Clinical trial results:
A 24 week treatment, multicenter, randomized, double blinded, double dummy, parallel-group, clinical trial evaluating the efficacy and safety of aclidinium bromide 400 g/formoterol fumarate 12 g fixed-dose combination BID compared with each monotherapy (aclidinium bromide 400 g BID and formoterol fumarate 12 g BID) and tiotropium 18 g QD when administered to subjects with stable chronic obstructive pulmonary disease

Summary

EudraCT number	2015-005444-33
Trial protocol	GB HU CZ BG ES PL
Global end of trial date	08 June 2017

Results information

Result version number	v1 (current)
This version publication date	06 June 2018
First version publication date	06 June 2018

Trial information

Trial identification

Sponsor protocol code	D6571C00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02796677
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Södertälje, Södertälje, Sweden, 151 85
Public contact	Information Centre, AstraZeneca AB, Information Centre, AstraZeneca AB, +1 800 2369933, information.centre@astrazeneca.com
Scientific contact	Global Clinical Leader, AstraZeneca AB, +46 766 346712, clinicaltrialtransparency@astrazeneca.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 June 2017
Global end of trial reached?	Yes
Global end of trial date	08 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

For United States (US): To assess the bronchodilatory effect of Aclidinium bromide/Formoterol fumarate (AB/FF) 400/12 µg compared to each individual component when administered twice daily (BID) via inhalation to chronic obstructive pulmonary disease (COPD) subjects. Ffor Market Access: To assess the non-inferior bronchodilation of AB 400 µg BID as compared to Tiotropium (TIO) 18 µg once daily (QD) in COPD subjects.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation /Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics. Each subject was given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Each subject was notified that they were free to discontinue from the study at any time and were given the opportunity to ask questions and allowed time to consider the information provided. Each subject provided signed and dated ICF before conducting any procedure specifically for the study. A copy of the signed informed consent form (ICF) was given to the subject. Any incentives for subjects who participated in the study as well as any provisions for subjects harmed as a consequence of study participation were described in the ICF that was approved by an Ethics Committe.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 July 2016
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 States: 699
Country: Number of subjects enrolled	Germany: 349
Country: Number of subjects enrolled	Poland: 124
Country: Number of subjects enrolled	Hungary: 116
Country: Number of subjects enrolled	Bulgaria: 106
Country: Number of subjects enrolled	Ukraine: 110
Country: Number of subjects enrolled	United Kingdom: 34
Country: Number of subjects enrolled	Czech Republic: 32
Country: Number of subjects enrolled	Spain: 7

Country: Number of subjects enrolled	Israel: 17
Worldwide total number of subjects	1594
EEA total number of subjects	768

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)	795
From 65 to 84 years	793
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Study was conducted on subjects with stable COPD, in 11 countries: United States (US), Germany, Poland, Hungary, Bulgaria, Ukraine, United Kingdom (UK), Czech Republic, Spain, Israel & Russia (was not finally started).

Pre-assignment

Screening details:

Eligible subjects signed ICF; entered screening period (Run-in; 14 ± 3 days), inclusion/exclusion criteria were checked by medical & COPD history, physical examination, blood pressure, electrocardiogram, laboratory tests, concomitant drugs & COPD Assessment Test [CAT] & post-bronchodilator forced expiratory volume in 1 second [FEV1]

Period 1

Period 1 title	Period 1: Overall Study
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Aclidinium bromide (AB)/Formoterol fumarate (FF) 400/12 µg

Arm description:

Randomized subjects received AB 400 µg/FF 12 µg oral inhalation powder twice daily (BID) via dry powder inhaler (DPI).

Arm type	Experimental
Investigational medicinal product name	Aclidinium bromide/Formoterol fumarate
Investigational medicinal product code	
Other name	Pressair®/Genuair® Dry Powder Inhaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

AB/FF 400/12 µg inhalation powder twice daily (morning and evening) via DPI for 24 weeks

Arm title	AB 400 µg

Arm description:

Randomized subjects received AB 400 µg oral inhalation powder BID via DPI.

Arm type	Experimental
Investigational medicinal product name	Aclidinium bromide
Investigational medicinal product code	
Other name	Pressair®/Genuair® Dry Powder Inhaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

AB 400 µg inhalation powder twice daily (morning and evening) via DPI for 24 weeks

Arm title	FF 12 µg

Arm description:

Randomized subjects received FF 12 µg oral inhalation powder BID via DPI.

Arm type	Experimental

Investigational medicinal product name	Formoterol fumarate
Investigational medicinal product code	
Other name	Pressair®/Genuair® Dry Powder Inhaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

FF 12 µg inhalation powder twice daily (morning and evening) via DPI for 24 weeks

Arm title	Tiotropium (TIO) 18 µg

Arm description:

Randomized subjects received TIO 18 µg oral inhalation powder in capsule BID via DPI.

Arm type	Experimental
Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	HandiHaler® Dry Powder Inhaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

TIO 18 µg inhalation powder QD (morning) via DPI for 24 weeks

Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	Pressair®/Genuair® Dry Powder Inhaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

TIO 18 µg inhalation powder twice daily (morning and evening) via DPI for 24 weeks

Number of subjects in period 1	Aclidinium bromide (AB)/Formoterol fumarate (FF) 400/12 µg	AB 400 µg	FF 12 µg
Started	317	478	320
Completed	279	405	267
Not completed	38	73	53
Consent withdrawn by subject	4	14	6
Adverse event, non-fatal	11	22	14
Lost to follow-up	1	5	2
Progressive disease	6	15	13
Reason not mentioned	2	3	-
Protocol deviation	7	5	4
Lack of efficacy	7	9	14

Number of subjects in period 1	Tiotropium (TIO) 18 µg
Started	479
Completed	405
Not completed	74
Consent withdrawn by subject	7

Adverse event, non-fatal	14
Lost to follow-up	2
Progressive disease	18
Reason not mentioned	5
Protocol deviation	8
Lack of efficacy	20

Period 2

Period 2 title	Intent-to-treat (ITT) population
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	AB/FF 400/12 µg

Arm description:

Randomized subjects received orally AB 400 µg/FF 12 µg inhalation powder twice daily (BID) via dry powder inhaler (DPI).

Arm type	Experimental
Investigational medicinal product name	Aclidinium bromide/Formoterol fumarate
Investigational medicinal product code	
Other name	Pressair®/Genuair® Dry Powder Inhaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

AB/FF 400/12 µg inhalation powder twice daily (morning and evening) via DPI for 24 weeks

Arm title	AB 400 µg

Arm description:

Randomized subjects received AB 400 µg oral inhalation powder BID via DPI.

Arm type	Experimental
Investigational medicinal product name	Aclidinium bromide
Investigational medicinal product code	
Other name	Pressair®/Genuair® Dry Powder Inhaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

AB 400 µg inhalation powder twice daily (morning and evening) via DPI for 24 weeks

Arm title	FF 12 µg

Arm description:

Randomized subjects received FF 12 µg oral inhalation powder BID via DPI.

Arm type	Experimental

Investigational medicinal product name	Formoterol fumarate
Investigational medicinal product code	
Other name	Pressair®/Genuair® Dry Powder Inhaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

FF 12 µg inhalation powder twice daily (morning and evening) via DPI for 24 weeks

Arm title	TIO 18 µg

Arm description:

Randomized subjects received orally TIO 18 µg inhalation powder in capsule QD via DPI.

Arm type	Experimental
Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	HandiHaler® Dry Powder Inhaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

TIO 18 µg inhalation powder QD (morning) via DPI for 24 weeks

Notes:

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

Justification: Subject disposition (Period 1) data were presented for the randomized population (N = 1594). The baseline characteristics and endpoints data were presented for the safety population and Intent-to-treat population (ITT; Period 2), respectively; in these two population sets, the number of subjects (N) was 1583. Hence, period 2 (ITT) was mentioned as the baseline period.

Number of subjects in period 2[2]	AB/FF 400/12 µg	AB 400 µg	FF 12 µg
Started	314	475	319
Completed	314	475	319

Number of subjects in period 2[2]	TIO 18 µg
Started	475
Completed	475

Notes:

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

Justification: All screened subjects were mentioned in the worldwide population of the trial whereas subjects who received at least 1 dose of the investigational product were mentioned in the ITT population (baseline period). Non-eligible subjects were not randomized in the study.

Baseline characteristics

Reporting groups	
Reporting group title	AB/FF 400/12 µg
Reporting group description:	
Randomized subjects received orally AB 400 µg/FF 12 µg inhalation powder twice daily (BID) via dry powder inhaler (DPI).	
Reporting group title	AB 400 µg
Reporting group description:	
Randomized subjects received AB 400 µg oral inhalation powder BID via DPI.	
Reporting group title	FF 12 µg
Reporting group description:	
Randomized subjects received FF 12 µg oral inhalation powder BID via DPI.	
Reporting group title	TIO 18 µg
Reporting group description:	
Randomized subjects received orally TIO 18 µg inhalation powder in capsule QD via DPI.	

Reporting group values	AB/FF 400/12 µg	AB 400 µg	FF 12 µg
Number of subjects	314	475	319
Age categorical			
Safety analysis set: Defined as all randomized subjects who took at least one dose of the study drug.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	166	270	168
From 65-84 years	146	205	151
85 years and over	2	0	0
Age Continuous			
Safety analysis set: Defined as all randomized subjects who took at least one dose of the study drug.			
Units: years			
arithmetic mean	64.4	64.4	64.7
standard deviation	± 8.5	± 8.1	± 8.3
Sex: Female, Male			
Safety analysis set: Defined as all randomized subjects who took at least one dose of the study drug.			
Units: Subjects			
Female	121	171	129
Male	193	304	190

Reporting group values	TIO 18 µg	Total	
Number of subjects	475	1583	
Age categorical			
Safety analysis set: Defined as all randomized subjects who took at least one dose of the study drug.			
Units: Subjects			
In utero	0	0	

Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	263	867	
From 65-84 years	209	711	
85 years and over	3	5	
Age Continuous			
Safety analysis set: Defined as all randomized subjects who took at least one dose of the study drug.			
Units: years			
arithmetic mean	64.0		
standard deviation	± 8.6	-	
Sex: Female, Male			
Safety analysis set: Defined as all randomized subjects who took at least one dose of the study drug.			
Units: Subjects			
Female	199	620	
Male	276	963	

End points

End points reporting groups

Reporting group title	Aclidinium bromide (AB)/Formoterol fumarate (FF) 400/12 µg
Reporting group description:	
Randomized subjects received AB 400 µg/FF 12 µg oral inhalation powder twice daily (BID) via dry powder inhaler (DPI).	
Reporting group title	AB 400 µg
Reporting group description:	
Randomized subjects received AB 400 µg oral inhalation powder BID via DPI.	
Reporting group title	FF 12 µg
Reporting group description:	
Randomized subjects received FF 12 µg oral inhalation powder BID via DPI.	
Reporting group title	Tiotropium (TIO) 18 µg
Reporting group description:	
Randomized subjects received TIO 18 µg oral inhalation powder in capsule BID via DPI.	
Reporting group title	AB/FF 400/12 µg
Reporting group description:	
Randomized subjects received orally AB 400 µg/FF 12 µg inhalation powder twice daily (BID) via dry powder inhaler (DPI).	
Reporting group title	AB 400 µg
Reporting group description:	
Randomized subjects received AB 400 µg oral inhalation powder BID via DPI.	
Reporting group title	FF 12 µg
Reporting group description:	
Randomized subjects received FF 12 µg oral inhalation powder BID via DPI.	
Reporting group title	TIO 18 µg
Reporting group description:	
Randomized subjects received orally TIO 18 µg inhalation powder in capsule QD via DPI.	
Subject analysis set title	AB/FF 400/12 µg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Randomized subjects received orally AB 400 µg/FF 12 µg inhalation powder BID via DPI.	
Subject analysis set title	AB 400 µg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Randomized subjects received AB 400 µg oral inhalation powder BID via DPI.	
Subject analysis set title	AB 400 µg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Randomized subjects received AB 400 µg oral inhalation powder BID via DPI.	
Subject analysis set title	FF 12 µg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Randomized subjects received FF 12 µg oral inhalation powder BID via DPI.	
Subject analysis set title	TIO 18 µg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Randomized subjects received orally TIO 18 µg inhalation powder in capsule QD via DPI.	
Subject analysis set title	TIO 18 µg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Randomized subjects received orally TIO 18 µg inhalation powder in capsule QD via DPI.

Primary: Change from baseline in 1-hour morning post-dose dose forced expiratory volume in 1 second (FEV1) of AB/FF 400/12 µg compared to AB 400 µg at week 24

End point title	Change from baseline in 1-hour morning post-dose dose forced expiratory volume in 1 second (FEV1) of AB/FF 400/12 µg compared to AB 400 µg at week 24

End point description:

To assess the bronchodilatory effect by evaluating the mean changes from baseline in FEV1 at 1 hour post-dose of AB/FF 400/12 µg compared to AB 400 µg after administration of oral inhalation powder BID via DIP to subjects with COPD. Baseline was defined as the average of the two FEV1 values measured just prior to the administration of the first dose of investigational product (IP) at randomization Visit. If one of the two was missing, then the available one would be used as baseline value.

End point type	Primary

End point timeframe:

At baseline 1-hour postdose and Week 24

End point values	AB/FF 400/12 µg	AB 400 µg	FF 12 µg	TIO 18 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	274	398	258	400
Units: Litres				
least squares mean (standard error)	0.253 (± 0.013)	0.169 (± 0.011)	0.168 (± 0.013)	0.161 (± 0.011)

Statistical analyses

Statistical analysis title	AB/FF 400/12 µg versus AB 400 µg

Statistical analysis description:

Number of subjects analyzed were 274 in AB/FF 400/12 µg arm and 398 in AB 400 µg arm.

Comparison groups	AB/FF 400/12 µg v AB 400 µg
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed model for repeated measures
Parameter estimate	LS mean difference
Point estimate	0.084
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.051
upper limit	0.117

Primary: Change from baseline in morning predose (trough) FEV1 of AB/FF 400/12

µg compared to FF 12 µg at week 24	
End point title	Change from baseline in morning predose (trough) FEV1 of AB/FF 400/12 µg compared to FF 12 µg at week 24

End point description:

To assess the bronchodilatory effect by evaluating the mean changes from baseline in FEV1 in morning pre-dose (trough) of AB/FF 400/12 µg compared to FF 12 µg after administration of oral inhalation powder BID via DPI to subjects with COPD. Morning pre-dose (trough) FEV1 was defined as the average of the corresponding -30 minute and 0 minute before the morning study medication administration at Week 24. If one time-point was missing then the available one would be used as morning pre-dose.

End point type	Primary

End point timeframe:

At baseline morning predose and Week 24

End point values	AB/FF 400/12 µg	AB 400 µg	FF 12 µg	TIO 18 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	274	401	259	401
Units: Litres				
least squares mean (standard error)	0.080 (± 0.014)	0.066 (± 0.012)	0.025 (± 0.014)	0.060 (± 0.012)

Statistical analyses

Statistical analysis title	AB/FF 400/12 µg versus FF 12 µg

Statistical analysis description:

Number of subjects analyzed were 274 in AB/FF 400/12 µg arm and 259 in AB 400 µg arm.

Comparison groups	AB/FF 400/12 µg v FF 12 µg
Number of subjects included in analysis	533
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009
Method	Mixed model for repeated measures
Parameter estimate	LS mean difference
Point estimate	0.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.088

Primary: Change from baseline in morning predose (trough) FEV1 at week 24 comparing AB 400 µg versus TIO 18 µg to demonstrate non-inferiority	
End point title	Change from baseline in morning predose (trough) FEV1 at week 24 comparing AB 400 µg versus TIO 18 µg to demonstrate non-inferiority

End point description:

To assess the non-inferior bronchodilatory effect by evaluating the mean changes from baseline in FEV1 in morning pre-dose (trough) of AB 400 µg BID compared to TIO 18 µg QD after administration of oral inhalation powder via DPI to subjects with COPD.

End point type	Primary

End point timeframe:

At baseline morning predose and Week 24

End point values	AB 400 µg	TIO 18 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	369	369		
Units: Litres				
least squares mean (standard error)	0.064 (± 0.013)	0.057 (± 0.013)		

Statistical analyses

Statistical analysis title	AB 400 µg versus TIO 18 µg

Statistical analysis description:

Number of subjects analyzed were 369 in AB 400 µg arm and 369 in TIO 18 µg arm.

Comparison groups	AB 400 µg v TIO 18 µg
Number of subjects included in analysis	738
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.6377
Method	Mixed model for repeated measures
Parameter estimate	LS mean difference
Point estimate	0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.021
upper limit	0.035

Notes:

[1] - Non-inferiority was established by showing that the lower bound of the two-sided 95% confidence interval for change from baseline in morning pre-dose (trough) FEV1 at week 24 when compared AB 400 µg versus TIO 18 µg was higher than -50 mL (non-inferiority limit).

Secondary: Change from baseline in normalized Area under curve 3 hours post-dose (nAUC0-3/3h) FEV1 of AB/FF 400/12 µg compared to AB 400 µg and and FF 12 µg at Week 24

End point title	Change from baseline in normalized Area under curve 3 hours post-dose (nAUC0-3/3h) FEV1 of AB/FF 400/12 µg compared to AB 400 µg and and FF 12 µg at Week 24

End point description:

To assess the bronchodilatory effect by evaluating the mean changes from baseline in normalized AUC0-3/3h FEV1 of AB/FF 400/12 µg compared to AB 400 µg and and FF 12 µg after administration of oral inhalation powder BID via DPI to subjects with COPD.

End point type	Secondary

End point timeframe:
At baseline and Week 24

End point values	AB/FF 400/12 µg	AB 400 µg	FF 12 µg	TIO 18 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	273	396	257	398
Units: Litres				
least squares mean (standard error)	0.237 (± 0.013)	0.162 (± 0.010)	0.149 (± 0.013)	0.151 (± 0.010)

Statistical analyses

Statistical analysis title	AB/FF 400/12 µg versus AB 400 µg
Statistical analysis description: Number of subjects analyzed were 273 in AB/FF 400/12 µg arm and 396 in AB 400 µg arm.	
Comparison groups	AB/FF 400/12 µg v AB 400 µg
Number of subjects included in analysis	669
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed model for repeated measures
Parameter estimate	LS mean difference
Point estimate	0.075
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.043
upper limit	0.107

Statistical analysis title	AB/FF 400/12 µg versus FF 12 µg
Statistical analysis description: Number of subjects analyzed were 273 in AB/FF 400/12 µg arm and 257 in FF 12 µg arm.	
Comparison groups	AB/FF 400/12 µg v FF 12 µg
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed model for repeated measures
Parameter estimate	LS mean difference
Point estimate	0.087

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.052
upper limit	0.122

Secondary: Responder (number [%] of subjects) analysis of St. George's Respiratory Questionnaire (SGRQ) total score with AB/FF 400/12 µg versus AB 400 µg and FF 12 µg.

End point title	Responder (number [%] of subjects) analysis of St. George's Respiratory Questionnaire (SGRQ) total score with AB/FF 400/12 µg versus AB 400 µg and FF 12 µg.

End point description:

SGRQ was a standardized self-completed tool used to measure impaired health and perceived well-being ("quality of life") in respiratory diseases. The questionnaire contained 50 items divided into 3 (symptoms, activity and impacts) dimensions. Each of the 3 dimensions of the questionnaire was scored separately in the range from 0 to 100% (score 0 - no impairment and higher score - poorer health). A summary score utilized responses of all items as the total SGRQ score. SGRQ responders were those with a decrease in SGRQ total score of at least 4 units (criterion for minimal meaningful improvement) from baseline.

End point type	Secondary

End point timeframe:

At baseline and Week 24

End point values	AB/FF 400/12 µg	AB 400 µg	FF 12 µg	TIO 18 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	314	475	319	475
Units: Percentages				
Yes|	130	188	128	197
Percentages of "Yes"|	48	49	50	51
No|	140	195	130	192
Percentages of "No"|	52	51	50	49

Statistical analyses

Statistical analysis title	AB/FF 400/12 µg versus AB 400 µg

Statistical analysis description:

Number of subjects analyzed were 314 in AB/FF 400/12 µg arm and 475 in AB 400 µg arm.

Comparison groups	AB/FF 400/12 µg v AB 400 µg
Number of subjects included in analysis	789
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8714
Method	Logistic random-effect model
Parameter estimate	Odds ratio
Point estimate	0.96

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.51

Statistical analysis title	AB/FF 400/12 µg versus FF 12 µg
Statistical analysis description: Number of subjects analyzed were 314 in AB/FF 400/12 µg arm and 319 in AB 400 µg arm.	
Comparison groups	AB/FF 400/12 µg v FF 12 µg
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8873
Method	Logistic random-effect model
Parameter estimate	Odds ratio
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.58

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From time of signature of the ICF throughout the treatment period and including the follow-up period (2 weeks after the last study drug administration)

Adverse event reporting additional description:

An adverse event – An undesirable medical condition/deterioration of pre-existing medical condition following/during exposure to pharmaceutical product, whether/not considered causally related to product. An undesirable medical condition - symptoms (e.g. nausea), signs (e.g. tachycardia)/ abnormal investigation results (e.g. laboratory findings)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	AB/FF 400/12 µg

Reporting group description:

Randomized subjects received orally AB 400 µg/FF 12 µg inhalation powder BID via DPI.

Reporting group title	AB 400 µg

Reporting group description:

Randomized subjects received AB 400 µg oral inhalation powder BID via DPI.

Reporting group title	FF 12 µg

Reporting group description:

Randomized subjects received orally FF 12 µg inhalation powder BID via DPI.

Reporting group title	TIO 18 µg

Reporting group description:

Randomized subjects received orally TIO 18 µg inhalation powder in capsule QD via DPI.

Serious adverse events	AB/FF 400/12 µg	AB 400 µg	FF 12 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 314 (7.32%)	41 / 475 (8.63%)	22 / 319 (6.90%)
number of deaths (all causes)	1	1	4
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine carcinoma			

subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal meningioma benign			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic neoplasm			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma stage IV			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal cell carcinoma			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis			

subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose vein			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Complication associated with device			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Impaired healing			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			

subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	7 / 314 (2.23%)	11 / 475 (2.32%)	10 / 319 (3.13%)
occurrences causally related to treatment / all	0 / 8	0 / 11	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 314 (0.32%)	1 / 475 (0.21%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar disorder			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arterial bypass occlusion			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Foreign body			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 314 (0.32%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol poisoning			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc injury			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Coronary artery stenosis			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 314 (0.00%)	2 / 475 (0.42%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			

subjects affected / exposed	0 / 314 (0.00%)	2 / 475 (0.42%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cor pulmonale chronic			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			

subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar infarction			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar stroke			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 314 (0.32%)	1 / 475 (0.21%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			

subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Polycythaemia			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholelithiasis			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oliguria			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
End stage renal disease			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 314 (0.32%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	4 / 314 (1.27%)	3 / 475 (0.63%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 314 (0.32%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	1 / 319 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			

subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	0 / 314 (0.00%)	1 / 475 (0.21%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis viral			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 314 (0.00%)	0 / 475 (0.00%)	0 / 319 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	TIO 18 µg		
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 475 (7.79%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neuroendocrine carcinoma			

subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal meningioma benign				
subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastatic neoplasm				
subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of lung				
subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal carcinoma				
subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma stage IV				
subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal cell carcinoma				
subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertensive crisis				
subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arteriosclerosis				

subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral artery stenosis			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Varicose vein			
subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Complication associated with device			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Impaired healing			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest pain			

subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	14 / 475 (2.95%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atelectasis			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary mass			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			

Anxiety			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bipolar disorder			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Arterial bypass occlusion			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tendon rupture			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Foreign body			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alcohol poisoning			
subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc injury			
subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thermal burn			
subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Coronary artery stenosis			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure acute			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			

subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	1 / 475 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	1 / 475 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina unstable				
subjects affected / exposed	1 / 475 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	3 / 475 (0.63%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Cor pulmonale chronic				
subjects affected / exposed	1 / 475 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Atrial tachycardia				
subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	2 / 475 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				

subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebellar infarction			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lacunar stroke			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Carotid artery stenosis			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hydrocephalus			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sciatica			

subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Polycythaemia			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Cholelithiasis			
subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oliguria			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
End stage renal disease			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar spinal stenosis			
subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			

subjects affected / exposed	2 / 475 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural infection				
subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	0 / 475 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngitis				

subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonsillar abscess			
subjects affected / exposed	0 / 475 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis viral			
subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 475 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	AB/FF 400/12 µg	AB 400 µg	FF 12 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	173 / 314 (55.10%)	222 / 475 (46.74%)	178 / 319 (55.80%)
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 314 (2.23%)	8 / 475 (1.68%)	9 / 319 (2.82%)
occurrences (all)	7	8	10
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 314 (5.10%)	19 / 475 (4.00%)	17 / 319 (5.33%)
occurrences (all)	27	20	19
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	6 / 314 (1.91%)	9 / 475 (1.89%)	7 / 319 (2.19%)
occurrences (all)	6	9	7
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary			
subjects affected / exposed	49 / 314 (15.61%)	79 / 475 (16.63%)	58 / 319 (18.18%)
occurrences (all)	60	90	74
Dyspnoea			
subjects affected / exposed	6 / 314 (1.91%)	13 / 475 (2.74%)	6 / 319 (1.88%)
occurrences (all)	6	18	7
Cough			
subjects affected / exposed	6 / 314 (1.91%)	7 / 475 (1.47%)	4 / 319 (1.25%)
occurrences (all)	7	7	4
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	15 / 314 (4.78%)	7 / 475 (1.47%)	8 / 319 (2.51%)
occurrences (all)	22	7	12
Arthralgia			
subjects affected / exposed	8 / 314 (2.55%)	4 / 475 (0.84%)	3 / 319 (0.94%)
occurrences (all)	9	4	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	36 / 314 (11.46%)	47 / 475 (9.89%)	39 / 319 (12.23%)
occurrences (all)	42	56	45
Upper respiratory tract infection			
subjects affected / exposed	8 / 314 (2.55%)	13 / 475 (2.74%)	7 / 319 (2.19%)
occurrences (all)	9	15	7
Sinusitis			
subjects affected / exposed	8 / 314 (2.55%)	10 / 475 (2.11%)	6 / 319 (1.88%)
occurrences (all)	8	10	6
Pneumonia			
subjects affected / exposed	4 / 314 (1.27%)	1 / 475 (0.21%)	6 / 319 (1.88%)
occurrences (all)	4	1	6
Urinary tract infection			
subjects affected / exposed	4 / 314 (1.27%)	5 / 475 (1.05%)	8 / 319 (2.51%)
occurrences (all)	4	5	8

Non-serious adverse events	TIO 18 µg		
Total subjects affected by non-serious adverse events subjects affected / exposed	241 / 475 (50.74%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	7 / 475 (1.47%) 9		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	25 / 475 (5.26%) 31		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	7 / 475 (1.47%) 7		
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	61 / 475 (12.84%) 70 12 / 475 (2.53%) 12 17 / 475 (3.58%) 19		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	7 / 475 (1.47%) 8 8 / 475 (1.68%) 10		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	64 / 475 (13.47%) 67		

Upper respiratory tract infection subjects affected / exposed occurrences (all)	17 / 475 (3.58%) 21		
Sinusitis subjects affected / exposed occurrences (all)	7 / 475 (1.47%) 7		
Pneumonia subjects affected / exposed occurrences (all)	6 / 475 (1.26%) 6		
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 475 (0.63%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2016	Protocol version 2.0: - Defined primary objective for Market Access and statistical analysis (Synopsis, Sections 4.1, 5.2, 5.5,5.7, 7.1.1) - Included reference for Bretaris® Genuair® and Bretaris® Genuair® Summary of Product Characteristics (SmPC) (Section 3, list of references) - Corrected doses for Atrovent and specified brand names for US and non-US countries (Synopsis, Sections 5.1, 5.4) - Replaced Visit 8 by follow-up phone call (Section 5.1, 5.3, 6.1) - Added clarification on procedures for the end of treatment (EOT) and end of study (EOS) visits, including 1h post-dose pulmonary function test (PFT) after COPD prescribed treatment (Section 5.1) - Added red blood cells morphology, white blood cells differential and mean corpuscular volume (MCV) in the laboratory assessments (Section 8.4.1)
21 March 2016	Protocol version 3.0: The collection of IP intake was included in the e-diary (Section 5.1)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported