Sponsor

Novartis

Generic drug name

Tiotropium bromide

Trial indication(s)

Chronic Obstructive Pulmonary Disease (COPD)

Protocol number

CPJMR0052203

Protocol title

A randomized, open-label, multicenter, two-period crossover study to evaluate the 24 hour bronchodilator profile of Tiotropium Bromide Respimat® administered once daily versus twice daily in patients with Chronic Obstructive Pulmonary Disease (COPD)

Clinical trial phase

Phase II

Study Start/End Dates

26 Jan 2009 to 06 May 2009

Study Design/Methodology

This was a randomized, open-label, multicenter, two-period crossover study to evaluate the 24 hour bronchodilator profile of tiotropium bromide Respimat® administered once daily versus twice daily in patients with COPD.

Centers

The study was conducted at 8 centers in 3 countries; Germany (3), France (2), United kingdoms (3).

Objectives:

Primary objective

To compare the bronchodilator profile over 24 hours, measured in terms of the standardized 24 h forced expiratory volume in 1 second (FEV1) area under the curve (AUC), of tiotropium bromide administered either 2.5 µg twice daily (b.i.d.) or 5 µg once daily (q.d.) following 14 days treatment.

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

Patients were with tiotropium bromide solution in either 2.5 µg b.i.d. or 5 µg q.d. via the Respimat® inhaler for 14 days.

Statistical Methods

The Day 14 FEV1 AUC $_{0\text{-}24h}$ was calculated using the trapezoidal rule using observed and imputed FEV1 between -15min and 23h 45min post-dose. This calculation was standardized by dividing by the actual length of time the AUC covered; actual times were used. Parameters were summarized descriptively by treatment and time point.

The Day 14 FEV1 $AUC_{0\text{-}24h/24}$ was analyzed using a 2-way crossover linear mixed effects model for the pharmacodynamics (PD) analysis set. The model contained Day 14 standardized 24 h FEV1 AUC as the dependent variable and sequence, patient (sequence), treatment, period, and period baseline FEV1. All effects were fixed except patient (sequence). Mean difference between the two dosing regimens (tiotropium bromide 5 µg q.d. vs. tiotropium bromide 2.5 µg b.i.d.) was derived.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Male or female adult patients aged ≥40 years, who signed an Informed Consent Form prior to initiation of any study-related procedure.

- Patients with moderate to severe COPD (Stage II or Stage III) according to the Gold guidelines 2007.
- Patients had to be current or ex-smokers with a smoking history of at least 10 pack years.
- Patients with a post-bronchodilator FEV1 ≥30% and < 80% of the predicted normal, and post-bronchodilator ratio of FEV1 to forced vital capacity (FVC) < 0.7 at Visit 1 and Visit 3.

Exclusion criteria:

- Pregnant women or nursing mothers and women of child-bearing potential,
- Patients requiring oxygen therapy on a daily basis for chronic hypoxemia, or who had been hospitalized for an exacerbation of their airways disease in the 6 weeks prior to Visit 1 or between Visit 1 and Visit 4.
- Patients who had a respiratory tract infection within 6 weeks prior to Visit 1. Patients who developed a respiratory tract infection or COPD exacerbation during the screening period (up to Visit 4) were not eligible, but were permitted to be re-screened at a later date (at least 6 weeks after the resolution of the respiratory tract infection).
- Patients with a clinically relevant laboratory abnormality or a clinically significant condition such as (but not limited to):
    - unstable ischemic heart disease, left ventricular failure, history of myocardial infarction, arrhythmia (excluding stable atrial fibrillation),
    - long term prednisone therapy (defined as ≥ 10mg daily for at least 1 month prior to Visit1),
    - history of malignancy of any organ system (including lung cancer), treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
    - narrow-angle glaucoma (diagnosed prior to or at Visit 1)
    - symptomatic prostatic hyperplasia or bladder-neck obstruction or moderate to severe renal impairment or urinary retention
    - uncontrolled hypo- and hyperthyroidism, hypokalemia, hyper adrenergic state
    - any condition which might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study.
- Patients with a history of asthma indicated by (but not limited to) onset of symptoms prior to age 40 years.
- Patients contraindicated for tiotropium treatment or who had shown an untoward reaction to inhaled anticholinergic agents.
- Patients with a history of untoward reactions to sympathomimetic amines or inhaled medication or any component thereof.

- Patients with a history of long QT syndrome or whose QTc measured at Visit 1 (Fridericia method) was prolonged (>450 ms for males or >470 for females).
- Patients who needed the following treatments for COPD and allied conditions unless they had been stabilized for at least one month prior to Visit 1: cromoglycate, nedocromil, ketotifen, inhaled corticosteroids in recommended and constant doses and dose regimens.
- Patients taking beta-blocking agents.
- Patients unable to use the Respimat® device or a pMDI (rescue medication) or perform spirometry measurements.
- Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of Visit 1, whichever was longer.
- Participation in any clinical investigation within 4 weeks prior to initial dosing or longer if required by local regulations.

Other protocol-defined inclusion/exclusion criteria may apply

Patient Flow Table:

Patient disposition – n (%) of patients

	Safety population
Patients	
Randomized	67 (100.0%)
Completed	66 (98.5%)
Discontinued	1 (1.5%)
Main cause of discontinuation	
Adverse event(s)	1 (100.0%)

Baseline Characteristics

Demographic and disease characteristics at baseline by treatment group (safety analysis set)

Demographic or disease characteristic		Safety analysis set N=67
Age (years)	Mean (SD)	60.7 (8.04)
	Median	61.0
	Range	40–80
Height (cm)	Mean (SD)	172.4 (9.13)
	Median	174.0
	Range	147–192
Gender - n(%)	Male	51 (76.1%)
	Female	16 (23.9%)
Race - n(%)	Caucasian	67 (100.0%)
Ethnicity - n(%)	Hispanic/Latino	2 (3.0%)
	Other	65 (97.0%)
Stage of COPD - n(%)	Stage II	45 (67.2%)
	Stage III	22 (32.8%)
Time since diagnosis of COPD	Mean (SD)	10.1 (6.89)
	Median	8.0
	Range	0–29
Smoking history - n(%)	Ex-smoker	32 (47.8%)
	Current smoker	35 (52.2%)
Pack years for current or ex-smokers	Mean (SD)	45.7 (23.95)
	Median	40.0
	Range	10–132

Summary of Efficacy

Primary Outcome Result(s):

Least squares means for Day 14 FEV 1 AUC $_{0\text{-}24h}$ (PD analysis set)

	Tiotropium bromide 5 µg q.d. N=67		Tiotropium bromide 2.5 µg b.i.d. N=67			
Primary endpoint	**n**	**LS means (SE)**	**n**	**LS means (SE)**	**Estimate (SE)**	**90% CI**
Day 14 FEV_1 $AUC_{0\text{-}24h}$ (L)	65	1.572 (0.0210)	65	1.601 (0.0210)	-0.030 (0.0217)	(-0.066,0.007)

n = number of patients with non-missing baseline and relevant time point data.

Summary of Safety

Safety Results

Adverse events overall and by system organ class and treatment (Safety analysis set)

Primary system organ class	**Tiotropium bromide 5 µg q.d. N=67 n(%)**	**Tiotropium bromide 2.5 µg b.i.d. N=67 n(%)**
n (%) of patients with AEs	**10 (14.9)**	**16 (23.9)**
Respiratory, thoracic and mediastinal disorders	4 (6.0)	6 (9.0)
Nervous system disorders	2 (3.0)	4 (6.0)
Gastrointestinal disorders	2 (3.0)	3 (4.5)
Infections and infestations	1 (1.5)	2 (3.0)
Musculoskeletal and connective tissue disorders	1 (1.5)	2 (3.0)
Skin and subcutaneous tissue disorders	0	1 (1.5)
Surgical and medical procedures	0	1 (1.5)
Investigations	1 (1.5)	0

Adverse events overall and by preferred term and treatment (Safety analysis set)

Preferred term	Tiotropium bromide 5 µg q.d. N=67 n(%)	Tiotropium bromide 2.5 µg b.i.d. N=67 n(%)
n (%) of patients with AEs	**10 (14.9)**	**16 (23.9)**
Headache	1 (1.5)	3 (4.5)
Dry mouth	1 (1.5)	2 (3.0)
Dyspnea	0	2 (3.0)
Nasopharyngitis	1 (1.5)	2 (3.0)
Back pain	1 (1.5)	1 (1.5)
Cough	2 (3.0)	1 (1.5)
Dizziness	1 (1.5)	1 (1.5)
Dysphonia	1 (1.5)	1 (1.5)
Bone pain	0	1 (1.5)
Chronic obstructive pulmonary disease	0	1 (1.5)
Diarrhea	0	1 (1.5)
Dry throat	0	1 (1.5)
Photodermatosis	0	1 (1.5)
Rhinorrhea	0	1 (1.5)
Tooth extraction	0	1 (1.5)
Wheezing	0	1 (1.5)
Abdominal pain upper	1 (1.5)	0
Heart rate irregular	1 (1.5)	0
Oropharyngeal pain	1 (1.5)	0

Deaths, other serious adverse events, and other significant adverse events

- No deaths reported during the study
- No serious adverse events reported during the study.
- One patient was permanently discontinued study drug due to an adverse event.

Other Relevant Findings

Least squares means for Day 14 FEV 1 and FVC endpoints (PD analysis set)

	Tiotropium bromide 5 µg q.d. N=67		Tiotropium bromide 2.5 µg b.i.d. N=67			
Day 14 endpoint	n	LS means (SE)	n	LS means (SE)	Estimate (SE)	90% CI
FEV_1 AUC_{0-4h} (L)	67	1.696 (0.0241)	66	1.716 (0.0242)	-0.020 (0.0261)	(-0.063, 0.024)
FEV_1 AUC_{0-12h} (L)	66	1.647 (0.0224)	66	1.655 (0.0224)	-0.008 (0.0238)	(-0.048, 0.032)
FEV_1 AUC_{12-24h} (L)	65	1.495 (0.0219)	65	1.545 (0.0219)	-0.050 (0.0218)	(-0.086, -0.014)*
FEV_1 trough	67	1.573 (0.0250)	66	1.613 (0.0252)	-0.040 (0.0312)	(-0.093, 0.012)
FEV_1 peak	67	1.829 (0.0278)	67	1.861 (0.0278)	-0.033 (0.0311)	(-0.085, 0.019)
FVC AUC_{0-4h} (L)	67	3.594 (0.0455)	66	3.630 (0.0457)	-0.036 (0.0424)	(-0.107, 0.035)
FVC AUC_{0-12h} (L)	66	3.502 (0.0425)	66	3.531 (0.0425)	-0.029 (0.0411)	(-0.098, 0.040)
FVC AUC_{12-24h} (L)	65	3.273 (0.0397)	65	3.374 (0.0397)	-0.102 (0.0430)	(-0.174, -0.030)*
FVC AUC_{0-24h} (L)	65	3.387 (0.0393)	65	3.456 (0.0393)	-0.069 (0.0406)	(-0.137, -0.001)
FVC trough	67	3.421 (0.0465)	66	3.461 (0.0468)	-0.040 (0.0579)	(-0.136, 0.057)
FVC peak	67	3.828 (0.0491)	67	3.880 (0.0491)	-0.052 (0.0499)	(-0.135, 0.031)

n = number of patients with non-missing baseline and relevant time point data
* Statistically significant difference for q.d. vs. b.i.d. according to two-sided p-value

Date of Clinical Trial Report

30 Oct 2009