Clinical trial results:
A 12-month, open label, randomised, effectiveness study to evaluate fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) Inhalation Powder delivered once daily via a Novel Dry Powder Inhaler compared with usual maintenance therapy in subjects with Asthma

Summary

EudraCT number	2011-005553-31
Trial protocol	GB
Global end of trial date	16 December 2016

Results information

Result version number	v2 (current)
This version publication date	11 August 2018
First version publication date	22 December 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	115150

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study is to compare the effectiveness of fluticasone furoate(FF)/vilanterol (VI) Inhalation Powder (FF 100 micrograms [mcg]/VI 25mcg or FF 200mcg/VI 25mcg) with usual asthma maintenance therapy over twelve months in a large United Kingdom primary care population of subjects with Asthma. FF/VI will be administered once-daily (QD) via the Novel Dry Powder Inhaler (NDPI).

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 4233
Worldwide total number of subjects	4233
EEA total number of subjects	4233

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)	3352
From 65 to 84 years	844
85 years and over	37

Subject disposition

Recruitment

Recruitment details:

This was a multi-center, randomized, open label study to evaluate the effectiveness of fluticasone furoate (FF)/vilanterol (VI) Inhalation Powder (FF 100 micrograms [mcg]/VI 25 mcg or FF 200 mcg/VI 25 mcg) compared with usual asthma maintenance therapy in participants with asthma in a localized geographical region of United Kingdom.

Pre-assignment

Screening details:

A total of 4725 participants were screened of which 4233 participants were randomized to either initiate with FF/VI or continue their usual asthma maintenance therapy in a ratio of 1:1. The total duration of study was approximately 12 months (52 weeks).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Usual Care

Arm description:

Participants continued their usual asthma maintenance therapy that is, inhaled corticosteroid without a long acting beta2-agonist or inhaled corticosteroid with long acting beta2-agonist combination (either as a fixed dose combination or an inhaled corticosteroid/long acting beta2-agonist provided in two separate inhalers).

Arm type	Active comparator
Investigational medicinal product name	Inhaled corticosteroid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants continued their usual asthma maintenance therapy with inhaled corticosteroid.

Investigational medicinal product name	Inhaled corticosteroid/long acting beta2-agonist
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants continued their usual asthma maintenance with inhaled corticosteroid/long acting beta2-agonist as a fixed drug combination or via two separate inhalers.

Arm title	FF/VI

Arm description:

Participants initiated with an appropriate dose of inhaled FF/VI (100 mcg/25 mcg or 200 mcg/25 mcg per actuation) once daily via Novel Dry Powder Inhaler.

Arm type	Experimental

Investigational medicinal product name	FF/VI (200/25 mcg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

200 mcg of FF blended with lactose in the first strip and 25 mcg of VI blended with lactose and magnesium stearate in the second strip was administered via a novel dry powder inhaler.

Investigational medicinal product name	FF/VI (100/25 mcg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

100 mcg of FF blended with lactose in the first strip and 25 mcg of VI blended with lactose and magnesium stearate in the second strip was administered via a novel dry powder inhaler.

Number of subjects in period 1	Usual Care	FF/VI
Started	2119	2114
Completed	1946	1920
Not completed	173	194
Physician decision	23	37
Consent withdrawn by subject	23	31
Adverse event, non-fatal	12	15
Lost to follow-up	97	93
Other: Subject reached stopping criteria	11	13
Protocol deviation	7	5

Baseline characteristics

Reporting groups	
Reporting group title	Usual Care
Reporting group description:	
Participants continued their usual asthma maintenance therapy that is, inhaled corticosteroid without a long acting beta2-agonist or inhaled corticosteroid with long acting beta2-agonist combination (either as a fixed dose combination or an inhaled corticosteroid/long acting beta2-agonist provided in two separate inhalers).	
Reporting group title	FF/VI
Reporting group description:	
Participants initiated with an appropriate dose of inhaled FF/VI (100 mcg/25 mcg or 200 mcg/25 mcg per actuation) once daily via Novel Dry Powder Inhaler.	

Reporting group values	Usual Care	FF/VI	Total
Number of subjects	2119	2114	4233
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	49.7	49.9	
standard deviation	± 16.69	± 16.05	-
Gender categorical Units: Subjects			
Female	1241	1257	2498
Male	878	857	1735
Race, Customized Units: Subjects			
African American/African Heritage	25	40	65
Asian - Central/South Asian Heritage	35	46	81
Asian - East Asian Heritage	4	9	13
Asian - Japanese Heritage	2	0	2
Asian - South East Asian Heritage	9	18	27
Native Hawaiian or Other Pacific Islander	1	1	2
White - Arabic/North African Heritage	6	5	11
White - White/Caucasian/European Heritage	2002	1971	3973
Mixed race	33	23	56
Unknown	2	1	3

End points

End points reporting groups

Reporting group title	Usual Care

Reporting group description:

Participants continued their usual asthma maintenance therapy that is, inhaled corticosteroid without a long acting beta2-agonist or inhaled corticosteroid with long acting beta2-agonist combination (either as a fixed dose combination or an inhaled corticosteroid/long acting beta2-agonist provided in two separate inhalers).

Reporting group title	FF/VI

Reporting group description:

Participants initiated with an appropriate dose of inhaled FF/VI (100 mcg/25 mcg or 200 mcg/25 mcg per actuation) once daily via Novel Dry Powder Inhaler.

Primary: Percentage of participants who have either an Asthma Control Test (ACT) total score of >=20 or an increase from Baseline of >=3 in ACT total score at Week 24.

End point title	Percentage of participants who have either an Asthma Control Test (ACT) total score of >=20 or an increase from Baseline of >=3 in ACT total score at Week 24.

End point description:

The ACT is a validated self-administered questionnaire utilizing 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5). By answering all 5 questions, participants with asthma obtained an ACT score ranging between 5 and 25. Higher scores indicated better control of asthma. An ACT score of <=15 showed poorly controlled asthma; 16 to 19 showed partly controlled asthma and >=20 showed well controlled asthma. The total score was calculated as the sum of the scores from all 5 questions. The primary efficacy analysis (PEA) Population is defined as all Intent-to-Treat (ITT) participants (that is, all participants who were randomized and received at least one prescription of study medication) who have an ACT total score of <20 at Baseline (Day 0). The percentage of responders that is participants with an ACT total score >=20 or an increase from Baseline of >=3 has been presented

End point type	Primary

End point timeframe:

Baseline (Day 0) and Week 24

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1399[1]	1373[2]		
Units: Percentage of participants				
Percentage of participants	56	71		

Notes:

[1] - PEA Population. Only participants with non-missing ACT score were analyzed.

[2] - PEA Population. Only participants with non-missing ACT score were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Adjusted odds ratio comparing FF/VI with Usual Care has been presented.

Comparison groups	Usual Care v FF/VI

Number of subjects included in analysis	2772
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [3]
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	2.34

Notes:

[3] - The analysis method was logistic regression adjusted for randomized treatment, asthma maintenance therapy (AMT) at Baseline per randomization stratification, Baseline ACT total score, Baseline ACT total score squared, gender and age.

Secondary: Percentage of participants who have either an ACT total score of >=20 or an increase from Baseline of >=3 in ACT total score at Week 12, 40 and 52.

End point title	Percentage of participants who have either an ACT total score of >=20 or an increase from Baseline of >=3 in ACT total score at Week 12, 40 and 52.

End point description:

The ACT is a validated self-administered questionnaire utilizing 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5). By answering all 5 questions, participants with asthma obtained an ACT score ranging between 5 and 25. Higher scores indicated better control of asthma. An ACT score of <=15 showed poorly controlled asthma; 16 to 19 showed partly controlled asthma and >=20 showed well controlled asthma. The total score was calculated as the sum of the scores from all 5 questions. ITT Population comprised of all participants who were randomized and received at least one prescription of study medication. The percentage of responders that is participants with an ACT total score >=20 or an increase from Baseline of >=3 has been presented. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Weeks 12, 40 and 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[4]	2114[5]		
Units: Percentage of participants				
Week 12, n=2032, 2009	62	75		
Week 40, n=1938, 1904	60	71		
Week 52, n=1922, 1896	58	70		

Notes:

[4] - ITT Population

[5] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Adjusted odds ratio comparing FF/VI with Usual Care for Week 12 has been presented. The correct

Number of Subjects Included in Analysis is 4041. Due to a system limitation, the value 4233 is incorrectly auto-populated.

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [6]
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	1.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.67
upper limit	2.2

Notes:

[6] - Logistic regression adjusted for randomized treatment, AMT at Baseline per randomization stratification, Baseline ACT total score, Baseline ACT total score squared, gender and age.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Adjusted odds ratio comparing FF/VI with Usual Care for Week 40 has been presented. The correct Number of Subjects Included in Analysis is 3842. Due to a system limitation, the value 4233 is incorrectly auto-populated.

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [7]
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.45
upper limit	1.91

Notes:

[7] - Logistic regression adjusted for randomized treatment, AMT at Baseline per randomization stratification, Baseline ACT total score, Baseline ACT total score squared, gender and age.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Adjusted odds ratio comparing FF/VI with Usual Care for Week 52 has been presented. The correct Number of Subjects Included in Analysis is 3818. Due to a system limitation, the value 4233 is incorrectly auto-populated.

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [8]
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	1.76

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.54
upper limit	2.02

Notes:

[8] - Logistic regression adjusted for randomized treatment, AMT at Baseline per randomization stratification, Baseline ACT total score, Baseline ACT total score squared, gender and age.

Secondary: Percentage of participants with asthma control (ACT total score >=20) at Weeks 12, 24, 40 and 52.

End point title	Percentage of participants with asthma control (ACT total score >=20) at Weeks 12, 24, 40 and 52.

End point description:

The ACT is a validated self-administered questionnaire utilizing 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5). By answering all 5 questions, participants with asthma obtained an ACT score ranging between 5 and 25. Higher scores indicated better control of asthma. An ACT score of <=15 showed poorly controlled asthma; 16 to 19 showed partly controlled asthma and >=20 showed well controlled asthma. The total score was calculated as the sum of the scores from all 5 questions. The percentage of participants with an ACT total score >=20 has been presented. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Weeks 12, 24, 40 and 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[9]	2114[10]		
Units: Percentage of participants				
Week 12, n=2032, 2009	46	61		
Week 24, n=1957, 1936	46	60		
Week 40, n=1938, 1904	45	58		
Week 52, n=1922, 1896	44	58		

Notes:

[9] - ITT Population

[10] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Adjusted odds ratio comparing FF/VI with Usual Care at Week 12 has been presented. The correct Number of Subjects Included in Analysis is 4041. Due to a system limitation, the value 4233 is incorrectly auto-populated.

Comparison groups	FF/VI v Usual Care

Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [11]
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.82
upper limit	2.4

Notes:

[11] - The analysis method was logistic regression adjusted for randomized treatment, AMT at Baseline per randomization stratification, Baseline ACT total score, gender and age.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Adjusted odds ratio comparing FF/VI with Usual Care at Week 24 has been presented. The correct Number of Subjects Included in Analysis is 3893. Due to a system limitation, the value 4233 is incorrectly auto-populated.

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [12]
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	2.25

Notes:

[12] - The analysis method was logistic regression adjusted for randomized treatment, AMT at Baseline per randomization stratification, Baseline ACT total score, gender and age.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Adjusted odds ratio comparing FF/VI with Usual Care at Week 40 has been presented. The correct Number of Subjects Included in Analysis is 3842. Due to a system limitation, the value 4233 is incorrectly auto-populated.

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [13]
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	1.79

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.56
upper limit	2.06

Notes:

[13] - The analysis method was logistic regression adjusted for randomized treatment, AMT at Baseline per randomization stratification, Baseline ACT total score, gender and age.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Adjusted odds ratio comparing FF/VI with Usual Care at Week 52 has been presented. The correct Number of Subjects Included in Analysis is 3818. Due to a system limitation, the value 4233 is incorrectly auto-populated.

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [14]
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.69
upper limit	2.24

Notes:

[14] - The analysis method was logistic regression adjusted for randomized treatment, AMT at Baseline per randomization stratification, Baseline ACT total score, gender and age.

Secondary: Percentage of participants who have an increase from Baseline of >=3 in ACT total score at Weeks 12, 24, 40 and 52.

End point title	Percentage of participants who have an increase from Baseline of >=3 in ACT total score at Weeks 12, 24, 40 and 52.

End point description:

The ACT is a validated self-administered questionnaire utilizing 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5). By answering all 5 questions, participants with asthma obtained an ACT score ranging between 5 and 25. Higher scores indicated better control of asthma. An ACT score of <=15 showed poorly controlled asthma; 16 to 19 showed partly controlled asthma and >=20 showed well controlled asthma. The total score was calculated as the sum of the scores from all 5 questions. The percentage of participants with an increase in ACT total score >=3 from Baseline has been presented. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Weeks 12, 24, 40 and 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[15]	2114[16]		
Units: Percentage of participants				
Week 12, n=2032, 2009	39	55		
Week 24, n=1957, 1936	40	54		
Week 40, n=1938, 1904	42	53		
Week 52, n=1922, 1896	37	50		

Notes:

[15] - ITT Population

[16] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Adjusted odds ratio comparing FF/VI with Usual Care at Week 12 has been presented. The correct Number of Subjects Included in Analysis is 4041. Due to a system limitation, the value 4233 is incorrectly auto-populated

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [17]
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	2.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.98
upper limit	2.62

Notes:

[17] - The analysis method was logistic regression adjusted for randomized treatment, AMT at Baseline per randomization stratification, Baseline ACT total score, gender and age.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Adjusted odds ratio comparing FF/VI with Usual Care at Week 24 has been presented. The correct Number of Subjects Included in Analysis is 3893. Due to a system limitation, the value 4233 is incorrectly auto-populated

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [18]
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	2.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.81
upper limit	2.41

Notes:

[18] - The analysis method was logistic regression adjusted for randomized treatment, AMT at Baseline per randomization stratification, Baseline ACT total score, gender and age.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Adjusted odds ratio comparing FF/VI with Usual Care at Week 40 has been presented. The correct Number of Subjects Included in Analysis is 3842. Due to a system limitation, the value 4233 is incorrectly auto-populated

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [19]
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.53
upper limit	2.02

Notes:

[19] - The analysis method was logistic regression adjusted for randomized treatment, AMT at Baseline per randomization stratification, Baseline ACT total score, gender and age.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Adjusted odds ratio comparing FF/VI with Usual Care at Week 52 has been presented. The correct Number of Subjects Included in Analysis is 3818. Due to a system limitation, the value 4233 is incorrectly auto-populated.

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [20]
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	1.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.66
upper limit	2.21

Notes:

[20] - The analysis method was logistic regression adjusted for randomized treatment, AMT at Baseline per randomization stratification, Baseline ACT total score, gender and age.

Secondary: Mean change from Baseline in ACT total score at Weeks 12, 24, 40 and

52.

End point title	Mean change from Baseline in ACT total score at Weeks 12, 24, 40 and 52.

End point description:

The ACT is a validated self-administered questionnaire utilizing 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5). By answering all 5 questions, participants with asthma obtained an ACT score ranging between 5 and 25. Higher scores indicated better control of asthma. An ACT score of <=15 showed poorly controlled asthma; 16 to 19 showed partly controlled asthma and >=20 showed well controlled asthma. The total score was calculated as the sum of the scores from all 5 questions. Baseline value is the value at Visit 2 (Day 0) assessment. Change from Baseline is the value at post-dose visit minus Baseline. The least square mean change in ACT scores has been presented. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Weeks 12, 24, 40 and 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[21]	2114[22]		
Units: Scores on ACT scale				
least squares mean (standard error)				
Week 12, n=2032, 2009	1.77 (± 0.087)	3.31 (± 0.087)		
Week 24, n=1957, 1936	1.70 (± 0.093)	3.20 (± 0.094)		
Week 40, n=1938, 1904	1.63 (± 0.096)	3.00 (± 0.097)		
Week 52, n=1922, 1896	1.49 (± 0.094)	2.99 (± 0.095)		

Notes:

[21] - ITT Population

[22] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Treatment difference of FF/VI versus Usual Care at Week 12 has been presented. The correct Number of Subjects Included in Analysis is 4041. Due to a system limitation, the value 4233 is incorrectly auto-populated.

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [23]
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Mean difference (net)
Point estimate	1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	1.77

Notes:

[23] - MMRM adjusted for randomized treatment, AMT at Baseline per randomization stratification, Baseline ACT total score, randomized treatment-by-Baseline ACT total score interaction, gender, age, visit and randomized treatment by visit interaction.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Treatment difference of FF/VI versus Usual Care at Week 24 has been presented. The correct Number of Subjects Included in Analysis is 3893. Due to a system limitation, the value 4233 is incorrectly auto-populated.

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [24]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.25
upper limit	1.76

Notes:

[24] - MMRM adjusted for randomized treatment, AMT at Baseline per randomization stratification, Baseline ACT total score, randomized treatment-by-Baseline ACT total score interaction, gender, age, visit and randomized treatment by visit interaction.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Treatment difference of FF/VI versus Usual Care at Week 40 has been presented. The correct Number of Subjects Included in Analysis is 3842. Due to a system limitation, the value 4233 is incorrectly auto-populated.

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [25]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	1.63

Notes:

[25] - MMRM adjusted for randomized treatment, AMT at Baseline per randomization stratification, Baseline ACT total score, randomized treatment-by-Baseline ACT total score interaction, gender, age, visit and randomized treatment by visit interaction.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Treatment difference of FF/VI versus Usual Care at Week 52 has been presented. The correct Number of Subjects Included in Analysis is 3818. Due to a system limitation, the value 4233 is incorrectly auto-populated.

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [26]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.24
upper limit	1.76

Notes:

[26] - MMRM adjusted for randomized treatment, AMT at Baseline per randomization stratification, Baseline ACT total score, randomized treatment-by-Baseline ACT total score interaction, gender, age, visit and randomized treatment by visit interaction.

Secondary: Percentage of participants in each ACT total score category (>=20, 16 to 19, <=15) at Weeks 12, 24, 40 and 52.

End point title	Percentage of participants in each ACT total score category (>=20, 16 to 19, <=15) at Weeks 12, 24, 40 and 52.

End point description:

The ACT is a validated self-administered questionnaire utilizing 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5). By answering all 5 questions, participants with asthma obtained an ACT score ranging between 5 and 25. Higher scores indicated better control of asthma. An ACT score of <=15 showed poorly controlled asthma; 16 to 19 showed partly controlled asthma; and >=20 showed well controlled asthma. The total score was calculated as the sum of the scores from all 5 questions. The percentage of participants under each ACT total score category that is >=20, 16 to 19 and <=15 has been presented. Only those participants with data available at the specified data points were analyzed (represented by n=X in category title).

End point type	Secondary

End point timeframe:

Weeks 12, 24, 40 and 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[27]	2114[28]		
Units: Percentage of participants				
>=20, Week 12, n=2032, 2009	46	61		
16 to 19, Week 12, n=2032, 2009	26	20		
<=15, Week 12, n=2032, 2009	28	18		
>=20, Week 24, n=1957, 1936	46	60		
16 to 19, Week 24, n=1957, 1936	25	20		
<=15, Week 24, n=1957, 1936	29	20		
>=20, Week 40, n=1938, 1904	45	58		
16 to 19, Week 40, n=1938, 1904	24	21		
<=15, Week 40, n=1938, 1904	31	21		
>=20, Week 52, n=1922, 1896	44	58		
16 to 19, Week 52, n=1922, 1896	26	20		
<=15, Week 52, n=1922, 1896	30	21		

Notes:

[27] - ITT Population

[28] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Annual rate of asthma-related secondary care contacts

End point title	Annual rate of asthma-related secondary care contacts

End point description:

All contacts are defined as any encounter the participant may have with a doctor, nurse or other healthcare professionals working as part of the National Health Service (NHS) as identified in the electronic medical records (EMR). Contacts were defined to be asthma-related if the most prominent signs and symptoms that the participant presented were a direct result of the participant's asthma. An asthma-related secondary care contact is defined as an inpatient admission or a specialist outpatient visit or an accident and emergency (A&E) contact. A participant with an A&E contact and subsequent inpatient admission was considered to have had two healthcare contacts. The least square mean annual rate of all asthma-related secondary care contacts along with 95% confidence interval has been presented.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[29]	2114[30]		
Units: Contacts per participant per year				
least squares mean (confidence interval 95%)				
Contacts per participant per year	0.30 (0.25 to 0.34)	0.30 (0.26 to 0.36)		

Notes:

[29] - ITT Population

[30] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Ratio comparing FF/VI with Usual Care has been presented.

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.786 [31]
Method	Generalized Linear Model (GLM)
Parameter estimate	Ratio
Point estimate	1.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.28

Notes:

[31] - GLM assuming negative binomial distribution (NBD) adjusted for randomized treatment, asthma maintenance therapy at Baseline per randomization stratification, ACT total score at Baseline per randomization stratification, gender and age

Secondary: Annual rate of asthma-related primary care contacts

End point title	Annual rate of asthma-related primary care contacts

End point description:

All contacts are defined as any encounter the participant may have with a doctor, nurse or other healthcare professionals working as part of the NHS as identified in the EMR. Contacts were defined to be asthma-related if the most prominent signs and symptoms that the participant presented were a direct result of the participant's asthma. Asthma-related primary care contacts is defined as the sum of primary care contacts on a given calendar date with either a nurse, General Practitioner or other healthcare professional that can be considered as asthma-related as per Read codes. The least square mean annual rate of all asthma-related primary care contacts along with 95% confidence interval has been presented.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[32]	2114[33]		
Units: Contacts per participant per year				
least squares mean (confidence interval 95%)				
Contacts per participant per year	1.42 (1.36 to 1.47)	1.45 (1.39 to 1.51)		

Notes:

[32] - ITT Population

[33] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Ratio comparing FF/VI with Usual Care has been presented.

Comparison groups	Usual Care v FF/VI
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.461 [34]
Method	Generalized Linear Model (GLM)
Parameter estimate	Ratio
Point estimate	1.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.08

Notes:

[34] - GLM assuming NBD adjusted for randomized treatment, asthma maintenance therapy at Baseline per randomization stratification, ACT total score at Baseline per randomization stratification, gender and age

Secondary: Number of participants with time to first asthma-related primary care contact

End point title	Number of participants with time to first asthma-related primary care contact

End point description:

Asthma-related primary care contact is defined as the sum of primary care contacts on a given calendar date with either a nurse, General Practitioner or other healthcare professional that can be considered as asthma-related as per Read codes. Time to first asthma-related primary care contact was measured from the date of randomization (that is, study treatment start date) to the date of first asthma-related primary care contact, or study treatment stop date for participants who completed the study without any asthma-related primary care contacts (censored). Analyses of time to first asthma-related primary care contact was censored at Day 364. The number of participants at risk at Weeks 0, 13, 26, 39 and 52 has been presented. Kaplan Meier method of analysis was used. Study related primary care contacts (that is, contacts scheduled solely due to the participant taking part in clinical trial) were excluded from this analysis.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[35]	2114[36]		
Units: Participants				
Week 0	2119	2114		
Week 13	1621	1599		
Week 26	1208	1214		
Week 39	907	932		
Week 52	479	488		

Notes:

[35] - ITT Population

[36] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Annual rate of all on-treatment secondary care contacts

End point title	Annual rate of all on-treatment secondary care contacts

End point description:

A secondary care contact is defined as an inpatient admission or a specialist outpatient visit or an A&E contact. A participant with an A&E contact and subsequent inpatient admission was considered to have had two healthcare contacts. The inpatient admissions recorded at two hospitals on the same day, were counted as a single (inpatient admission) secondary care contact. In the situation where inpatient admission periods overlapped (example, a new inpatient admission was recorded within the dates of an

existing inpatient admission period), it was counted as a single (inpatient admission) healthcare contact with start date defined as the earliest inpatient admission date for either of the overlapping admissions and end date defined as the latest discharge date for either of the overlapping admissions. The least square mean annual rate of all on-treatment secondary care contacts along with 95% confidence interval has been summarized.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[37]	2114[38]		
Units: Contacts per participant per year				
least squares mean (confidence interval 95%)				
Contacts per participant per year	5.23 (4.91 to 5.57)	5.17 (4.86 to 5.51)		

Notes:

[37] - ITT Population

[38] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Ratio comparing FF/VI with Usual Care has been presented.

Comparison groups	Usual Care v FF/VI
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.822 [39]
Method	Generalized Linear Model (GLM)
Parameter estimate	Ratio
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.08

Notes:

[39] - GLM assuming NBD adjusted for randomized treatment, asthma maintenance therapy at Baseline per randomization stratification, ACT total score at Baseline per randomization stratification, gender and age

Secondary: Annual rate of all on-treatment primary care contacts

End point title	Annual rate of all on-treatment primary care contacts

End point description:

All contacts are defined as any encounter the participant may have with a doctor, nurse or other healthcare professionals working as part of the NHS as identified in the EMR. Total primary care contacts is defined as the sum of primary care contacts on a given calendar date with either a nurse, General Practitioner or other healthcare professional. The least square mean annual rate of all on-treatment primary care contacts along with 95% confidence interval has been presented.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[40]	2114[41]		
Units: Contacts per participant per year				
least squares mean (confidence interval 95%)				
Contacts per participant per year	10.61 (10.26 to 10.98)	11.64 (11.25 to 12.04)		

Notes:

[40] - ITT Population

[41] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Ratio comparing FF/VI with Usual Care has been presented.

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [42]
Method	Generalized Linear Model (GLM)
Parameter estimate	Ratio
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	1.15

Notes:

[42] - GLM assuming NBD adjusted for randomized treatment, asthma maintenance therapy at Baseline per randomization stratification, ACT total score at Baseline per randomization stratification, gender and age

Secondary: Number of participants with time to first primary care contact

End point title	Number of participants with time to first primary care contact

End point description:

Time to first primary care contact is measured from the date of randomization (that is, study treatment start date) to the date of first primary care contact, or study treatment stop date for participants who completed the study without any primary care contacts (censored). Analyses of time to first primary care contact will be censored at Day 364. The number of participants at risk at Weeks 0, 13, 26, 39 and 52 has been presented. Kaplan Meier method of analysis was used. Study related primary care contacts (that is, contacts scheduled solely due to the participant taking part in clinical trial) were excluded from this analysis.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[43]	2114[44]		
Units: Participants				
Week 0	2119	2114		
Week 13	513	483		
Week 26	245	242		
Week 39	160	178		
Week 52	79	96		

Notes:

[43] - ITT Population

[44] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean annual rate of severe asthma exacerbations

End point title	Mean annual rate of severe asthma exacerbations

End point description:

A severe asthma exacerbation is defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) or antibiotics, and inpatient hospitalization, or emergency department visit due to asthma that required systemic corticosteroids or antibiotics. Least square mean for annual rate of severe asthma exacerbation along with 95% confidence interval has been presented.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[45]	2114[46]		
Units: Exacerbations per participant per year				
least squares mean (confidence interval 95%)				
Exacerbations per participant per year	0.41 (0.38 to 0.44)	0.40 (0.37 to 0.43)		

Notes:

[45] - ITT Population

[46] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Ratio comparing FF/VI with Usual Care has been presented.

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.697 [47]
Method	Generalized Linear Model (GLM)
Parameter estimate	Ratio
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.09

Notes:

[47] - GLM assuming NBD adjusted for randomized treatment; asthma maintenance therapy and ACT total score at Baseline per randomization stratification; number of severe asthma exacerbations in previous year prior to randomization categorized; gender & age

Secondary: Time to first severe asthma exacerbation.

End point title	Time to first severe asthma exacerbation.

End point description:

A severe asthma exacerbation is defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) or antibiotics, and inpatient hospitalization, or emergency department visit due to asthma that required systemic corticosteroids or antibiotics. The date of a severe asthma exacerbation was defined as the exacerbation onset date. Participants who completed the study without a severe asthma exacerbation were censored. Time to first severe asthma exacerbation was measured from the date of randomization (that is, study treatment start date) to the onset date of first severe asthma exacerbation, or study treatment stop date for participants who completed the study without any severe asthma exacerbations (censored). Analyses of time to first severe asthma exacerbation was censored at Day 364. The number of participants with severe asthma exacerbation has been presented.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[48]	2114[49]		
Units: Participants				
Participants	654	634		

Notes:

[48] - ITT Population

[49] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

A hazard ratio <1 indicated a lower risk with FF/VI compared with Usual Care

Comparison groups	FF/VI v Usual Care

Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.504 [50]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.07

Notes:

[50] - Cox proportional hazards model with randomized treatment, asthma maintenance therapy at Baseline per randomization stratification, ACT total score at Baseline per randomization stratification, gender and age as covariates

Secondary: Mean number of salbutamol inhalers prescribed for each participant over the 12 month treatment period.

End point title	Mean number of salbutamol inhalers prescribed for each participant over the 12 month treatment period.

End point description:

Salbutamol was prescribed as a rescue medication to be used as and when necessary throughout the study. The number of salbutamol inhalers used by each participant during the study was calculated based on the total number of inhalers (adjusted to an equivalence of 200 metered actuations) prescribed. Number of salbutamol inhalers prescribed during the study was derived taking the participants time on study medication into account so it corresponds to 12 months on treatment The least square mean number of salbutamol inhalers prescribed per participant during the study has been presented. Only participants exposed to study drug for at least 30 days were included in the analysis.

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2116[51]	2108[52]		
Units: Mean number of inhalers per participant				
least squares mean (standard error)				
Mean number of inhalers per participant	8.0 (± 0.11)	7.2 (± 0.11)		

Notes:

[51] - ITT Population

[52] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Difference of FF/VI versus Usual Care has been presented.

Comparison groups	FF/VI v Usual Care

Number of subjects included in analysis	4224
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [53]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.5

Notes:

[53] - ANCOVA adjusted for randomized treatment, asthma maintenance therapy at Baseline per randomization stratification, ACT total score at Baseline per randomization stratification, gender,age & number of salbutamol inhalers in year prior to randomization

Secondary: Time to modification of initial therapy

End point title	Time to modification of initial therapy

End point description:

Initial therapy is defined as the treatment that the participant was prescribed at randomization. Modification of initial therapy included any change in brand, dose or frequency of inhaler, that is, stepping up in class, dose or frequency, stepping down in class, dose or frequency, switching to another brand of inhaler, switching treatment arm or withdrawal from the study. Time to modification of initial therapy was measured from the date of randomization (that is, exposure start date) to the date of modification of initial therapy or date of treatment termination for participants who completed the study without modifiying initial therapy (censored). The number of participants with modification of initial therapy has been presented.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[54]	2114[55]		
Units: Participants				
Participants	488	563		

Notes:

[54] - ITT Population

[55] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Hazard ratio for FF/VI versus Usual Care has been presented

Comparison groups	Usual Care v FF/VI

Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [56]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	1.38

Notes:

[56] - Cox proportional hazards model with randomized treatment, asthma maintenance therapy at Baseline per randomization stratification, ACT total score at Baseline per randomization stratification, gender and age as covariates

Secondary: Percentage of participants who have an increase from Baseline of >=0.5 in Standardized Asthma Quality of Life Questionnaire [AQLQ(S)] total score at Week 52.

End point title	Percentage of participants who have an increase from Baseline of >=0.5 in Standardized Asthma Quality of Life Questionnaire [AQLQ(S)] total score at Week 52.

End point description:

The AQLQ(S) contained 32 items under the following four domains: activity limitation (11 items), symptoms (12 items), emotional function (5 items) and environmental stimuli (4 items). The response format consisted of a seven-point scale where a value of 1 indicated "total impairment" and a value of 7 indicated "no impairment". The total AQLQ(S) score is the mean of all 32 items in the questionnaire and each individual domain score was calculated as the mean of the items within that domain. Hence, the total and domain scores were each defined on a range from 1 to 7 with higher scores indicating a higher quality of life. Baseline value is the value at Day 0 assessment. Change from Baseline is post dose visit value minus Baseline. The percentage of responders that is, participants with an increase from Baseline of >=0.5 in AQLQ(S) total score has been presented.

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Week 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1922[57]	1896[58]		
Units: Percentage of participants				
Percentage of participants	43	55		

Notes:

[57] - ITT Population

[58] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Adjusted odds ratio of FF/VI with Usual Care has been presented.

Comparison groups	Usual Care v FF/VI

Number of subjects included in analysis	3818
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [59]
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.55
upper limit	2.06

Notes:

[59] - Logistic regression adjusted for randomized treatment, asthma maintenance therapy at Baseline per randomization stratification, ACT total score at Baseline per randomization stratification, gender, age and Baseline score.

Secondary: Percentage of participants who have an increase from Baseline of >=0.5 in AQLQ(S) environmental stimuli domain score at Week 52.

End point title	Percentage of participants who have an increase from Baseline of >=0.5 in AQLQ(S) environmental stimuli domain score at Week 52.

End point description:

The AQLQ(S) contained 32 items under the following four domains: activity limitation (11 items), symptoms (12 items), emotional function (5 items) and environmental stimuli (4 items). The response format consisted of a seven-point scale where a value of 1 indicated "total impairment" and a value of 7 indicated "no impairment". The total environmental stimuli domain score was calculated as the mean of the items within the environmental stimuli domain. Hence, the environmental stimuli domain scores were each defined on a range from 1 to 7 with higher scores indicating a higher quality of life. Baseline value is the value at Day 0 assessment. Change from Baseline is post dose visit value minus Baseline. The percentage of responders that is, participants with an increase from Baseline of >=0.5 in AQLQ(S) environmental stimuli domain score has been presented.

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Week 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1922[60]	1896[61]		
Units: Percentage of participants				
Percentage of participants	50	59		

Notes:

[60] - ITT Population

[61] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Adjusted odds ratio of FF/VI versus Usual Care has been presented.

Comparison groups	Usual Care v FF/VI

Number of subjects included in analysis	3818
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [62]
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.31
upper limit	1.73

Notes:

[62] - Logistic regression adjusted for randomized treatment, asthma maintenance therapy at Baseline per randomization stratification, ACT total score at Baseline per randomization stratification, gender, age and Baseline score.

Secondary: Percentage of participants with serious adverse event (SAE) of pneumonia

End point title	Percentage of participants with serious adverse event (SAE) of pneumonia

End point description:

A serious advent event (SAE) of pneumonia was defined as any SAE in the adverse event special interest (AESI) group of "pneumonia". The incidence of the SAEs of pneumonia for each treatment group is defined as the percentage of participants in that group who have experienced at least one SAE of pneumonia from start date of study treatment to the stop date of exposure + 28 days or date of study discontinuation, whichever is earliest. The percentage of participants with SAE of pneumonia has been presented.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[63]	2114[64]		
Units: Percentage of participants				
Percentage of participants	1	1		

Notes:

[63] - ITT Population

[64] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Incidence ratio was calculated as percentage of participants who had at least one SAE of pneumonia in the FF/VI group divided by the percentage of participants who had at least one SAE of pneumonia in the Usual Care group.

Comparison groups	Usual Care v FF/VI

Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	non-inferiority[65]
Parameter estimate	Incidence ratio
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	2.7

Notes:

[65] - Non-inferiority is demonstrated if the upper limit of the two-sided 95% confidence interval for the incidence ratio is less than 2.

Secondary: Time to first SAE of pneumonia

End point title	Time to first SAE of pneumonia

End point description:

An SAE of pneumonia was defined as any SAE in the AESI group of "pneumonia". The date of an event for an SAE of pneumonia was the AE onset date. Participants who do not have an SAE of pneumonia during the first 364 days of the treatment period (start date of exposure to min [end date of exposure + 28 days, date of study discontinuation, start date of exposure + 363]) were censored. Time to first SAE of pneumonia was measured from the date of randomization (that is, study treatment start date) to the onset date of first SAE of pneumonia. The number of participants with first on-treatment SAE of pneumonia has been presented.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[66]	2114[67]		
Units: Participants				
Participants	16	23		

Notes:

[66] - ITT Population

[67] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Hazard ratio for FF/VI versus Usual Care has been presented.

Comparison groups	FF/VI v Usual Care
Number of subjects included in analysis	4233
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.255 [68]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.45

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	2.74

Notes:

[68] - Cox proportional hazards model with randomized treatment, asthma maintenance therapy at Baseline per randomization stratification, ACT total score at Baseline per randomization stratification, gender and age as covariates.

Secondary: Number of participants with fatal SAEs of pneumonia

End point title	Number of participants with fatal SAEs of pneumonia

End point description:

All SAEs included in the AESI group of "pneumonia" were considered as an SAE of pneumonia. Fatal SAEs of pneumonia are SAEs that led to death of participants. The number of participants with fatal SAEs of pneumonia has been presented.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[69]	2114[70]		
Units: Participants				
Participants	3	1		

Notes:

[69] - ITT Population

[70] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with SAEs

End point title	Number of participants with SAEs

End point description:

An SAE is any untoward medical occurrence that, at any dose: results in death; is life-threatening; requires hospitalization or prolongation of existing hospitalization; results in disability/incapacity; is a congenital anomaly/birth defect; important medical events which may require medical or surgical intervention for example, invasive or malignant cancers; all events of possible drug-induced liver injury with hyperbilirubinemia. The number of participants with on-treatment SAEs has been summarized.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[71]	2114[72]		
Units: Participants				
Participants	284	284		

Notes:

[71] - ITT Population

[72] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse drug reactions (ADRs)

End point title	Number of participants with adverse drug reactions (ADRs)

End point description:

An ADR is any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a medicinal product, for which there is a reasonable possibility that the untoward occurrence is causally related to the medicinal product. ADRs are a subset of AEs for a given medicinal product.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Usual Care	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2119[73]	2114[74]		
Units: Participants				
Participants	109	326		

Notes:

[73] - ITT Population

[74] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse drug reactions (ADRs) were collected from the start of study treatment and until the follow up contact (Up to Week 52).

Adverse event reporting additional description:

ITT Population comprised of all randomized participants who received at least one prescription of study medication

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	FF/VI

Reporting group description:

Participants initiated with an appropriate dose of inhaled FF/VI (100 mcg/25 mcg or 200 mcg/25 mcg per actuation) once daily via Novel Dry Powder Inhaler.

Reporting group title	Usual Care

Reporting group description:

Participants continued their usual asthma maintenance therapy that is, inhaled corticosteroid without a long acting beta2-agonist or inhaled corticosteroid with long acting beta2-agonist combination (either as a fixed dose combination or an inhaled corticosteroid/long acting beta2-agonist provided in two separate inhalers).

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no non-serious adverse events above 3% threshold.

Serious adverse events	FF/VI	Usual Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	284 / 2114 (13.43%)	284 / 2119 (13.40%)	
number of deaths (all causes)	15	27	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acinic cell carcinoma of salivary gland			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoma benign			

subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma recurrent			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	4 / 2114 (0.19%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain cancer metastatic			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	2 / 2114 (0.09%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer metastatic			

subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lymphoma			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chondrosarcoma			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer metastatic			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal carcinoma			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stromal tumour			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			

subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Invasive ductal breast carcinoma				
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Lentigo maligna				
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Lung cancer metastatic				
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Lung neoplasm malignant				
subjects affected / exposed	2 / 2114 (0.09%)	0 / 2119 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Malignant melanoma				
subjects affected / exposed	2 / 2114 (0.09%)	0 / 2119 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Malignant melanoma in situ				
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Metastases to central nervous system				
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Metastases to liver				

subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to lung			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastatic renal cell carcinoma			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Penile squamous cell carcinoma			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phyllodes tumour			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Precursor B-lymphoblastic lymphoma			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			

subjects affected / exposed	3 / 2114 (0.14%)	4 / 2119 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	2 / 2114 (0.09%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer recurrent			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	2 / 2114 (0.09%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric cancer			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Angiodysplasia			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			

subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Circulatory collapse			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	5 / 2114 (0.24%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Essential hypertension			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 2114 (0.00%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypotension			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Raynaud's phenomenon			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava occlusion			

subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Temporal arteritis			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous			
subjects affected / exposed	2 / 2114 (0.09%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unintended pregnancy			
subjects affected / exposed	3 / 2114 (0.14%)	3 / 2119 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unwanted pregnancy			
subjects affected / exposed	2 / 2114 (0.09%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	1 / 2114 (0.05%)	4 / 2119 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 2114 (0.05%)	3 / 2119 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical failure			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 2114 (0.00%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycotic allergy			

subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema genital			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst torsion			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	24 / 2114 (1.14%)	30 / 2119 (1.42%)	
occurrences causally related to treatment / all	2 / 30	0 / 34	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atelectasis			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 2114 (0.05%)	5 / 2119 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Emphysema			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 2114 (0.05%)	3 / 2119 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pharyngeal inflammation			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pickwickian syndrome			

subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	2 / 2114 (0.09%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary eosinophilia			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 2114 (0.00%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reflux laryngitis			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	2 / 2114 (0.09%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	2 / 2114 (0.09%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcoholism			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Antisocial personality disorder			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorder			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusion			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed mood			

subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	4 / 2114 (0.19%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression suicidal			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eating disorder			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomania			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Persistent depressive disorder			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic stress disorder			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	2 / 2114 (0.09%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizoaffective disorder			

subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	3 / 2114 (0.14%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 2114 (0.05%)	3 / 2119 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	3 / 2114 (0.14%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 2114 (0.05%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Hepatic failure			

subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic function abnormal			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood potassium decreased			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio abnormal			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	11 / 2114 (0.52%)	7 / 2119 (0.33%)	
occurrences causally related to treatment / all	0 / 11	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal function test abnormal			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Accidental overdose			
subjects affected / exposed	2 / 2114 (0.09%)	3 / 2119 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	8 / 2114 (0.38%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns third degree			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted fracture			
subjects affected / exposed	0 / 2114 (0.00%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal abrasion			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			

subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	6 / 2114 (0.28%)	5 / 2119 (0.24%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	2 / 2114 (0.09%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 2114 (0.05%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	3 / 2114 (0.14%)	3 / 2119 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			

subjects affected / exposed	1 / 2114 (0.05%)	4 / 2119 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 2114 (0.05%)	3 / 2119 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	2 / 2114 (0.09%)	5 / 2119 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	5 / 2114 (0.24%)	5 / 2119 (0.24%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intentional product misuse			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 2114 (0.00%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb crushing injury			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			

subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	2 / 2114 (0.09%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 2114 (0.05%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	2 / 2114 (0.09%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	4 / 2114 (0.19%)	9 / 2119 (0.42%)	
occurrences causally related to treatment / all	0 / 4	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	2 / 2114 (0.09%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fractured base			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	2 / 2114 (0.09%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	2 / 2114 (0.09%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			

subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	2 / 2114 (0.09%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Ulna fracture			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound secretion			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	5 / 2114 (0.24%)	3 / 2119 (0.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Branchial cyst			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocardial fibroelastosis			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute coronary syndrome			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	4 / 2114 (0.19%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	5 / 2114 (0.24%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 2114 (0.00%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	2 / 2114 (0.09%)	3 / 2119 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Atrial fibrillation			
subjects affected / exposed	7 / 2114 (0.33%)	14 / 2119 (0.66%)	
occurrences causally related to treatment / all	0 / 7	2 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block first degree			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	2 / 2114 (0.09%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 2114 (0.05%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery thrombosis			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diastolic dysfunction			
subjects affected / exposed	0 / 2114 (0.00%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive heart disease			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Left ventricular dysfunction			

subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	3 / 2114 (0.14%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular hypertrophy			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	2 / 2114 (0.09%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	5 / 2114 (0.24%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocarditis			
subjects affected / exposed	2 / 2114 (0.09%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			

subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tricuspid valve incompetence			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anosmia			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	5 / 2114 (0.24%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			

subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	2 / 2114 (0.09%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 2114 (0.00%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug withdrawal convulsions			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 2114 (0.05%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 2114 (0.09%)	4 / 2119 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	3 / 2114 (0.14%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	5 / 2114 (0.24%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis relapse			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	0 / 2114 (0.00%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			

subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	5 / 2114 (0.24%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory disturbance			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural hygroma			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 2114 (0.14%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	2 / 2114 (0.09%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIth nerve paralysis			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular dementia			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral artery dissection			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 2114 (0.14%)	3 / 2119 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of chronic disease			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy mediastinal			

subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tinnitus			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Angle closure glaucoma			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	6 / 2114 (0.28%)	4 / 2119 (0.19%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis allergic			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	4 / 2114 (0.19%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ocular hyperaemia			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			

subjects affected / exposed	5 / 2114 (0.24%)	4 / 2119 (0.19%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 2114 (0.05%)	5 / 2119 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 2114 (0.19%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	2 / 2114 (0.09%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			

subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 2114 (0.05%)	5 / 2119 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 2114 (0.14%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 2114 (0.00%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated umbilical hernia			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	3 / 2114 (0.14%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia, obstructive			

subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 2114 (0.09%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema			
subjects affected / exposed	1 / 2114 (0.05%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	3 / 2114 (0.14%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			

subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 2114 (0.28%)	9 / 2119 (0.42%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	3 / 2114 (0.14%)	5 / 2119 (0.24%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 2114 (0.05%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	2 / 2114 (0.09%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loin pain haematuria syndrome			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	2 / 2114 (0.09%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	3 / 2114 (0.14%)	3 / 2119 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 2114 (0.09%)	4 / 2119 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary hypogonadism			

subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 2114 (0.14%)	8 / 2119 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibromyalgia			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 2114 (0.00%)	3 / 2119 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metatarsalgia			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			

subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 2114 (0.00%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteopenia			
subjects affected / exposed	2 / 2114 (0.09%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	5 / 2114 (0.24%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palindromic rheumatism			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			

subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 2114 (0.05%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	7 / 2114 (0.33%)	11 / 2119 (0.52%)	
occurrences causally related to treatment / all	0 / 8	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic hepatitis C			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	3 / 2114 (0.14%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			

subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 2114 (0.09%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital herpes			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital infection			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected dermal cyst			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	0 / 2114 (0.00%)	3 / 2119 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	2 / 2114 (0.09%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			

subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	5 / 2114 (0.24%)	7 / 2119 (0.33%)	
occurrences causally related to treatment / all	1 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenic sepsis			
subjects affected / exposed	2 / 2114 (0.09%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ophthalmic herpes simplex			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic inflammatory disease			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			

subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	1 / 2114 (0.05%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	23 / 2114 (1.09%)	13 / 2119 (0.61%)	
occurrences causally related to treatment / all	6 / 24	0 / 14	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural sepsis			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	2 / 2114 (0.09%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			

subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis			
subjects affected / exposed	1 / 2114 (0.05%)	3 / 2119 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 2114 (0.14%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 2114 (0.14%)	7 / 2119 (0.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sialoadenitis			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	12 / 2114 (0.57%)	4 / 2119 (0.19%)	
occurrences causally related to treatment / all	0 / 13	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 2114 (0.05%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 2114 (0.05%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral labyrinthitis			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval abscess			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 2114 (0.05%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 2114 (0.05%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			

subjects affected / exposed	3 / 2114 (0.14%)	3 / 2119 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 2114 (0.05%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glucose tolerance impaired			
subjects affected / exposed	0 / 2114 (0.00%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 2114 (0.00%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	4 / 2114 (0.19%)	1 / 2119 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 2114 (0.00%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 2114 (0.00%)	2 / 2119 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 2114 (0.05%)	0 / 2119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	12 / 2114 (0.57%)	13 / 2119 (0.61%)	
occurrences causally related to treatment / all	2 / 12	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	FF/VI	Usual Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 2114 (0.00%)	0 / 2119 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2013	Amendment No. 01: Protocol summary; headings formatted; Secondary objective added; The secondary objective is to compare the incidence serious adverse events of pneumonia during the study of FF 100mcg/VI 25mcg or FF 200mcg/VI 25mcg with usual asthma maintenance therapy over twelve months; Throughout; Salford, Greater Manchester changed to Salford and South Manchester; Sample size changed; from 4820 to 4036; Contacts defined to include; other healthcare professionals; New endpoint deleted from other efficacy endpoints; Safety endpoint added; Incidence of serious adverse events of pneumonia during the study; Rationale; text changed to include collection of data from pharmacy EMR; Throughout; with National Health Service (NHS) contact changed to with or without NHS contact; Inclusion criteria 1 amended to include; Subjects must be able to complete the electronic subject questionnaires or allow a proxy to do so on their behalf; Additional exclusion criteria added; 8. Subjects whose current medications include RELVAR® ELLIPTA® are not eligible to enter the study; Withdrawal criteria; updated to reflect ECG no longer performed at visit 2; Treatment assignment: text added; Subjects with hepatic impairment should be given a maximum dose of FF/VI 100mcg/25mcg; Conmeds and other medications amended to include all medications and trade name not collected; Treatment changes; updated to reflect if the patient is changed to RELVAR® ELLIPTA® they should be withdrawn; Table 4 time and events; updated to remove ECG requirement at V2 and add in Smoking status questions at V2, V6 and early withdrawal, and add in genetic sampling at V6; details of crude patient history to be collected added; Liver stopping and follow up criteria clarified; Section about genetics added; Hypotheses updated to reflect change in endpoint; Sample size calculations and justification updated; Details around data collection and analysis of pneumonia SAEs; Additional references added; Genetics added
11 March 2014	Amendment No. 02: - Updated author list - Secondary Objectives amended to clarify that all hospitals will use 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD 10) codes - Data Analysis and Statistical considerations updated to reflect request from Committee for Medicinal Products for Human Use (CHMP) re Pneumonias - Safety Endpoints updated to reflect request from CHMP re Pneumonia

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported