Clinical trial results:
A 12-week treatment, multi-center, randomized, double-blind, parallel-group, placebo and active controlled study to assess the efficacy, safety, and tolerability of indacaterol maleate / glycopyrronium bromide in COPD patients with moderate to severe airflow limitation

Summary

EudraCT number	2012-003347-30
Trial protocol	HU SI SK
Global end of trial date	28 February 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	25 July 2015

Trial information

Trial identification

Sponsor protocol code	CQVA149A2337

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01712516
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 Pharmas AG, 41 613241111,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2014
Global end of trial reached?	Yes
Global end of trial date	28 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of QVA149 27.5/12.5 µg b.i.d. compared to monotherapy components, QAB149 27.5 µg b.i.d. and NVA237 12.5 µg b.i.d., in terms of standardized FEV1AUC0-12h at Week 12.

Protection of trial subjects:

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

Background therapy:

Salmeterol/albuterol inhaler

Evidence for comparator: -

Actual start date of recruitment	03 December 2012
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	Colombia: 8
Country: Number of subjects enrolled	Egypt: 1
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Guatemala: 40
Country: Number of subjects enrolled	Hungary: 142
Country: Number of subjects enrolled	Panama: 12
Country: Number of subjects enrolled	Slovakia: 167
Country: Number of subjects enrolled	Slovenia: 20
Country: Number of subjects enrolled	United States: 597
Worldwide total number of subjects	1001
EEA total number of subjects	343

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)	565
From 65 to 84 years	429
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Participants were randomized to each treatment arm in a 1:1:1:1 ratio.

Pre-assignment

Screening details:

One thousand one participants were randomized. (One participant was randomized twice, took study drug twice and was counted twice in the randomized and safety sets). In the safety set, participants were analyzed according to the treatment received.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	QVA149

Arm description:

27.5/12.5 ug twice daily (b.i.d.) via Single Dose Dry Powder Inhaler (SDDPI)

Arm type	Experimental
Investigational medicinal product name	QVA149
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Dosage and administration details:

27.5/12.5 ug twice daily (b.i.d.) via Single Dose Dry Powder Inhaler (SDDPI)

Arm title	QAB149

Arm description:

27.5 ug b.i.d.

Arm type	Active comparator
Investigational medicinal product name	QAB149
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Dosage and administration details:

27.5 ug b.i.d.

Arm title	NVA237

Arm description:

12.5 ug b.i.d.

Arm type	Active comparator

Investigational medicinal product name	NVA237
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Dosage and administration details:
12.5 ug b.i.d.

Arm title	Placebo

Arm description:
b.i.d.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Dosage and administration details:
b.i.d.

Number of subjects in period 1	QVA149	QAB149	NVA237
Started	250	251	251
Full analysis set	250	251	250
Safety set	250	251	251
Completed	244	241	245
Not completed	6	10	6
Adverse event, serious fatal	-	1	-
Physician decision	2	-	-
Consent withdrawn by subject	3	9	3
Technical problems	-	-	-
Protocol deviation	1	-	1
Lost to follow-up	-	-	2

Number of subjects in period 1	Placebo
Started	249
Full analysis set	247
Safety set	248
Completed	236
Not completed	13
Adverse event, serious fatal	-
Physician decision	1
Consent withdrawn by subject	9
Technical problems	2

Protocol deviation	-
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	QVA149
Reporting group description:	
27.5/12.5 ug twice daily (b.i.d.) via Single Dose Dry Powder Inhaler (SDDPI)	
Reporting group title	QAB149
Reporting group description:	
27.5 ug b.i.d.	
Reporting group title	NVA237
Reporting group description:	
12.5 ug b.i.d.	
Reporting group title	Placebo
Reporting group description:	
b.i.d.	

Reporting group values	QVA149	QAB149	NVA237
Number of subjects	250	251	251
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	143	130	144
From 65-84 years	106	118	104
85 years and over	1	3	3
Age Continuous | Units: Years			
arithmetic mean	62.8	63.7	63.1
standard deviation	± 8.46	± 8.58	± 8.53
Gender, Male/Female Units: Participants			
Female	96	101	107
Male	154	150	144

Reporting group values	Placebo	Total	
Number of subjects	249	1001	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	

Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	148	565	
From 65-84 years	101	429	
85 years and over	0	7	
Age Continuous |			
Units: Years			
arithmetic mean	62.5		
standard deviation	± 8.07	-	
Gender, Male/Female			
Units: Participants			
Female	111	415	
Male	138	586	

End points

End points reporting groups	
Reporting group title	QVA149
Reporting group description:	
27.5/12.5 ug twice daily (b.i.d.) via Single Dose Dry Powder Inhaler (SDDPI)	
Reporting group title	QAB149
Reporting group description:	
27.5 ug b.i.d.	
Reporting group title	NVA237
Reporting group description:	
12.5 ug b.i.d.	
Reporting group title	Placebo
Reporting group description:	
b.i.d.	

Primary: Primary: Change from baseline in standardized forced expiratory volume in 1 second (FEV1) Area Under the Curve (AUC) (0-12 hours (h))

End point title	Primary: Change from baseline in standardized forced expiratory volume in 1 second (FEV1) Area Under the Curve (AUC) (0-12 hours (h))

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. Missing values of FEV1 AUC0-12 at Day 1 and Week 12 will not imputed. The trapezoidal rule was used to calculate FEV1 AUC and then normalized to the length of time.

End point type	Primary

End point timeframe:

baseline (BL), 12 weeks

End point values	QVA149	QAB149	NVA237	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	249	251	250	246
Units: Liters				
least squares mean (standard error)	0.234 (± 0.0134)	0.122 (± 0.0134)	0.155 (± 0.0134)	-0.028 (± 0.0137)

Statistical analyses

Statistical analysis title	FEV1 (L) AUC(0-12h) change from baseline
Comparison groups	QAB149 v QVA149

Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed model for repeated measures (MMRM)

Statistical analysis title	FEV1 (L) AUC(0-12h) change from baseline
Comparison groups	QVA149 v NVA237
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed model for repeated measures (MMRM)

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

End point title	Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score

End point description:

Participants reported change in health status by using the SGRQ. The SGRQ contains 50 items divided into 2 parts covering 3 aspects of health related to COPD: Part I covers "Symptoms" and is concerned with respiratory symptoms, their frequency and severity; Part II covers "Activity" and is concerned with activities that cause or are limited by breathlessness; Part II is also concerned with "Impacts", which covers a range of aspects concerned with social functioning and psychological disturbances resulting from airways disease. A score was calculated for each of these 3 subscales and a "Total" score was calculated. In each case the lowest possible value is zero and the highest 100. Higher values correspond to greater impairment of health status. Missing week 12 data were imputed with Last Observation Carried Forward (LOCF) method but only if measured at day >= 29. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

BL, 12 Weeks

End point values	QVA149	QAB149	NVA237	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	238	234	237	226
Units: score on a scale				
least squares mean (standard error)	-7.5 (± 0.85)	-5.9 (± 0.86)	-6 (± 0.86)	-1.1 (± 0.88)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a clinically important improvement of at

least 4 units in the SGRQ total score

End point title	Percentage of participants with a clinically important improvement of at least 4 units in the SGRQ total score

End point description:

Participants reported change in health status by using the SGRQ. The SGRQ contains 50 items divided into 2 parts covering 3 aspects of health related to COPD: Part I covers "Symptoms" and is concerned with respiratory symptoms, their frequency and severity; Part II covers "Activity" and is concerned with activities that cause or are limited by breathlessness; Part II is also concerned with "Impacts", which covers a range of aspects concerned with social functioning and psychological disturbances resulting from airways disease. A score was calculated for each of these 3 subscales and a "Total" score was calculated. In each case the lowest possible value is zero and the highest 100. Higher values correspond to greater impairment of health status.

End point type	Secondary

End point timeframe:

12 weeks

End point values	QVA149	QAB149	NVA237	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	238	234	237	226
Units: Percentage of participants				
number (not applicable)	59.2	56.8	51.5	34.5

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in trough FEV1

End point title	Change from baseline in trough FEV1

End point description:

Pulmonary function assessments were performed using centralized spirometry according to international standards. Trough FEV1 was analyzed using the same MMRM as specified for FEV1. Trough FEV1 was defined as the mean of FEV1 at 23 h 15 min and 23 h 45 min after the morning dose of the previous day. Before the mean was calculated, a time window of 10 – 13 hours post-evening dose was applied to these 2 measurements. Recordings outside the time window were set to missing.

End point type	Secondary

End point timeframe:

BL, day 2, day 86

End point values	QVA149	QAB149	NVA237	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	246	251	249	245
Units: Liters				
least squares mean (standard error)				
day 2	0.208 (± 0.0107)	0.111 (± 0.0106)	0.132 (± 0.0107)	0.01 (± 0.0107)

day 86	0.216 (± 0.0142)	0.138 (± 0.0141)	0.128 (± 0.0142)	-0.017 (± 0.0145)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in pre-dose trough FEV1

End point title	Change from baseline in pre-dose trough FEV1

End point description:

Pulmonary function assessments were performed using centralized spirometry according to international standards. Pre-dose trough FEV1 was analyzed using the same MMRM as specified for FEV1. Pre-dose trough FEV1 was defined as the mean of FEV1 at -45 min and -15 min before the morning dose. Since the time of evening dose of the previous day was not recorded at these visits, no time window was applied.

End point type	Secondary

End point timeframe:

BL, day 85

End point values	QVA149	QAB149	NVA237	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	243	249	246	241
Units: Liters				
least squares mean (standard error)	0.193 (± 0.0132)	0.1 (± 0.0132)	0.108 (± 0.0133)	-0.027 (± 0.0135)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in FEV1

End point title	Change from baseline in FEV1

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.

End point type	Secondary

End point timeframe:

BL, Day 1: 5min, 15min, 1h, 2h, 4h, 6h, 8h, 11h55 min; Day 2: 23h15min, 23h45min; Day 15: -45min, -15min, 1h; Day 29: -45 min, -15min, 1h; Day 57: -45min, -15min, 1h; day 85: -45min, -15min, 5min, 15min, 1h, 2h, 4h, 6h, 8h, 11h; day 86: 23h15min; 23h45min

End point values	QVA149	QAB149	NVA237	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	250	251	250	247
Units: Liters				
least squares mean (standard error)				
day 1, 5 min (n=248,249,249,243)	0.117 (± 0.0061)	0.076 (± 0.006)	0.072 (± 0.0061)	-0.001 (± 0.0062)
day 1, 15 min (n=248,251,249,244)	0.16 (± 0.007)	0.09 (± 0.0069)	0.126 (± 0.007)	0.005 (± 0.007)
day 1, 1 h (n=249,251,249,246)	0.199 (± 0.0082)	0.089 (± 0.0082)	0.176 (± 0.0083)	0.008 (± 0.0083)
day 1, 2 h (n=249,249,248,246)	0.237 (± 0.0091)	0.109 (± 0.0091)	0.197 (± 0.0092)	0.03 (± 0.0092)
day 1, 4 h (n=247,247,248,237)	0.22 (± 0.0099)	0.108 (± 0.0099)	0.167 (± 0.0099)	0.019 (± 0.0101)
day 1, 6 h (n=247,246,244,239)	0.181 (± 0.0103)	0.085 (± 0.0104)	0.135 (± 0.0104)	-0.005 (± 0.0106)
day 1, 8 h (n=248,247,245,242)	0.165 (± 0.0102)	0.077 (± 0.0101)	0.112 (± 0.0103)	-0.019 (± 0.0104)
day 1, 11 h 55 min(n=242,243,244,239)	0.116 (± 0.0114)	0.029 (± 0.0114)	0.066 (± 0.0114)	-0.045 (± 0.0115)
day 2, 23 h 15 min (n=241,246,245,241)	0.201 (± 0.0111)	0.105 (± 0.011)	0.128 (± 0.0111)	0.002 (± 0.0111)
day 2, 23 h 45 min (n= 246,251,248,244)	0.216 (± 0.0111)	0.118 (± 0.0109)	0.137 (± 0.0111)	0.018 (± 0.0111)
day 15, - 45 min (243,249,246,240)	0.208 (± 0.0126)	0.114 (± 0.0124)	0.108 (± 0.0126)	-0.045 (± 0.0127)
day 15, -15 min (n=243,248,246,241)	0.238 (± 0.0124)	0.143 (± 0.0123)	0.132 (± 0.0124)	-0.025 (± 0.0124)
day 15, 1 h (n=249,251,249,246)	0.321 (± 0.0134)	0.179 (± 0.0133)	0.212 (± 0.0134)	-0.019 (± 0.0135)
day 29, -45 min (n=243,249,246,240)	0.213 (± 0.0132)	0.127 (± 0.0131)	0.117 (± 0.0132)	-0.03 (± 0.0133)
day 29, -15 min (n=243,248,246,241)	0.235 (± 0.0132)	0.147 (± 0.0131)	0.138 (± 0.0132)	-0.013 (± 0.0134)
day 29, 1 h (n=249,251,249,246)	0.32 (± 0.0135)	0.17 (± 0.0135)	0.216 (± 0.0136)	-0.004 (± 0.0137)
day 57, -45 min (n=243,249,246,240)	0.203 (± 0.0136)	0.104 (± 0.0136)	0.117 (± 0.0137)	-0.037 (± 0.014)
day 57, -15 min (n=243,248,246,241)	0.224 (± 0.0136)	0.125 (± 0.0135)	0.147 (± 0.0136)	-0.014 (± 0.0139)
day 57, 1 h (n=249,251,249,246)	0.319 (± 0.0143)	0.163 (± 0.0143)	0.221 (± 0.0144)	-0.016 (± 0.0146)
day 85, -45 min (n=243,249,246,240)	0.187 (± 0.0134)	0.09 (± 0.0135)	0.096 (± 0.0135)	-0.032 (± 0.0138)
day 85, - 15 min (n=243,248,246,241)	0.199 (± 0.0138)	0.109 (± 0.0137)	0.123 (± 0.0138)	-0.018 (± 0.0141)
day 85, 5 min (n=248,249,249,243)	0.246 (± 0.0142)	0.151 (± 0.0143)	0.143 (± 0.0142)	-0.02 (± 0.0144)
day 85, 15 min (n=248,251,249,244)	0.269 (± 0.0141)	0.153 (± 0.0142)	0.179 (± 0.0141)	-0.001 (± 0.0145)
day 85, 1 h (n=249,251,249,246)	0.293 (± 0.0144)	0.141 (± 0.0144)	0.208 (± 0.0144)	-0.018 (± 0.0147)
day 85, 2 h (n=249,249,248,246)	0.315 (± 0.0146)	0.159 (± 0.0147)	0.216 (± 0.0148)	-0.001 (± 0.015)

day 85, 4 h (n=247,247,248,237)	0.26 (± 0.015)	0.145 (± 0.0151)	0.172 (± 0.0151)	-0.004 (± 0.0157)
day 85, 6 h (n=247,246,244,239)	0.226 (± 0.0149)	0.122 (± 0.015)	0.139 (± 0.0151)	-0.011 (± 0.0155)
day 85, 8 h (n=248,247,245,242)	0.198 (± 0.0146)	0.107 (± 0.0147)	0.133 (± 0.0149)	-0.039 (± 0.0153)
day 85, 11 h 55 min(n=242,243,244,239)	0.163 (± 0.0147)	0.078 (± 0.015)	0.105 (± 0.015)	-0.073 (± 0.0154)
day 86, 23 h 15 min (n=241,246,245,241)	0.206 (± 0.0148)	0.13 (± 0.0147)	0.117 (± 0.0149)	-0.023 (± 0.015)
day 86, 23 h 45 min (n=246,251,248,244)	0.221 (± 0.0144)	0.144 (± 0.0144)	0.132 (± 0.0146)	-0.012 (± 0.0149)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in FVC

End point title	Change from baseline in FVC

End point description:

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 baseline, baseline inhaled corticosteroid (ICS) use, region, baseline FEV1 * visit interaction, and visit, treatment * visit interaction.

End point type	Secondary

End point timeframe:

BL, Day 1: 5min, 15min, 1h, 2h, 4h, 6h, 8h, 11h55 min; Day 2: 23h15min, 23h45min; Day 15: -45min, -15min, 1h; Day 29: -45 min, -15min, 1h; Day 57: -45min, -15min, 1h; day 85: -45min, -15min, 5min, 15min, 1h, 2h, 4h, 6h, 8h, 11h; day 86: 23h15min; 23h45min

End point values	QVA149	QAB149	NVA237	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	250	251	250	247
Units: Liters				
least squares mean (standard error)				
day 1, 5 min (n=248,249,249,243)	0.245 (± 0.0138)	0.175 (± 0.0136)	0.158 (± 0.0137)	-0.006 (± 0.014)
day 1, 15 min (n=248,251,249,244)	0.318 (± 0.0154)	0.185 (± 0.0153)	0.238 (± 0.0155)	0.009 (± 0.0155)
day 1, 1 h (n=249,251,249,246)	0.355 (± 0.0165)	0.153 (± 0.0164)	0.309 (± 0.0166)	0.013 (± 0.0166)
day 1, 2 h (n=249,249,248,246)	0.395 (± 0.0181)	0.214 (± 0.018)	0.324 (± 0.0182)	0.044 (± 0.0183)
day 1, 4 h (n=247,247,248,237)	0.364 (± 0.0187)	0.189 (± 0.0187)	0.271 (± 0.0188)	0.026 (± 0.0192)
day 1, 6 h (n=247,246,244,239)	0.316 (± 0.0186)	0.159 (± 0.0188)	0.244 (± 0.0189)	0.004 (± 0.0192)
day 1, 8 h (n=248,247,245,242)	0.285 (± 0.0179)	0.154 (± 0.0178)	0.212 (± 0.0182)	-0.021 (± 0.0183)
day 1, 11 h 55 min (n=242,243,244,239)	0.235 (± 0.0188)	0.093 (± 0.0188)	0.125 (± 0.0188)	-0.06 (± 0.019)

day 2, 23 h 15 min (n=241,246,245,241)	0.343 (± 0.0193)	0.191 (± 0.0191)	0.217 (± 0.0194)	0.001 (± 0.0194)
day 2, 23 h 45 min (n=246,251,248,244)	0.355 (± 0.0195)	0.196 (± 0.0192)	0.229 (± 0.0194)	0.027 (± 0.0195)
day 15, -45 min (n=243,249,246,240)	0.313 (± 0.0205)	0.163 (± 0.0201)	0.168 (± 0.0204)	-0.047 (± 0.0206)
day 15, -15 min (n=243,248,246,241)	0.358 (± 0.0207)	0.201 (± 0.0204)	0.198 (± 0.0207)	-0.02 (± 0.0207)
day 15, 1 h (n=249,251,249,246)	0.473 (± 0.0025)	0.269 (± 0.0223)	0.311 (± 0.0225)	-0.009 (± 0.0227)
day 29, -45 min (n=243,249,246,240)	0.32 (± 0.0217)	0.194 (± 0.0216)	0.188 (± 0.0217)	-0.025 (± 0.022)
day 29, -15 min (n=243,248,246,241)	0.332 (± 0.0216)	0.218 (± 0.0215)	0.197 (± 0.0216)	-0.004 (± 0.0219)
day 29, 1 h (n=249,251,249,246)	0.449 (± 0.0224)	0.259 (± 0.0223)	0.322 (± 0.0225)	0.008 (± 0.0227)
day 57, -45 min (n=243,249,246,240)	0.293 (± 0.0215)	0.142 (± 0.0215)	0.173 (± 0.0217)	-0.034 (± 0.0221)
day 57, -15 min (n=243,248,246,241)	0.298 (± 0.0223)	0.167 (± 0.0222)	0.222 (± 0.0224)	-0.009 (± 0.0229)
day 57, 1 h (n=249,251,249,246)	0.445 (± 0.0233)	0.227 (± 0.0233)	0.326 (± 0.0234)	-0.011 (± 0.0238)
day 85, -45 min (n=243,249,246,240)	0.252 (± 0.0223)	0.121 (± 0.0224)	0.143 (± 0.0225)	-0.029 (± 0.0229)
day 85, -15 min (n=243,248,246,241)	0.263 (± 0.0224)	0.142 (± 0.0223)	0.18 (± 0.0225)	-0.031 (± 0.0229)
day 85, 5 min (n=248,249,249,243)	0.331 (± 0.0243)	0.215 (± 0.0244)	0.225 (± 0.0243)	-0.048 (± 0.0247)
day 85, 15 min (n=248,251,249,244)	0.377 (± 0.0242)	0.223 (± 0.0243)	0.276 (± 0.0243)	-0.004 (± 0.0248)
day 85, 1 h (n=249,251,249,246)	0.4 (± 0.0243)	0.209 (± 0.0243)	0.295 (± 0.0244)	-0.023 (± 0.0248)
day 85, 2h (n=249,249,248,246)	0.414 (± 0.0244)	0.218 (± 0.0245)	0.301 (± 0.0247)	-0.001 (± 0.0251)
day 85, 4 h (n=247,247,248,237)	0.338 (± 0.0247)	0.203 (± 0.0249)	0.261 (± 0.025)	0.002 (± 0.0259)
day 85, 6 h (n=247,246,244,239)	0.305 (± 0.0239)	0.164 (± 0.024)	0.211 (± 0.0241)	-0.011 (± 0.0248)
day 85, 8 h (n=248,247,245,242)	0.273 (± 0.0233)	0.152 (± 0.0235)	0.213 (± 0.0237)	-0.038 (± 0.0244)
day 85, 11 55 min (n=242,243,244,239)	0.233 (± 0.0239)	0.131 (± 0.0243)	0.197 (± 0.0243)	-0.093 (± 0.025)
day 86, 23 h 15 min (n=241,246,245,241)	0.278 (± 0.0248)	0.172 (± 0.0247)	0.176 (± 0.025)	-0.021 (± 0.0251)
day 86, 23 h 45 min (n=246,251,248,244)	0.298 (± 0.024)	0.199 (± 0.0239)	0.21 (± 0.0244)	-0.017 (± 0.0248)

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Change from baseline in standardized FEV1 AUC (0-4 h), FEV1 AUC (4-8h), FEV1 AUC (8-12h) and FEV1 AUC (0-12 h)

End point title	Secondary: Change from baseline in standardized FEV1 AUC (0-4 h), FEV1 AUC (4-8h), FEV1 AUC (8-12h) and FEV1 AUC (0-12 h)

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

End point timeframe:

BL, day 1, 12 weeks

End point values	QVA149	QAB149	NVA237	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	250	251	250	247
Units: Liters				
least squares mean (standard error)				
Day 1, AUC 0-4h (n=249,251,250,246)	0.213 (± 0.0077)	0.101 (± 0.0077)	0.174 (± 0.0077)	0.019 (± 0.0078)
Day 1, AUC 4-8h (n=248,248,250,243)	0.187 (± 0.0093)	0.09 (± 0.0093)	0.134 (± 0.0093)	-0.003 (± 0.0095)
Day 1, AUC 8-12h (n=248,249,249,245)	0.143 (± 0.0099)	0.054 (± 0.0099)	0.092 (± 0.01)	-0.031 (± 0.0101)
Day 1, AUC 0-12h (n=249,251,250,246)	0.184 (± 0.0084)	0.08 (± 0.0084)	0.135 (± 0.0084)	-0.003 (± 0.0085)
Week 12, AUC 0-4h (n=249,251,250,246)	0.289 (± 0.0138)	0.147 (± 0.0138)	0.196 (± 0.0138)	-0.008 (± 0.0141)
Week 12, AUC 4-8h (n=248,248,250,243)	0.229 (± 0.014)	0.12 (± 0.0141)	0.148 (± 0.0141)	-0.021 (± 0.0145)
Week 12, AUC 8-12h (n=248,249,249,245)	0.182 (± 0.0141)	0.095 (± 0.0142)	0.123 (± 0.0143)	-0.055 (± 0.0146)
Week 12, AUC 0-12h (n=249,251,250,246)	0.234 (± 0.0134)	0.122 (± 0.0134)	0.155 (± 0.0134)	-0.028 (± 0.0137)

Statistical analyses

No statistical analyses for this end point

Secondary: Transitional Dyspnea Index (TDI) focal score

End point title	Transitional Dyspnea Index (TDI) focal score

End point description:

The Baseline Dyspnea Index (BDI) / TDI is an instrument used to assess a participant's level of dyspnea. The BDI and TDI each have three domains: functional impairment, magnitude of task and magnitude of effort. BDI domains were rated from 0 (severe) to 4 (unimpaired) and rates summed for baseline focal score ranged from 0 to 12; lower scores mean worse severity. TDI domains were rated from -3 (major deterioration) to 3 (major improvement) and rates summed for transition focal score ranged from -9 to 9; negative scores indicate deterioration. A TDI focal score of ≥1 was defined as a clinically important improvement from baseline.

End point type	Secondary

End point timeframe:

BL, 12 weeks

End point values	QVA149	QAB149	NVA237	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	233	238	232	222
Units: score on a scale				
least squares mean (standard error)	2.88 (± 0.251)	1.98 (± 0.252)	1.88 (± 0.252)	0.85 (± 0.256)

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Change from baseline in mean daily number of puffs of rescue medication

End point title	Secondary: Change from baseline in mean daily number of puffs of rescue medication

End point description:

Participants completed an electronic diary (eDiary) twice daily at the same time in the morning and evening to record the number of puffs of rescue medication taken in the previous 12 hours. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

BL, 12 weeks

End point values	QVA149	QAB149	NVA237	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	243	242	242	235
Units: number of puffs				
least squares mean (standard error)	-2.19 (± 0.15)	-2.05 (± 0.15)	-1.78 (± 0.151)	-1.04 (± 0.153)

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Change from baseline in mean total daily symptom score, mean daytime total symptom score and mean nighttime total symptom score

End point title	Secondary: Change from baseline in mean total daily symptom score, mean daytime total symptom score and mean nighttime total symptom score

End point description:

The participant recorded symptom scores twice daily in the eDiary. The daily clinical symptoms included: cough, wheezing, shortness of breath, sputum volume, sputum color, and night time awakening. The range of scores for each assessment is 0 to 3 where 0 indications No symptom and 3 indicates a Severe symptom. The total daily symptom score is obtained by adding the scores for the morning and evening symptoms for each day. The maximum possible total daily score is 54. A negative change from baseline indicated improvement.

End point type	Secondary

End point timeframe:
BL, 12 weeks

End point values	QVA149	QAB149	NVA237	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	250	251	250	247
Units: score on a scale				
least squares mean (standard error)				
total daily (n=243,242,242,235)	-1.34 (± 0.108)	-1.22 (± 0.108)	-1.09 (± 0.108)	-0.61 (± 0.11)
total daytime (n=242,239,240,234)	-1.16 (± 0.105)	-1.05 (± 0.105)	-0.96 (± 0.105)	-0.53 (± 0.106)
total nighttime (n=243,239,238,234)	-1.09 (± 0.107)	-1.01 (± 0.107)	-0.9 (± 0.108)	-0.41 (± 0.109)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	QVA149 27.5/12.5 mcg

Reporting group description:

QVA149 27.5/12.5 mcg

Reporting group title	QAB149 27.5 mcg

Reporting group description:

QAB149 27.5 mcg

Reporting group title	NVA237 12.5 mcg

Reporting group description:

NVA237 12.5 mcg

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	QVA149 27.5/12.5 mcg	QAB149 27.5 mcg	NVA237 12.5 mcg
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 250 (2.40%)	5 / 251 (1.99%)	12 / 251 (4.78%)
number of deaths (all causes)	0	1	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	1 / 250 (0.40%)	0 / 251 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC CANCER			

subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METASTATIC MALIGNANT MELANOMA			
subjects affected / exposed	1 / 250 (0.40%)	0 / 251 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NON-SMALL CELL LUNG CANCER			
subjects affected / exposed	1 / 250 (0.40%)	0 / 251 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROSTATE CANCER			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
HYPERTENSIVE CRISIS			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	1 / 250 (0.40%)	0 / 251 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OEDEMA PERIPHERAL			

subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	1 / 250 (0.40%)	1 / 251 (0.40%)	5 / 251 (1.99%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOPTYSIS			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG INFILTRATION			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
FEMUR FRACTURE			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GUN SHOT WOUND			

subjects affected / exposed	0 / 250 (0.00%)	1 / 251 (0.40%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac disorders			
ANGINA PECTORIS			
subjects affected / exposed	0 / 250 (0.00%)	1 / 251 (0.40%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
CARDIOPULMONARY FAILURE			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 250 (0.40%)	0 / 251 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
INGUINAL HERNIA			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

PNEUMOPERITONEUM			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
HEPATIC FUNCTION ABNORMAL			
subjects affected / exposed	0 / 250 (0.00%)	1 / 251 (0.40%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
ERYTHEMA			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
OSTEOARTHRITIS			
subjects affected / exposed	0 / 250 (0.00%)	1 / 251 (0.40%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
EPIGLOTTITIS			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 250 (0.00%)	1 / 251 (0.40%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIRECTAL ABSCESS			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			

subjects affected / exposed	1 / 250 (0.40%)	0 / 251 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SINUSITIS			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER RESPIRATORY TRACT INFECTION BACTERIAL			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 250 (0.00%)	0 / 251 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 248 (5.24%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HEPATIC CANCER			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
METASTATIC MALIGNANT MELANOMA			

subjects affected / exposed	0 / 248 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
NON-SMALL CELL LUNG CANCER				
subjects affected / exposed	0 / 248 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PROSTATE CANCER				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SQUAMOUS CELL CARCINOMA OF SKIN				
subjects affected / exposed	0 / 248 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
HYPERTENSIVE CRISIS				
subjects affected / exposed	0 / 248 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
CHEST PAIN				
subjects affected / exposed	0 / 248 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
OEDEMA PERIPHERAL				
subjects affected / exposed	0 / 248 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
CHRONIC OBSTRUCTIVE PULMONARY DISEASE				

subjects affected / exposed	7 / 248 (2.82%)			
occurrences causally related to treatment / all	1 / 8			
deaths causally related to treatment / all	0 / 0			
HAEMOPTYSIS				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
LUNG INFILTRATION				
subjects affected / exposed	0 / 248 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
RESPIRATORY FAILURE				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
HEPATIC ENZYME INCREASED				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
FEMUR FRACTURE				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GUN SHOT WOUND				
subjects affected / exposed	0 / 248 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
ANGINA PECTORIS				
subjects affected / exposed	0 / 248 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

CARDIAC FAILURE			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CARDIOPULMONARY FAILURE			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
INGUINAL HERNIA			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PNEUMOPERITONEUM			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
HEPATIC FUNCTION ABNORMAL			

subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
ERYTHEMA			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
OSTEOARTHRITIS			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
EPIGLOTTITIS			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PERIRECTAL ABSCESS			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SINUSITIS			

subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
UPPER RESPIRATORY TRACT INFECTION BACTERIAL			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	QVA149 27.5/12.5 mcg	QAB149 27.5 mcg	NVA237 12.5 mcg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 250 (11.20%)	23 / 251 (9.16%)	23 / 251 (9.16%)
Respiratory, thoracic and mediastinal disorders			
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	28 / 250 (11.20%)	23 / 251 (9.16%)	23 / 251 (9.16%)
occurrences (all)	38	30	33

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 248 (14.52%)		
Respiratory, thoracic and mediastinal disorders			
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	36 / 248 (14.52%)		
occurrences (all)	50		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2013	Amendment 1: The purpose of this amendment was to ensure that there was no overlap of patients between this trial and the replicate trial QVA149A2336, which would protect the integrity of both trials. An exclusion criterion was added to the current trial, which excluded patients that had previously been enrolled in QVA149A2336. Changes were made to the model used to evaluate the primary endpoint and to the sensitivity analysis, in order to ensure that it was analyzed appropriately. Changes were made to the analyses used to evaluate the primary endpoint as follows: 1) a 2-way interaction between baseline and visit in the model was added in order to account for the difference in correlation between the outcome and baseline at each visit; and 2) the sensitivity analysis based only on the completers at Week 12 was removed as the underlying assumption of data being missing completely at random was too restrictive. In addition, patients with moderate renal impairment were allowed to participate in the trial, ensuring that the protocol population was not overly restrictive.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported