pre-dose at Day 1) and Week 24

| End point values | FF/VI 100/25 mcg | FF/UMEC/VI 100/ 31.25/25 mcg | FF/UMEC/VI 100/62.5/25 mcg | FF/VI 200/25 mcg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 401[44] | 398 | 399 | 397 |
| Units: Beats per minute | | | | |
| least squares mean (standard error) | -1.1 (± 0.43) | 0.2 (± 0.43) | -1.0 (± 0.43) | -0.7 (± 0.43) |

Notes:

[44] - ITT Population

| End point values | FF/UMEC/VI 200/ 31.25/25 mcg | FF/UMEC/VI 200/62.5/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 399 | 402 | | |
| Units: Beats per minute | | | | |
| least squares mean (standard error) | -1.3 (± 0.44) | -0.5 (± 0.43) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | FF/VI 100/25 mcg v FF/UMEC/VI 100/ 31.25/25 mcg |
| Number of subjects included in analysis | 799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.034 [45] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1 |
| upper limit | 2.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.61 |

Notes:

[45] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | FF/VI 100/25 mcg v FF/UMEC/VI 100/62.5/25 mcg |
| Number of subjects included in analysis | 800 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.839 [46] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 1.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.61 |

Notes:

[46] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

| **Statistical analysis title** | Statistical Analysis 3 |
|---|---|
| Comparison groups | FF/VI 200/25 mcg v FF/UMEC/VI 200/ 31.25/25 mcg |

| | |
|---|---|
| Number of subjects included in analysis | 796 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.349 [47] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.8 |
| upper limit | 0.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.61 |

Notes:

[47] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

| **Statistical analysis title** | Statistical Analysis 4 |
|---|---|
| Comparison groups | FF/VI 200/25 mcg v FF/UMEC/VI 200/62.5/25 mcg |
| Number of subjects included in analysis | 799 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.768 [48] |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 1.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.61 |

Notes:

[48] - p-value was calculated using MMRM with covariates of treatment, age, sex, region, Baseline value, pre-study ICS dosage at screening, and visit, interaction terms for Baseline value by visit and treatment by visit.

## Secondary: Number of Participants With Abnormal Clinical Chemistry Values

| End point title | Number of Participants With Abnormal Clinical Chemistry Values |
|---|---|

End point description:

Blood samples were collected for assessment of clinical chemistry parameters, which included albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), direct bilirubin, total bilirubin, calcium, creatinine, glucose, potassium, protein, sodium and urea. Abnormal laboratory results are categorized as high or low with respect to their normal ranges. Participants having High and Low values from normal ranges for any parameter at any time post-baseline visits are presented. Only those participants with data available at the specified time point were analyzed.

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

End point timeframe:

Up to Week 52

| End point values | FF/VI 100/25 mcg | FF/UMEC/VI 100/ 31.25/25 mcg | FF/UMEC/VI 100/62.5/25 mcg | FF/VI 200/25 mcg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 391[49] | 392 | 394 | 390 |
| Units: Participants | | | | |
| Albumin, low | 2 | 0 | 0 | 1 |
| Albumin, high | 1 | 6 | 5 | 2 |
| ALT, low | 0 | 0 | 0 | 0 |
| ALT, high | 41 | 29 | 24 | 28 |
| AST, low | 0 | 0 | 0 | 0 |
| AST, high | 29 | 27 | 14 | 21 |
| ALP, low | 1 | 0 | 0 | 0 |
| ALP, high | 21 | 15 | 10 | 12 |
| Direct bilirubin, low | 0 | 0 | 0 | 0 |
| Direct bilirubin, high | 1 | 1 | 0 | 2 |
| Bilirubin, low | 0 | 0 | 0 | 0 |
| Bilirubin, high | 9 | 12 | 5 | 15 |
| Calcium, low | 4 | 9 | 7 | 7 |
| Calcium, high | 4 | 12 | 10 | 11 |
| Creatinine, low | 54 | 62 | 49 | 63 |
| Creatinine, high | 7 | 7 | 8 | 6 |
| Glucose, low | 15 | 11 | 11 | 7 |
| Glucose, high | 74 | 71 | 70 | 76 |
| Potassium, low | 2 | 3 | 1 | 7 |
| Potassium, high | 15 | 13 | 11 | 9 |
| Protein, low | 3 | 0 | 5 | 3 |
| Protein, high | 0 | 1 | 3 | 2 |
| Sodium, low | 5 | 7 | 3 | 5 |
| Sodium, high | 6 | 7 | 7 | 4 |
| Urea, low | 3 | 4 | 5 | 3 |
| Urea, high | 13 | 17 | 3 | 11 |

Notes:

[49] - ITT Population

| End point values | FF/UMEC/VI 200/ 31.25/25 mcg | FF/UMEC/VI 200/62.5/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 391 | 397 | | |
| Units: Participants | | | | |
| Albumin, low | 0 | 0 | | |
| Albumin, high | 3 | 1 | | |
| ALT, low | 0 | 0 | | |
| ALT, high | 27 | 30 | | |
| AST, low | 0 | 0 | | |
| AST, high | 23 | 16 | | |
| ALP, low | 1 | 0 | | |

| | | | | |
|---|---|---|---|---|
| ALP, high | 16 | 12 | | |
| Direct bilirubin, low | 0 | 0 | | |
| Direct bilirubin, high | 2 | 1 | | |
| Bilirubin, low | 0 | 0 | | |
| Bilirubin, high | 17 | 13 | | |
| Calcium, low | 4 | 3 | | |
| Calcium, high | 8 | 7 | | |
| Creatinine, low | 60 | 64 | | |
| Creatinine, high | 9 | 8 | | |
| Glucose, low | 12 | 7 | | |
| Glucose, high | 66 | 73 | | |
| Potassium, low | 7 | 6 | | |
| Potassium, high | 12 | 19 | | |
| Protein, low | 1 | 2 | | |
| Protein, high | 3 | 1 | | |
| Sodium, low | 7 | 3 | | |
| Sodium, high | 5 | 7 | | |
| Urea, low | 3 | 1 | | |
| Urea, high | 11 | 13 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Abnormal hematology values

| End point title | Number of Participants With Abnormal hematology values |
|---|---|

End point description:

Blood samples were collected for assessment of hematology parameters, which included Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Erythrocytes, Hematocrit, Hemoglobin, Leukocytes, Platelets, Mean Corpuscular Hemoglobin (MCH) and Mean Corpuscular Volume (MCV). Abnormal laboratory results are categorized as high or low with respect to their normal ranges. Participants having High and Low values from normal ranges for any parameter at any time post-baseline visits are presented. Only those participants with data available at the specified time point were analyzed (represented by n=X in category titles).

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

End point timeframe:

Up to Week 52

| End point values | FF/VI 100/25 mcg | FF/UMEC/VI 100/ 31.25/25 mcg | FF/UMEC/VI 100/62.5/25 mcg | FF/VI 200/25 mcg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 391[50] | 390 | 392 | 391 |
| Units: Participants | | | | |
| Basophils, low, n=390,390,391,389,389,396 | 0 | 0 | 0 | 0 |
| Basophils, high, n=390,390,391,389,389,396 | 1 | 0 | 0 | 0 |

| | | | | |
|---|---|---|---|---|
| Eosinophils, low, n=390,390,391,389,389,396 | 26 | 27 | 25 | 31 |
| Eosinophils, high, n=390,390,391,389,389,396 | 111 | 84 | 102 | 84 |
| Lymphocytes, low, n=390,390,391,389,389,396 | 13 | 11 | 13 | 8 |
| Lymphocytes, high, n=390,390,391,389,389,396 | 2 | 5 | 1 | 7 |
| Monocytes, low, n=390,390,391,389,389,396 | 60 | 68 | 57 | 64 |
| Monocytes, high, n=390,390,391,389,389,396 | 7 | 1 | 4 | 2 |
| Neutrophils, low, n=390,390,391,389,389,396 | 14 | 10 | 16 | 10 |
| Neutrophils, high, n=390,390,391,389,389,396 | 21 | 20 | 15 | 19 |
| Erythrocytes, low, n=391,390,392,391,391,397 | 14 | 16 | 11 | 15 |
| Erythrocytes, high, n=391,390,392,391,391,397 | 24 | 21 | 13 | 12 |
| Hematocrit, low, n=391,390,392,391,391,397 | 21 | 28 | 16 | 20 |
| Hematocrit, high, n=391,390,392,391,391,397 | 60 | 52 | 50 | 47 |
| Hemoglobin, low, n=391,390,392,391,391,397 | 32 | 47 | 40 | 40 |
| Hemoglobin, high, n=391,390,392,391,391,397 | 14 | 13 | 8 | 17 |
| Leukocytes, low, n=391,390,391,389,391,396 | 9 | 12 | 14 | 9 |
| Leukocytes, high, n=391,390,391,389,391,396 | 38 | 29 | 20 | 31 |
| Platelets, low, n=391,388,389,391,388,396 | 4 | 2 | 3 | 4 |
| Platelets, high, n=391,388,389,391,388,396 | 17 | 16 | 19 | 21 |
| MCH, low, n=391,390,392,391,391,397 | 40 | 47 | 24 | 34 |
| MCH, high, n=391,390,392,391,391,397 | 18 | 32 | 22 | 17 |
| MCV, low, n=391,390,392,391,391,397 | 20 | 22 | 10 | 15 |
| MCV, high, n=391,390,392,391,391,397 | 29 | 41 | 25 | 29 |

Notes:

[50] - ITT Population

| **End point values** | FF/UMEC/VI 200/ 31.25/25 mcg | FF/UMEC/VI 200/62.5/25 mcg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 391 | 397 | | |
| Units: Participants | | | | |
| Basophils, low, n=390,390,391,389,389,396 | 0 | 0 | | |
| Basophils, high, n=390,390,391,389,389,396 | 0 | 0 | | |
| Eosinophils, low, n=390,390,391,389,389,396 | 32 | 28 | | |
| Eosinophils, high, n=390,390,391,389,389,396 | 85 | 78 | | |
| Lymphocytes, low, n=390,390,391,389,389,396 | 13 | 10 | | |

| | | | | |
|---|---|---|---|---|
| Lymphocytes, high, n=390,390,391,389,389,396 | 6 | 6 | | |
| Monocytes, low, n=390,390,391,389,389,396 | 51 | 63 | | |
| Monocytes, high, n=390,390,391,389,389,396 | 7 | 4 | | |
| Neutrophils, low, n=390,390,391,389,389,396 | 12 | 9 | | |
| Neutrophils, high, n=390,390,391,389,389,396 | 15 | 34 | | |
| Erythrocytes, low, n=391,390,392,391,391,397 | 21 | 22 | | |
| Erythrocytes, high, n=391,390,392,391,391,397 | 17 | 17 | | |
| Hematocrit, low, n=391,390,392,391,391,397 | 20 | 26 | | |
| Hematocrit, high, n=391,390,392,391,391,397 | 49 | 49 | | |
| Hemoglobin, low, n=391,390,392,391,391,397 | 37 | 34 | | |
| Hemoglobin, high, n=391,390,392,391,391,397 | 10 | 13 | | |
| Leukocytes, low, n=391,390,391,389,391,396 | 12 | 8 | | |
| Leukocytes, high, n=391,390,391,389,391,396 | 26 | 40 | | |
| Platelets, low, n=391,388,389,391,388,396 | 5 | 4 | | |
| Platelets, high, n=391,388,389,391,388,396 | 19 | 21 | | |
| MCH, low, n=391,390,392,391,391,397 | 41 | 25 | | |
| MCH, high, n=391,390,392,391,391,397 | 25 | 32 | | |
| MCV, low, n=391,390,392,391,391,397 | 19 | 14 | | |
| MCV, high, n=391,390,392,391,391,397 | 26 | 37 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Non-serious AEs and serious AEs were collected from start of study treatment (Week 0) up to Week 52

Adverse event reporting additional description:

Non-serious AEs and serious AEs were collected for ITT Population.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | FF/VI 100/25 mcg |

Reporting group description:

Participants received Fluticasone Furoate/ Vilanterol (FF/VI) 100/25 micrograms (mcg) inhalation powder via dry powder inhaler (DPI), once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Reporting group title | FF/UMEC/VI 100/ 31.25/25 mcg |

Reporting group description:

Participants received Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) 100/31.25/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Reporting group title | FF/UMEC/VI 100/62.5/25 mcg |

Reporting group description:

Participants received FF/UMEC/VI 100/62.5/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Reporting group title | FF/VI 200/25 mcg |

Reporting group description:

Participants received FF/VI 200/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Reporting group title | FF/UMEC/VI 200/ 31.25/25 mcg |

Reporting group description:

Participants received FF/UMEC/VI 200/31.25/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| | |
|---|---|
| Reporting group title | FF/UMEC/VI 200/62.5/25 mcg |

Reporting group description:

Participants received FF/UMEC/VI 200/62.5/25 mcg inhalation powder via DPI, once daily in the morning up to 52 weeks. Participants were allowed to take albuterol/salbutamol as a rescue medication when needed during the treatment period.

| Serious adverse events | FF/VI 100/25 mcg | FF/UMEC/VI 100/ 31.25/25 mcg | FF/UMEC/VI 100/62.5/25 mcg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 25 / 407 (6.14%) | 18 / 405 (4.44%) | 23 / 406 (5.67%) |
| number of deaths (all causes) | 0 | 2 | 0 |
| number of deaths resulting from adverse events | | | |

| | | | |
|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 407 (0.25%) | 1 / 405 (0.25%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 1 / 406 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometrial cancer | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lip and/or oral cavity cancer | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 1 / 406 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 1 / 407 (0.25%) | 0 / 405 (0.00%) | 0 / 406 (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 |
| Rectal cancer | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 1 / 405 (0.25%) | 1 / 406 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 1 / 405 (0.25%) | 0 / 406 (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 |
| Uterine haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 407 (0.25%) | 0 / 405 (0.00%) | 0 / 406 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 7 / 407 (1.72%) | 7 / 405 (1.73%) | 7 / 406 (1.72%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 8 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal polyps | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 2 / 406 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 1 / 405 (0.25%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Chronic rhinosinusitis with nasal polyps | | | |
| subjects affected / exposed | 1 / 407 (0.25%) | 0 / 405 (0.00%) | 0 / 406 (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 |
| Status asthmaticus | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 407 (0.25%) | 0 / 405 (0.00%) | 0 / 406 (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 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 407 (0.25%) | 0 / 405 (0.00%) | 1 / 406 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 1 / 406 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 1 / 405 (0.25%) | 0 / 406 (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 |
| Facial bones fracture | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 407 (0.25%) | 0 / 405 (0.00%) | 0 / 406 (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 |
| Jaw fracture | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint injury | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 1 / 406 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 1 / 405 (0.25%) | 0 / 406 (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 |
| Ligament sprain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal foreign body | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 1 / 406 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary contusion | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 1 / 405 (0.25%) | 0 / 406 (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 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Hypertrophic cardiomyopathy | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 1 / 405 (0.25%) | 0 / 406 (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 |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 2 / 407 (0.49%) | 1 / 405 (0.25%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 2 / 406 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 1 / 405 (0.25%) | 0 / 406 (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 |

| | | | |
|---|---|---|---|
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 1 / 406 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 407 (0.25%) | 0 / 405 (0.00%) | 0 / 406 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular disorder | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial paralysis | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 1 / 405 (0.25%) | 0 / 406 (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 |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 1 / 405 (0.25%) | 0 / 406 (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 |
| Hypertensive encephalopathy | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 1 / 406 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sciatica | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 407 (0.25%) | 0 / 405 (0.00%) | 0 / 406 (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 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic gastritis | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 407 (0.25%) | 0 / 405 (0.00%) | 0 / 406 (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 |
| Gastrointestinal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 1 / 406 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hiatus hernia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 1 / 406 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 407 (0.25%) | 0 / 405 (0.00%) | 0 / 406 (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 |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 1 / 407 (0.25%) | 0 / 405 (0.00%) | 0 / 406 (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 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 407 (0.25%) | 0 / 405 (0.00%) | 0 / 406 (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 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 407 (0.25%) | 0 / 405 (0.00%) | 0 / 406 (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 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Nephropathy toxic | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 1 / 405 (0.25%) | 0 / 406 (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 |
| Stress urinary incontinence | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Musculoskeletal and connective tissue disorders** | | | |
| Foot deformity | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 1 / 406 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 1 / 405 (0.25%) | 0 / 406 (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 |
| Polymyalgia rheumatica | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal disorder | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Trigger finger | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Infections and infestations** | | | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 407 (0.49%) | 0 / 405 (0.00%) | 3 / 406 (0.74%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 1 / 405 (0.25%) | 0 / 406 (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 |
| Acute sinusitis | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 1 / 405 (0.25%) | 0 / 406 (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 |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic sinusitis | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 407 (0.25%) | 0 / 405 (0.00%) | 0 / 406 (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 |
| Metapneumovirus infection | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periodontitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia influenzal | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Soft tissue infection | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 1 / 406 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound sepsis | | | |
| subjects affected / exposed | 1 / 407 (0.25%) | 0 / 405 (0.00%) | 0 / 406 (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 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 407 (0.00%) | 1 / 405 (0.25%) | 0 / 406 (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 |
| Hyperglycaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 407 (0.00%) | 0 / 405 (0.00%) | 0 / 406 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | FF/VI 200/25 mcg | FF/UMEC/VI 200/ 31.25/25 mcg | FF/UMEC/VI 200/62.5/25 mcg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 406 (5.17%) | 23 / 404 (5.69%) | 21 / 408 (5.15%) |
| number of deaths (all causes) | 1 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder cancer | | | |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 404 (0.00%) | 0 / 408 (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 |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometrial cancer | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 |
| Intestinal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 |

| | | | |
|---|---|---|---|
| Lip and/or oral cavity cancer | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal cancer | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Reproductive system and breast disorders | | | |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine haemorrhage | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 6 / 406 (1.48%) | 5 / 404 (1.24%) | 4 / 408 (0.98%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 5 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal polyps | | | |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 404 (0.00%) | 0 / 408 (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 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 2 / 408 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic rhinosinusitis with nasal polyps | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status asthmaticus | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Hepatic enzyme increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limb injury | | | |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 404 (0.00%) | 0 / 408 (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 |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial bones fracture | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaw fracture | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 |
| Joint injury | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 |
| Musculoskeletal foreign body | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary contusion | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 404 (0.00%) | 0 / 408 (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 |
| Congenital, familial and genetic disorders | | | |
| Hypertrophic cardiomyopathy | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 404 (0.00%) | 0 / 408 (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 |
| Nervous system disorders | | | |
| Cerebrovascular disorder | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial paralysis | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive encephalopathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sciatica | | | |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 404 (0.00%) | 0 / 408 (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 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 | | | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 |
| Chronic gastritis | | | |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 404 (0.00%) | 0 / 408 (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 |
| Colitis | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal ulcer haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |

| | | | |
|---|---|---|---|
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 404 (0.00%) | 0 / 408 (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 |
| Nephropathy toxic | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stress urinary incontinence | | | |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 404 (0.00%) | 0 / 408 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Foot deformity | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Polymyalgia rheumatica | | | |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 404 (0.00%) | 0 / 408 (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 |
| Spinal disorder | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 |
| Trigger finger | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 406 (0.74%) | 4 / 404 (0.99%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 |
| Acute sinusitis | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 |
| Chronic sinusitis | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metapneumovirus infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periodontitis | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia influenzal | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 404 (0.25%) | 0 / 408 (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 |
| Soft tissue infection | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 1 / 408 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound sepsis | | | |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus inadequate control | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 404 (0.00%) | 0 / 408 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 404 (0.00%) | 0 / 408 (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 |

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

| **Non-serious adverse events** | FF/VI 100/25 mcg | FF/UMEC/VI 100/ 31.25/25 mcg | FF/UMEC/VI 100/62.5/25 mcg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 136 / 407 (33.42%) | 150 / 405 (37.04%) | 135 / 406 (33.25%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 30 / 407 (7.37%) | 31 / 405 (7.65%) | 36 / 406 (8.87%) |
| occurrences (all) | 46 | 51 | 52 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 16 / 407 (3.93%) | 12 / 405 (2.96%) | 13 / 406 (3.20%) |
| occurrences (all) | 16 | 14 | 19 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 63 / 407 (15.48%) | 56 / 405 (13.83%) | 60 / 406 (14.78%) |
| occurrences (all) | 76 | 68 | 73 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 21 / 407 (5.16%) | 24 / 405 (5.93%) | 15 / 406 (3.69%) |
| occurrences (all) | 26 | 35 | 16 |
| Bronchitis | | | |
| subjects affected / exposed | 14 / 407 (3.44%) | 18 / 405 (4.44%) | 15 / 406 (3.69%) |
| occurrences (all) | 15 | 22 | 15 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 11 / 407 (2.70%) | 17 / 405 (4.20%) | 10 / 406 (2.46%) |
| occurrences (all) | 14 | 20 | 10 |
| Influenza | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 13 / 407 (3.19%) | 12 / 405 (2.96%) | 15 / 406 (3.69%) |
| occurrences (all) | 14 | 12 | 16 |
| Pharyngitis | | | |
| subjects affected / exposed | 8 / 407 (1.97%) | 10 / 405 (2.47%) | 9 / 406 (2.22%) |
| occurrences (all) | 11 | 11 | 11 |

| **Non-serious adverse events** | FF/VI 200/25 mcg | FF/UMEC/VI 200/ 31.25/25 mcg | FF/UMEC/VI 200/62.5/25 mcg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 122 / 406 (30.05%) | 127 / 404 (31.44%) | 122 / 408 (29.90%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 23 / 406 (5.67%) | 27 / 404 (6.68%) | 19 / 408 (4.66%) |
| occurrences (all) | 47 | 38 | 25 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 6 / 406 (1.48%) | 14 / 404 (3.47%) | 9 / 408 (2.21%) |
| occurrences (all) | 8 | 20 | 10 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 53 / 406 (13.05%) | 51 / 404 (12.62%) | 51 / 408 (12.50%) |
| occurrences (all) | 70 | 58 | 67 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 13 / 406 (3.20%) | 15 / 404 (3.71%) | 19 / 408 (4.66%) |
| occurrences (all) | 16 | 19 | 21 |
| Bronchitis | | | |
| subjects affected / exposed | 19 / 406 (4.68%) | 16 / 404 (3.96%) | 22 / 408 (5.39%) |
| occurrences (all) | 26 | 19 | 24 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 7 / 406 (1.72%) | 12 / 404 (2.97%) | 9 / 408 (2.21%) |
| occurrences (all) | 13 | 17 | 9 |
| Influenza | | | |
| subjects affected / exposed | 9 / 406 (2.22%) | 8 / 404 (1.98%) | 6 / 408 (1.47%) |
| occurrences (all) | 9 | 8 | 6 |
| Pharyngitis | | | |
| subjects affected / exposed | 14 / 406 (3.45%) | 11 / 404 (2.72%) | 9 / 408 (2.21%) |
| occurrences (all) | 15 | 14 | 10 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 09 June 2016 | Re-Publishing: Following publication of the original protocol but prior to distribution of the document, an exploratory analysis of the psychometric properties of the Evaluating Respiratory Symptoms (E-RS) and Supplemental asthma items was included in the protocol. This necessitated a re-publishing of the protocol. |
| 13 December 2016 | Amendment 01 was approved on 13 December 2016, and involved the following changes: one other secondary endpoint assessment time point; clarification of patient-reported outcome (PRO)other efficacy endpoint definitions and minimum clinically important differences (MCIDs); clarification of inclusion/exclusion criteria; clarification of the QT interval corrected for heart rate (QTc)stopping criterion; clarification of the use of study-provided fluticasone propionate (FP) for treatment of the symptoms of a moderate asthma exacerbation; clarification of concomitant medications and non-drug therapies; amending the order and timing of the assessments; amended power of the secondary endpoint analyses; updating of the multiplicity plan. |
| 23 June 2017 | Amendment 02was approved on 23 June 2017, and involved correction of the other objective; clarification of PRO other efficacy endpoint definitions and MCIDs; broadening of the inclusion criteria; clarification of Baseline definition for the electronic diary (eDiary) alerts (Section 4.6.2.7); updating of the multiplicity plan (re-ordering of the hierarchy and removal of FEV1 3 hour post-study treatment [IP]endpoint from the hierarchy). |
| 29 September 2017 | Amendment 03 was approved on 29 September 2017 and involved updating and defining the variable treatment period and transition date to determine the planned end of study (EOS) Visit for each participant; removal of the country-specific minimum requirements for Japanese participants (Protocol Appendix 7). |
| 05 December 2017 | Amendment 04 was approved on 05 December 2017 and involved clarification of details regarding the dispensing and administering of the study-provided FP at the investigator’s discretion, to a participant for treatment of the symptoms of a moderate asthma exacerbation. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported