Clinical trial results:
A prospective, multicenter, 12-week, randomized open label study to evaluate the efficacy and safety of glycopyrronium (50 micrograms o.d.) or indacaterol maleate and glycopyrronium bromide fixed-dose combination (110/50 micrograms o.d.) regarding symptoms and health status in patients with moderate chronic obstructive pulmonary disease (COPD) switching from treatment with any standard COPD regimen

Summary

EudraCT number	2013-003127-11
Trial protocol	CZ LT SK BE EE LV IE SE AT PT IT GB DK GR HU PL ES DE SI
Global end of trial date	29 April 2016

Results information

Result version number	v1 (current)
This version publication date	22 April 2017
First version publication date	22 April 2017

Trial information

Trial identification

Sponsor protocol code	CQVA149A3401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01985334
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH_4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To show the superiority of glycopyrronium (50 µg o.d.) vs. short-acting bronchodilators (SABA and/or SAMA as monotherapy or in free or FDC) on trough FEV1 at week 12.
- To show the non-inferiority of glycopyrronium (50 µg o.d.) vs. long-acting bronchodilators (LABA or LAMA monotherapy) on trough FEV1 at week 12.
- To show the superiority of indacaterol maleate and glycopyrronium bromide FDC (110/50 µg o. d.) vs. LABA and ICS in free or FDC on trough FEV1 at week 12.
- To show the superiority of indacaterol maleate and glycopyrronium bromide FDC (110/50 µg o. d.) vs. long-acting bronchodilators (LABA or LAMA monotherapy) on trough FEV1 at week 12.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 84
Country: Number of subjects enrolled	Belgium: 209
Country: Number of subjects enrolled	Czech Republic: 531
Country: Number of subjects enrolled	Denmark: 13
Country: Number of subjects enrolled	Estonia: 92
Country: Number of subjects enrolled	France: 51
Country: Number of subjects enrolled	Germany: 1689
Country: Number of subjects enrolled	Hungary: 143
Country: Number of subjects enrolled	Ireland: 16
Country: Number of subjects enrolled	Italy: 210
Country: Number of subjects enrolled	Latvia: 72
Country: Number of subjects enrolled	Lithuania: 109
Country: Number of subjects enrolled	Norway: 46
Country: Number of subjects enrolled	Poland: 103
Country: Number of subjects enrolled	Portugal: 35

Country: Number of subjects enrolled	Romania: 120
Country: Number of subjects enrolled	Russian Federation: 198
Country: Number of subjects enrolled	Slovakia: 178
Country: Number of subjects enrolled	Slovenia: 53
Country: Number of subjects enrolled	Spain: 178
Country: Number of subjects enrolled	Sweden: 63
Country: Number of subjects enrolled	United Kingdom: 180
Country: Number of subjects enrolled	Greece: 16
Worldwide total number of subjects	4389
EEA total number of subjects	4191

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)	2110
From 65 to 84 years	2267
85 years and over	12

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study used a multicenter, parallel-group, randomized 3:1, open-label design. The treatment epoch lasted 12 weeks (i.e. 90 days). The total duration of the study for each patient was 12 weeks (from randomization) plus 30 days of safety follow-up.

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	A1 (any SABA and/or SAMA)

Arm description:

Patients treated with any SABA and/or SAMA as monotherapy or in free or fixed dose combination at enrollment and randomized to remain in their baseline therapy with any SABA and/or SAMA

Arm type	Experimental
Investigational medicinal product name	any SABA and/or SAMA
Investigational medicinal product code	any SABA and/or SAMA
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Oral inhalation

Arm title	A2 (glycopyrronium)

Arm description:

Patients treated with any SABA and/or SAMA as monotherapy or in free or FDC at enrollment and randomized to switch in treatment with glycopyrronium (50 µg o.d.)

Arm type	Experimental
Investigational medicinal product name	glycopyrronium
Investigational medicinal product code	glycopyrronium
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Oral inhalation

Arm title	B1 (any LAMA or LABA and mMRC=1)

Arm description:

Patients treated with any LABA or LAMA monotherapy and mMRC score =1 point at Visit 1 and randomized to remain in their baseline treatment with LABA or LAMA

Arm type	Experimental

Investigational medicinal product name	LAMA or LABA
Investigational medicinal product code	LAMA or LABA
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Oral inhalation

Arm title	B2 (glycopyrronium and mMRC=1)

Arm description:

Patients treated with any LABA or LAMA monotherapy and mMRC score =1 point at Visit 1 and randomized to switch in treatment with glycopyrronium (50 µg o.d.)

Arm type	Experimental
Investigational medicinal product name	glycopyrronium and mMRC=1
Investigational medicinal product code	glycopyrronium and mMRC=1
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Oral inhalation

Arm title	C1 (any LABA and ICS)

Arm description:

Patients treated with any LABA and ICS in free or FDC at enrollment and randomized to remain in their baseline treatment with LABA and ICS in free or FDC

Arm type	Experimental
Investigational medicinal product name	any LABA and ICS
Investigational medicinal product code	any LABA and ICS
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Oral inhalation

Arm title	C2 (indacaterol/glycopyrronium)

Arm description:

Patients treated with any LABA and ICS in free or FDC at enrollment and randomized to switch in treatment with indacaterol maleate and glycopyrronium bromide FDC (110/50 µg o.d.)

Arm type	Experimental
Investigational medicinal product name	indacaterol/glycopyrronium
Investigational medicinal product code	
Other name	indacaterol/glycopyrronium
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Oral inhalation

Arm title	D1 (any LAMA or LABA and mMRC>1)

Arm description:

Patients treated with any LABA or LAMA monotherapy and mMRC score >1 point at Visit 1 and randomized to remain their baseline in treatment with LABA or LAMA

Arm type	Experimental

Investigational medicinal product name	any LAMA or LABA and mMRC>1
Investigational medicinal product code	
Other name	any LAMA or LABA and mMRC>1
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Oral inhalation

Arm title	D2 (indacaterol/glycopyrronium and mMRC>1)

Arm description:

Patients treated with any LABA or LAMA monotherapy and mMRC score >1 point at Visit 1 and randomized to switch in treatment with indacaterol maleate and glycopyrronium bromide FDC (110/50 µg o.d.).

Arm type	Experimental
Investigational medicinal product name	indacaterol/glycopyrronium and mMRC>1
Investigational medicinal product code	
Other name	indacaterol/glycopyrronium and mMRC>1
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Oral inhalation

Number of subjects in period 1	A1 (any SABA and/or SAMA)	A2 (glycopyrronium)	B1 (any LAMA or LABA and mMRC=1)
Started	130	387	420
The intention-to-treat (ITT) population	122	369	420
Completed	107	303	367
Not completed	23	84	53
Adverse event, serious fatal	1	-	-
Moderate / severe COPD exacerbation	5	14	12
Use of prohibited treatment	1	4	1
Medication non-compliance	-	4	1
Worsening of disease	-	-	-
Administrative problems	1	1	-
Adverse event, non-fatal	-	8	2
Other	2	9	7
Protocol deviation	6	31	25
Unknown	4	2	3
Investigator decision	-	3	-
Lost to follow-up	-	2	-
Subject withdrawal of consent	3	6	2

Number of subjects in period 1	B2 (glycopyrronium and mMRC=1)	C1 (any LABA and ICS)	C2 (indacaterol/glycopyrronium)
Started	1262	274	822

The intention-to-treat (ITT) population	1254	269	811
Completed	1033	234	666
Not completed	229	40	156
Adverse event, serious fatal	3	-	-
Moderate / severe COPD exacerbation	40	6	40
Use of prohibited treatment	2	1	6
Medication non-compliance	6	2	3
Worsening of disease	1	-	3
Administrative problems	2	-	1
Adverse event, non-fatal	26	3	18
Other	17	4	8
Protocol deviation	84	17	47
Unknown	10	1	6
Investigator decision	7	1	1
Lost to follow-up	3	1	4
Subject withdrawal of consent	28	4	19

Number of subjects in period 1	D1 (any LAMA or LABA and mMRC>1)	D2 (indacaterol/glycopyrronium and mMRC>1)
Started	274	820
The intention-to-treat (ITT) population	268	811
Completed	237	699
Not completed	37	121
Adverse event, serious fatal	1	2
Moderate / severe COPD exacerbation	8	19
Use of prohibited treatment	2	-
Medication non-compliance	1	3
Worsening of disease	-	1
Administrative problems	1	3
Adverse event, non-fatal	3	15
Other	4	7
Protocol deviation	15	42
Unknown	2	2
Investigator decision	-	4
Lost to follow-up	-	3
Subject withdrawal of consent	-	20

Baseline characteristics

Reporting groups	
Reporting group title	A1 (any SABA and/or SAMA)
Reporting group description:	
Patients treated with any SABA and/or SAMA as monotherapy or in free or fixed dose combination at enrollment and randomized to remain in their baseline therapy with any SABA and/or SAMA	
Reporting group title	A2 (glycopyrronium)
Reporting group description:	
Patients treated with any SABA and/or SAMA as monotherapy or in free or FDC at enrollment and randomized to switch in treatment with glycopyrronium (50 µg o.d.)	
Reporting group title	B1 (any LAMA or LABA and mMRC=1)
Reporting group description:	
Patients treated with any LABA or LAMA monotherapy and mMRC score =1 point at Visit 1 and randomized to remain in their baseline treatment with LABA or LAMA	
Reporting group title	B2 (glycopyrronium and mMRC=1)
Reporting group description:	
Patients treated with any LABA or LAMA monotherapy and mMRC score =1 point at Visit 1 and randomized to switch in treatment with glycopyrronium (50 µg o.d.)	
Reporting group title	C1 (any LABA and ICS)
Reporting group description:	
Patients treated with any LABA and ICS in free or FDC at enrollment and randomized to remain in their baseline treatment with LABA and ICS in free or FDC	
Reporting group title	C2 (indacaterol/glycopyrronium)
Reporting group description:	
Patients treated with any LABA and ICS in free or FDC at enrollment and randomized to switch in treatment with indacaterol maleate and glycopyrronium bromide FDC (110/50 µg o.d.)	
Reporting group title	D1 (any LAMA or LABA and mMRC>1)
Reporting group description:	
Patients treated with any LABA or LAMA monotherapy and mMRC score >1 point at Visit 1 and randomized to remain their baseline in treatment with LABA or LAMA	
Reporting group title	D2 (indacaterol/glycopyrronium and mMRC>1)
Reporting group description:	
Patients treated with any LABA or LAMA monotherapy and mMRC score >1 point at Visit 1 and randomized to switch in treatment with indacaterol maleate and glycopyrronium bromide FDC (110/50 µg o.d.).	

Reporting group values	A1 (any SABA and/or SAMA)	A2 (glycopyrronium)	B1 (any LAMA or LABA and mMRC=1)
Number of subjects	130	387	420
Age categorical 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)	67	214	204
From 65-84 years	63	173	216
85 years and over	0	0	0

Age Continuous			
Units: years			
arithmetic mean	64.1	63.1	64.6
standard deviation	± 7.8	± 8.4	± 8.2
Gender, Male/Female			
Units: Subjects			
Female	48	119	131
Male	82	268	289

Reporting group values	B2 (glycopyrronium and mMRC=1)	C1 (any LABA and ICS)	C2 (indacaterol/glycopyrronium)
Number of subjects	1262	274	822
Age categorical			
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)	622	131	396
From 65-84 years	635	142	425
85 years and over	5	1	1
Age Continuous			
Units: years			
arithmetic mean	64.4	64.4	64.6
standard deviation	± 8.2	± 8.9	± 8.7
Gender, Male/Female			
Units: Subjects			
Female	376	106	286
Male	886	168	536

Reporting group values	D1 (any LAMA or LABA and mMRC>1)	D2 (indacaterol/glycopyrronium and mMRC>1)	Total
Number of subjects	274	820	4389
Age categorical			
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)	119	357	2110
From 65-84 years	154	459	2267
85 years and over	1	4	12

Age Continuous Units: years			
arithmetic mean	65.2	65.4	
standard deviation	± 7.6	± 8.3	-
Gender, Male/Female Units: Subjects			
Female	95	276	1437
Male	179	544	2952

End points

End points reporting groups

Reporting group title	A1 (any SABA and/or SAMA)
Reporting group description:	
Patients treated with any SABA and/or SAMA as monotherapy or in free or fixed dose combination at enrollment and randomized to remain in their baseline therapy with any SABA and/or SAMA	
Reporting group title	A2 (glycopyrronium)
Reporting group description:	
Patients treated with any SABA and/or SAMA as monotherapy or in free or FDC at enrollment and randomized to switch in treatment with glycopyrronium (50 µg o.d.)	
Reporting group title	B1 (any LAMA or LABA and mMRC=1)
Reporting group description:	
Patients treated with any LABA or LAMA monotherapy and mMRC score =1 point at Visit 1 and randomized to remain in their baseline treatment with LABA or LAMA	
Reporting group title	B2 (glycopyrronium and mMRC=1)
Reporting group description:	
Patients treated with any LABA or LAMA monotherapy and mMRC score =1 point at Visit 1 and randomized to switch in treatment with glycopyrronium (50 µg o.d.)	
Reporting group title	C1 (any LABA and ICS)
Reporting group description:	
Patients treated with any LABA and ICS in free or FDC at enrollment and randomized to remain in their baseline treatment with LABA and ICS in free or FDC	
Reporting group title	C2 (indacaterol/glycopyrronium)
Reporting group description:	
Patients treated with any LABA and ICS in free or FDC at enrollment and randomized to switch in treatment with indacaterol maleate and glycopyrronium bromide FDC (110/50 µg o.d.)	
Reporting group title	D1 (any LAMA or LABA and mMRC>1)
Reporting group description:	
Patients treated with any LABA or LAMA monotherapy and mMRC score >1 point at Visit 1 and randomized to remain their baseline in treatment with LABA or LAMA	
Reporting group title	D2 (indacaterol/glycopyrronium and mMRC>1)
Reporting group description:	
Patients treated with any LABA or LAMA monotherapy and mMRC score >1 point at Visit 1 and randomized to switch in treatment with indacaterol maleate and glycopyrronium bromide FDC (110/50 µg o.d.).	
Subject analysis set title	A2 + B2
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
A2 (glycopyrronium)+B2 (glycopyrronium and mMRC=1	
Subject analysis set title	A1 + B1
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
A1(any SABA and/or SAMA+B1 (any LAMA or LABA and mMRC=1	
Subject analysis set title	A2 +B2
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
A2 (glycopyrronium)+B2 (glycopyrronium and mMRC=1	
Subject analysis set title	A1 +B1
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
A1(any SABA and/or SAMA+B1 (any LAMA or LABA and mMRC=1)	
Subject analysis set title	C2 +D2

Subject analysis set type	Intention-to-treat
Subject analysis set description: C2 (indacaterol/glycopyrronium)+D2 (indacaterol/glycopyrronium and mMRC>1)	
Subject analysis set title	C1 + D1
Subject analysis set type	Intention-to-treat
Subject analysis set description: C1 (any LABA and ICS)+D1 (any LAMA or LABA and mMRC>1)	
Subject analysis set title	C2 +D2
Subject analysis set type	Intention-to-treat
Subject analysis set description: C2 (indacaterol/glycopyrronium) + D2 (indacaterol/glycopyrronium and mMRC>1)	
Subject analysis set title	C1 + D1
Subject analysis set type	Intention-to-treat
Subject analysis set description: C1 (any LABA and ICS) + D1 (any LAMA or LABA and mMRC>1)	

Primary: Trough FEV1 at week 12 for group: glycopyrronium vs. short-acting bronchodilators (SABA and/or SAMA as monotherapy or in free or FDC)

End point title	Trough FEV1 at week 12 for group: glycopyrronium vs. short-acting bronchodilators (SABA and/or SAMA as monotherapy or in free or FDC)[1]
End point description: Trough FEV1 at visit 4 is defined as FEV1, computed as the mean of forced expiratory volume in 1 second 15min and 45 min pre dose measurements, at the end of the dosing interval	
End point type	Primary
End point timeframe: Day 1 (baseline) and week 12 (Visit 4)	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this outcome measure

End point values	A1 (any SABA and/or SAMA)	A2 (glycopyrroniu m)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	369		
Units: Liters				
least squares mean (confidence interval 95%)	1.8264 (1.7797 to 1.8732)	1.8916 (1.8647 to 1.9185)		

Statistical analyses

Statistical analysis title	Trough FEV1 at visit 4
Comparison groups	A2 (glycopyrronium) v A1 (any SABA and/or SAMA)

Number of subjects included in analysis	491
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.018
Method	linear mixed model

Primary: Trough FEV1 at week 12 for group: glycopyrronium vs. long-acting bronchodilators (LABA or LAMA monotherapy)

End point title	Trough FEV1 at week 12 for group: glycopyrronium vs. long-acting bronchodilators (LABA or LAMA monotherapy)[2]

End point description:

Trough FEV1 at visit 4 is defined as FEV1, computed as the mean of forced expiratory volume in 1 second 15min and 45 min pre dose measurements, at the end of the dosing interval

End point type	Primary

End point timeframe:

Day 1 (baseline) and week 12 (Visit 4)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this outcome measure

End point values	B1 (any LAMA or LABA and mMRC=1)	B2 (glycopyrronium and mMRC=1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	420	1254		
Units: Liters				
least squares mean (confidence interval 95%)	1.8004 (1.7768 to 1.8239)	1.8215 (1.8078 to 1.8352)		

Statistical analyses

Statistical analysis title	Trough FEV1 at week 12
Comparison groups	B1 (any LAMA or LABA and mMRC=1) v B2 (glycopyrronium and mMRC=1)
Number of subjects included in analysis	1674
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	linear mixed model

Primary: Trough FEV1 at week 12 for group: indacaterol maleate and glycopyrronium bromide FDC vs. LABA and ICS in free or FDC

End point title	Trough FEV1 at week 12 for group: indacaterol maleate and glycopyrronium bromide FDC vs. LABA and ICS in free or FDC[3]

End point description:

Trough FEV1 at visit 4 is defined as FEV1, computed as the mean of forced expiratory volume in 1 second 15min and 45 min pre dose measurements, at the end of the dosing interval.

End point type	Primary

End point timeframe:

Day 1 (baseline) and week 12 (Visit 4)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this outcome measure

End point values	C1 (any LABA and ICS)	C2 (indacaterol/glycopyrronium)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	811		
Units: Liters				
least squares mean (confidence interval 95%)	1.6847 (1.6542 to 1.7153)	1.7558 (1.7378 to 1.7737)		

Statistical analyses

Statistical analysis title	Trough FEV1 at week 12
Comparison groups	C1 (any LABA and ICS) v C2 (indacaterol/glycopyrronium)
Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	linear mixed model

Primary: Trough FEV1 at week 12 for group: indacaterol maleate and glycopyrronium bromide FDC vs. long-acting bronchodilators (LABA or LAMA monotherapy)

End point title	Trough FEV1 at week 12 for group: indacaterol maleate and glycopyrronium bromide FDC vs. long-acting bronchodilators (LABA or LAMA monotherapy)[4]

End point description:

Trough FEV1 at visit 4 is defined as FEV1, computed as the mean of forced expiratory volume in 1 second 15min and 45 min pre dose measurements, at the end of the dosing interval.

End point type	Primary

End point timeframe:

Day 1 (baseline) and week 12 (Visit 4)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this outcome measure

End point values	D1 (any LAMA or LABA and mMRC>1)	D2 (indacaterol/glycopyrronium and mMRC>1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	811		
Units: Liters				
least squares mean (confidence interval 95%)	1.6728 (1.6461 to 1.6994)	1.7742 (1.7587 to 1.7896)		

Statistical analyses

Statistical analysis title	Trough FEV1 at week 12
Comparison groups	D1 (any LAMA or LABA and mMRC>1) v D2 (indacaterol/glycopyrronium and mMRC>1)
Number of subjects included in analysis	1079
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	linear mixed model

Primary: Change from baseline on Transition Dyspnea Index (TDI) for groups: glycopyrronium vs. short-acting bronchodilators (SABA and/or SAMA as monotherapy or in free or FDC)

End point title	Change from baseline on Transition Dyspnea Index (TDI) for groups: glycopyrronium vs. short-acting bronchodilators (SABA and/or SAMA as monotherapy or in free or FDC)[5]

End point description:

Transition Dyspnea Index (TDI) captures changes from baseline. The TDI score is based on three domains with each domain scored from -3 (major deterioration) to +3 (major improvement), to give an overall score of -9 to +9, a negative score indicating a deterioration from baseline. A TDI focal score of 1 is considered to be a clinically significant improvement from baseline.

End point type	Primary

End point timeframe:

Day 1 (baseline) and week 12

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this outcome measure

End point values	A1 (any SABA and/or SAMA)	A2 (glycopyrronium)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	369		
Units: Units on a scale				
least squares mean (confidence interval 95%)	0.5117 (-0.0073 to 1.0306)	2.3005 (2.0015 to 2.5995)		

Statistical analyses

Statistical analysis title	Transition Dyspnea Index (TDI)
Comparison groups	A1 (any SABA and/or SAMA) v A2 (glycopyrronium)
Number of subjects included in analysis	491
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	linear mixed model

Primary: Change from baseline on Transition Dyspnea Index (TDI) for groups: glycopyrronium vs. long-acting bronchodilators (LABA or LAMA monotherapy)

End point title	Change from baseline on Transition Dyspnea Index (TDI) for groups: glycopyrronium vs. long-acting bronchodilators (LABA or LAMA monotherapy)[6]

End point description:

Transition Dyspnea Index (TDI) captures changes from baseline. The TDI score is based on three domains with each domain scored from -3 (major deterioration) to +3 (major improvement), to give an overall score of -9 to +9, a negative score indicating a deterioration from baseline. A TDI focal score of 1 is considered to be a clinically significant improvement from baseline.

End point type	Primary

End point timeframe:

Day 1 (baseline) and week 12

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this outcome measure

End point values	B1 (any LAMA or LABA and mMRC=1)	B2 (glycopyrronium and mMRC=1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	420	1254		
Units: Units on a scale				
least squares mean (confidence interval 95%)	0.6969 (0.4169 to 0.9769)	1.4351 (1.2718 to 1.5984)		

Statistical analyses

Statistical analysis title	Transition Dyspnea Index (TDI)
Comparison groups	B1 (any LAMA or LABA and mMRC=1) v B2 (glycopyrronium and mMRC=1)

Number of subjects included in analysis	1674
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	linear mixed model

Primary: Change from baseline on Transition Dyspnea Index (TDI) for groups: indacaterol maleate and glycopyrronium bromide FDC vs. LABA and ICS in free or FDC

End point title	Change from baseline on Transition Dyspnea Index (TDI) for groups: indacaterol maleate and glycopyrronium bromide FDC vs. LABA and ICS in free or FDC[7]

End point description:

Transition Dyspnea Index (TDI) captures changes from baseline. The TDI score is based on three domains with each domain scored from -3 (major deterioration) to +3 (major improvement), to give an overall score of -9 to +9, a negative score indicating a deterioration from baseline. A TDI focal score of 1 is considered to be a clinically significant improvement from baseline.

End point type	Primary

End point timeframe:

Day 1 (baseline) and week 12

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this outcome measure

End point values	C1 (any LABA and ICS)	C2 (indacaterol/glycopyrronium)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	811		
Units: Units on a scale				
least squares mean (confidence interval 95%)	0.8508 (0.4676 to 1.234)	1.9491 (1.7207 to 2.1775)		

Statistical analyses

Statistical analysis title	Transition Dyspnea Index (TDI)
Comparison groups	C1 (any LABA and ICS) v C2 (indacaterol/glycopyrronium)
Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	linear mixed model

Primary: Change from baseline on Transition Dyspnea Index (TDI) for groups: indacaterol maleate and glycopyrronium bromide FDC vs. long-acting bronchodilators (LABA or LAMA monotherapy)

End point title	Change from baseline on Transition Dyspnea Index (TDI) for groups: indacaterol maleate and glycopyrronium bromide FDC vs. long-acting bronchodilators (LABA or LAMA monotherapy)[8]

End point description:

Transition Dyspnea Index (TDI) captures changes from baseline. The TDI score is based on three domains with each domain scored from -3 (major deterioration) to +3 (major improvement), to give an overall score of -9 to +9, a negative score indicating a deterioration from baseline. A TDI focal score of 1 is considered to be a clinically significant improvement from baseline.

End point type	Primary

End point timeframe:

Day 1 (baseline) and week 12

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to this outcome measure

End point values	D1 (any LAMA or LABA and mMRC>1)	D2 (indacaterol/glycopyrronium and mMRC>1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	811		
Units: Units on a scale				
least squares mean (confidence interval 95%)	0.8632 (0.5098 to 1.2166)	2.1209 (1.913 to 2.3288)		

Statistical analyses

Statistical analysis title	Transition Dyspnea Index (TDI)
Comparison groups	D1 (any LAMA or LABA and mMRC>1) v D2 (indacaterol/glycopyrronium and mMRC>1)
Number of subjects included in analysis	1079
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	linear mixed model

Secondary: Trough FEV1 at week 12 for group: glycopyrronium vs. short-acting bronchodilators (SABA and/or SAMA as monotherapy or in free or FDC) or vs. long-acting bronchodilators (LABA or LAMA monotherapy)

End point title	Trough FEV1 at week 12 for group: glycopyrronium vs. short-acting bronchodilators (SABA and/or SAMA as monotherapy or in free or FDC) or vs. long-acting bronchodilators (LABA or LAMA monotherapy)

End point description:

Trough FEV1 at visit 4 is defined as FEV1, computed as the mean of forced expiratory volume in 1 second 15min and 45 min pre dose measurements, at the end of the dosing interval

End point type	Secondary

End point timeframe:

12 Weeks

End point values	A2 + B2	A1 + B1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1623	542		
Units: Liters				
least squares mean (confidence interval 95%)	1.8373 (1.825 to 1.8496)	1.8065 (1.7853 to 1.8276)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline on on Transition Dyspnea Index (TDI) for groups: glycopyrronium vs. short-acting bronchodilators (SABA and/or SAMA as monotherapy or in free or FDC) or long-acting bronchodilators (LABA or LAMA monotherapy)

End point title	Change from baseline on on Transition Dyspnea Index (TDI) for groups: glycopyrronium vs. short-acting bronchodilators (SABA and/or SAMA as monotherapy or in free or FDC) or long-acting bronchodilators (LABA or LAMA monotherapy)

End point description:

Transition Dyspnea Index (TDI) captures changes from baseline. The TDI score is based on three domains with each domain scored from -3 (major deterioration) to +3 (major improvement), to give an overall score of -9 to +9, a negative score indicating a deterioration from baseline. A TDI focal score of 1 is considered to be a clinically significant improvement from baseline.

End point type	Secondary

End point timeframe:

Day 1 (baseline) and week 12

End point values	A2 +B2	A1 +B1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1623	542		
Units: Score on a scale				
least squares mean (confidence interval 95%)	1.6315 (1.4874 to 1.7756)	0.6562 (0.4085 to 0.9039)		

Statistical analyses

No statistical analyses for this end point

Secondary: Trough FEV1 at week 12 for group: indacaterol maleate and glycopyrronium bromide FDC vs. LABA or LAMA monotherapy or LABA and ICS in

free or FDC on trough FEV1 at week 12.

End point title	Trough FEV1 at week 12 for group: indacaterol maleate and glycopyrronium bromide FDC vs. LABA or LAMA monotherapy or LABA and ICS in free or FDC on trough FEV1 at week 12.

End point description:

Trough FEV1 at visit 4 is defined as FEV1, computed as the mean of forced expiratory volume in 1 second 15min and 45 min pre dose measurements, at the end of the dosing interval.

End point type	Secondary

End point timeframe:

12 Weeks

End point values	C2 +D2	C1 + D1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1622	537		
Units: Liters				
least squares mean (confidence interval 95%)	1.765 (1.7532 to 1.7768)	1.6789 (1.6587 to 1.6992)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline on Transition Dyspnea Index (TDI) for groups: indacaterol maleate and glycopyrronium bromide FDC vs. LABA or LAMA monotherapy or LABA and ICS in free or FDC

End point title	Change from baseline on Transition Dyspnea Index (TDI) for groups: indacaterol maleate and glycopyrronium bromide FDC vs. LABA or LAMA monotherapy or LABA and ICS in free or FDC

End point description:

Transition Dyspnea Index (TDI) captures changes from baseline. The TDI score is based on three domains with each domain scored from -3 (major deterioration) to +3 (major improvement), to give an overall score of -9 to +9, a negative score indicating a deterioration from baseline. A TDI focal score of 1 is considered to be a clinically significant improvement from baseline.

End point type	Secondary

End point timeframe:

Day 1 (baseline) and week 12

End point values	C2 +D2	C1 + D1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1622	537		
Units: Score on a scale				
least squares mean (confidence interval 95%)	2.0354 (1.8811 to 2.1896)	0.8588 (0.5983 to 1.1192)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline on Total score of COPD Assessment Test (CAT) for groups: glycopyrronium and indacaterol maleate and glycopyrronium bromide FDC

End point title	Change from baseline on Total score of COPD Assessment Test (CAT) for groups: glycopyrronium and indacaterol maleate and glycopyrronium bromide FDC

End point description:

Total score of COPD Assessment Test (CAT) will be measured at baseline and at week 12. This questionnaire is completed by the patient. The score ranges from 0-40 where higher scores represent worse health status. CAT scores ≥ 10 are associated with significantly impaired health status.

End point type	Secondary

End point timeframe:

Day 1 (baseline) and Week 12

End point values	A1 (any SABA and/or SAMA)	A2 (glycopyrronium)	B1 (any LAMA or LABA and mMRC=1)	B2 (glycopyrronium and mMRC=1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	122	369	420	1254
Units: Score				
arithmetic mean (standard deviation)	0.1 (± 4.6)	-1.8 (± 5.3)	0.1 (± 4.9)	-0.5 (± 4.6)

End point values	C1 (any LABA and ICS)	C2 (indacaterol/glycopyrronium)	D1 (any LAMA or LABA and mMRC>1)	D2 (indacaterol/glycopyrronium and mMRC>1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	269	811	268	811
Units: Score				
arithmetic mean (standard deviation)	-0.4 (± 4.8)	-1.4 (± 5.4)	-0.9 (± 5)	-1.9 (± 5.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline on Total score of Clinical COPD Questionnaire

(CCQ) for groups: glycopyrronium and indacaterol maleate and glycopyrronium bromide FDC

End point title	Change from baseline on Total score of Clinical COPD Questionnaire (CCQ) for groups: glycopyrronium and indacaterol maleate and glycopyrronium bromide FDC

End point description:

The Clinical COPD Questionnaire (CCQ) is a self-administered 10-item questionnaire developed to measure clinical control in patients with COPD. Patients will be instructed to recall their experiences during the previous week. They respond to each question using a 7-point scale from 0 = asymptomatic/no imitation to 6 = extremely symptomatic/totally limited. The questionnaire is divided into 3 domains (symptoms [items 1, 2, 5, and 6] functional [items 7, 8, 9, and 10] and mental state [items 3 and 4]). The overall clinical COPD control score and the scores of the domains are calculated by adding all the scores together and dividing this sum by the number of questions. Thus, the overall clinical COPD control score as well as the score on each of the three domains varies between 0 (very good control) to 6 (extremely poor control).

End point type	Secondary

End point timeframe:

Day 1 (baseline) and Week 12

End point values	A1 (any SABA and/or SAMA)	A2 (glycopyrronium)	B1 (any LAMA or LABA and mMRC=1)	B2 (glycopyrronium and mMRC=1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	122	369	420	1254
Units: Score				
arithmetic mean (standard deviation)	0 (± 0.6)	-0.3 (± 0.7)	0 (± 0.7)	-0.1 (± 0.7)

End point values	C1 (any LABA and ICS)	C2 (indacaterol/glycopyrronium)	D1 (any LAMA or LABA and mMRC>1)	D2 (indacaterol/glycopyrronium and mMRC>1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	269	811	268	811
Units: Score				
arithmetic mean (standard deviation)	-0.1 (± 0.7)	-0.2 (± 0.8)	-0.1 (± 0.8)	-0.3 (± 0.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of puffs of rescue medication use for groups: glycopyrronium and indacaterol maleate and glycopyrronium bromide FDC

End point title	Mean number of puffs of rescue medication use for groups: glycopyrronium and indacaterol maleate and glycopyrronium bromide FDC

End point description:

Mean number of puffs of rescue medication use will be measured using eDiary data over 12 weeks of treatment.

End point type	Secondary
End point timeframe: 12 weeks	

End point values	A1 (any SABA and/or SAMA)	A2 (glycopyrronium)	B1 (any LAMA or LABA and mMRC=1)	B2 (glycopyrronium and mMRC=1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	122	369	420	1254
Units: Number of puffs				
arithmetic mean (standard deviation)	1.8 (± 1.7)	1 (± 1.3)	0.8 (± 1.2)	0.7 (± 1.1)

End point values	C1 (any LABA and ICS)	C2 (indacaterol/glycopyrronium)	D1 (any LAMA or LABA and mMRC>1)	D2 (indacaterol/glycopyrronium and mMRC>1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	269	811	268	811
Units: Number of puffs				
arithmetic mean (standard deviation)	1.6 (± 1.7)	1.1 (± 1.4)	1.4 (± 1.4)	1.1 (± 1.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of reported symptoms of COPD for groups: glycopyrronium and indacaterol maleate and glycopyrronium bromide FDC

End point title	Number of reported symptoms of COPD for groups: glycopyrronium and indacaterol maleate and glycopyrronium bromide FDC
End point description: Patient-reported symptoms of COPD combined will be measured using eDiary data reported over the 12 week treatment period.	
End point type	Secondary
End point timeframe: 12 weeks	

End point values	A1 (any SABA and/or SAMA)	A2 (glycopyrronium)	B1 (any LAMA or LABA and mMRC=1)	B2 (glycopyrronium and mMRC=1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	122	369	420	1254
Units: Score				
arithmetic mean (standard deviation)	-0.04 (± 0.15)	-0.1 (± 0.22)	-0.03 (± 0.19)	-0.05 (± 0.2)

End point values	C1 (any LABA and ICS)	C2 (indacaterol/glycopyrronium)	D1 (any LAMA or LABA and mMRC>1)	D2 (indacaterol/glycopyrronium and mMRC>1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	269	811	268	811
Units: Score				
arithmetic mean (standard deviation)	-0.05 (± 0.19)	-0.07 (± 0.22)	-0.04 (± 0.19)	-0.09 (± 0.21)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	any SABA and/or SAMA
Reporting group description:	
any SABA and/or SAMA	
Reporting group title	any LAMA or@ LABA and mMRC eq 1
Reporting group description:	
any LAMA or@ LABA and mMRC eq 1	
Reporting group title	glycopyrronium
Reporting group description:	
glycopyrronium	
Reporting group title	glycopyrronium@ and mMRC eq 1
Reporting group description:	
glycopyrronium@ and mMRC eq 1	
Reporting group title	any LABA and ICS
Reporting group description:	
any LABA and ICS	
Reporting group title	indacaterol/@glycopyrronium
Reporting group description:	
indacaterol/@glycopyrronium	
Reporting group title	indacaterol/@glycopyrronium and@ mMRC gt 1
Reporting group description:	
indacaterol/@glycopyrronium and@ mMRC gt 1	
Reporting group title	any LAMA or@ LABA and mMRC gt 1
Reporting group description:	
any LAMA or@ LABA and mMRC gt 1	

Serious adverse events	any SABA and/or SAMA	any LAMA or@ LABA and mMRC eq 1	glycopyrronium
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 125 (3.20%)	11 / 417 (2.64%)	9 / 385 (2.34%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Brain neoplasm			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Bronchial carcinoma			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	1 / 385 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Laryngeal cancer			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	1 / 125 (0.80%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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

Oropharyngeal cancer			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Prostate cancer			
subjects affected / exposed	0 / 125 (0.00%)	1 / 417 (0.24%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the tongue			
subjects affected / exposed	0 / 125 (0.00%)	1 / 417 (0.24%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	1 / 385 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	1 / 385 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	0 / 125 (0.00%)	1 / 417 (0.24%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Femoral artery aneurysm			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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

Hypertension			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Intermittent claudication			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Ischaemia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	1 / 385 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Peripheral artery aneurysm			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Peripheral artery stenosis			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Peripheral artery thrombosis			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Shock			

subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Thrombophlebitis superficial			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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			
Chest pain			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	1 / 385 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 125 (0.00%)	1 / 417 (0.24%)	1 / 385 (0.26%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 125 (0.00%)	1 / 417 (0.24%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	1 / 385 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 125 (0.00%)	1 / 417 (0.24%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	1 / 125 (0.80%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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 depression			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Depression			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Heart rate decreased			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			

complications			
Ankle fracture			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Bursa injury			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Femoral neck fracture			
subjects affected / exposed	0 / 125 (0.00%)	1 / 417 (0.24%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Fracture			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			

subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Splenic rupture			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Congenital central nervous system anomaly			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Hydrocele			
subjects affected / exposed	1 / 125 (0.80%)	0 / 417 (0.00%)	0 / 385 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute myocardial infarction			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Aortic valve incompetence			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Aortic valve stenosis			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Arrhythmia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	1 / 385 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	1 / 125 (0.80%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Coronary artery disease			
subjects affected / exposed	0 / 125 (0.00%)	1 / 417 (0.24%)	2 / 385 (0.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Left ventricular failure			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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	1 / 125 (0.80%)	0 / 417 (0.00%)	0 / 385 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Tachycardia			

subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	1 / 385 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Cerebrovascular disorder			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Embolic cerebral infarction			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Loss of consciousness			
subjects affected / exposed	0 / 125 (0.00%)	1 / 417 (0.24%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ruptured cerebral aneurysm			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Syncope			

subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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	1 / 125 (0.80%)	0 / 417 (0.00%)	0 / 385 (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
Vascular dementia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular encephalopathy			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	1 / 385 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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 incarcerated hernia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	1 / 385 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 125 (0.00%)	1 / 417 (0.24%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum oesophageal			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	1 / 385 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Inguinal hernia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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			
Bile duct stone			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Biliary tract disorder			

subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Hepatic cirrhosis			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Fatigue			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Hernia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Sudden death			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Ulcer			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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

Back pain			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Pseudarthrosis			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Synovitis			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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			
Bronchitis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 417 (0.24%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 417 (0.24%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Mediastinal abscess			

subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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
Oesophageal candidiasis			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	1 / 385 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	0 / 385 (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	glycopyrronium@ and mMRC eq 1	any LABA and ICS	indacaterol/@glycopyrronium
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 1248 (2.40%)	6 / 269 (2.23%)	22 / 816 (2.70%)
number of deaths (all causes)	3	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Brain neoplasm			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Breast cancer			

subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Bronchial carcinoma			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Colon cancer			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Laryngeal cancer			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Lung adenocarcinoma			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Metastases to bone			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Oropharyngeal cancer			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Prostate cancer			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Squamous cell carcinoma of the tongue			

subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Aortic stenosis			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Circulatory collapse			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Femoral artery aneurysm			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Hypertension			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Intermittent claudication			

subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Ischaemia			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Peripheral artery aneurysm			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Peripheral artery stenosis			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Peripheral artery thrombosis			
subjects affected / exposed	0 / 1248 (0.00%)	1 / 269 (0.37%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Thrombophlebitis superficial			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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			
Chest pain			

subjects affected / exposed	2 / 1248 (0.16%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 1248 (0.24%)	1 / 269 (0.37%)	3 / 816 (0.37%)
occurrences causally related to treatment / all	3 / 3	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Drug hypersensitivity			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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			
Pneumothorax			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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

Respiratory depression			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Depression			
subjects affected / exposed	0 / 1248 (0.00%)	1 / 269 (0.37%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart rate decreased			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursa injury			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			

subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Femoral neck fracture			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Femur fracture			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Splenic rupture			

subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Congenital central nervous system anomaly			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocele			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Acute myocardial infarction			
subjects affected / exposed	2 / 1248 (0.16%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Aortic valve incompetence			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Aortic valve stenosis			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Arrhythmia			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 1248 (0.00%)	1 / 269 (0.37%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Coronary artery disease			

subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Left ventricular failure			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Cerebrovascular accident			

subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular disorder			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Cerebrovascular insufficiency			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Embolic cerebral infarction			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Loss of consciousness			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Ruptured cerebral aneurysm			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Syncope			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular dementia			

subjects affected / exposed	0 / 1248 (0.00%)	1 / 269 (0.37%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular encephalopathy			
subjects affected / exposed	0 / 1248 (0.00%)	1 / 269 (0.37%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	2 / 816 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Abdominal incarcerated hernia			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Constipation			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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

Diverticulum oesophageal			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Faecaloma			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Inguinal hernia			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Pancreatitis			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Biliary tract disorder			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Hepatic cirrhosis			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Blister			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Fatigue			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernia			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Sudden death			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Ulcer			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Back pain			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Osteoarthritis			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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

Pseudarthrosis			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	0 / 816 (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
Synovitis			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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			
Bronchitis			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Cystitis			
subjects affected / exposed	0 / 1248 (0.00%)	1 / 269 (0.37%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Influenza			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Mediastinal abscess			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (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
Oesophageal candidiasis			
subjects affected / exposed	0 / 1248 (0.00%)	0 / 269 (0.00%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	2 / 1248 (0.16%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 1248 (0.00%)	1 / 269 (0.37%)	0 / 816 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	indacaterol/@glycopyrronium and@ mMRC gt 1	any LAMA or@ LABA and mMRC gt 1	
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 814 (4.18%)	10 / 269 (3.72%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	2 / 814 (0.25%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			

subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal cancer			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the tongue			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			

subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 814 (0.25%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery aneurysm			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 814 (0.12%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	0 / 814 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemia			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			

subjects affected / exposed	3 / 814 (0.37%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	3 / 814 (0.37%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 814 (0.37%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Anaphylactic shock			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 814 (0.12%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory depression			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Depression			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart rate decreased			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursa injury			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fracture			
subjects affected / exposed	0 / 814 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hip fracture			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	0 / 814 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 814 (0.12%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Splenic rupture			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 814 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Wound dehiscence			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			

Congenital central nervous system anomaly			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocele			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 814 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arrhythmia			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 814 (0.12%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 814 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 814 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic cerebral infarction			

subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured cerebral aneurysm			
subjects affected / exposed	0 / 814 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular dementia			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular encephalopathy			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenic purpura			

subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal incarcerated hernia			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum oesophageal			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract disorder			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fatigue			

subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ulcer			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudarthrosis			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			

subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinal abscess			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 814 (0.12%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 814 (0.86%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	7 / 7	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 814 (0.00%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	any SABA and/or SAMA	any LAMA or@ LABA and mMRC eq 1	glycopyrronium
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 125 (15.20%)	63 / 417 (15.11%)	67 / 385 (17.40%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 125 (0.80%)	7 / 417 (1.68%)	3 / 385 (0.78%)
occurrences (all)	1	7	3
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 125 (0.00%)	3 / 417 (0.72%)	7 / 385 (1.82%)
occurrences (all)	0	3	8
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	2 / 125 (1.60%)	1 / 417 (0.24%)	0 / 385 (0.00%)
occurrences (all)	2	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 125 (2.40%)	13 / 417 (3.12%)	5 / 385 (1.30%)
occurrences (all)	3	13	6
Dyspnoea			
subjects affected / exposed	1 / 125 (0.80%)	6 / 417 (1.44%)	5 / 385 (1.30%)
occurrences (all)	1	6	5
Oropharyngeal pain			
subjects affected / exposed	0 / 125 (0.00%)	3 / 417 (0.72%)	4 / 385 (1.04%)
occurrences (all)	0	3	4
Productive cough			
subjects affected / exposed	0 / 125 (0.00%)	0 / 417 (0.00%)	4 / 385 (1.04%)
occurrences (all)	0	0	4
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 125 (1.60%)	3 / 417 (0.72%)	6 / 385 (1.56%)
occurrences (all)	2	3	6
Infections and infestations			

Bronchitis			
subjects affected / exposed	0 / 125 (0.00%)	4 / 417 (0.96%)	4 / 385 (1.04%)
occurrences (all)	0	5	4
Nasopharyngitis			
subjects affected / exposed	8 / 125 (6.40%)	24 / 417 (5.76%)	38 / 385 (9.87%)
occurrences (all)	8	26	40
Pharyngitis			
subjects affected / exposed	3 / 125 (2.40%)	0 / 417 (0.00%)	1 / 385 (0.26%)
occurrences (all)	3	0	1
Rhinitis			
subjects affected / exposed	0 / 125 (0.00%)	7 / 417 (1.68%)	1 / 385 (0.26%)
occurrences (all)	0	7	1
Tracheitis			
subjects affected / exposed	2 / 125 (1.60%)	2 / 417 (0.48%)	0 / 385 (0.00%)
occurrences (all)	3	2	0
Urinary tract infection			
subjects affected / exposed	2 / 125 (1.60%)	1 / 417 (0.24%)	2 / 385 (0.52%)
occurrences (all)	2	1	2

Non-serious adverse events	glycopyrronium@ and mMRC eq 1	any LABA and ICS	indacaterol/@glycopyrronium
Total subjects affected by non-serious adverse events			
subjects affected / exposed	163 / 1248 (13.06%)	29 / 269 (10.78%)	119 / 816 (14.58%)
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 1248 (0.56%)	2 / 269 (0.74%)	5 / 816 (0.61%)
occurrences (all)	8	2	5
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 1248 (0.72%)	1 / 269 (0.37%)	12 / 816 (1.47%)
occurrences (all)	13	1	16
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	3 / 1248 (0.24%)	0 / 269 (0.00%)	2 / 816 (0.25%)
occurrences (all)	3	0	3
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	33 / 1248 (2.64%)	5 / 269 (1.86%)	44 / 816 (5.39%)
occurrences (all)	35	7	47
Dyspnoea			
subjects affected / exposed	13 / 1248 (1.04%)	6 / 269 (2.23%)	7 / 816 (0.86%)
occurrences (all)	14	7	7
Oropharyngeal pain			
subjects affected / exposed	10 / 1248 (0.80%)	4 / 269 (1.49%)	3 / 816 (0.37%)
occurrences (all)	10	4	3
Productive cough			
subjects affected / exposed	1 / 1248 (0.08%)	0 / 269 (0.00%)	2 / 816 (0.25%)
occurrences (all)	1	0	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 1248 (0.64%)	2 / 269 (0.74%)	10 / 816 (1.23%)
occurrences (all)	8	2	10
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 1248 (0.32%)	1 / 269 (0.37%)	1 / 816 (0.12%)
occurrences (all)	4	1	1
Nasopharyngitis			
subjects affected / exposed	71 / 1248 (5.69%)	11 / 269 (4.09%)	37 / 816 (4.53%)
occurrences (all)	81	12	39
Pharyngitis			
subjects affected / exposed	7 / 1248 (0.56%)	0 / 269 (0.00%)	3 / 816 (0.37%)
occurrences (all)	8	0	3
Rhinitis			
subjects affected / exposed	12 / 1248 (0.96%)	2 / 269 (0.74%)	5 / 816 (0.61%)
occurrences (all)	12	2	5
Tracheitis			
subjects affected / exposed	2 / 1248 (0.16%)	0 / 269 (0.00%)	2 / 816 (0.25%)
occurrences (all)	2	0	2
Urinary tract infection			
subjects affected / exposed	5 / 1248 (0.40%)	0 / 269 (0.00%)	1 / 816 (0.12%)
occurrences (all)	5	0	1

Non-serious adverse events	indacaterol/@glycopyrronium and@ mMRC gt 1	any LAMA or@ LABA and mMRC gt 1	
Total subjects affected by non-serious adverse events subjects affected / exposed	120 / 814 (14.74%)	20 / 269 (7.43%)	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	7 / 814 (0.86%) 7	0 / 269 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	8 / 814 (0.98%) 8	1 / 269 (0.37%) 1	
Gastrointestinal disorders Dyspepsia subjects affected / exposed occurrences (all)	1 / 814 (0.12%) 1	0 / 269 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	27 / 814 (3.32%) 29	4 / 269 (1.49%) 4	
Dyspnoea subjects affected / exposed occurrences (all)	7 / 814 (0.86%) 7	2 / 269 (0.74%) 2	
Oropharyngeal pain subjects affected / exposed occurrences (all)	4 / 814 (0.49%) 4	1 / 269 (0.37%) 1	
Productive cough subjects affected / exposed occurrences (all)	0 / 814 (0.00%) 0	2 / 269 (0.74%) 2	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	11 / 814 (1.35%) 12	2 / 269 (0.74%) 2	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	3 / 814 (0.37%) 3	1 / 269 (0.37%) 1	

Nasopharyngitis			
subjects affected / exposed	54 / 814 (6.63%)	10 / 269 (3.72%)	
occurrences (all)	59	12	
Pharyngitis			
subjects affected / exposed	5 / 814 (0.61%)	1 / 269 (0.37%)	
occurrences (all)	6	1	
Rhinitis			
subjects affected / exposed	10 / 814 (1.23%)	1 / 269 (0.37%)	
occurrences (all)	11	1	
Tracheitis			
subjects affected / exposed	2 / 814 (0.25%)	0 / 269 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	3 / 814 (0.37%)	0 / 269 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2014	introduced the following changes to be aligned with the requests included in the List of Grounds for Non-acceptance following the results of the assessment during Voluntary Harmonization Procedures VHP419 (VHP2013136): • Addition of Exclusion Criterion 8: "Patients on non-selective beta-blockers. Those patients may enter the study after non-selective beta-blocker withdrawal during a 7-day wash-out period". Addition of Exclusion Criterion 9: "Patients receiving any other prohibited COPD-related medications.
05 March 2014	introduced the following change requested by Regulatory Authorities: • A secondary endpoint was added: "To evaluate the effect of glycopyrronium (50 µg o.d.) and indacaterol maleate and glycopyrronium bromide FDC (110/50 µg o.d) vs. baseline therapy on: Trough FEV1 at Visit 4 (after 12 weeks of treatment)".
28 March 2014	introduced the following change requested by Regulatory Authorities (Voluntary Harmonization Procedure): • To promote FEV1 as primary endpoint maintaining BDI/TDI as co-primary endpoint since FEV1 is a well-established parameter to measure treatment efficacy and is a well-recognized endpoint in COPD clinical trials
03 February 2015	introduced the following changes to clarify some issues identified during the trial conduct: • Protocol Requested Treatment (Inclusion Criterion 6) was updated following the intention to clarify that all formulations of inhaled medication commercially available with an indication for use in patients with COPD in the therapeutic categories included in the study protocol were eligible for study inclusion. • Spirometry Guidance was updated to clarify the steps to be taken while performing a spirometry test during the study and how the related results should be interpreted before confirming the patient eligibility for the study.
27 July 2015	• Due to low recruitment in Groups A and B that would lead to a significant delay of trial completion, a decision was made to close the recruitment of Groups A and B at the time the randomization in Groups C and D would be completed. Recruitment of the Groups C and D continued as originally planned. To guarantee appropriate power, the drop-out rate was updated (from 5% to 10%) according to the approximate number of early terminated patients in the trial at the time when this amendment was written. • Addition of Exclusion Criterion 5: "Patients who have a post-bronchodilator FEV1 decrease more than 10% compared to pre-bronchodilator FEV1 result at Visit 2" to provide further clarity to investigators and support the proper implementation of the reversibility testing criterion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported