



Clinical trial results:

A 52-week treatment, multi-center, randomized, doubleblind, double dummy, parallel-group, active controlled study to compare the effect of QVA149 (indacaterol maleate / glycopyrronium bromide) with salmeterol/fluticasone on the rate of exacerbations in subjects with moderate to very severe COPD.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

Summary

EudraCT number	2012-004966-16
Trial protocol	SK HU SE ES AT LT NL CZ FI DE BE IS IT PT NO PL EE DK BG
Global end of trial date	15 September 2015

Results information

Result version number	v1 (current)
This version publication date	12 July 2018
First version publication date	12 July 2018

Trial information

Trial identification

Sponsor protocol code	CQVA149A2318
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01782326
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
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that QVA149 (110/50 µg o.d.) was at least non-inferior to salmeterol/fluticasone (50/500 µg b.i.d.) in terms of rate of Chronic Obstructive Pulmonary Disease (COPD) exacerbations (mild/moderate/severe) during 52 weeks of treatment

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	29 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 180
Country: Number of subjects enrolled	Austria: 94
Country: Number of subjects enrolled	Belgium: 84
Country: Number of subjects enrolled	Bulgaria: 105
Country: Number of subjects enrolled	Canada: 51
Country: Number of subjects enrolled	Chile: 14
Country: Number of subjects enrolled	China: 295
Country: Number of subjects enrolled	Colombia: 29
Country: Number of subjects enrolled	Croatia: 36
Country: Number of subjects enrolled	Czech Republic: 167
Country: Number of subjects enrolled	Denmark: 60
Country: Number of subjects enrolled	Estonia: 31
Country: Number of subjects enrolled	Finland: 22
Country: Number of subjects enrolled	France: 24

Country: Number of subjects enrolled	Germany: 525
Country: Number of subjects enrolled	United Kingdom: 41
Country: Number of subjects enrolled	Greece: 72
Country: Number of subjects enrolled	Guatemala: 49
Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Hungary: 73
Country: Number of subjects enrolled	Iceland: 21
Country: Number of subjects enrolled	India: 103
Country: Number of subjects enrolled	Italy: 98
Country: Number of subjects enrolled	Japan: 80
Country: Number of subjects enrolled	Korea, Republic of: 71
Country: Number of subjects enrolled	Latvia: 17
Country: Number of subjects enrolled	Lithuania: 57
Country: Number of subjects enrolled	Mexico: 32
Country: Number of subjects enrolled	Netherlands: 58
Country: Number of subjects enrolled	Norway: 26
Country: Number of subjects enrolled	Philippines: 35
Country: Number of subjects enrolled	Poland: 95
Country: Number of subjects enrolled	Portugal: 31
Country: Number of subjects enrolled	Romania: 172
Country: Number of subjects enrolled	Russian Federation: 94
Country: Number of subjects enrolled	Serbia: 69
Country: Number of subjects enrolled	Slovakia: 104
Country: Number of subjects enrolled	South Africa: 96
Country: Number of subjects enrolled	Spain: 87
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Taiwan: 16
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	Turkey: 25
Worldwide total number of subjects	3358
EEA total number of subjects	2106

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)	1650
From 65 to 84 years	1700
85 years and over	8

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This was a 52- week treatment, multi-center, randomized, double-blind, double-dummy, parallel-group, non-inferiority, active controlled study to evaluate the effect of QVA149 (110/50 µg o.d.) compared to salmeterol/fluticasone (50/500 µg b.i.d.) on exacerbations (mild/moderate/severe) in patients with moderate to very severe COPD.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	QVA149

Arm description:

QVA149 (110/50 µg) once daily

Arm type	Experimental
Investigational medicinal product name	indacaterol maleate / glycopyrronium bromide
Investigational medicinal product code	QVA149
Other name	indacaterol maleate / glycopyrronium bromide
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Dosage and administration details:

110/50 µg capsules

Arm title	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
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Arm description:

Salmeterol/fluticasone (50/500µg) twice a day

Arm type	Active comparator
Investigational medicinal product name	Salmeterol/fluticasone
Investigational medicinal product code	
Other name	Salmeterol/fluticasone
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

110/50 µg o.d powder for multi dose administration

Number of subjects in period 1	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Started	1678	1680
Completed	1400	1360
Not completed	278	320
Adverse event, serious fatal	129	145
Physician decision	13	16
Technical problems	-	5
Protocol deviation	8	7
Lack of efficacy	17	22

Baseline characteristics

Reporting groups

Reporting group title	QVA149
Reporting group description: QVA149 (110/50 µg) once daily	
Reporting group title	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Reporting group description: Salmeterol/fluticasone (50/500µg) twice a day	

Reporting group values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)	Total
Number of subjects	1678	1680	3358
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)	816	834	1650
From 65-84 years	860	840	1700
85 years and over	2	6	8
Age Continuous Units: years			
arithmetic mean	64.6	64.5	
standard deviation	± 7.89	± 7.7	-
Gender, Male/Female Units: Participants			
Female	1297	1256	2553
Male	381	424	805

End points

End points reporting groups

Reporting group title	QVA149
Reporting group description:	
QVA149 (110/50 µg) once daily	
Reporting group title	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Reporting group description:	
Salmeterol/fluticasone (50/500µg) twice a day	

Primary: Rate of COPD exacerbations

End point title	Rate of COPD exacerbations
End point description:	
COPD exacerbations starting between first dose and one day after last treatment are included. COPD exacerbations that occurred within 7 days of each other are collapsed as one event. Estimates are from a generalized linear model assuming a negative binomial distribution with terms for treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during the past 12 months prior to study), smoking status at screening, ICS use at screening, airflow limitation severity, and region. As the offset variable log(exposure time in years) was used.	
End point type	Primary
End point timeframe:	
52 weeks	

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1528	1556		
Units: COPD Exacerbations/year				
least squares mean (confidence interval 95%)	3.59 (3.28 to 3.94)	4.03 (3.68 to 4.41)		

Statistical analyses

Statistical analysis title	Rate of COPD exacerbations
Comparison groups	QVA149 v Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of subjects included in analysis	3084
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Method	Generalized linear model
Parameter estimate	Rate Ratio
Point estimate	0.89

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	0.96

Notes:

[1] - Study was designed to have >95% power to rule out a 1.15-fold increase in the rate exacerbations for QVA149 vs. salmeterol/fluticasone.

Statistical analysis title	Rate of COPD exacerbations
Comparison groups	QVA149 v Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of subjects included in analysis	3084
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Generalized linear method
Parameter estimate	Rate Ratio
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	0.96

Secondary: Time to first COPD exacerbation.

End point title	Time to first COPD exacerbation.
End point description:	
First COPD exacerbations starting between first dose and one day after last treatment are included. Cox regression model includes terms for treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during the past 12 months prior to study), smoking status at screening, ICS use at screening, airflow limitation severity, and region.	
End point type	Secondary
End point timeframe:	
52 weeks	

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1675	1679		
Units: Days				
median (confidence interval 95%)	71 (60 to 82)	51 (46 to 57)		

Statistical analyses

Statistical analysis title	Time to first COPD exacerbation.
Comparison groups	QVA149 v Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of subjects included in analysis	3354
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	0.91

Secondary: Rate of moderate to severe COPD exacerbations.

End point title	Rate of moderate to severe COPD exacerbations.
End point description: COPD exacerbations starting between date of first dose and one day after last treatment are included. COPD exacerbations that occurred within 7 days of each other are collapsed as one event with the worst severity. A COPD exacerbation of moderate severity meets the symptoms definition in the protocol and requires treatment with systemic corticosteroids and/or antibiotics. A severe COPD exacerbation requires hospitalization. Estimates are from a generalized linear model assuming a negative binomial distribution with terms for treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during the past 12 months prior to study), smoking status at screening, ICS use at screening, airflow limitation severity, and region. The offset variable log(exposure time in years) was used.	
End point type	Secondary
End point timeframe: 52 weeks	

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1651	1656		
Units: COPD Exacerbation/year				
least squares mean (confidence interval 95%)	0.98 (0.88 to 1.1)	1.19 (1.07 to 1.32)		

Statistical analyses

Statistical analysis title	Rate of moderate to severe COPD exacerbations
Comparison groups	QVA149 v Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of subjects included in analysis	3307
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Generalized linear model
Parameter estimate	Rate Ratio
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	0.91

Secondary: Time to first moderate to severe COPD exacerbation.

End point title	Time to first moderate to severe COPD exacerbation.
End point description: First COPD exacerbations starting between first dose and one day after last treatment are included. Cox regression model includes terms for treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during the past 12 months prior to study), smoking status at screening, ICS use at screening, airflow limitation severity, and region.	
End point type	Secondary
End point timeframe: 52 weeks.	

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1675	1679		
Units: Days				
median (confidence interval 95%)	999 (99 to 9999)	308 (283 to 352)		

Statistical analyses

Statistical analysis title	Time to first moderate to severe COPD exacerbation
Comparison groups	QVA149 v Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)

Number of subjects included in analysis	3354
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	0.86

Secondary: Rate of moderate to severe COPD exacerbations requiring treatment with systemic corticosteroids

End point title	Rate of moderate to severe COPD exacerbations requiring treatment with systemic corticosteroids
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End point description:

COPD exacerbations starting between date of first dose and one day after last treatment are included. COPD exacerbations that occurred within 7 days of each other are collapsed as one event with the worst severity. Estimates are from a generalized linear model assuming a negative binomial distribution with fixed effects of treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during the past 12 months prior to study), smoking status at screening, ICS use at screening, airflow limitation severity, and region. The offset variable log(exposure time in years) was used.

End point type	Secondary
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End point timeframe:

52 weeks

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1651	1656		
Units: COPD Exacerbation/year				
least squares mean (confidence interval 95%)	0.18 (0.14 to 0.22)	0.18 (0.14 to 0.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of moderate to severe COPD exacerbations requiring treatment with antibiotics

End point title	Rate of moderate to severe COPD exacerbations requiring treatment with antibiotics
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End point description:

Estimates are from a generalized linear model assuming a negative binomial distribution with terms for treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during the past 12 months prior to study), smoking status at screening, ICS use at screening, airflow limitation severity, and region. The offset variable log(exposure time in years) was used. COPD exacerbations starting between first dose and one day after last treatment are included .

End point type	Secondary
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End point timeframe:

52 weeks

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1651	1656		
Units: COPD Exacerbation/year				
least squares mean (confidence interval 95%)	0.17 (0.13 to 0.22)	0.22 (0.17 to 0.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of moderate to severe COPD exacerbations requiring hospitalization. COPD exacerbations starting between first dose and one day after last treatment are included.

End point title	Rate of moderate to severe COPD exacerbations requiring hospitalization. COPD exacerbations starting between first dose and one day after last treatment are included.
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End point description:

All exacerbations requiring hospitalization are considered severe according to protocol definitions so this is the rate of severe COPD exacerbations only. Note - an ER visit of longer than 24 hours was considered a hospitalization.

End point type	Secondary
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End point timeframe:

52 weeks

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1651	1656		
Units: COPD Exacerbation/year				
least squares mean (confidence interval 95%)	0.15 (0.11 to 0.19)	0.17 (0.13 to 0.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of moderate to severe COPD exacerbations requiring re-hospitalization within 30 days

End point title	Rate of moderate to severe COPD exacerbations requiring re-hospitalization within 30 days
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End point description:

Re-hospitalizations are defined as hospitalizations starting within the first 30 days after a severe COPD exacerbation and between first dose and one day after date of last treatment. Generalized linear model assuming a negative binomial distribution with terms for treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during the past 12 months prior to study), smoking status at screening, ICS use at screening, airflow limitation severity, and region. The offset variable log(exposure time in years) was used. COPD exacerbations starting between first dose and one day after last treatment are included.

End point type	Secondary
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End point timeframe:

52 weeks

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1675	1679		
Units: COPD Exacerbation/year				
arithmetic mean (standard deviation)	0 (± 0.15)	0 (± 0.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first moderate to severe COPD exacerbations requiring treatment with systemic corticosteroids

End point title	Time to first moderate to severe COPD exacerbations requiring treatment with systemic corticosteroids
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End point description:

Cox regression model includes terms for treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during the past 12 months prior to study), smoking status at screening, ICS use at screening, airflow limitation severity, and region. COPD exacerbations starting between first dose and one day after date of last treatment are included.

End point type	Secondary
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End point timeframe:

52 weeks

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1675	1679		
Units: Days				
median (confidence interval 95%)	999 (99 to 9999)	999 (99 to 9999)		

Statistical analyses

Statistical analysis title	Exacerbations requiring systemic corticosteroids
Comparison groups	QVA149 v Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of subjects included in analysis	3354
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.256
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.08

Secondary: Time to first moderate to severe COPD exacerbations requiring treatment with antibiotics

End point title	Time to first moderate to severe COPD exacerbations requiring treatment with antibiotics
End point description: Cox regression model includes terms for treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during the past 12 months prior to study), smoking status at screening, ICS use at screening, airflow limitation severity, and region. COPD exacerbations starting between first dose and one day after date of last treatment are included.	
End point type	Secondary
End point timeframe: 52 weeks	

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1675	1679		
Units: Days				
median (confidence interval 95%)	999 (99 to 9999)	999 (99 to 9999)		

Statistical analyses

Statistical analysis title	Exacerbations requiring treatment with antibiotics
Comparison groups	QVA149 v Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of subjects included in analysis	3354
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.008
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	0.95

Secondary: Time to first moderate to severe COPD exacerbations requiring hospitalization

End point title	Time to first moderate to severe COPD exacerbations requiring hospitalization
End point description:	
Cox regression model includes terms for treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during the past 12 months prior to study), smoking status at screening, ICS use at screening, airflow limitation severity, and region. COPD exacerbations starting between first dose and one day after date of last treatment are included.	
End point type	Secondary
End point timeframe:	
52 weeks	

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1675	1679		
Units: Days				
median (confidence interval 95%)	999 (99 to 9999)	999 (99 to 9999)		

Statistical analyses

Statistical analysis title	Exacerbations requiring hospitalization
Comparison groups	QVA149 v Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of subjects included in analysis	3354
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.046
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1

Secondary: Time to first moderate to severe COPD exacerbations requiring re-hospitalization within 30 days

End point title	Time to first moderate to severe COPD exacerbations requiring re-hospitalization within 30 days
End point description:	Cox regression model includes terms for treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during the past 12 months prior to study), smoking status at screening, ICS use at screening, airflow limitation severity, and region. COPD exacerbations starting between first dose and one day after date of last treatment are included.
End point type	Secondary
End point timeframe:	52 weeks

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1675	1679		
Units: Days				
median (confidence interval 95%)	999 (99 to 9999)	999 (99 to 9999)		

Statistical analyses

Statistical analysis title	Exacerbations requiring re-hospitalization
Comparison groups	QVA149 v Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of subjects included in analysis	3354
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.79
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	2.1

Secondary: Forced expiratory volume in 1 second

End point title	Forced expiratory volume in 1 second
End point description:	Change from baseline. Pulmonary function assessments were performed using centralized spirometry according to international standards. Baseline FEV1 was defined as the average of the pre-dose FEV1 measured at -45 minutes (min) and -15 min at day 1. A mixed model for repeated measures (MMRM), used for this analysis, included terms of treatment, baseline FEV1 measurements, smoking status at baseline, baseline inhaled corticosteroid (ICS) use, airflow limitation severity, region, visit, treatment-by-visit interaction, and baseline FEV1-by-visit interaction.
End point type	Secondary
End point timeframe:	Baseline, day 1 (30 min and one hour post dose)

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1675	1679		
Units: Liters				
least squares mean (standard error)				
Day 1, 30 min post-dose (n=1659, 1663)	0.121 (± 0.0049)	0.076 (± 0.0049)		
Day 1, one hour post-dose (n=1657, 1664)	0.147 (± 0.0054)	0.092 (± 0.0054)		

Statistical analyses

No statistical analyses for this end point

Secondary: Forced expiratory volume in 1 second

End point title	Forced expiratory volume in 1 second
End point description:	
Change from baseline in trough value. Pulmonary function assessments were performed using centralized spirometry according to international standards. Baseline FEV1 was defined as the average of the pre-dose FEV1 measured at -45 minutes (min) and -15 min at day 1. A mixed model for repeated measures (MMRM), used for this analysis, included terms of treatment, baseline FEV1 measurements, smoking status at baseline, baseline inhaled corticosteroid (ICS) use, region, airflow limitation severity, visit, treatment-by-visit interaction, and baseline FEV1-by-visit interaction.	
End point type	Secondary
End point timeframe:	
Baseline, 4 weeks	

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1597	1595		
Units: Liters				
least squares mean (standard error)	0.079 (± 0.007)	0.006 (± 0.007)		

Statistical analyses

No statistical analyses for this end point

Secondary: Forced expiratory volume in 1 second

End point title	Forced expiratory volume in 1 second
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End point description:

Change from baseline in trough value. Pulmonary function assessments were performed using centralized spirometry according to international standards. Baseline FEV1 was defined as the average of the pre-dose FEV1 measured at -45 minutes (min) and -15 min at day 1. A mixed model for repeated measures (MMRM), used for this analysis, included terms of treatment, baseline FEV1 measurements, smoking status at baseline, baseline inhaled corticosteroid (ICS) use, region, airflow limitation severity, visit, treatment-by-visit interaction, and baseline FEV1-by-visit interaction.

End point type	Secondary
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End point timeframe:

Baseline, 12 weeks

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1597	1595		
Units: Liters				
least squares mean (standard error)	0.07 (± 0.0072)	-0.008 (± 0.0072)		

Statistical analyses

No statistical analyses for this end point

Secondary: Forced expiratory volume in 1 second

End point title	Forced expiratory volume in 1 second
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End point description:

Change from baseline in trough value. Pulmonary function assessments were performed using centralized spirometry according to international standards. Baseline FEV1 was defined as the average of the pre-dose FEV1 measured at -45 minutes (min) and -15 min at day 1. A mixed model for repeated measures (MMRM), used for this analysis, included terms of treatment, baseline FEV1 measurements, smoking status at baseline, baseline inhaled corticosteroid (ICS) use, region, airflow limitation severity, visit, treatment-by-visit interaction, and baseline FEV1-by-visit interaction.

End point type	Secondary
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End point timeframe:

Baseline, 26 weeks

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1597	1595		
Units: Liters				
least squares mean (standard error)	0.049 (± 0.0073)	-0.037 (± 0.0074)		

Statistical analyses

No statistical analyses for this end point

Secondary: Forced expiratory volume in 1 second

End point title	Forced expiratory volume in 1 second
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End point description:

Change from baseline in trough value. Pulmonary function assessments were performed using centralized spirometry according to international standards. Baseline FEV1 was defined as the average of the pre-dose FEV1 measured at -45 minutes (min) and -15 min at day 1. A mixed model for repeated measures (MMRM), used for this analysis, included terms of treatment, baseline FEV1 measurements, smoking status at baseline, baseline inhaled corticosteroid (ICS) use, region, airflow limitation severity, visit, treatment-by-visit interaction, and baseline FEV1-by-visit interaction.

End point type	Secondary
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End point timeframe:

Baseline, 38 weeks

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1597	1595		
Units: Liters				
least squares mean (standard error)	0.034 (± 0.0074)	-0.039 (± 0.0075)		

Statistical analyses

No statistical analyses for this end point

Secondary: Forced expiratory volume in 1 second

End point title	Forced expiratory volume in 1 second
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End point description:

Change from baseline in trough value. Pulmonary function assessments were performed using centralized spirometry according to international standards. Baseline FEV1 was defined as the average of the pre-dose FEV1 measured at -45 minutes (min) and -15 min at day 1. A mixed model for repeated measures (MMRM), used for this analysis, included terms of treatment, baseline FEV1 measurements, smoking status at baseline, baseline inhaled corticosteroid (ICS) use, region, airflow limitation severity, visit, treatment-by-visit interaction, and baseline FEV1-by-visit interaction.

End point type	Secondary
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End point timeframe:

Baseline, 52 weeks

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1597	1595		
Units: Liters				
least squares mean (standard error)	0.015 (± 0.0075)	-0.048 (± 0.0076)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Forced expiratory volume in 1 second AUC (0-12h)

End point title	Change from baseline in Forced expiratory volume in 1 second AUC (0-12h)
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End point description:

Pulmonary function assessments were performed using centralized spirometry according to international standards. Baseline FEV1 was defined as the average of the pre-dose FEV1 measured at -45 minutes (min) and -15 min at day 1. A mixed model for repeated measures (MMRM), used for this analysis, included terms of treatment, baseline FEV1 measurements, smoking status at baseline, baseline inhaled corticosteroid (ICS) use, region, baseline FEV1 * visit interaction, and visit, treatment * visit interaction. The trapezoidal rule was used to calculate FEV1 AUC and then normalized to the length of time"

End point type	Secondary
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End point timeframe:

Baseline, 52 weeks

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	279	277		
Units: Liters				
least squares mean (standard error)	0.078 (± 0.0174)	-0.032 (± 0.0176)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in total St. George's Respiratory Questionnaire score

End point title	Change from baseline in total St. George's Respiratory Questionnaire score
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End point description:

The St. George Respiratory Questionnaire C (SGRQ-C) is a disease-specific measure of health status for use in COPD that was used to provide the health status measurements in this study. A mixed model for repeated measures (MMRM), used for this analysis, included terms of treatment, baseline SGRQ-C total score, smoking status at baseline, baseline inhaled corticosteroid (ICS) use, airflow limitation severity, visit, treatment*visit Interaction, baseline SGRQ-C total score*visit + region. lowest possible value is zero and the highest 100. Higher values correspond to greater impairment of health status. A negative change from baseline indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline, 4 weeks

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1602	1593		
Units: Score on a scale				
least squares mean (standard error)	-2.3 (± 0.36)	-2.3 (± 0.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in total St. George's Respiratory Questionnaire score

End point title	Change from baseline in total St. George's Respiratory Questionnaire score
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End point description:

The St. George Respiratory Questionnaire C (SGRQ-C) is a disease-specific measure of health status for use in COPD that was used to provide the health status measurements in this study. A mixed model for repeated measures (MMRM), used for this analysis, included terms of treatment, baseline SGRQ-C total score, smoking status at baseline, baseline inhaled corticosteroid (ICS) use, airflow limitation severity, visit, treatment*visit Interaction, baseline SGRQ-C total score*visit + region. lowest possible value is zero and the highest 100. Higher values correspond to greater impairment of health status. A negative change from baseline indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline, 12 weeks

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1602	1593		
Units: Score on a scale				
least squares mean (standard error)	-3.2 (± 0.38)	-1.9 (± 0.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in total St. George's Respiratory Questionnaire score

End point title	Change from baseline in total St. George's Respiratory Questionnaire score
End point description: The St. George Respiratory Questionnaire C (SGRQ-C) is a disease-specific measure of health status for use in COPD that was used to provide the health status measurements in this study. A mixed model for repeated measures (MMRM), used for this analysis, included terms of treatment, baseline SGRQ-C total score, smoking status at baseline, baseline inhaled corticosteroid (ICS) use, airflow limitation severity, visit, treatment*visit Interaction, baseline SGRQ-C total score*visit + region. lowest possible value is zero and the highest 100. Higher values correspond to greater impairment of health status. A negative change from baseline indicates improvement.	
End point type	Secondary
End point timeframe: Baseline, 26 weeks	

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1602	1593		
Units: Score on a scale				
least squares mean (standard error)	-3.5 (± 0.39)	-2.3 (± 0.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in total St. George's Respiratory Questionnaire score

End point title	Change from baseline in total St. George's Respiratory Questionnaire score
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End point description:

The St. George Respiratory Questionnaire C (SGRQ-C) is a disease-specific measure of health status for use in COPD that was used to provide the health status measurements in this study. A mixed model for repeated measures (MMRM), used for this analysis, included terms of treatment, baseline SGRQ-C total score, smoking status at baseline, baseline inhaled corticosteroid (ICS) use, airflow limitation severity, visit, treatment*visit Interaction, baseline SGRQ-C total score*visit + region. lowest possible value is zero and the highest 100. Higher values correspond to greater impairment of health status. A negative change from baseline indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline, 38 weeks

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1602	1593		
Units: Score on a scale				
least squares mean (standard error)	-3.5 (± 0.4)	-1.7 (± 0.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in total St. George's Respiratory Questionnaire score

End point title	Change from baseline in total St. George's Respiratory Questionnaire score
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End point description:

The St. George Respiratory Questionnaire C (SGRQ-C) is a disease-specific measure of health status for use in COPD that was used to provide the health status measurements in this study. A mixed model for repeated measures (MMRM), used for this analysis, included terms of treatment, baseline SGRQ-C total score, smoking status at baseline, baseline inhaled corticosteroid (ICS) use, airflow limitation severity, visit, treatment*visit Interaction, baseline SGRQ-C total score*visit + region. lowest possible value is zero and the highest 100. Higher values correspond to greater impairment of health status. A negative change from baseline indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline, 52 weeks

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1602	1593		
Units: Score on a scale				

least squares mean (standard error)	-3.1 (\pm 0.41)	-1.9 (\pm 0.41)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the number of puffs of rescue medication

End point title	Change from baseline in the number of puffs of rescue medication
End point description: A linear mixed model (LMM) was used for this analysis Change from baseline in mean number of puffs. LMM including: treatment, baseline value, smoking status at screening, ICS use at screening, airflow limitation severity, region and random effect of center nested within region.	
End point type	Secondary
End point timeframe: Baseline, 52 weeks	

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1675	1679		
Units: Number of puffs per day				
least squares mean (standard error)	-1.01 (\pm 0.097)	-0.76 (\pm 0.097)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the safety of QVA149 ((110/50 µg o.d.) vs fluticasone/salmeterol (500/50µg bid) in terms of HPA axis function, as determined by collection of 24-hour urine cortisol.

End point title	Change from baseline in the safety of QVA149 ((110/50 µg o.d.) vs fluticasone/salmeterol (500/50µg bid) in terms of HPA axis function, as determined by collection of 24-hour urine cortisol.
End point description: Urine cortisol/creatinine ratio	
End point type	Secondary
End point timeframe: Baseline, 52 Weeks	

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	154		
Units: ng/mL				
median (full range (min-max))	5.615 (-96.93 to 509.17)	-10.39 (-97.76 to 4444.65)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Forced Vital Capacity

End point title	Change From Baseline in Forced Vital Capacity
End point description:	
Change from baseline in trough value (average of values measured 45 and 15 minutes prior to the morning dose). Pulmonary function assessments were performed using centralized spirometry according to international standards. Baseline FVC was defined as the average of the pre-dose FVC measured at -45 minutes (min) and -15 min at day 1. A mixed model for repeated measures (MMRM), used for this analysis, included terms of treatment, baseline FVC measurements, smoking status at screening, screening inhaled corticosteroid (ICS) use, region, baseline FVC * visit interaction, and visit, treatment * visit interaction	
End point type	Secondary
End point timeframe:	
4 Weeks, 12 Weeks, 26 Weeks, 38 Weeks, 52 Weeks	

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1597	1595		
Units: Liters				
least squares mean (standard error)				
4 weeks	0.146 (± 0.0127)	-0.032 (± 0.0128)		
12 weeks	0.134 (± 0.0131)	-0.071 (± 0.0131)		
26 weeks	0.088 (± 0.0135)	-0.121 (± 0.0136)		
38 weeks	0.071 (± 0.0137)	-0.111 (± 0.0137)		
52 weeks	0.022 (± 0.0139)	-0.138 (± 0.014)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with adverse events, serious adverse events, and death

End point title	Number of patients with adverse events, serious adverse events, and death
End point description: The overall rate of adverse events reported from initiation through 30 days post last dose.	
End point type	Secondary
End point timeframe: 52 weeks of treatment + 30 days	

End point values	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1678	1680		
Units: Number of participants				
Patients with at least one SAEs	308	334		
Patients with at least one AE	1459	1498		
Death	24	24		

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	QVA149
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Reporting group description:

QVA149

Reporting group title	Salm/Flut
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Reporting group description:

Salm/Flut

Serious adverse events	QVA149	Salm/Flut	
Total subjects affected by serious adverse events			
subjects affected / exposed	308 / 1678 (18.36%)	334 / 1680 (19.88%)	
number of deaths (all causes)	24	24	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACUTE MYELOID LEUKAEMIA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
ADENOCARCINOMA GASTRIC			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ADENOCARCINOMA OF COLON			

subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
ADRENAL GLAND CANCER			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-CELL LYMPHOMA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BASAL CELL CARCINOMA			
subjects affected / exposed	2 / 1678 (0.12%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST CANCER			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHIAL CARCINOMA			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CHRONIC MYELOID LEUKAEMIA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLON CANCER			
subjects affected / exposed	1 / 1678 (0.06%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
DIFFUSE LARGE B-CELL LYMPHOMA			

subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
GASTRIC CANCER			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC CANCER			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOPHARYNGEAL CANCER			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
LARGE INTESTINE BENIGN NEOPLASM			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARYNGEAL CANCER			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARYNGEAL SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG ADENOCARCINOMA METASTATIC			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG NEOPLASM MALIGNANT			

subjects affected / exposed	3 / 1678 (0.18%)	6 / 1680 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT MESENCHYMOMA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTASES TO LIVER			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYELOID LEUKAEMIA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEOPLASM MALIGNANT			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
NON-HODGKIN'S LYMPHOMA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON-SMALL CELL LUNG CANCER			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL CARCINOMA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PENILE NEOPLASM			

subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLASMA CELL MYELOMA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROSTATE CANCER			
subjects affected / exposed	4 / 1678 (0.24%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL ADENOCARCINOMA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL CANCER			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL CANCER			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL CELL CARCINOMA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL CELL LUNG CANCER			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SQUAMOUS CELL CARCINOMA			

subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF LUNG			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TONGUE NEOPLASM MALIGNANT STAGE UNSPECIFIED			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETHRAL CANCER			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
AORTIC ANEURYSM			
subjects affected / exposed	2 / 1678 (0.12%)	3 / 1680 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
AORTIC ANEURYSM RUPTURE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
AORTIC CALCIFICATION			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTERIOSCLEROSIS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CIRCULATORY COLLAPSE			

subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEEP VEIN THROMBOSIS			
subjects affected / exposed	2 / 1678 (0.12%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLISM ARTERIAL			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSION			
subjects affected / exposed	3 / 1678 (0.18%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSIVE CRISIS			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	2 / 1678 (0.12%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LERICHE SYNDROME			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE			

subjects affected / exposed	4 / 1678 (0.24%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL EMBOLISM			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TEMPORAL ARTERITIS			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOPHLEBITIS			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOSIS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VARICOSE ULCERATION			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENOUS THROMBOSIS			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			

subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
LOCAL SWELLING			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTI-ORGAN FAILURE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 1678 (0.06%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
OEDEMA PERIPHERAL			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	1 / 1678 (0.06%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN CARDIAC DEATH			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
SUDDEN DEATH			
subjects affected / exposed	1 / 1678 (0.06%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Immune system disorders			
FOOD ALLERGY			

subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	0 / 1678 (0.00%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
TESTICULAR TORSION			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UTERINE POLYP			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE PULMONARY OEDEMA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	5 / 1678 (0.30%)	4 / 1680 (0.24%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
ASTHMA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS CHRONIC			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

BRONCHOPLEURAL FISTULA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHOSPASM			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	182 / 1678 (10.85%)	207 / 1680 (12.32%)	
occurrences causally related to treatment / all	5 / 237	8 / 264	
deaths causally related to treatment / all	0 / 10	0 / 13	
CHRONIC RESPIRATORY FAILURE			
subjects affected / exposed	4 / 1678 (0.24%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
COUGH			
subjects affected / exposed	0 / 1678 (0.00%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	8 / 1678 (0.48%)	4 / 1680 (0.24%)	
occurrences causally related to treatment / all	1 / 8	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
EMPHYSEMA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOPTYSIS			

subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOTHORAX			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERCAPNIA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOXIA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARYNGEAL OEDEMA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG CONSOLIDATION			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PLEURISY			
subjects affected / exposed	2 / 1678 (0.12%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PNEUMONITIS			

subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	2 / 1678 (0.12%)	5 / 1680 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX SPONTANEOUS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	4 / 1678 (0.24%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
PULMONARY HAEMORRHAGE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PULMONARY HILAR ENLARGEMENT			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY HYPERTENSION			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY OEDEMA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
RESPIRATORY ACIDOSIS			

subjects affected / exposed	2 / 1678 (0.12%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	11 / 1678 (0.66%)	6 / 1680 (0.36%)	
occurrences causally related to treatment / all	0 / 11	0 / 7	
deaths causally related to treatment / all	0 / 3	0 / 4	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COMPLETED SUICIDE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
DELIRIUM TREMENS			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEPRESSION			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HALLUCINATION			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SLEEP DISORDER			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 1678 (0.06%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
BLOOD POTASSIUM INCREASED			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT DECREASED			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ANAEMIA POSTOPERATIVE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANKLE FRACTURE			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN HERNIATION			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CARBON MONOXIDE POISONING			

subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CLAVICLE FRACTURE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COMPRESSION FRACTURE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEAD INJURY			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	2 / 1678 (0.12%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			

subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIMB INJURY			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENISCUS INJURY			
subjects affected / exposed	0 / 1678 (0.00%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
OVERDOSE			
subjects affected / exposed	2 / 1678 (0.12%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PATELLA FRACTURE			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC FRACTURE			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POSTOPERATIVE WOUND COMPLICATION			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROCEDURAL INTESTINAL PERFORATION			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIB FRACTURE			

subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL FRACTURE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TIBIA FRACTURE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND DECOMPOSITION			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
PROGRESSIVE CEREBELLAR DEGENERATION			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	1 / 1678 (0.06%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	4 / 1678 (0.24%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	

ANGINA PECTORIS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANGINA UNSTABLE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARRHYTHMIA			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	5 / 1678 (0.30%)	7 / 1680 (0.42%)	
occurrences causally related to treatment / all	4 / 5	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FLUTTER			
subjects affected / exposed	2 / 1678 (0.12%)	3 / 1680 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL TACHYCARDIA			
subjects affected / exposed	2 / 1678 (0.12%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRADYCARDIA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	5 / 1678 (0.30%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	1 / 5	1 / 1	
deaths causally related to treatment / all	1 / 3	0 / 0	
CARDIAC FAILURE			

subjects affected / exposed	5 / 1678 (0.30%)	7 / 1680 (0.42%)	
occurrences causally related to treatment / all	0 / 5	1 / 7	
deaths causally related to treatment / all	0 / 3	0 / 0	
CARDIAC FAILURE ACUTE			
subjects affected / exposed	0 / 1678 (0.00%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	1 / 1678 (0.06%)	3 / 1680 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
CARDIAC TAMPONADE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	1 / 1678 (0.06%)	3 / 1680 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
CARDIOVASCULAR DISORDER			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONGESTIVE CARDIOMYOPATHY			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COR PULMONALE			
subjects affected / exposed	0 / 1678 (0.00%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COR PULMONALE CHRONIC			

subjects affected / exposed	0 / 1678 (0.00%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
CORONARY ARTERY DISEASE			
subjects affected / exposed	2 / 1678 (0.12%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY STENOSIS			
subjects affected / exposed	1 / 1678 (0.06%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC CARDIOMYOPATHY			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEFT VENTRICULAR DYSFUNCTION			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEFT VENTRICULAR FAILURE			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	6 / 1678 (0.36%)	5 / 1680 (0.30%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 4	
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	1 / 1678 (0.06%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
MYOCARDIAL RUPTURE			

subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PERICARDIAL EFFUSION			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERICARDIAL HAEMORRHAGE			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIGHT VENTRICULAR FAILURE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINUS TACHYCARDIA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENTRICULAR ARRHYTHMIA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
BASAL GANGLIA STROKE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN INJURY			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN STEM HAEMORRHAGE			

subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CAROTID ARTERIOSCLEROSIS			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CAROTID ARTERY OCCLUSION			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CENTRAL NERVOUS SYSTEM LESION			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBELLAR INFARCTION			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL INFARCTION			
subjects affected / exposed	2 / 1678 (0.12%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL ISCHAEMIA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL THROMBOSIS			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			

subjects affected / exposed	0 / 1678 (0.00%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLUSTER HEADACHE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEPRESSED LEVEL OF CONSCIOUSNESS			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIZZINESS			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPILEPSY			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEMIPARESIS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYDROCEPHALUS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC STROKE			

subjects affected / exposed	2 / 1678 (0.12%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LACUNAR INFARCTION			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	2 / 1678 (0.12%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIITH NERVE PARALYSIS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPARIN-INDUCED THROMBOCYTOPENIA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOCHROMIC ANAEMIA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

ANGLE CLOSURE GLAUCOMA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OPHTHALMOPLEGIA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OPTIC ISCHAEMIC NEUROPATHY			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RETINAL DETACHMENT			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL HERNIA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACID PEPTIC DISEASE			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASCITES			

subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPHAGIA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FAECALOMA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			

subjects affected / exposed	0 / 1678 (0.00%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 1678 (0.00%)	3 / 1680 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATEMESIS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILEUS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILEUS PARALYTIC			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INGUINAL HERNIA			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL PERFORATION			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL STENOSIS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINE POLYP			

subjects affected / exposed	0 / 1678 (0.00%)	4 / 1680 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGITIS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
subjects affected / exposed	2 / 1678 (0.12%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PANCREATITIS ACUTE			
subjects affected / exposed	1 / 1678 (0.06%)	3 / 1680 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
STOMATITIS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UMBILICAL HERNIA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			

subjects affected / exposed	0 / 1678 (0.00%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLELITHIASIS			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC CIRRHOSIS			
subjects affected / exposed	2 / 1678 (0.12%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC CYST RUPTURED			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC FUNCTION ABNORMAL			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER DISORDER			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
LINEAR IGA DISEASE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAPSORIASIS			

subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SWELLING FACE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URTICARIA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CALCULUS URINARY			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC KIDNEY DISEASE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEPHROLITHIASIS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
URETHRAL STENOSIS			

subjects affected / exposed	2 / 1678 (0.12%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY RETENTION			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
GOITRE			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTHROPATHY			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GROIN PAIN			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCLE HAEMORRHAGE			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

OSTEOARTHRITIS			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOLYSIS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOPOROTIC FRACTURE			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POLYMYALGIA RHEUMATICA			
subjects affected / exposed	2 / 1678 (0.12%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL PAIN			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ABSCCESS JAW			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABSCCESS LIMB			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATYPICAL MYCOBACTERIAL			

INFECTION			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERAEemia			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	0 / 1678 (0.00%)	4 / 1680 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS INFECTIVE			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
subjects affected / exposed	2 / 1678 (0.12%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ECZEMA INFECTED			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOLITIS INFECTIOUS			

subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	0 / 1678 (0.00%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS ROTAVIRUS			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 INFLUENZA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
HERPES ZOSTER			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
INFECTED SKIN ULCER			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIOUS PLEURAL EFFUSION			
subjects affected / exposed	2 / 1678 (0.12%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIVE ANEURYSM			

subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	8 / 1678 (0.48%)	7 / 1680 (0.42%)	
occurrences causally related to treatment / all	1 / 9	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
LOWER RESPIRATORY TRACT INFECTION BACTERIAL			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFECTION			
subjects affected / exposed	0 / 1678 (0.00%)	3 / 1680 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
MENINGITIS VIRAL			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

NASOPHARYNGITIS			
subjects affected / exposed	0 / 1678 (0.00%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORAL VIRAL INFECTION			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OTITIS EXTERNA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OTITIS MEDIA CHRONIC			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITONITIS			
subjects affected / exposed	1 / 1678 (0.06%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHARYNGITIS			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCOCCAL INFECTION			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	34 / 1678 (2.03%)	54 / 1680 (3.21%)	
occurrences causally related to treatment / all	0 / 36	3 / 60	
deaths causally related to treatment / all	0 / 4	1 / 3	
PNEUMONIA BACTERIAL			

subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSEUDOMONAS INFECTION			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY SEPSIS			
subjects affected / exposed	4 / 1678 (0.24%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
PULMONARY TUBERCULOSIS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 1678 (0.12%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION BACTERIAL			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SEPTIC SHOCK			

subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
SINUSITIS			
subjects affected / exposed	2 / 1678 (0.12%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPUTUM PURULENT			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUBERCULOUS PLEURISY			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 1678 (0.12%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
UPPER RESPIRATORY TRACT INFECTION BACTERIAL			
subjects affected / exposed	9 / 1678 (0.54%)	15 / 1680 (0.89%)	
occurrences causally related to treatment / all	0 / 10	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETERITIS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			

subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL INFECTION			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 1678 (0.06%)	2 / 1680 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
ACIDOSIS			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CACHEXIA			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS			
subjects affected / exposed	1 / 1678 (0.06%)	3 / 1680 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIET REFUSAL			
subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ELECTROLYTE IMBALANCE			

subjects affected / exposed	1 / 1678 (0.06%)	0 / 1680 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 1678 (0.06%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERKALAEMIA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	0 / 1678 (0.00%)	1 / 1680 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	QVA149	Salm/Flut	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1285 / 1678 (76.58%)	1351 / 1680 (80.42%)	
Respiratory, thoracic and mediastinal disorders			
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	1262 / 1678 (75.21%)	1331 / 1680 (79.23%)	
occurrences (all)	5182	5694	
Infections and infestations			
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	76 / 1678 (4.53%)	91 / 1680 (5.42%)	
occurrences (all)	104	115	
NASOPHARYNGITIS			
subjects affected / exposed	197 / 1678 (11.74%)	194 / 1680 (11.55%)	
occurrences (all)	274	263	
UPPER RESPIRATORY TRACT			

INFECTION BACTERIAL			
subjects affected / exposed	121 / 1678 (7.21%)	157 / 1680 (9.35%)	
occurrences (all)	170	220	
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	131 / 1678 (7.81%)	136 / 1680 (8.10%)	
occurrences (all)	210	243	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 May 2013	Issued when approximately 3000 patients had been screened and approximately 1350 patients had been randomized in 38 countries, was prepared to remove the Sub-Study Data Analysis and to include the collection of the CAT (COPD Assessment Test) score at Visit 1
04 March 2014	Issued to remove serum cortisol analyses from the study as data from a previous QVA149 clinical trial demonstrated that there were no clinically significant changes in serum cortisol levels, when QVA149 was compared to salmeterol/fluticasone, following 26 weeks of treatment. In addition, published data on the effect of inhaled corticosteroid therapy on serum cortisol levels has been varied, with minimal effects reported in most studies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

Notes: