Sponsor

Novartis

Generic Drug Name

Indacaterol maleate and glycopyrronium bromide

Therapeutic Area of Trial

Chronic obstructive pulmonary disease (COPD)

Approved Indication

Not approved yet

Protocol Number

CQVA149A1301

Title

A 52-week treatment, multi-center, randomized, open label, parallel group study to assess the long term safety and tolerability of QVA149 (110 mcg indacaterol / 50 mcg glycopyrrolate o.d.) using tiotropium (18 mcg o.d.) as an active control in Japanese patients with moderate to severe chronic obstructive pulmonary disease (COPD)

Study Phase

Phase III

Study Start/End Dates

28 Jan 2011 to 07 Sep 2012

Study Design/Methodology

This was a 52-weeks, multi-center, randomized, open label, parallel group study to assess the long term safety and tolerability of QVA149 (110 µg indacaterol / 50 µg glycopyrronium o.d.), using tiotropium (18 µg o.d.) as an active control in Japanese patients with moderate to severe COPD. Eligible patients were randomized 3:1 to receive QVA149 110/50 µg o.d., or tiotropium 18 µg o.d. for 52 weeks. There was a pre-screening visit (Visit 1) where informed consent was obtained and current COPD medications were reviewed and in suitable patients, if necessary, arrangements were made to adjust prohibited COPD therapy to allowable COPD therapy. The interval between Visit 2 and 3 was a 7-days run-in period used to assess eligibility of patients for the study and to collect baseline values. At Visit 3, patients whose eligibility was confirmed were randomized to one of the treatment groups, QVA149 and tiotropium (randomization ratio 3:1).

Centers

35 centers in Japan

Publication

None

Test Product (s), Dose(s), and Mode(s) of Administration

QVA149 (110 µg indacaterol / 50 µg glycopyrronium o.d.), delivered via Concept1. QVA149 was administered once daily in the morning between 8 a.m. and 11 a.m.

Statistical Methods

The primary objective of this study was to provide data on the long-term safety of QVA149 o.d. via Concept1 with regard to treatment emergent adverse event reporting in Japanese patients with moderate to severe COPD following 52 weeks treatment.

Adverse events: All adverse emergent events in this study were recorded and listed in the safety set. Adverse events starting on or after the time of the first inhalation of study drug were classified as a treatment emergent adverse event. Treatment-emergent adverse events were coded using MedDRA (Version 14.1) and summarized by primary system organ class, preferred term, severity and relationship to study drug. For patients either being prematurely withdrawn from the study or completing the study, only AEs reported within 7 days of the last dose (within 30 days for SAEs) were included in the summary tables.

Laboratory data: All laboratory data were listed with abnormal values flagged. The laboratory values and the change from baseline for continuous laboratory parameters were summarized at each time point and visit. A frequency table of results for categories laboratory parameters was produced by time point and visit. Shift tables relative to the normal reference ranges were used to summarize the change from baseline to the worst case post first dosing for each laboratory parameter.

Electrocardiogram (ECG) and vital signs: Data from the ECG (including QT interval, RR interval, PR interval, QRS duration, ventricular rate, Fridericia's QTc and Bazett's QTc) was summarized by treatment at all time points (ECGs comprising a single measurement at Visit 2, a mean of two 25 minute pre-dose measurements at Visit 7 and 9, and a mean of two 1 h post-dose measurements at Visit 7 and 9). The baseline measurement for ECGs was the single measurement at Visit 2. Vital signs (blood pressure, radial pulse rate) were summarized by treatment at 25 min pre-dose in the morning. The baseline measurement for vital signs was the 25 min pre-dose measurement at Visit 3. The maximum (QTc, systolic blood pressure, radial pulse rate) or minimum (diastolic blood pressure) post first dosing (i.e., post-baseline) value was also summarized. The changes from baseline were also summarized by treatment. Notable values for vital signs and QTc were summarized.

Pre-dose FEV1 and FVC: The pre-dose FEV1 and FVC were defined as the mean of the pre-dose 45 and 15 min values. The pre-dose FEV1 and the change from baseline for each post-baseline visit, were summarized with descriptive statistics by treatment group. Summaries were repeated for FVC.

FEV1 and FVC at each time-point: FEV1 and the change from baseline at each time-point, for each visit, were similarly summarized. The means for FEV1 were displayed graphically over time by treatment group. These analyses were repeated for FVC.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

Patients with moderate to severe stable COPD (Stage II or Stage III) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines 2008.

Current or ex-smokers who have a smoking history of at least 10 pack years. (Ten pack years are defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years etc.)

Patients with postbronchodilator forced expiratory volume in one second (FEV1) ≥30% and < 80% of the predicted normal, and postbronchodilator FEV1/forced vital capacity (FVC) < 0.7 at Visit 2.

Exclusion Criteria

Pregnant women or nursing mothers or women of child-bearing potential not using an acceptable method of contraception -Patients requiring long term oxygen therapy -Patients who have had a lower respiratory tract infection within 4 weeks prior to Visit

Patients with concomitant pulmonary disease -Patients with a history of asthma

Any patient with history of malignancy of any organ system (including lung cancer), treated or untreated, within the past 5 years

Patients with a history of certain cardiovascular comorbid conditions

Patients with a known history and diagnosis of alpha-1 antitrypsin deficiency

Patients in the active phase of a supervised pulmonary rehabilitation program

Patients contraindicated for treatment with, or having a history of reactions/ hypersensitivity to anticholinergic agents, long and short acting beta-2 agonists, sympathomimetic amines Other protocol-defined inclusion/exclusion criteria may apply

- **Participant Flow**

Disposition Reason	QVA149		Tio		Total	
	n	(%)	n	(%)	n	(%)
Screened					230	

Disposition Reason	QVA149		Tio		Total	
	n	(%)	n	(%)	n	(%)
Randomized	121	(100)	39	(100)	160	(100)
Completed	104	(86.0)	38	(97.4)	142	(88.8)
Discontinued	17	(14.0)	1	(2.6)	18	(11.3)
Primary reason for premature discontinuation						
Adverse Event(s)	11	(9.1)	0		11	(6.9)
Protocol deviation	3	(2.5)	0		3	(1.9)
Subject withdrew consent	2	(1.7)	1	(2.6)	3	(1.9)
Death	1	(0.8)	0		1	(0.6)

Percentages of patients completed and discontinued are calculated with the number of randomized patients as the denominator. Percentages of categories under "Primary reason from premature discontinuation" are calculated with the number of randomized patients as the denominator.

Baseline Characteristics

Variable	Statistic	QVA149 N = 119	Tio N = 39	Total N = 158
Age (years)	n	119	39	158
	Mean (SD)	69.3 (6.79)	69.4 (6.90)	69.3 (6.80)
	Median	70.0	68.0	69.0
	Min - Max	46 - 83	57 – 84	46 - 84
Age				
< 65 years	n (%)	24 (20.2)	10 (25.6)	34 (21.5)
65 - < 75 years	n (%)	69 (58.0)	18 (46.2)	87 (55.1)
≥ 75 years	n (%)	26 (21.8)	11 (28.2)	37 (23.4)
Gender				
Male	n (%)	114 (95.8)	37 (94.9)	151 (95.6)
Female	n (%)	5 (4.2)	2 (5.1)	7 (4.4)
Race				
Asian	n (%)	119 (100)	39 (100)	158 (100)
Ethnicity				
Japanese	n (%)	119 (100)	39 (100)	158 (100)
Baseline weight (kg)	n	119	39	158
	Mean (SD)	60.38 (9.613)	61.44 (8.788)	60.64 (9.400)
	Median	61.70	61.50	61.60
	Min - Max	31.2 - 81.0	46.5 - 79.0	31.2 - 81.0
Baseline height (cm)	n	119	39	158
	Mean (SD)	164.4 (7.08)	163.3 (6.38)	164.1 (6.91)
	Median	165.0	163.0	164.5
	Min - Max	144 - 183	148 – 181	144 - 183
Baseline body mass index (kg/m^2)	n	119	39	158
	Mean (SD)	22.31 (3.067)	23.02 (2.919)	22.49 (3.037)
	Median	22.43	23.10	22.59
	Min - Max	13.9 - 32.2	17.7 - 29.0	13.9 - 32.2
Baseline body mass index				
≤ 18.5 kg/m^2	n (%)	13 (10.9)	3 (7.7)	16 (10.1)
> 18.5 kg/m^2	n (%)	106 (89.1)	36 (92.3)	142 (89.9)
≤ 30.0 kg/m^2	n (%)	118 (99.2)	39 (100)	157 (99.4)
> 30.0 kg/m^2	n (%)	1 (0.8)	0	1 (0.6)

Baseline height and weight are defined as the measurements taken at the screening visit. Body Mass Index (kg/m^2) = weight (kg)/[height $(m)^2$].

Outcome measures

Primary Outcome Result(s)

Number of participants with adverse events, serious adverse events or death

	QVA149 N = 119 n (%)	Tio N = 39 n (%)
Patients with at least one AE	101 (84.9)	28 (71.8)
Serious AE(s) or significant AE(s)		
Death	1 (0.8)	0
SAE(s)	19 (16.0)	2 (5.1)
Discontinuation due to AE(s)	11 (9.2)	0
Discontinuation due to SAE(s)	5 (4.2)	0
Discontinuation due to non-SAE(s)	6 (5.0)	0
AE leading to dose adjustment or interruption	0	0
AE requiring significant additional therapy	91 (76.5)	24 (61.5)
AE leading to hospitalization or prolonged hospitalization	18 (15.1)	2 (5.1)

Deaths reported during the active treatment period plus the following 30 days are included. All adverse events starting on or after the time of the first administration of study drug but not later than 7 days (30 days in the case of a SAE) after the last administration are included.

Secondary Outcome Result(s)

Number of patients with newly occurring or worsening clinically notable hematology values at any timepoint over the whole treatment period

Parameter	Criterion	QVA149 N = 119 n/N'(%)	Tio N = 39 n/N'(%)
Hemoglobin (g/dL)	Male < 11.5	3/113 (2.7)	0/36 (0)
	Female < 9.5	0/5 (0)	0/2 (0)
	Total	3/118 (2.5)	0/38 (0)
Hematocrit (%)	Male < 37	6/113 (5.3)	0/36 (0)
	Female < 32	0/5 (0)	0/2 (0)
	Total	6/118 (5.1)	0/38 (0)
White Cell Count (/uL)	< 2800	0/118 (0)	0/38 (0)
	> 16000	0/118 (0)	0/38 (0)
Platelets (10^4/uL)	< 7.5	0/118 (0)	0/38 (0)
	> 70.0	0/118 (0)	0/38 (0)

n = Number of patients meeting the criterion, i.e. who had a newly occurring clinically notable value or had a worsening of a value during treatment which was already notable at baseline. For patients with a missing value at baseline, any post-baseline notable value is considered as newly occurring. Data from unscheduled visits and premature discontinuation visits are included. N' = Number of patients with a post-baseline value for the specified parameter. The denominators used to calculate the percentages are presented as N'. Measurements taken more than 7 days after the last dose of study drug are excluded.

Number of patients with newly occurring or worsening clinically notable biochemistry values at any time-point over the treatment period

Parameter	Criterion	QVA149 N = 119 n/N' (%)	Tio N = 39 n/N' (%)
Total protein (g/dL)	< 4.0	0/118 (0)	0/38 (0)
	> 9.5	0/118 (0)	0/38 (0)
Albumin (g/dL)	< 2.5	0/118 (0)	0/38 (0)
Bilirubin (total) (mg/dL)	> 1.9	0/118 (0)	0/38 (0)
BUN (mg/dL)	> 27	1/118 (0.8)	0/38 (0)
Creatinine (mg/dL)	> 1.99	0/118 (0)	0/38 (0)
AST (U/L)	> 3 × ULN	0/118 (0)	0/38 (0)
ALT (U/L)	> 3 × ULN	0/118 (0)	0/38 (0)
ALP (U/L)	> 3 × ULN	0/118 (0)	0/38 (0)
γ-GTP (U/L)	> 3 × ULN	2/118 (1.7)	2/38 (5.3)
Sodium (mEq/L)	< 125	0/118 (0)	0/38 (0)
	> 160	0/118 (0)	0/38 (0)
Potassium (mEq/L)	< 3.0	0/118 (0)	0/38 (0)
	> 6.0	0/118 (0)	0/38 (0)
Glucose (mg/dL)	< 51.0	0/118 (0)	0/38 (0)
	> 180.0	7/118 (5.9)	3/38 (7.9)

n = Number of patients meeting the criterion, i.e. who had a newly occurring clinically notable value or had a worsening of a value during treatment which was already notable at baseline. For patients with a missing value at baseline, any post-baseline notable value is considered as newly occurring. Data from unscheduled visits and premature discontinuation visits are included. N' = Number of patients with a post-baseline value for the specified parameter. The denominators used to calculate the percentages are presented as N'. Measurements taken more than 7 days after the last dose of study drug are excluded.

Number of patients with newly occurring or worsening clinically notable vital signs values at any time-point over the whole treatment period

Parameter	Criterion	QVA149 N = 119 n/N' (%)	Tio N = 39 n/N' (%)
Pulse rate	Low: < 40 bpm, or ≤ 50 bpm and decrease from baseline ≥ 15 bpm	0/119	0/39
	High: > 130 bpm, or ≥ 120 bpm and increase from baseline ≥ 15 bpm	0/119	0/39
	Low or high	0/119	0/39
Systolic blood pressure	Low: < 75 mmHg, or ≤ 90 mmHg and decrease from baseline ≥ 20 mmHg	4/119 (3.4)	0/39
	High: > 200 mmHg, or ≥ 180 mmHg and increase from baseline ≥ 20 mmHg	0/119	1/39 (2.6)
	Low or high	4/119 (3.4)	1/39 (2.6)
Diastolic blood pressure	Low: < 40 mmHg, or ≤ 50 mmHg and decrease from baseline ≥ 15 mmHg	3/119 (2.5)	0/39
	High: > 115 mmHg, or ≥ 105 mmHg and increase from baseline ≥ 15 mmHg	2/119 (1.7)	1/39 (2.6)
	Low or high	5/119 (4.2)	1/39 (2.6)

n = Number of patients meeting the criterion, i.e. who had a newly occurring clinically notable value or had a worsening of a value during treatment which was already notable at baseline. For patients with a missing value at baseline, any post-baseline notable value is considered as newly occurring. Data from premature discontinuation visits are included. N' = Number of patients with a post-baseline value for the specified vital sign. The denominators used to calculate the percentages are presented as N'. Measurements taken more than 7 days after the last dose of study drug are excluded.

Number of patients with newly occurring or worsening clinically notable Fridericia's QTc values at any timepoint over the whole treatment period

Criterion	QVA149 N = 119 n/N' (%)	Tio N = 39 n/N' (%)
Males: QTc > 450 ms	6/111 (5.4)	0/36
Females: QTc > 470 ms	0/5	0/2
Increase from baseline 30 - 60 ms	12/116 (10.3)	3/38 (7.9)
Increase from baseline > 60 ms	1/116 (0.9)	0/38

n = Number of patients meeting the criterion, i.e. who had a newly occurring clinically notable value or had a worsening of a value during treatment which was already notable at baseline. For patients with a missing value at baseline, any post-baseline notable value is considered as newly occurring. Data from unscheduled visits and premature discontinuation visits are included. N' = Number of patients with a post-baseline value for the specified parameter. The denominators used to calculate the percentages are presented as N'. Measurements taken more than 7 days after the last dose of study drug are excluded.

Change in pre-dose FEV1 from baseline

Visit	Statistic	QVA149 N = 119	Tio N = 39

		Base	Post	Change	Base	Post	Change
Week 3	n	117	117	117	38	38	38
	Mean	1.312	1.517	0.206	1.388	1.481	0.093
	SD	0.4737	0.4829	0.1534	0.3697	0.3734	0.0977
	Min	0.58	0.66	−0.29	0.84	0.91	−0.13
	Median	1.220	1.480	0.190	1.405	1.500	0.103
	Max	2.58	2.89	0.70	2.23	2.40	0.27
Week 6	n	115	115	115	38	38	38
	Mean	1.312	1.514	0.202	1.388	1.471	0.083
	SD	0.4788	0.4953	0.1668	0.3697	0.3980	0.1201
	Min	0.58	0.71	−0.23	0.84	0.86	−0.18
	Median	1.220	1.470	0.185	1.405	1.468	0.100
	Max	2.58	3.02	0.96	2.23	2.39	0.50
Week 12	n	113	113	113	38	38	38
	Mean	1.314	1.523	0.209	1.388	1.526	0.139
	SD	0.4811	0.5023	0.1725	0.3697	0.3850	0.1562
	Min	0.58	0.60	−0.27	0.84	0.85	−0.28
	Median	1.220	1.495	0.195	1.405	1.560	0.130
	Max	2.58	2.98	1.03	2.23	2.32	0.66
Week 24	n	113	113	113	37	37	37
	Mean	1.303	1.501	0.198	1.387	1.502	0.115
	SD	0.4697	0.5027	0.1735	0.3748	0.4228	0.1400
	Min	0.58	0.68	−0.23	0.84	0.87	−0.18
	Median	1.220	1.450	0.175	1.385	1.520	0.110
	Max	2.58	3.05	0.68	2.23	2.31	0.48
Week 36	n	105	105	105	37	37	37
	Mean	1.305	1.487	0.182	1.384	1.466	0.082
	SD	0.4620	0.5078	0.1619	0.3741	0.4056	0.1465
	Min	0.58	0.64	−0.23	0.84	0.88	−0.32
	Median	1.220	1.460	0.175	1.385	1.455	0.085
	Max	2.58	2.93	0.62	2.23	2.36	0.41

		QVA149 N = 119			Tio N = 39		
Visit	**Statistic**	**Base**	**Post**	**Change**	**Base**	**Post**	**Change**
Week 52	n	104	104	104	37	37	37
	Mean	1.316	1.504	0.189	1.385	1.437	0.052
	SD	0.4686	0.5038	0.1762	0.3744	0.4419	0.1688
	Min	0.58	0.61	−0.29	0.84	0.78	−0.34
	Median	1.220	1.428	0.178	1.385	1.375	0.050
	Max	2.58	2.85	0.81	2.23	2.37	0.37

Base = Baseline, Change = Post baseline − baseline. Only patients with a value at both baseline and the respective post-baseline visit are included. Pre-dose FEV_1 is defined as the average of the measurements at 45 and 15 min pre-dose. Baseline is defined as the pre-dose FEV_1 value on Day 1 (Week 1). If one of the pre-dose 45 and 15 min values are missing then the remaining non-missing value is taken as pre-dose FEV_1. If both values are missing, then their pre-dose FEV_1 is regarded as missing. Any missing pre-dose FEV_1 measurements are not imputed.

Change in pre-dose FVC from baseline

		QVA149 N = 119			Tio N = 39		
Visit	**Statistic**	**Base**	**Post**	**Change**	**Base**	**Post**	**Change**
Week 3	n	117	117	117	38	38	38
	Mean	2.781	3.095	0.314	2.774	2.987	0.213
	SD	0.7871	0.7340	0.2882	0.5797	0.5355	0.2369
	Min	1.37	1.51	−0.36	1.83	1.94	−0.18
	Median	2.680	2.995	0.280	2.695	2.948	0.175
	Max	4.98	5.04	1.17	4.56	4.72	0.74

		QVA149 N = 119			Tio N = 39		
Visit	**Statistic**	**Base**	**Post**	**Change**	**Base**	**Post**	**Change**
Week 6	n	115	115	115	38	38	38
	Mean	2.778	3.088	0.310	2.774	2.947	0.173
	SD	0.7867	0.7402	0.3178	0.5797	0.5455	0.2162
	Min	1.37	1.53	−0.52	1.83	1.93	−0.32
	Median	2.680	3.020	0.285	2.695	2.925	0.220
	Max	4.98	5.17	1.39	4.56	4.75	0.61
Week 12	n	113	113	113	38	38	38
	Mean	2.801	3.136	0.335	2.774	3.053	0.279
	SD	0.7916	0.7508	0.2948	0.5797	0.5360	0.2942
	Min	1.37	1.61	−0.19	1.83	1.99	−0.35
	Median	2.725	3.075	0.280	2.695	3.058	0.215
	Max	4.98	4.99	1.21	4.56	4.70	1.02
Week 24	n	113	113	113	37	37	37
	Mean	2.784	3.114	0.330	2.776	2.982	0.206
	SD	0.7681	0.7566	0.3248	0.5876	0.5482	0.2367
	Min	1.37	1.56	−0.88	1.83	2.03	−0.32
	Median	2.725	3.045	0.295	2.690	2.910	0.195
	Max	4.98	5.03	1.18	4.56	4.56	0.75
Week 36	n	105	105	105	37	37	37
	Mean	2.795	3.059	0.264	2.765	2.932	0.167
	SD	0.7810	0.7667	0.2706	0.5849	0.5733	0.2438
	Min	1.37	1.43	−0.25	1.83	2.01	−0.26
	Median	2.725	3.070	0.240	2.690	2.875	0.175
	Max	4.98	4.94	1.15	4.56	4.70	0.69
Week 52	n	104	104	104	37	37	37
	Mean	2.805	3.066	0.261	2.781	2.893	0.112
	SD	0.7839	0.7419	0.3047	0.5862	0.5391	0.2462
	Min	1.37	1.45	−0.85	1.83	1.94	−0.58
	Median	2.733	3.010	0.238	2.700	2.860	0.095
	Max	4.98	5.08	1.25	4.56	4.63	0.70

Base = Baseline, Change = Post baseline − baseline. Only patients with a value at both baseline and the respective post-baseline visit are included. Pre-dose FVC is defined as the average of the measurements at 45 and 15 min pre-dose. Baseline is defined as the pre-dose FVC value on Day 1 (Week 1). If one of the pre-dose 45 and 15 min values are missing then the remaining non-missing value is taken as pre-dose FVC. If both values are missing, then their pre-dose FVC is regarded as missing. Any missing pre-dose FVC measurements are not imputed.

Safety Results

Incidence of AEs by primary SOC (Safety set)

Primary MedDRA SOC	QVA149 N = 119 n (%)	Tio N = 39 n (%)
Any adverse event	101 (84.9)	28 (71.8)
Infections and infestations	62 (52.1)	19 (48.7)
Respiratory, thoracic and mediastinal disorders	44 (37.0)	13 (33.3)
Gastrointestinal disorders	22 (18.5)	8 (20.5)
Musculoskeletal and connective tissue disorders	17 (14.3)	7 (17.9)
Skin and subcutaneous tissue disorders	17 (14.3)	6 (15.4)
Nervous system disorders	14 (11.8)	2 (5.1)
Injury, poisoning and procedural complications	9 (7.6)	6 (15.4)
Metabolism and nutrition disorders	7 (5.9)	0
Ear and labyrinth disorders	6 (5.0)	1 (2.6)
Eye disorders	6 (5.0)	1 (2.6)
General disorders and administration site conditions	6 (5.0)	2 (5.1)
Vascular disorders	6 (5.0)	0
Cardiac disorders	4 (3.4)	0
Investigations	4 (3.4)	4 (10.3)
Psychiatric disorders	4 (3.4)	2 (5.1)
Renal and urinary disorders	4 (3.4)	2 (5.1)
Reproductive system and breast disorders	4 (3.4)	0
Hepatobiliary disorders	3 (2.5)	1 (2.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (2.5)	0
Blood and lymphatic system disorders	2 (1.7)	0
Immune system disorders	2 (1.7)	0
Congenital, familial and genetic disorders	1 (0.8)	0

Primary SOCs are sorted in descending order of frequency in QVA149 group. Any adverse event (AE) includes all AEs, with patients who experienced more than one AE only counted once. If a patient reported more than one adverse event with the same SOC, the patient is counted once for that SOC. All adverse events starting on or after the time of the first administration of study drug but not later than 7 days (30 days in the case of a SAE) after the last administration are included.

Most Frequently Reported AEs Overall by Preferred Term (at least 3% incidence in any group)

MedDRA PT	QVA149 N = 119 n (%)	Tio N = 39 n (%)
Any adverse event	101 (84.9)	28 (71.8)
Nasopharyngitis	40 (33.6)	12 (30.8)
Chronic obstructive pulmonary disease	32 (26.9)	8 (20.5)
Pneumonia	9 (7.6)	1 (2.6)
Upper respiratory tract infection	9 (7.6)	6 (15.4)

MedDRA PT	QVA149 N = 119 n (%)	Tio N = 39 n (%)
Back pain	6 (5.0)	1 (2.6)
Bronchitis	5 (4.2)	3 (7.7)
Dysphonia	5 (4.2)	1 (2.6)
Pharyngitis	5 (4.2)	1 (2.6)
Colonic polyp	4 (3.4)	0
Headache	4 (3.4)	1 (2.6)
Insomnia	4 (3.4)	2 (5.1)
Diarrhoea	3 (2.5)	2 (5.1)
Influenza	2 (1.7)	2 (5.1)
Rash	2 (1.7)	2 (5.1)
Blood alkaline phosphatase increased	0	2 (5.1)
Gastritis	0	2 (5.1)
Rib fracture	0	3 (7.7)

PTs are sorted in descending order of percentage according to the QVA149 group. Any adverse event (AE) includes all AEs, with patients who experienced more than one AE only counted once. If a patient reported more than one adverse event with the same PT, the patient is counted once for that PT. Chronic obstructive pulmonary disease was reported as an AE when the condition worsened from baseline. All adverse events starting on or after the time of the first administration of study drug but not later than 7 days (30 days in the case of a SAE) after the last administration are included.

Serious Adverse Events and Deaths

	QVA149 N = 119 n (%)	Tio N = 39 n (%)
Death	1 (0.8)	0
SAE(s)	19 (16.0)	2 (5.1)
Discontinuation due to SAE(s)	5 (4.2)	0

Deaths reported during the active treatment period plus the following 30 days are included. All adverse events starting on or after the time of the first administration of study drug but not later than 7 days (30 days in the case of a SAE) after the last administration are included.

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

13 February 2013

Date Inclusion on Novartis Clinical Trial Results Database

4 September 2013

Date of Latest Update