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 Units: Subjects			
All Participants	407	405	406
Age Continuous Units: Years			
arithmetic mean	53.3	51.7	52.9
standard deviation	± 13.03	± 13.27	± 13.39
Sex: Female, Male Units: Participants			
Female	254	262	248
Male	153	143	158
Race/Ethnicity, Customized 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 Units: Subjects			
All Participants	406	404	408
Age Continuous Units: Years			
arithmetic mean	53.9	53.5	53.7
standard deviation	± 13.30	± 13.12	± 12.50
Sex: Female, Male Units: Participants			
Female	252	240	258
Male	154	164	150
Race/Ethnicity, Customized 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 Units: Subjects			
All Participants	2436		
Age Continuous Units: Years arithmetic mean standard deviation	 -		
Sex: Female, Male Units: Participants			
Female	1514		
Male	922		
Race/Ethnicity, Customized 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