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Web Page/Link to Prescribing/Label Information

N/A

Generic Drug Name

Formoterol

Therapeutic Area of Trial

Chronic Obstructive Pulmonary Disease (COPD)

Approved Indication

Investigational

Study Number

CFOR258F2402

Title

A randomized, multi-center, placebo controlled 24 week study to compare the efficacy and safety of formoterol Certihaler 10µg b.i.d., tiotropium HandiHaler 18µg o.d. and tiotropium HandiHaler 18µg o.d. in combination with formoterol Certihaler 10µg b.i.d. in patients with stable Chronic Obstructive Pulmonary Disease.

Phase of Development

Phase IIIb

Study Start/End Dates

20-Oct-2004 to 29-Nov-2005

Study Design/Methodology

Multicenter, partially double-blind, randomized, parallel group trial, using a placebo control and active comparator. Patients were treated for 24 weeks with formoterol, placebo, tiotropium, or tiotropium plus formoterol. Treatment comparisons were made, each against each other; formoterol vs. placebo and tiotropium plus formoterol vs. tiotropium monotherapy were double-blind. Efficacy was determined by analysis of peak forced expiratory volume in 1 second (FEV1) at various timepoints.

Centres

86 centers in 8 countries – Czech Republic (4), Germany (30), Spain (4), Hungary (4), Italy (19),

Netherlands (9), Poland (7), Russian Federation (9).

Publication

Ongoing.

Objectives

Primary outcome/efficacy objective(s)

To investigate the efficacy of formoterol Certihaler 10µg twice-daily compared with placebo, following 24 weeks of treatment, in terms of Forced Expiratory Volume in 1 second (FEV1 - a standard respiratory function testing methodology) at 2 hours after dosing.

Secondary outcome/efficacy objective(s)

To explore the efficacy of tiotropium 18µg o.d. administered with formoterol Certihaler 10µg compared to tiotropium 18µg once daily in terms of COPD-related "Bad Days" over 24 weeks of treatment.

To explore the speed of onset of action of formoterol Certihaler 10µg, twice daily (compared to placebo); with tiotropium 18µg, once daily, (compared to placebo), in terms of bronchodilation at 5 minutes after dosing.

To provide safety data for formoterol 10 µg b.i.d. delivered by the Certihaler in patients with COPD, including elderly patients, and to compare this safety data with tiotropium 18 µg o.d. (Handihaler).

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

Formoterol 10 µg or placebo, delivered via the Certihaler, a breath-actuated multi-dose dry powder inhaler.

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

Tiotropium 18µg delivered by the HandiHaler, a breath-actuated, single-dose dry powder inhaler.

Criteria for Evaluation

Primary efficacy:

FEV1 measured at 2 hours after dosing following 24 weeks treatment

Secondary efficacy

- FEV_1 measured:
  - 5 minutes after the first dose.

- pre-dose, 5 mins, 2h and 3h post-dose at other study visits.
- COPD “Bad Days” derived from patient diary data.
- COPD “Exacerbation days” derived from patient diary data.
- COPD symptom-free days
- Quality of Life (QOL) scores derived from the St Georges Respiratory Questionnaire (SGRQ).

Safety/tolerability:

Safety assessments consisted of monitoring and recording all adverse events, serious adverse events (with their severity and relationship to study drug), and pregnancies, the monitoring of hematology and blood chemistry performed at a central laboratory at the start and end of the study, and regular assessments of vital signs, electrocardiogram (ECG), and physical condition

Pharmacology:

N/A

Other: N/A

Statistical Methods

The intent-to-treat (ITT) population consisted of all randomized patients who received at least one dose of study medication. This population was used for efficacy and safety analyses. For safety analyses the subgroup of elderly patients aged 65 years and over was also considered.

For the primary efficacy variable, superiority of formoterol Certihaler over placebo was demonstrated if the null hypothesis H0 “There is no difference between formoterol Certihaler 10µg b.i.d. and placebo in terms of FEV1 measured at 2 hours post dosing following 24 weeks of treatment” was rejected in favor of formoterol using a two-sided test at the 5% significance level.

The analysis was performed on the ITT population using the following analysis of covariance (ANCOVA) model:

FEV_1 = country + gender + reversibility + baseline smoking status + treatment + baseline FEV_1

All other efficacy outcomes reported here were analyzed using a similar model.

Safety analyses were performed for the safety population and repeated for the subgroup of elderly patients.

Treatment emergent adverse events were summarized by treatment group, using the MedDRA system organ class and preferred term. Summaries were provided for all AEs, and by most frequent, by worst severity, suspected drug-related AEs, serious AEs, those which led to permanent discontinuation of study drug, and COPD related adverse events.

Study Population: Inclusion/Exclusion Criteria and Demographics

Patients included were males or females who were current or previous smokers with a smoking history of =10 pack-years, and with a diagnosis of COPD as per the GOLD criteria with an age at onset > 40 years. They were required to have a pre-bronchodilator FEV1 < 70% of patient's predicted normal value and = 1.00 L, with FEV1/FVC< 70 % at Visit 2, and a total symptom score from the patient diary of more than 0 on at least 4 of the last 7 days prior to Visit 3.

Patients were excluded if they had concomitant pulmonary disease, had been hospitalized for an acute exacerbation of their airways disease in the month prior to Visit 1 or during screening, or had a respiratory tract infection within 1 month prior to Visit 1.

Number of Subjects

	Formoterol	Placebo	Tiotropium	Tio + For
Planned N	200	200	200	200
Randomised n	210	209	221	207
Completed n (%)	185 (88.1)	179 (85.6)	192 (86.9)	182 (87.9)
Withdrawn n (%)	25 (11.9)	30 (14.4)	29 (13.1)	25 (12.1)
Withdrawn due to adverse events n (%)	6 (2.9)	8 (3.8)	13 (5.9)	8 (3.9)
Withdrawn due to lack of efficacy n (%)	0	3 (1.4)	2 (0.9)	0
Withdrawn for other reasons n (%)	19 (9.0)	19 (9.1)	14 (6.3)	17 (8.2)

Demographic and Background Characteristics

	Formoterol	Placebo	Tiotropium	Tio + For
N (ITT)	210	209	221	207
Females:males	1:3.1	1:3.4	1:3.8	1:3.8
Mean age, years (SD)	61.8 (8.8)	62.5 (8.6)	63.4 (9.5)	62.6 (8.8)
Race White n (%) Black n (%) Asian n (%) Other n (%)	 209 (99.5) 0 0 1 (0.5)	 209 (100.0) 0 0 0	 221 (100.0) 0 0 0	 206 (99.5) 1 (0.5) 0 0
Mean FEV1 % predicted (SD)	51.6 (10.6)	51.1 (11.0)	51.6 (11.2)	50.4 (10.5)
Mean reversibility, % (SD)	11.4 (12.9)	11.4 (14.1)	9.9 (11.4)	11.0 (10.4)

Primary Efficacy Result(s)

FEV_1 (L) 2 h post-dose after 24 weeks of treatment (ITT population)				
Treatment effect	**N**	**LS mean**	**SE**	**95% CI**
Formoterol	192	1.73	0.03	1.67 – 1.78
Placebo	190	1.56	0.03	1.50 – 1.61
Tiotropium	193	1.73	0.03	1.68 – 1.79
Tio + For	183	1.80	0.03	1.74 – 1.85
Treatment contrast	**LS mean**	**SE**	**95% CI**	**P-value**

Formoterol – Placebo	0.17	0.03	0.11 – 0.24	<0.001
Tiotropium – Placebo	0.18	0.03	0.11 – 0.25	<0.001
Tio + For – Placebo	0.24	0.03	0.17 – 0.31	<0.001
Tio + For – Tiotropium	0.06	0.03	-0.00 – 0.13	0.066
Tio + For – Formoterol	0.07	0.03	0.00 – 0.14	0.044
Formoterol - Tiotropium	-0.01	0.03	-0.07 – 0.06	0.855
Secondary efficacy result(s)				
FEV_1 (L) 5 minutes after first dose of treatment (visit 3)				
Treatment effect	**N**	**LS mean**	**SE**	**95% CI**
Formoterol	207	1.63	0.01	1.61 – 1.65
Placebo	205	1.53	0.01	1.51 – 1.55
Tiotropium	215	1.54	0.01	1.52 – 1.57
Tio + For	201	1.63	0.01	1.60 – 1.65
Treatment contrast	**LS mean**	**SE**	**95% CI**	**P-value**
Formoterol – Placebo	0.10	0.02	0.07 – 0.13	<0.001
Tiotropium - Placebo	0.01	0.02	-0.02 – 0.04	0.341
Tio + For – Placebo	0.10	0.02	0.07 – 0.13	<0.001
Tio + For – Tiotropium	0.08	0.02	0.05 – 0.11	<0.001
Tio + For – Formoterol	-0.00	0.02	-0.03 – 0.03	0.840
Formoterol - Tiotropium	0.08	0.02	0.05 – 0.11	<0.001
Percentage of COPD related 'bad days' over 24 weeks of treatment (ITT population)				
Treatment effect	**N**	**LS mean**	**SE**	**95% CI**
Formoterol	204	24.9	2.1	20.8 – 29.0
Placebo	203	33.9	2.1	29.8 – 38.1
Tiotropium	209	25.6	2.1	21.5 – 29.7
Tio + For	196	26.3	2.1	22.2 – 30.5
Treatment contrast	**LS mean**	**SE**	**95% CI**	**P-value**
Formoterol – Placebo	-9.0	2.6	-14.1 - -3.9	<0.001

Tiotropium - Placebo	-8.4	2.6	-13.4 – 3.3	0.001
Tio + For – Placebo	-7.6	2.6	-12.7 - -2.5	0.004
Tio + For – Tiotropium	0.8	2.6	-4.3 – 5.9	0.767
Tio + For – Formoterol	1.4	2.6	-3.7 _6.6	0.585
Formoterol - Tiotropium	-0.7	2.6	-5.7 – 4.4	0.798
Percentage of COPD related 'exacerbation days' over 24 weeks of treatment (ITT population)				
Treatment effect	**N**	**LS mean**	**SE**	**95% CI**
Formoterol	204	2.4	0.7	1.0 – 3.8
Placebo	203	4.7	0.7	3.4 – 6.1
Tiotropium	209	3.3	0.7	1.9 – 4.7
Tio + For	196	3.3	0.7	1.9 – 4.7
Treatment contrast	**LS mean**	**SE**	**95% CI**	**P-value**
Formoterol – Placebo	-2.3	0.9	-4.0 - -0.6	0.007
Tiotropium - Placebo	-1.4	0.9	-3.1 – 0.2	0.093
Tio + For – Placebo	-1.4	0.9	-3.2 – 0.3	0.102
Tio + For – Tiotropium	0.0	0.9	-1.7 – 1.7	0.987
Tio + For – Formoterol	0.9	0.9	-0.8 – 2.6	0.304
Formoterol - Tiotropium	-0.9	0.9	-2.6 – 0.8	0.304
Percentage of Symptom-free days over 24 weeks of treatment (ITT population)				
Treatment effect	**N**	**LS mean**	**SE**	**95% CI**
Formoterol	204	8.4	1.3	5.8 – 11.0
Placebo	203	6.6	1.3	4.0 – 9.2
Tiotropium	209	7.8	1.3	5.2 – 10.4
Tio + For	196	7.9	1.3	5.3 – 10.5
Treatment contrast	**LS mean**	**SE**	**95% CI**	**P-value**
Formoterol – Placebo	1.8	1.6	-1.4 – 5.0	0.262
Tiotropium - Placebo	1.3	1.6	-1.9 – 4.5	0.438
Tio + For – Placebo	1.3	1.7	-1.9 – 4.6	0.419
Tio + For – Tiotropium	0.1	1.6	-3.1 – 3.3	0.963
Tio + For – Formoterol	-0.5	1.7	-3.7 – 2.7	0.763
Formoterol - Tiotropium	0.6	1.6	-2.6 – 3.8	0.723

Quality of life: SGRQ total score (%) at the end of the study (ITT population)				
Treatment effect	**N**	**LS mean**	**SE**	**95% CI**
Formoterol	176	38.2	1.0	36.2 – 40.2
Placebo	177	41.1	1.0	39.0 – 43.1
Tiotropium	180	39.2	1.0	37.2 – 41.2
Tio + For	170	38.1	1.1	36.1 – 40.2
Treatment contrast	**LS mean**	**SE**	**95% CI**	**P-value**
Formoterol – Placebo	-2.9	1.3	-5.4 - -0.3	0.027
Tiotropium - Placebo	-1.9	1.3	-4.4 – 0.6	0.143
Tio + For – Placebo	-2.9	1.3	-5.5 - -0.4	0.025
Tio + For – Tiotropium	-1.0	1.3	-3.6 – 1.5	0.419
Tio + For – Formoterol	-0.1	1.3	-2.6 – 2.5	0.953
Formoterol - Tiotropium	-1.0	1.3	-3.5 – 1.6	0.450

Adverse Events by System Organ Class

	Formoterol n (%)	**Placebo n (%)**	**Tiotropium n (%)**	**Tio + For n (%)**
Patients studied				
Total no. of patients	210 (100)	209 (100)	221 (100)	207 (100)
Total no. of patients with AEs	72 (34.3)	82 (39.2)	79 (35.7)	70 (33.8)
Primary system organ class affected				
Infections and infestations	36 (17.1)	30 (14.4)	31 (14.0)	25 (12.1)
Respiratory, thoracic and mediastinal disorders	25 (11.9)	40 (19.1)	38 (17.2)	27 (13.0)
Gastrointestinal disorders	11 (5.2)	8 (3.8)	10 (4.5)	5 (2.4)
Nervous system disorders	11 (5.2)	4 (1.9)	4 (1.8)	9 (4.3)
Musculoskeletal and connective tissue disorders	7 (3.3)	9 (4.3)	3 (1.4)	9 (4.3)
Cardiac disorders	6 (2.9)	7 (3.3)	9 (4.1)	6 (2.9)
General disorders and admin. site conditions	5 (2.4)	5 (2.4)	6 (2.7)	9 (4.3)
Metabolism and nutrition disorders	5 (2.4)	1 (0.5)	3 (1.4)	4 (1.9)
Vascular disorders	5 (2.4)	6 (2.9)	5 (2.3)	4 (1.9)
Hepatobiliary disorders	2 (1.0)	2 (1.0)	0	0
Investigations	2 (1.0)	2 (1.0)	1 (0.5)	0
Psychiatric disorders	2 (1.0)	2 (1.0)	0	0
Renal and urinary disorders	2 (1.0)	0	4 (1.8)	0
Skin and subcutaneous tissue disorders	2 (1.0)	3 (1.4)	7 (3.2)	2 (1.0)
Blood and lymphatic system disorders	1 (0.5)	0	0	0
Ear and labyrinth disorders	1 (0.5)	0	2 (0.9)	0
Immune system disorders	1 (0.5)	0	1 (0.5)	0
Injury, poisoning and procedural complications	1 (0.5)	6 (2.9)	1 (0.5)	4 (1.9)
Reproductive system and breast disorders	1 (0.5)	0	0	1 (0.5)
Surgical and medical procedures	1 (0.5)	0	0	0
Eye disorders	0	0	2 (0.9)	1 (0.5)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	3 (1.4)	0	2 (1.0)

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

Adverse event (MedDRA preferred term)	Formoterol n (%)	Placebo n (%)	Tiotropium n (%)	Tio + For n (%)
Chronic obstructive pulmonary disease	20 (9.5)	34 (16.3)	28 (12.7)	16 (7.7)
Nasopharyngitis	15 (7.1)	11 (5.3)	11 (5.0)	13 (6.3)
Hypertension	4 (1.9)	5 (2.4)	5 (2.3)	3 (1.4)
Back pain	3 (1.4)	3 (1.4)	1 (0.5)	3 (1.4)
Bronchitis	3 (1.4)	1 (0.5)	4 (1.8)	1 (0.5)
Cough	3 (1.4)	4 (1.9)	5 (2.3)	5 (2.4)
Hypercholesterolemia	3 (1.4)	1 (0.5)	1 (0.5)	0
Influenza	3 (1.4)	5 (2.4)	1 (0.5)	2 (1.0)
Respiratory tract infection	3 (1.4)	3 (1.4)	4 (1.8)	1 (0.5)
Tremor	3 (1.4)	0	2 (0.9)	1 (0.5)

Serious Adverse Events and Deaths

	Formoterol n (%)	**Placebo n (%)**	**Tiotropium n (%)**	**Tio + For n (%)**
Patients studied				
Total no. of patients	210 (100)	209 (100)	221 (100)	207 (100)
Total no. of patients with AEs	72 (34.3)	82 (39.2)	79 (35.7)	70 (33.8)
Serious or clinically significant adverse events				
Death	0	1 (0.5)	0	0
Non-fatal SAE	8 (3.8)	11 (5.3)	10 (4.5)	10 (4.8)
Any AE leading to discontinuation	6 (2.9)	8 (3.8)	11 (5.0)	8 (3.9)

Events reported are not mutually exclusive. A SAE could also be an AE leading to discontinuation.

SAE details	**Formoterol n (%)**	**Placebo n (%)**	**Tiotropium n (%)**	**Tio + For n (%)**
Coronary artery disease	2 (1.0)	0	0	0
Angina pectoris	1 (0.5)	0	2(0.9)	0
Acute coronary syndrome	0	1 (0.5)	0	0
Atrial fibrillation	0	0	0	1 (0.5)
Myocardial ischemia	0	0	1 (0.5)	1 (0.5)
Tachycardia	0	1 (0.5)	0	0
Cerebrovascular accident	2 (1.0)	0	0	0
Carotid artery stenosis	1 (0.5)	0	0	0
Cerebral Haemorrhage	0	1 (0.5)	0	0
Tremor	0	0	0	1 (0.5)
Bronchopneumonia	1 (0.5)	0	0	0
Influenza	0	2 (1.0)	0	0
Respiratory tract infection	0	0	1 (0.5)	0
Chronic obstructive pulmonary disease	1 (0.5)	3 (1.4)	6 (2.7)	3 (1.4)
Dyspnoea	1 (0.5)	2 (1.0)	1 (0.5)	0
Cough	0	0	1 (0.5)	0
Pleural effusion	0	0	1 (0.5)	0
Pulmonary embolism	0	0	0	1 (0.5)
Hypertension	1 (0.5)	0	0	0
Gastric Haemorrhage	0	1 (0.5)	0	0
Gastrointestinal inflammation Intestinal perforation	0 0	1 (0.5) 0	0 0	0 1 (0.5)
Asthenia	O	O	1 (0.5)	0
Chills	0	1 (0.5)	0	0
Pyrexia	0	1 (0.5)	0	0
Accidental overdose	0	0	0	1 (0.5)
Fall	0	1 (0.5)	0	0
Humerus fracture	0	1 (0.5)	0	0
Bronchial carcinoma	0	0	0	1 (0.5)
Lung neoplasm malignant	0	0	0	1 (0.5)
Metastases to bone	0	1 (0.5)	0	0
Non-Hodgkin's lymphoma	0	1 (0.5)	0	0
Oesophageal Squamous cell carcinoma	0	1 (0.5)	0	0
Anxiety	0	1 (0.5)	0	0

Other Relevant Findings

None

Date of Clinical Trial Report

Not yet finalised

Date Inclusion on Novartis Clinical Trial Results Database

24 April 2007

Date of Latest Update April 2007