Sponsor

Novartis

Generic Drug Name

Indacaterol

Therapeutic Area of Trial

Chronic Obstructive Pulmonary Disease (COPD)

Approved Indication

Maintenance bronchodilator treatment of airflow obstruction in adult patients with COPD.

Protocol Number

CQAB149BFR01

Title

Correlation between the reversibility of airways obstruction and the clinical efficacy of indacaterol 150 µg OD in moderate-to-severe COPD patients. The REVERBREZ study.

Study Phase

Phase IV

Study Start/End Dates

17 Dec 2010 to 30 May 2012

Study Design/Methodology

Multicenter, open study in male and female adult patients (≥ 40 years of age) with stable COPD and a FEV1 ≤ 80% of the predicted value.

Patients were to attend 5 study visits. During the selection visit (Visit 1) a reversibility test with salbutamol was performed and the selection criteria were checked. Treatment with indacaterol 150 µg OD was initiated at Visit 2 and continued up to Visit 5 (treatment period). During Visit 2 and each subsequent visit a spirometry test was performed before inhalation of indacaterol.

Between Visit 1 and Visit 2, the only bronchodilator treatment allowed was salbutamol. Any other bronchodilator was prohibited during the study except for salbutamol which was provided as rescue medication and could be use on demand (daily dosage limited to 8 inhalations of 100 µg).

Centers

177 centers in France.

Publication

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

Indacaterol: Hard capsule of 150 µg indacaterol maleate dry powder for inhalation administered once daily (OD) using Onbrez® Breezhaler® inhaler. Treatment was to be inhaled preferably in the morning, always at the same time (± 2 hours) for 5 months (148 to 169 days).

Salbutamol: Metered-dose inhaler (MDI) containing the equivalent of 200 inhalations of 100 µg salbutamol. One dose (400 µg) was administered at Visit 1 to evaluate reversibility of airway obstruction. Salbutamol was also provided as rescue medication to use on demand with a limit of 800 µg per day (8 puffs per day).

Statistical Methods

Descriptive statistics consisting of mean, standard deviation (SD), Min, Max and median for quantitative variables and of frequency tables for qualitative variables were presented for each study time point. 95% CI were provided for main criteria.

Statistical test was bilateral with a significant threshold of 0.05. However, as there was no comparison group in this study, analyses were mainly exploratory and descriptive and p-values were provided only as an indication.

Populations

Safety population: All patients enrolled in the study, having received at least one dose of study medication and for whom at least one tolerability assessment after treatment administration was available.

Intent to Treat (ITT): All patients enrolled in the study, having received at least one dose of study medication and for whom at least one efficacy assessment after treatment administration was available. This was the reference population for the efficacy analyses.

Per Protocol (PP): Patients included in the ITT population, having completed the study and for whom no major protocol deviation was reported.

The following 2 populations were added to those planned in the protocol, to limit the number of exclusions, focusing on either Visit 3 or Visit 5.

PP at Visit 3 (PPV3): Patients included in the ITT population, having completed the study until Visit 3 without any major protocol deviations.

PP at Visit 5 (PPV5): Patients included in the ITT population, having completed the study until Visit 5 without any major protocol deviations, irrespective of a possible S01 deviation at Visit 3 (S01 deviation: temporary interruption of treatment resulting in Visit 3 evaluations > 7 days after last dose).

Study Population: Inclusion/Exclusion Criteria and Demographics

- Age eligible for study: 40 years and older
- Genders eligible for study: male and female
- Accepts healthy volunteers: No

Inclusion criteria

- Diagnosis of COPD (moderate to severe as per Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2009 recommendations) and :
  - Post-bronchodilator $FEV_1 < 80\%$ and $\geq 30\%$ of the predicted value.
  - Post-bronchodilator FEV1/forced vital capacity (FVC) < 70%.
- Smokers history of at least 10 pack-years.

Exclusion criteria

- Patients who have had a COPD exacerbation in the 6 weeks prior to screening.
- Patients who have had a respiratory tract infection within 4 weeks prior to screening.
- Patients with concomitant pulmonary disease.
- Patients with a history of asthma.
- Patients with diabetes Type I or uncontrolled diabetes Type II.
- Any patient with lung cancer or a history of lung cancer.
- Patients with a history of certain cardiovascular comorbid conditions.

Participant Flow

	Treated patients	Not treated patients	Total
Number (%) of patients			
Enrolled	543	59	602
End of study at V3	7 (1.7)	0 (0.0)	7 (1.7)
End of study at V5	400 (98.3)	0 (0.0)	400 (98.3)
Discontinued	136 (25.0)	59 (100.0)	195 (32.4)
Main reason for discontinuation	n (%)	n (%)	n (%)
Not meeting protocol criteria	64 (47.1)	31 (52.5)	95 (48.7)
Adverse event(s)	30 (22.1)	7 (11.9)	37 (19.0)
Consent withdrawal	11 (8.1)	15 (25.4)	26 (13.3)
Lack of efficacy	18 (13.2)	2 (3.4)	20 (10.3)
Lost to follow-up	6 (4.4)	2 (3.4)	8 (4.1)
Death	4 (2.9)	0 (0.0)	4 (2.1)
Administrative reasons	2 (1.5)	1 (1.7)	3 (1.5)
Patient no longer required study treatment	1 (0.7)	1 (1.7)	2 (1.0)

Baseline Characteristics

Age (years)	N	543
	Mean	62.7
	SD	9.58
	Range	33.0;87.0
Age group – n (%)	N	543
	< 65 years	310 (57.1)
	65 to 75 years	177 (32.6)
	> 75	56 (10.3)
Gender – n (%)	N	543
	Male	404 (74.4)
	Female	139 (25.6)
Weight (kg)(a)	N	525
	Mean	75.5
	SD	18.08
	Range	38.0;172.0
BMI (kg/m2)[(a)]	N	525
	Mean	26.1
	SD	5.37
	Range	14.9;51.4
Heart rate (bpm)	N	541
	Mean	77.2
	SD	10.84
	Range	45.0;120.0

Systolic blood pressure (mmHg)	N	540
	Mean	130.9
	SD	14.96
	Range	95.0;250.0
Diastolic blood pressure (mmHg)	N	540
	Mean	75.6
	SD	9.24
	Range	45.0;120.0
Peak expiratory flow rate (L/min)	N	536
	Mean	273.2
	SD	93.69
	Range	69.6;580.0
Tobacco consumption		
Smoking status – n(%)	N	543
	Smokers	196 (36.1)
	Ex-smokers	347 (63.9)
Number of pack-years	N	541
	Mean	40.3
	SD	19.34
	Range	10.0;200.0
COPD		
Time from COPD diagnosis	N	541
	Mean	9.1
	SD	7.39
	Range	0.0;41.0
Type – n (%)		542
	Chronic obstructive bronchitis and emphysema	156 (28.7)
	Chronic obstructive bronchitis	317 (58.4)
	Emphysema	69 (12.7)

[a] Baseline data for weight and BMI were collected at Visit 2. Others data were collected at Visit 1.

Outcome Measures

Primary Outcome Results

Immediate reversibility of FEV1 with 400 µg salbutamol, 30 minutes after inhalation, measured at Visit 1

		Before salbutalmol	After salbutamol	Absolute reversibility[a,d]	Relative reversibility[b,e]
All patients					
FEV1 (L)	N	542	537	537	537
	Mean	1.54	1.65	0.11	7.8
	SD	0.50	0.53	0.17	12.13
	Range	0.52;3.65	0.48;4.08	-0.43;1.07	-26.9;118.1
Significant Reversibility [c]	N	-	537	537	537
	Yes	-	106 (19.5)	117 (21.5)	150 (27.6)
	No	-	431 (79.4)	420 (77.3)	387 (71.3)
Group R					
FEV1 (L)	N	106	106	106	106
	Mean	1.54	1.88	0.34	23.7
	SD	0.45	0.51	0.16	13.38
	Range	0.77;3.01	1.07;4.08	0.20;1.07	12.0;118.1
Group NR					
FEV1 (L)	N	431	431	431	431
	Mean	1.54	1.59	0.05	3.8
	SD	0.51	0.52	0.11	7.84
	Range	0.52;3.65	0.48;3.29	-0.43;0.29	-26.9;37.0

[a] Absolute reversibility (L): value after salbutamol – value before salbutamol

[b] Relative reversibility (%): (absolute reversibility/value before salbutamol)x100

[c] Significant reversibility after salbutamol

Yes = R Patients (Group R): if absolute reversibility ≥ 200 mL AND relative reversibility ≥ 12%

No = NR Patients (Group NR): if absolute reversibility < 200 mL OR relative reversibility < 12%

[d] Significant absolute reversibility if ≥ 200 mL

[e] Significant relative reversibility if ≥ 12%

One patient was excluded because he/she received salbutamol within 6 hours before reversibility testing.

Variation in FEV1 (Δ FEV1) between Visit 3 and Visit 2 in patients with COPD

	V2 N = 510	V3 N = 509	Absolute difference (V3-V2)	Relative difference (V3-V2)/V2x100
FEV1 (L)	505[(a)]	504[(a)]	501	501
Mean	1.45	1.55	0.10	9.2
SD	0.55	0.56	0.26	19.00
Median	1.36	1.48	0.09	6.9
Range	0.44;3.73	0.42;4.09	-1.38;1.59	-49.8;135.9
Absolute difference [Classes]				
< 100 mL		258 (50.7)		
≥ 100 mL		243 (47.7)		

[(a)] Patients having received salbutamol within 6 hours before reversibility testing were excluded from analysis (5 patients at V2 and 4 at V3).

Secondary Outcome Results

Correlation between the immediate reversibility of FEV1 with 400 µg salbutamol, 30 minutes after inhalation, measured at Visit 1 and the responsiveness of VQ11 as measured by the variation in the VQ11 score (Δ VQ11) between Visit 5 and Visit 2.

Change in VQ11 Total score over the 5 months of treatment

	V2 N = 510	V5 N = 420	Difference (V5-V2)
VQ11 (total score)			
	505	415	411
Mean	23.2	20.8	-2.1
SD	8.49	8.52	7.27
Median	22.0	19.0	-2.0
Range	11.0;49.0	11.0;53.0	-30.0;26.0
Difference category (Classes); n(%)			
	505	415	
< 22	243 (48.1)	252 (60.7)	
≥ 22	262 (51.9)	163 (39.3)	

Percentage are calculated on observed effective (missing data excluded)

Change in the 3 VQ11 sub-scores

Change in the VQ11 functional score over the 5 months of treatment – Group R – ITT Population

		V2 (N = 100)	V3 (N = 100)	V4 (N = 87)	V5 (N = 79)
VQ11 – Functional Score	N	99	98	86	79
	Mean	7.0	6.0	6.0	6.2
	SD	2.64	2.67	2.98	2.82
	Min	3.0	3.0	3.0	3.0
	Median	7.0	5.0	5.0	6.0
	Max	13.0	14.0	14.0	13.0
>>> difference from V2	N		97	85	78
	Mean		-1.0	-0.9	-0.8
	SD		2.02	2.51	2.34
	Min		-6.0	-7.0	-7.0
	Median		-1.0	0.0	-0.5
	Max		6.0	7.0	5.0

Change in the VQ11 functional score over the 5 months of treatment - Group NR – ITT Population

		V2 (N = 406)	V3 (N = 405)	V4 (N = 360)	V5 (N = 337)
VQ11 – Functional Score	N	402	393	356	332
	Mean	7.5	6.8	6.5	6.5
	SD	3.01	2.93	2.86	2.93
	Min	3.0	3.0	3.0	3.0
	Median	7.0	6.0	6.0	6.0
	Max	15.0	15.0	15.0	15.0
>>> difference from V2	N		390	353	329
	Mean		-0.7	-0.9	-0.7
	SD		2.23	2.46	2.59
	Min		-10.0	-8.0	-8.0
	Median		-1.0	-1.0	0.0
	Max		9.0	7.0	9.0

Change in the VQ11 psychological score over the 5 months of treatment - Group R – ITT Population

		V2 (N = 100)	V3 (N = 100)	V4 (N = 87)	V5 (N = 79)
VQ11 – Psychological score	N	99	98	86	79
	Mean	8.6	7.6	7.3	7.8
	SD	3.11	3.23	3.36	3.53
	Min	4.0	4.0	4.0	4.0
	Median	8.0	7.0	6.0	7.0
	Max	17.0	17.0	18.0	18.0
>>> difference from V2	N		97	85	78
	Mean		-1.0	-1.4	-0.7
	SD		2.42	2.62	2.75
	Min		-7.0	-11.0	-11.0
	Median		-1.0	-1.0	-1.0
	Max		6.0	4.0	9.0

Change in the VQ11 psychological score over the 5 months of treatment - Group NR – ITT Population

		V2 (N = 406)	V3 (N = 405)	V4 (N = 360)	V5 (N = 337)
VQ11 – Psychological score	N	402	393	356	332
	Mean	8.6	7.7	7.6	7.5
	SD	3.12	3.08	2.95	2.94
	Min	4.0	4.0	4.0	4.0
	Median	8.0	7.0	7.0	7.0
	Max	19.0	19.0	19.0	19.0
>>> difference from V2	N		390	353	329
	Mean		-0.8	-0.9	-0.9
	SD		2.48	2.65	2.79
	Min		-10.0	-10.0	-10.0
	Median		-1.0	-1.0	-1.0
	Max		7.0	8.0	7.0

Change in the VQ11 relational score over the 5 months of treatment - Group R – ITT Population

		V2 (N = 100)	V3 (N = 100)	V4 (N = 87)	V5 (N = 79)
VQ11 – Relational score	N	99	98	86	79
	Mean	7.1	6.5	6.3	6.4
	SD	3.16	3.01	3.13	3.26
	Min	4.0	4.0	4.0	4.0
	Median	6.0	5.0	5.0	5.0
	Max	16.0	16.0	19.0	16.0
>>> difference from V2	N		97	85	78
	Mean		-0.6	-0.7	-0.4
	SD		2.51	2.36	2.72
	Min		-8.0	-9.0	-10.0
	Median		0.0	0.0	0.0
	Max		11.0	7.0	12.0

Change in the VQ11 relational score over the 5 months of treatment - Group NR – ITT Population

		V2 (N = 406)	V3 (N = 405)	V4 (N = 360)	V5 (N = 337)
VQ11 – Relational score	N	402	393	356	332
	Mean	7.3	6.8	6.6	6.7
	SD	3.34	3.34	3.28	3.13
	Min	4.0	4.0	4.0	4.0
	Median	6.0	6.0	5.0	6.0
	Max	19.0	19.0	20.0	19.0
>>> difference from V2	N		390	353	329
	Mean		-0.4	-0.6	-0.5
	SD		2.39	2.53	2.94
	Min		-14.0	-15.0	-15.0
	Median		0.0	0.0	0.0
	Max		7.0	7.0	9.0

Patients achieving 5 points difference in VQ11 total score

patients achieving 5 points difference in total VQ11 score – difference from V2		V2 (N = 510)	V3 (N = 509)	V4 (N = 451)	V5 (N = 420)
	N		491	442	411
	Improvement		133 (27.1 %)	145 (32.8 %)	119 (29.0 %)
	No change (-5 to +5)		311 (63.3 %)	252 (57.0 %)	233 (56.7 %)
	Worsening		47 (9.6 %)	45 (10.2 %)	59 (14.4 %)
	Missing		18	9	9

Change in the peak expiratory flow rate (PEFR) and rescue medication use between the last 7 days before Visit 3 and the last 7 days before Visit 2.

		V2 (N = 504)	V3 (N = 509)	V3-V2 (N = 510)
Morning PEF (L/min)	N	482	468	452
	Mean	244.3	272.3	26.8
	SD	90.44	101.18	37.15
	Min	72.9	81.4	-107.1
	Median	232.9	255.0	22.9
	Max	578.6	647.1	184.3
	[IC95 mean]			[23.4;30.2]
Rescue medication use	N	476	451	436
	Mean	2.4	1.3	-1.1
	SD	2.59	2.09	1.94
	Min	0.0	0.0	-11.6
	Median	1.7	0.3	-0.4
	Max	16.1	14.7	6.3
	[IC95 mean]			[-1.3;-0.9]

Change in the peak expiratory flow rate (PEFR) and rescue medication use between the last 7 days before Visit 3 and the last 7 days before Visit 2 – Group R.

		V2 (N = 99)	V3 (N = 100)	V3-V2 (N = 100)
Morning PEF (L/min)	N	97	95	94
	Mean	249.0	286.1	34.0
	SD	88.12	102.73	39.45
	Min	75.7	84.3	-81.4
	Median	235.7	274.3	29.3
	Max	561.4	601.4	184.3
	[IC95 mean]			[26.0;42.0]
Rescue medication use	N	95	91	89
	Mean	2.5	1.4	-1.1
	SD	2.66	2.15	1.94
	Min	0.0	0.0	-6.6
	Median	2.0	0.2	-0.3
	Max	12.6	12.0	3.5
	[IC95 mean]			[-1.5;-0.7]

Change in the peak expiratory flow rate (PEFR) and rescue medication use between the last 7 days before Visit 3 and the last 7 days before Visit 2 – Group NR.

		V2 (N = 401)	V3 (N = 405)	V3-V2 (N = 406)
Morning PEF (L/min)	N	381	370	355
	Mean	242.8	268.9	25.4
	SD	91.40	100.97	35.70
	Min	72.9	81.4	-75.7
	Median	230.7	250.0	21.4
	Max	578.6	647.1	130.7
	[IC95 mean]			[21.7;29.2]
Rescue medication use	N	377	357	344
	Mean	2.4	1.3	-1.1
	SD	2.57	2.07	1.95
	Min	0.0	0.0	-11.6
	Median	1.6	0.3	-0.4
	Max	16.1	14.7	6.3
	[IC95 mean]			[-1.3;-0.9]

Change in symptom scores between the last 7 days before Visit 3 and the last 7 days before Visit 2

		V2 (N = 504)	V3 (N = 509)	V3-V2 (N = 510)
Symptomatic score (0 to 18)	N	490	474	462
	Mean	5.0	4.2	-0.8
	SD	3.06	3.00	2.18
	Min	0.0	0.0	-10.1
	Median	4.9	3.7	-0.5
	Max	16.5	16.6	6.1

Change in symptom scores between the last 7 days before Visit 3 and the last 7 days before Visit 2 – Group R

		V2 (N = 99)	V3 (N = 100)	V3-V2 (N = 100)
Symptomatic score (0 to 18)	N	97	95	94
	Mean	4.9	4.0	-0.9
	SD	3.05	3.27	1.97
	Min	0.0	0.0	-7.1
	Median	4.5	3.6	-0.9
	Max	16.5	16.6	3.9

Change in symptom scores between the last 7 days before Visit 3 and the last 7 days before Visit 2 – Group NR

		V2 (N = 401)	V3 (N = 405)	V3-V2 (N = 406)
Symptomatic score (0 to 18)	N	389	376	365
	Mean	5.0	4.2	-0.8
	SD	3.06	2.93	2.23
	Min	0.0	0.0	-10.1
	Median	4.9	3.7	-0.4
	Max	15.7	14.4	6.1

Change in the Medical Research Council breathless scale (MRC) between Visit 3 and Visit 2

		V2 (N = 510)	V3 (N = 509)
MRC Score	N	502	500
	Mean	1.4	1.1
	SD	0.84	0.82
	Min	0.0	0.0
	Median	1.0	1.0
	Max	4.0	4.0
difference from V2	N		495
	Mean		-0.3
	SD		0.79
	Min		-4.0
	Median		0.0
	Max		2.0
	[IC95 mean]		[-0.3;-0.2]

Change in the Medical Research Council breathless scale (MRC) between Visit 3 and Visit 2 – group R

		V2 (N = 100)	V3 (N = 100)
MRC Score	N	99	99
	Mean	1.3	1.0
	SD	0.85	0.79
	Min	0.0	0.0
	Median	1.0	1.0
	Max	3.0	3.0
difference from V2	N		98
	Mean		-0.3
	SD		0.85
	Min		-3.0
	Median		0.0
	Max		2.0
	[IC95 mean]		[-0.5;-0.2]

Change in the Medical Research Council breathless scale (MRC) between Visit 3 and Visit 2 – group NR

		V2 (N = 406)	V3 (N = 405)
MRC Score	N	399	398
	Mean	1.4	1.2
	SD	0.84	0.83
	Min	0.0	0.0
	Median	1.0	1.0
	Max	4.0	4.0
difference from V2	N		394
	Mean		-0.2
	SD		0.77
	Min		-4.0
	Median		0.0
	Max		2.0
	[IC95 mean]		[-0.3;-0.2]

Physician's opinion on the correct use of the inhaler

	V3 (N = 512)[a]	V5 (N = 420)[b]
Head retroflexion: n(%)	390 (76.2)	332 (79.0)
Simultaneous pressing of both buttons: n(%)	487 (95.1)	403 (96.0)
Ease of inhalation: n(%)	483 (94.3)	399 (95.0)
Speed of inhalation: n(%)	476 (93.0)	388 (92.4)
Maintenance of apnea at the end of inhalation: n(%)	420 (82.0)	376 (89.5)
Awareness of powder inhalation: n(%)	482 (94.1)	401 (95.5)
Perception of noise emitted by the capsule: n(%)	485 (94.7)	396 (94.3)
Check of the empty capsule: n(%)	474 (92.6)	388 (92.4)

[a] missing data = 23 except for maintenance of apnea at the end of inhalation for which data for 24 patients were missing
[b] missing data = 24
Percentage calculated on column effective (N=)

Safety Results

Adverse Events by System Organ Class – Safety population

	Total
No. (%) of patients enrolled in the safety population	543 (100.0)
No. (%) of patients with at least one AE	264 (48.6)
No (%) of patients with at least one AE considered as related to study treatment	52 (9.6)
System organ class affected	n (%)
Respiratory, thoracic and mediastinal disorders.	132 (24.3)
Infections and infestations	104 (19.2)
General disorders and administration site disorders	29 (5.3)
Nervous system disorders	22 (4.1)
Musculoskeletal and connective tissue disorders.	21 (3.9)
Gastrointestinal disorders	19 (3.5)
Cardiac disorders	12 (2.2)
Injury, poisoning and procedural complications	9 (1.7)
Neoplasms benign, malignant and unspecified	9 (1.7)
Vascular disorders	8 (1.5)
Investigations	6 (1.1)
Psychiatric disorders	5 (0.9)
Skin and subcutaneous tissue disorders	4 (0.7)
Eye disorders	3 (0.6)
Metabolism and nutrition disorders	3 (0.6)
Immune system disorders	2 (0.4)
Surgical and medical procedures	2 (0.4)
Blood and lymphatic system disorders	1 (0.2)
Ear and labyrinth disorders	1 (0.2)
Renal and urinary disorders	1 (0.2)
Reproductive system and breast disorders	1 (0.2)

Most Frequently Reported AEs (frequency > 1%) by Preferred Term n (%) – Safety population

No. (%) of patients enrolled in the safety population	543(100.0)
No. (%) of patients with at least one AE	264(48.6)
AE preferred term	n(%)
Chronic obstructive pulmonary disease	73 (13.4)
Bronchitis	50 (9.2)
Cough	25 (4.6)
Dyspnea	25 (4.6)
Rhinitis	15 (2.8)
Muscle spams	10 (1.8)
Chest pain	7 (1.3)
Headache	7 (1.3)
Nasopharyngitis	7 (1.3)
Palpitations	6 (1.1)
Productive cough	6 (1.1)
Throat irritation	6 (1.1)

Serious Adverse Events and Deaths

No. (%) of patients enrolled in the safety population	543 (100.0)
No. (%) of patients with at least one AE	264 (48.6)
Number (%) of patients with serious or other significant events	n (%)
Death	4 (0.7)
At least one SAE	33 (6.1)
AE(s) leading to premature discontinuation	34 (6.3)

Other Relevant Findings

Not applicable.

Date of Clinical Trial Report

16 Apr 2013

Date Inclusion on Novartis Clinical Trial Results Database

28 May 2013

Date of Latest Update