



## 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 LV GB GR LU
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
<b>Arm title</b>	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

<b>Arm title</b>	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 categorial 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 <sup>[1]</sup>
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.

<b>Statistical analysis title</b>	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	

<b>End point values</b>	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

<b>Statistical analysis title</b>	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

<b>End point values</b>	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

<b>Statistical analysis title</b>	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

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**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.

<b>End point values</b>	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**

<b>Statistical analysis title</b>	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

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**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  $\log(\text{exposure time in years})$  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

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**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

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.

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

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  $\log(\text{exposure time in years})$  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 ( $\pm$ 0.15)	0 ( $\pm$ 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

<b>End point values</b>	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

<b>Statistical analysis title</b>	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	

<b>End point values</b>	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

<b>Statistical analysis title</b>	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

<b>End point values</b>	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

<b>Statistical analysis title</b>	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

<b>End point values</b>	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

<b>Statistical analysis title</b>	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)

<b>End point values</b>	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	

<b>End point values</b>	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

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 ( $\pm$ 0.0072)	-0.008 ( $\pm$ 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

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, 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 ( $\pm$ 0.0073)	-0.037 ( $\pm$ 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

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, 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

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, 52 weeks

<b>End point values</b>	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 ( $\pm$ 0.0075)	-0.048 ( $\pm$ 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

<b>End point values</b>	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 ( $\pm$ 0.0174)	-0.032 ( $\pm$ 0.0176)		

### Statistical analyses

No statistical analyses for this end point

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

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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.

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End point type	Secondary
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End point timeframe:

Baseline, 4 weeks

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<b>End point values</b>	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)		

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**Statistical analyses**

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No statistical analyses for this end point

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

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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.

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End point type	Secondary
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End point timeframe:

Baseline, 12 weeks

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<b>End point values</b>	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
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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, 26 weeks

<b>End point values</b>	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 (± 0.41)	-1.9 (± 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 (± 0.097)	-0.76 (± 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	

<b>End point values</b>	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	

<b>End point values</b>	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

<b>Serious adverse events</b>	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	
<b>ADRENAL GLAND CANCER</b>			
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>B-CELL LYMPHOMA</b>			
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>BASAL CELL CARCINOMA</b>			
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	
<b>BREAST CANCER</b>			
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>BRONCHIAL CARCINOMA</b>			
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	
<b>CHRONIC MYELOID LEUKAEMIA</b>			
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	
<b>COLON CANCER</b>			
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	
<b>DIFFUSE LARGE B-CELL LYMPHOMA</b>			

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
<b>GASTRIC CANCER</b>		
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
<b>HEPATIC CANCER</b>		
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
<b>HYPOPHARYNGEAL CANCER</b>		
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
<b>LARGE INTESTINE BENIGN NEOPLASM</b>		
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
<b>LARYNGEAL CANCER</b>		
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
<b>LARYNGEAL SQUAMOUS CELL CARCINOMA</b>		
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>LUNG ADENOCARCINOMA METASTATIC</b>		
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
<b>LUNG NEOPLASM MALIGNANT</b>		

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
<b>MALIGNANT MESENCHYMOMA</b>		
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
<b>METASTASES TO LIVER</b>		
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
<b>MYELOID LEUKAEMIA</b>		
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>NEOPLASM MALIGNANT</b>		
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
<b>NON-HODGKIN'S LYMPHOMA</b>		
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
<b>NON-SMALL CELL LUNG CANCER</b>		
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
<b>OESOPHAGEAL CARCINOMA</b>		
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
<b>PENILE NEOPLASM</b>		

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>PLASMA CELL MYELOMA</b>		
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>PROSTATE CANCER</b>		
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
<b>RECTAL ADENOCARCINOMA</b>		
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
<b>RECTAL CANCER</b>		
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
<b>RENAL CANCER</b>		
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>SMALL CELL CARCINOMA</b>		
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
<b>SMALL CELL LUNG CANCER</b>		
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
<b>SQUAMOUS CELL CARCINOMA</b>		

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	
<b>SQUAMOUS CELL CARCINOMA OF LUNG</b>			
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	
<b>TONGUE NEOPLASM MALIGNANT STAGE UNSPECIFIED</b>			
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	
<b>URETHRAL CANCER</b>			
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	
<b>Vascular disorders</b>			
<b>AORTIC ANEURYSM</b>			
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	
<b>AORTIC ANEURYSM RUPTURE</b>			
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	
<b>AORTIC CALCIFICATION</b>			
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>ARTERIOSCLEROSIS</b>			
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>CIRCULATORY COLLAPSE</b>			

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
<b>DEEP VEIN THROMBOSIS</b>		
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
<b>EMBOLISM ARTERIAL</b>		
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>HYPERTENSION</b>		
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
<b>HYPERTENSIVE CRISIS</b>		
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
<b>HYPOTENSION</b>		
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
<b>LERICHE SYNDROME</b>		
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
<b>ORTHOSTATIC HYPOTENSION</b>		
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
<b>PERIPHERAL ARTERIAL OCCLUSIVE DISEASE</b>		

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	
<b>PERIPHERAL EMBOLISM</b>			
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>TEMPORAL ARTERITIS</b>			
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	
<b>THROMBOPHLEBITIS</b>			
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	
<b>THROMBOSIS</b>			
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>VARICOSE ULCERATION</b>			
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>VENOUS THROMBOSIS</b>			
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	
<b>General disorders and administration site conditions</b>			
<b>ASTHENIA</b>			
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	
<b>FATIGUE</b>			

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	
<b>LOCAL SWELLING</b>			
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	
<b>MULTI-ORGAN FAILURE</b>			
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	
<b>NON-CARDIAC CHEST PAIN</b>			
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	
<b>OEDEMA PERIPHERAL</b>			
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	
<b>PYREXIA</b>			
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	
<b>SUDDEN CARDIAC DEATH</b>			
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	
<b>SUDDEN DEATH</b>			
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	
<b>Immune system disorders</b>			
<b>FOOD ALLERGY</b>			

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	
<b>Reproductive system and breast disorders</b>			
<b>BENIGN PROSTATIC HYPERPLASIA</b>			
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	
<b>TESTICULAR TORSION</b>			
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	
<b>UTERINE POLYP</b>			
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>Respiratory, thoracic and mediastinal disorders</b>			
<b>ACUTE PULMONARY OEDEMA</b>			
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>ACUTE RESPIRATORY FAILURE</b>			
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	
<b>ASTHMA</b>			
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>BRONCHITIS CHRONIC</b>			
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
<b>HAEMOTHORAX</b>		
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>HYPERCAPNIA</b>		
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>HYPOXIA</b>		
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>LARYNGEAL OEDEMA</b>		
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
<b>LUNG CONSOLIDATION</b>		
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
<b>PLEURAL EFFUSION</b>		
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
<b>PLEURISY</b>		
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
<b>PNEUMONITIS</b>		

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>PNEUMOTHORAX</b>		
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
<b>PNEUMOTHORAX SPONTANEOUS</b>		
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>PULMONARY EMBOLISM</b>		
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
<b>PULMONARY HAEMORRHAGE</b>		
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
<b>PULMONARY HILAR ENLARGEMENT</b>		
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>PULMONARY HYPERTENSION</b>		
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
<b>PULMONARY OEDEMA</b>		
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
<b>RESPIRATORY ACIDOSIS</b>		

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	
<b>RESPIRATORY FAILURE</b>			
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	
<b>Psychiatric disorders</b>			
<b>ANXIETY</b>			
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	
<b>COMPLETED SUICIDE</b>			
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	
<b>DELIRIUM TREMENS</b>			
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	
<b>DEPRESSION</b>			
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	
<b>HALLUCINATION</b>			
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	
<b>SLEEP DISORDER</b>			
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>Investigations</b>			

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
<b>CLAVICLE FRACTURE</b>		
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>COMPRESSION FRACTURE</b>		
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>FALL</b>		
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>FEMORAL NECK FRACTURE</b>		
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
<b>FEMUR FRACTURE</b>		
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
<b>HEAD INJURY</b>		
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
<b>HIP FRACTURE</b>		
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
<b>HUMERUS FRACTURE</b>		

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
<b>LIMB INJURY</b>		
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>MENISCUS INJURY</b>		
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
<b>OVERDOSE</b>		
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
<b>PATELLA FRACTURE</b>		
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
<b>PELVIC FRACTURE</b>		
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
<b>POSTOPERATIVE WOUND COMPLICATION</b>		
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
<b>PROCEDURAL INTESTINAL PERFORATION</b>		
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>RIB FRACTURE</b>		

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>SPINAL COMPRESSION FRACTURE</b>			
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	
<b>SPINAL FRACTURE</b>			
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>TIBIA FRACTURE</b>			
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>WOUND DECOMPOSITION</b>			
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	
<b>Congenital, familial and genetic disorders</b>			
<b>PROGRESSIVE CEREBELLAR DEGENERATION</b>			
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	
<b>Cardiac disorders</b>			
<b>ACUTE CORONARY SYNDROME</b>			
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	
<b>ACUTE MYOCARDIAL INFARCTION</b>			
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
<b>CARDIAC FAILURE ACUTE</b>		
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
<b>CARDIAC FAILURE CONGESTIVE</b>		
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
<b>CARDIAC TAMPONADE</b>		
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
<b>CARDIO-RESPIRATORY ARREST</b>		
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
<b>CARDIOVASCULAR DISORDER</b>		
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
<b>CONGESTIVE CARDIOMYOPATHY</b>		
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
<b>COR PULMONALE</b>		
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
<b>COR PULMONALE CHRONIC</b>		

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
<b>CORONARY ARTERY DISEASE</b>		
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
<b>CORONARY ARTERY STENOSIS</b>		
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
<b>ISCHAEMIC CARDIOMYOPATHY</b>		
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
<b>LEFT VENTRICULAR DYSFUNCTION</b>		
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>LEFT VENTRICULAR FAILURE</b>		
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
<b>MYOCARDIAL INFARCTION</b>		
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
<b>MYOCARDIAL ISCHAEMIA</b>		
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
<b>MYOCARDIAL RUPTURE</b>		

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	
<b>PERICARDIAL EFFUSION</b>			
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>PERICARDIAL HAEMORRHAGE</b>			
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	
<b>RIGHT VENTRICULAR FAILURE</b>			
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>SINUS TACHYCARDIA</b>			
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	
<b>VENTRICULAR ARRHYTHMIA</b>			
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	
<b>Nervous system disorders</b>			
<b>BASAL GANGLIA STROKE</b>			
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>BRAIN INJURY</b>			
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	
<b>BRAIN STEM HAEMORRHAGE</b>			

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>CAROTID ARTERIOSCLEROSIS</b>		
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
<b>CAROTID ARTERY OCCLUSION</b>		
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>CENTRAL NERVOUS SYSTEM LESION</b>		
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>CEREBELLAR INFARCTION</b>		
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>CEREBRAL INFARCTION</b>		
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
<b>CEREBRAL ISCHAEMIA</b>		
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
<b>CEREBRAL THROMBOSIS</b>		
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
<b>CEREBROVASCULAR ACCIDENT</b>		

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
<b>CLUSTER HEADACHE</b>		
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>DEPRESSED LEVEL OF CONSCIOUSNESS</b>		
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
<b>DIZZINESS</b>		
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
<b>EPILEPSY</b>		
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
<b>HEADACHE</b>		
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>HEMIPARESIS</b>		
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>HYDROCEPHALUS</b>		
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>ISCHAEMIC STROKE</b>		

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	
<b>LACUNAR INFARCTION</b>			
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>SYNCOPE</b>			
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	
<b>TRANSIENT ISCHAEMIC ATTACK</b>			
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	
<b>VIITH NERVE PARALYSIS</b>			
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>Blood and lymphatic system disorders</b>			
<b>ANAEMIA</b>			
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	
<b>HEPARIN-INDUCED THROMBOCYTOPENIA</b>			
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	
<b>HYPOCHROMIC ANAEMIA</b>			
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>Eye disorders</b>			

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
<b>COLITIS</b>		
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
<b>CONSTIPATION</b>		
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
<b>DIARRHOEA</b>		
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
<b>DUODENAL ULCER</b>		
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
<b>DYSPHAGIA</b>		
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>FAECALOMA</b>		
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
<b>GASTRIC ULCER</b>		
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
<b>GASTRITIS</b>		

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
<b>GASTROESOPHAGEAL REFLUX DISEASE</b>		
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
<b>HAEMATEMESIS</b>		
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>ILEUS</b>		
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
<b>ILEUS PARALYTIC</b>		
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
<b>INGUINAL HERNIA</b>		
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
<b>INTESTINAL PERFORATION</b>		
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
<b>INTESTINAL STENOSIS</b>		
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>LARGE INTESTINE POLYP</b>		

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	
<b>NAUSEA</b>			
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>OESOPHAGITIS</b>			
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>PANCREATITIS</b>			
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	
<b>PANCREATITIS ACUTE</b>			
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	
<b>STOMATITIS</b>			
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	
<b>UMBILICAL HERNIA</b>			
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>VOMITING</b>			
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>Hepatobiliary disorders</b>			
<b>CHOLECYSTITIS</b>			

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	
<b>CHOLELITHIASIS</b>			
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	
<b>DRUG-INDUCED LIVER INJURY</b>			
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>HEPATIC CIRRHOSIS</b>			
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	
<b>HEPATIC CYST RUPTURED</b>			
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>HEPATIC FUNCTION ABNORMAL</b>			
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	
<b>LIVER DISORDER</b>			
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	
<b>Skin and subcutaneous tissue disorders</b>			
<b>LINEAR IGA DISEASE</b>			
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>PARAPSORIASIS</b>			

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>SWELLING FACE</b>			
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>URTICARIA</b>			
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	
<b>Renal and urinary disorders</b>			
<b>ACUTE KIDNEY INJURY</b>			
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	
<b>CALCULUS URINARY</b>			
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>CHRONIC KIDNEY DISEASE</b>			
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>NEPHROLITHIASIS</b>			
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>RENAL FAILURE</b>			
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	
<b>URETHRAL STENOSIS</b>			

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	
<b>URINARY RETENTION</b>			
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	
<b>Endocrine disorders</b>			
<b>GOITRE</b>			
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	
<b>Musculoskeletal and connective tissue disorders</b>			
<b>ARTHRALGIA</b>			
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>ARTHROPATHY</b>			
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	
<b>GROIN PAIN</b>			
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	
<b>INTERVERTEBRAL DISC PROTRUSION</b>			
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>MUSCLE HAEMORRHAGE</b>			
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	

<b>OSTEOARTHRITIS</b>			
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	
<b>OSTEOLYSIS</b>			
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>OSTEOPOROTIC FRACTURE</b>			
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	
<b>POLYMYALGIA RHEUMATICA</b>			
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	
<b>SPINAL PAIN</b>			
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>Infections and infestations</b>			
<b>ABSCESS JAW</b>			
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	
<b>ABSCESS LIMB</b>			
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>APPENDICITIS</b>			
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	
<b>ATYPICAL MYCOBACTERIAL</b>			

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
BACTERAEMIA		
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
<b>ERYSIPELAS</b>		
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
<b>GASTROENTERITIS</b>		
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>GASTROENTERITIS ROTAVIRUS</b>		
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
<b>H1N1 INFLUENZA</b>		
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
<b>HERPES ZOSTER</b>		
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
<b>INFECTED SKIN ULCER</b>		
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
<b>INFECTIOUS PLEURAL EFFUSION</b>		
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
<b>INFECTIVE ANEURYSM</b>		

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
<b>INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE</b>		
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
<b>INFLUENZA</b>		
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
<b>LOWER RESPIRATORY TRACT INFECTION</b>		
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
<b>LOWER RESPIRATORY TRACT INFECTION BACTERIAL</b>		
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
<b>LOWER RESPIRATORY TRACT INFECTION VIRAL</b>		
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
<b>LUNG INFECTION</b>		
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
<b>MENINGITIS VIRAL</b>		
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>NASOPHARYNGITIS</b>			
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	
<b>ORAL VIRAL INFECTION</b>			
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	
<b>OTITIS EXTERNA</b>			
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	
<b>OTITIS MEDIA CHRONIC</b>			
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	
<b>PERITONITIS</b>			
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	
<b>PHARYNGITIS</b>			
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	
<b>PNEUMOCOCCAL INFECTION</b>			
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>PNEUMONIA</b>			
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	
<b>PNEUMONIA BACTERIAL</b>			

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>PSEUDOMONAS INFECTION</b>		
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>PULMONARY SEPSIS</b>		
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
<b>PULMONARY TUBERCULOSIS</b>		
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>PYELONEPHRITIS</b>		
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>RESPIRATORY TRACT INFECTION</b>		
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
<b>RESPIRATORY TRACT INFECTION BACTERIAL</b>		
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
<b>SEPSIS</b>		
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
<b>SEPTIC SHOCK</b>		

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
<b>SINUSITIS</b>		
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
<b>SPUTUM PURULENT</b>		
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>TUBERCULOUS PLEURISY</b>		
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
<b>UPPER RESPIRATORY TRACT INFECTION</b>		
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
<b>UPPER RESPIRATORY TRACT INFECTION BACTERIAL</b>		
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
<b>URETERITIS</b>		
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>URINARY TRACT INFECTION</b>		
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
<b>UROSEPSIS</b>		

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	
<b>VIRAL INFECTION</b>			
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	
<b>VIRAL UPPER RESPIRATORY TRACT INFECTION</b>			
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	
<b>Metabolism and nutrition disorders</b>			
<b>ACIDOSIS</b>			
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>CACHEXIA</b>			
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	
<b>DEHYDRATION</b>			
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	
<b>DIABETES MELLITUS</b>			
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	
<b>DIET REFUSAL</b>			
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	
<b>ELECTROLYTE IMBALANCE</b>			

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	
<b>HYPERGLYCAEMIA</b>			
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	
<b>HYPERKALAEMIA</b>			
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	
<b>HYPONATRAEMIA</b>			
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 %

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

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:

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### 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> for complete trial results.

Notes: