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Data Article

Data on the safety and tolerability of revefenacin, in patients with moderate to very severe chronic obstructive pulmonary disease

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ABSTRACT

This article contains information on the experimental design and methods on how the safety and tolerability data concerning patients with moderate to very severe chronic obstructive pulmonary disease (COPD) were obtained. This is in addition to our original research article. [1] We have also provided information on the clinical laboratory tests that were conducted.

Further interpretation and discussion of the data are demonstrated in the article "Revefenacin, a Once-daily, Lung-selective, Long-acting Muscarinic Antagonist for Nebulized Therapy: Safety and Tolerability Results of a 52-week Phase 3 Trial in Moderate to Very Severe Chronic Obstructive Pulmonary Disease." [1]

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Specifications Table

Subject area	Pulmonary and Respiratory Medicine
More specific subject area	Chronic obstructive pulmonary disease
Type of data	Tables and Figure
How data was acquired	Clinical study report, adverse event collection
Data format	Raw and analyzed
Experimental factors	Phase 3, randomized partially double-blind, parallel-group, 52-week trial Active, open-label comparator
Experimental features	Subjects were randomized to 1 of 3 treatment groups (revefenacin 88 μg, revefenacin 175 μg, and tiotropium 18 μg) administered once daily in the morning for 52 weeks. Subject safety and tolerability were evaluated using the frequency and severity of adverse events, clinical laboratory measurements, physical examinations, and vital signs
Data source location	103 sites in the United States
Data accessibility	Data with this article
Related research article	Donohue, JF. Kerwin, E. Sethi, S. Haumann, B. Pendyala, S. Dean, L. Barnes, C., Moran, EJ. Crater, G. Revefenacin, a once-daily, lung-selective, long-acting muscarinic antagonist for nebulized therapy: Safety and tolerability results of a 52-week phase 3 trial in moderate to very severe chronic obstructive pulmonary disease. Respir Med. 153, 2019, 153:38–43 [1].

Value of the data

- The clinical laboratory tests and vital signs are important to determine the overall safety profile of treatments in patients with COPD.
- The experimental design and methods give further information on how the safety and tolerability data concerning patients with COPD were obtained.
- The safety profile of revefenacin was demonstrated in a broad population of patients with COPD of varying disease severity.

1. Data

A schematic overview, which included the screening, treatment period, and follow-up visits, is shown in the Fig. In Table 1, a detailed list of the medications that required washout or modification before screening and were prohibited. The full inclusion and exclusion criteria are shown in Table 2. Table 3 provides a detailed overview of how adverse events (AEs), serious AEs (SAEs), and vital signs were evaluated. Tables 4–7 include data on drug exposure (revefenacin or tiotropium), clinical laboratory measurements, and vital signs.

2. Experimental design, materials, and methods

2.1. Schematic overview

Overall, there were one or two screening visits (Visit 1A/Visit 1B; depending on whether a washout period was required) and 6 treatment period visits (Visits 2 [Day 1], 3 [Day 29], 4 [Day 92], 5 [Day 183], 6 [Day 274], and 7 [Day 365]), and a telephone follow-up visit (Visit 8, 7 ± 2 days after Visit 7 or early termination). Informed consent was obtained during the first screening visit (Visit 1A), and the subject's existing COPD medication was assessed to determine whether any adjustments were required to comply with the protocol.

If a washout period or a stable long-acting beta agonist (LABA)/inhaled corticosteroid (ICS) run-in period (at least 30 days) was required, the time from the Initial Screening Visit to Visit 1B was to be no longer than 45 days. If a washout period or a stable LABA/ICS run-in period (at least 30 days) was not required, then the two screening visits (Visit 1A and 1B) were conducted as a single screening visit (Visit 1A/B). The period from Visit 1B (i.e., the Ipratropium Reversibility Visit) to Day 1 of dosing (Visit

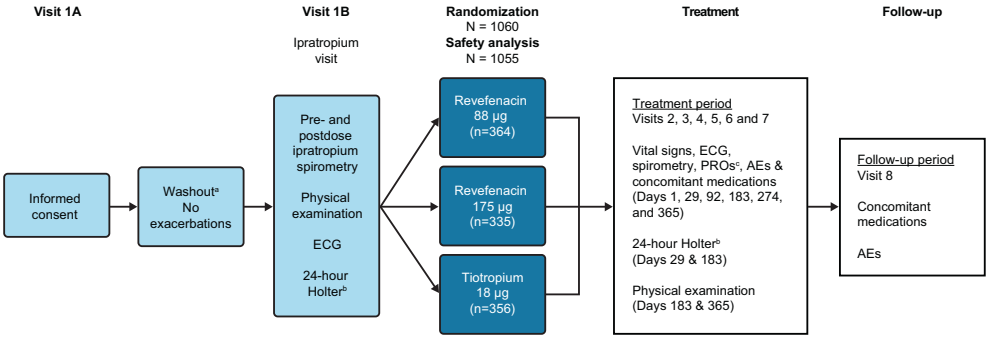

Fig. Schematic overview.

2) was 7−12 days (whether this was combined with Visit 1A or not). Eligible subjects were randomized on Visit 2 (Day 1 of dosing).

2.2. Medications that required washout or modification before Visit 1B and were prohibited

Table 1 lists medications that required a washout period before Visit 1B, and from Visit 1B to Visit 8 (24 hours after the last dose of revefenacin/tiotropium). Subjects were permitted to restart their routine medications after the completion of Visit 8.

Table 1
Medications that required washout/modification.

Medications	Washout or modification required
1. Any ICS at a dose of >1000 µg/day fluticasone propionate or equivalent	Subjects on a dose >1000 µg/day fluticasone propionate or equivalent should have their dose modified to be on a stable dose of ≤1000 µg fluticasone propionate or equivalent for at least 30 days before the ipratropium reversibility test at screening and continued through to Day 365.
2. LAMA 3. Roflumilast	14 days before the ipratropium reversibility test at screening and prohibited throughout the treatment period to Day 365
4. LABA 5. LABA/ICS 6. LAMA/LABA	Subjects on a LABA or LABA/ICS product do not need to be washed out provided they have been on a stable dose for at least 30 days before the ipratropium reversibility test at screening and continued through Day 365. The steroid component should be ≤ 1000 µg fluticasone propionate or equivalent.
7. Oral theophyllines 8. Oral leukotriene inhibitors 9. Other antimuscarinic medications	48 hours before the Ipratropium Reversibility test at screening and prohibited throughout the treatment period to Day 365
10. Sodium cromoglycate 11. Nedocromil sodium	24 hours before the Ipratropium Reversibility test at screening and prohibited throughout the treatment period to Day 365.
12. SABA 13. SAMA	6 hours before the ipratropium reversibility test at screening. Subjects will be provided with albuterol to be used as rescue medication during screening and throughout the treatment period. Albuterol must be withheld at least 6 hours before any spirometry performed. SAMA must be washed out before the ipratropium reversibility test and are prohibited throughout the treatment period.
14. Antibiotics	Any prophylactic use of antibiotics.

ICS; inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta-agonist; SAMA, short-acting muscarinic antagonist.

Table 2
Inclusion and exclusion criteria.

Inclusion criteria

1. Male and female subjects aged ≥40 years (age at Visit 1A).
2. Signed and dated written informed consent (Visit 1A) must be obtained before any assessments are performed.
3. The subject was capable of performing reproducible spirometry maneuvers as described by current American Thoracic Society Guidelines and had a post-ipratropium FEV_1/FVC ratio <0.7 at Visit 1B.
4. Subjects with moderate to very severe stable COPD and a post-ipratropium FEV_1 less than 80% of predicted normal and a post-ipratropium FEV_1 >700 mL at Visit 1B.
5. Subjects with a current/past cigarette smoking history (or equivalent for cigar or pipe smoking history) of at least 10 pack-years.
6. Subjects were willing and able to attend visits in accordance with the visit schedule.
7. Women of either childbearing potential or non-child bearing potential as follows:
   - Females of childbearing potential must have had documentation of a negative urine pregnancy test at Visit 1B and Visit 3 (before randomization). If a urine pregnancy test was positive, it must have been confirmed via a second urine pregnancy test. All female subjects of childbearing potential must have agreed to use a highly effective method of birth control during the trial and for at least 1 month after completion of drug dosing.
     - o A highly effective method of birth control was defined as one that results in a low failure rate (i.e., <1% per year) when used consistently and correctly, such as condom + diaphragm, condom + spermicide, diaphragm + spermicide, or intrauterine device with documented failure rate of <1% per year, or oral/injectable/implanted hormonal contraceptives used in combination with an additional barrier method.
   - Women were considered to be not of childbearing potential if they had a total hysterectomy and/or bilateral tubal ligation, (documentation for either must be provided before enrollment) or were at least 2 years postmenopausal.
8. Subjects (or caregivers) based on the investigator's assessment were able to properly prepare and administer medication based administered either by nebulizer or HandiHaler.

Exclusion criteria

1. Females who were pregnant, lactating, breastfeeding, or planning to become pregnant during the trial.
2. Subjects that had a significant respiratory disease or disorder other than COPD that, in the opinion of the investigator, would affect the interpretation of data from this trial, including, but not limited to, the following:
   - Restrictive lung disorders
   - Benign or malignant tumors of the lung
   - Chronic pulmonary infections (e.g., tuberculosis)
   - Occupational lung disease (e.g., silicosis, asbestosis)
   - Inflammatory disorders of the lung,
   - Alpha-1-antitrypsin deficiency,
   - Abnormalities of the chest wall or musculature (e.g., scoliosis, myasthenia gravis, phrenic nerve palsy).
3. Subjects that had a history of cancer of any organ treated or untreated in the 5 years before Visit 1A (excludes localized basal cell or squamous cell carcinoma of the skin; localized prostate cancer in situ of Grade 1; localized cervical cancer in situ of Grade 0).
4. Subjects that had a concurrent disease or condition that in the opinion of the investigator would interfere with trial participation or confound the evaluation of safety, tolerability, or PK of the drug (revefenacin or tiotropium).
5. Subjects that had a history of reactions or hypersensitivity to inhaled or nebulized anticholinergics or short-acting beta-agonists.
6. Subjects that have any medical condition that would preclude the use of inhaled anticholinergics, including narrow-angle glaucoma, symptomatic benign prostatic hyperplasia, bladder neck obstruction, or urinary retention.
7. Subjects that had a significantly increased risk of cardiovascular events, as indicated by a history at Visit 1A of myocardial infarction or unstable angina within the last 6 months, unstable or life-threatening cardiac arrhythmia requiring intervention in the last 3 months, or New York Heart Association Class IV heart failure.
8. Subjects that had clinically significant and uncontrolled hypertension, hypercholesterolemia, or type II diabetes mellitus.
9. Subjects that had been hospitalized for COPD or pneumonia within 8 weeks before Visit 1B.
10. Subjects that had used systemic corticosteroids within 6 weeks of Visit 1B.
11. Subjects that had used antibiotics for respiratory tract infections within 6 weeks of Visit 1B.
12. Subjects that had undergone lung volume reduction surgery or lobectomy within 12 months before Visit 1B.
13. Subjects that had an abnormal and clinically significant 12-lead ECG finding at Visit 1B according to the following criteria:
    - Atrial fibrillation with rapid ventricular rate >120 beats per minute
    - Sustained or non-sustained ventricular tachycardia
    - Second-degree heart block Mobitz type II
    - Third-degree heart block (unless pacemaker or defibrillator had been inserted)
    - QT interval corrected for heart rate using Fridericia's formula ≥500 msec.
14. Subjects that were unwilling or unable to stop the use of prohibited medications during the washout (if required), treatment period, or follow-up period.
15. Subjects that had participated in a previous revefenacin trial.

(*continued on next page*)

Table 2 (*continued*)

16. Subjects that had used any other investigational medication within 30 days or 5 drug half-lives (whichever was longer) of screening.
17. Subjects that had a history of known or suspected alcohol or drug abuse within 2 years before screening, in the opinion of the investigator.
18. Subjects that were affiliated with the investigator site (e.g., investigator, trial coordinator, site employee).
19. Subjects that required long-term oxygen therapy (>15 hours a day) daily for chronic hypoxemia.
20. Subjects who participated in the initiation phase of a supervised pulmonary rehabilitation program (subjects in the maintenance phase were eligible).

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 3
Assessments of adverse events and serious adverse events.

Adverse events	
Mild	Awareness of signs or symptoms, but easily tolerated
Moderate	Discomfort sufficient to cause interference with usual activities
Severe	Incapacitation with the inability to work or perform usual activities

Serious adverse events

1. Death
2. Life-threatening situation (subject was at immediate risk of death)
3. Inpatient hospitalization or prolongation of existing hospitalization (excluding those for therapy or placement of an indwelling catheter, unless associated with other serious events)
4. Congenital anomaly/birth defect in the offspring of a subject who received treatment
5. Other: Important medical events that may not have resulted in death, was immediately life-threatening, or required hospitalization, may have been considered an SAE when, based upon appropriate medical judgment, they may have jeopardized the subject and required medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events are as follows:
   - Intensive treatment in an emergency room or at home for allergic bronchospasm
   - Blood dyscrasias or convulsions that did not result in hospitalization
   - Development of drug dependency or drug abuse

Vital signs	
Systolic blood pressure	Diastolic blood pressure
<85	<45
>160	>100

Table 4
Drug exposure.

	Revefenacin 88 μg	Revefenacin 175 μg	Tiotropium 18 μg
Number of doses taken by subject			
Mean (standard deviation)	259.3 (130.35)	250.6 (136.16)	303.6 (103.16)
Median	337.0	335.0	356.0
Min, Max	2, 417	1, 420	6, 417
Duration of medication (days)			
Mean (standard deviation)	267.0 (134.61)	258.9 (138.17)	311.0 (105.49)
Median	363.0	362.0	364.0
Min, Max	1, 380	1, 386	1, 418

2.3. Inclusion and exclusion criteria

Subjects were eligible if they met the criteria in Table 2.

2.4. Assessment of treatment-emergent AEs (TEAEs) and SAEs

A TEAE was defined as an AE that began on or after the date of the first dose of treatment (revefenacin or tiotropium) up to the date of the last dose of treatment plus 7 ± 2 days in the follow-up

Table 5
Hematology assessments.

Mean (standard deviation) change from baseline at Day 365	Revefenacin 88 μg (N = 364)	Revefenacin 175 μg (N = 335)	Tiotropium 18 μg (N = 356)
Hemoglobin (g/L)	0.0 (10.18)	−1.4 (9.10)	−0.1 (9.48)
Hematocrit (L/L)	−0.005 (0.0316)	−0.009 (0.0292)	−0.007 (0.0297)
Erythrocyte mean corpuscular hemoglobin (pg)	0.13 (1.074)	0.14 (0.906)	0.27 (0.846)
Erythrocyte mean corpuscular hemoglobin concentration (g/L)	4.2 (7.47)	3.4 (7.72)	4.6 (7.69)
Erythrocyte mean corpuscular volume (fL)	−0.8 (2.94)	−0.5 (2.46)	−0.5 (2.48)
Erythrocytes (10^{12}/L)	−0.016 (0.3209)	−0.071 (0.3047)	−0.043 (0.3063)
Leukocytes (10^9/L)	0.387 (1.7634)	0.407 (1.7090)	0.274 (1.9666)
Basophils (10^9/L)	0.002 (0.0273)	0.007 (0.0246)	0.001 (0.0217)
Eosinophils (10^9/L)	0.017 (0.1462)	0.007 (0.1744)	0.008 (0.1517)
Lymphocytes (10^9/L)	0.009 (0.5742)	0.080 (0.4846)	0.023 (0.4919)
Monocytes (10^9/L)	0.033 (0.1679)	0.021 (0.1654)	0.027 (0.1638)
Neutrophils (10^9/L)	0.362 (1.7098)	0.294 (1.5869)	0.212 (1.7726)
Platelets (10^9/L)	6.2 (43.67)	4.1 (34.40)	−0.6 (39.77)

Table 6
Serum chemistry assessments.

Mean (standard deviation) change from baseline at Day 365	Revefenacin 88 μg (N = 364)	Revefenacin 175 μg (N = 335)	Tiotropium 18 μg (N = 356)
Carbon dioxide (mmol/L)	0.0 (2.80)	0.1 (2.75)	−0.2 (2.97)
Calcium (mmol/L)	−0.021 (0.0988)	0.006 (0.0980)	−0.010 (0.0952)
Chloride (mmol/L)	0.1 (2.90)	−0.1 (2.77)	−0.1 (2.75)
Magnesium (mmol/L)	−0.008 (0.0624)	−0.009 (0.0655)	−0.006 (0.0630)
Phosphate (mmol/L)	−0.004 (0.1775)	0.012 (0.1769)	0.007 (0.1856)
Potassium (mmol/L)	−0.06 (0.442)	−0.02 (0.429)	−0.06 (0.459)
Sodium (mmol/L)	−0.5 (2.80)	−0.6 (2.28)	−0.9 (2.72)
Alkaline phosphatase (IU/L)	2.3 (12.97)	1.6 (12.25)	1.0 (14.34)
Alanine aminotransferase (IU/L)	−0.5 (12.47)	0.0 (16.36)	0.6 (14.59)
Aspartate aminotransferase (IU/L)	0.4 (13.79)	0.3 (13.24)	0.7 (12.28)
Bilirubin (μmol/L)	−0.3 (3.10)	−0.4 (2.90)	−0.4 (3.09)
Gamma glutamyl transferase (IU/L)	1.4 (18.55)	0.0 (12.73)	0.8 (21.67)
Lactate dehydrogenase (IU/L)	1.1 (36.61)	−1.3 (23.51)	1.3 (28.26)
Blood urea nitrogen (mmol urea/L)	0.13 (2.005)	0.27 (1.679)	0.37 (2.039)
Creatinine (μmol/L)	2.0 (13.31)	1.6 (12.90)	1.2 (13.91)

Table 7
Vital signs assessments.

Mean (standard deviation) change from baseline at Day 365	Revefenacin 88 μg (N = 364)	Revefenacin 175 μg (N = 335)	Tiotropium 18 μg (N = 356)
Diastolic blood pressure (mmHg)	0.3 (10.12)	0.8 (9.43)	0.1 (9.79)
Systolic blood pressure (mmHg)	1.4 (18.03)	0.7 (17.18)	0.7 (17.56)

period. Clinical severity was recorded and graded using mild, moderate, or severe. An SAE was defined as any adverse drug experience that occurred at any dose that resulted in any of the following outcomes in Table 3. Clinical laboratory measurements and vital signs were performed non-fasting from Visit 1B to Visit 7 (and at Visit 8 if subject withdrew from subject early; Fig.). Abnormal laboratory findings or other abnormal assessments (such as vital signs) that were associated with signs and/or symptoms or were considered clinically significant in the judgment of the Investigator, were recorded as AEs or SAEs if they met the definition of an AE (or SAE). Vital signs were summarized in terms of observed values and changes from baseline. Vital signs outliers are shown in Table 3.

2.5. Drug exposure

Using drug administration data from the electronic case report form, estimates of exposure to revefenacin and tiotropium were summarized in Table 4.

2.6. Clinical laboratory measurements

Hematology and serum chemistry were assessed throughout the treatment period (Tables 5 and 6, respectively). A central laboratory (LabCorp Clinical Trials/COVANCE, Cranford, NJ) was used for all laboratory assessments.

2.7. Vital signs

Vital signs were assessed throughout the treatment period and were performed at approximately 60 minutes pre-dose and 10 minutes post-dose (Table 7). Heart rate was discussed in a separate paper [2].

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Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: BR, SP, LD, CNB, EJM and GC are current employees of Theravance Biopharma US, Inc; CNB was an employee of Theravance Biopharma US, Inc at the time the study was conducted; JD is a consultant and advisory committee member for Mylan Inc. and Sunovion Pharmaceuticals; SS is a consultant and advisory committee member for Theravance Biopharma US, Inc., and received research support from Mylan Inc; EK has participated in consulting, advisory boards, speaker panels, or received travel reimbursement for Amphastar, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Mylan, Novartis, Oriel, Pearl, Sunovion, Teva and Theravance Biopharma. He has conducted multicenter clinical research trials for approximately 40 pharmaceutical companies.

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