## 2. SYNOPSIS

**Title of Study:** A PHASE IIa, RANDOMISED, MULTICENTRE, EVALUATOR-BLINDED, 4-WAY CROSSOVER CLINICAL TRIAL TO STUDY THE PHARMACOKINETICS, SAFETY, TOLERABILITY AND EFFECTS ON LUNG FUNCTION OF ONE DAY TREATMENT OF FORMOTEROL 12 µg QD DELIVERED BY 2 DIFFERENT DRY POWDER INHALERS (AEROLIZER® AND INHALER), OF THE FIXED DOSE COMBINATION FORMOTEROL 12 µg + ACLIDINIUM BROMIDE 200 µg QD DELIVERED BY INHALER, AND OF FORMOTEROL 12 µg BID DELIVERED BY AEROLIZER®, IN MODERATE TO SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS.

**Investigators:**

**Study centre (s):**

**Publication (reference):**
None

| | |
|---|---|
| **Studied period (years):** 2007<br>Date study initiated (first screening): 27/09/07<br>Date study finalised (last patient last visit ): 12/12/07 | **Phase of development:** IIa |

**Objectives:**

- To assess, in moderate to severe Chronic Obstructive Pulmonary Disease (COPD) patients, the pharmacokinetics of:
  a) Formoterol 12 µg delivered by Foradil® Aerolizer® (AER), once a day (one puff) for one day.
  b) Formoterol 12 µg delivered by Genuair® (GEN), once a day (one puff) for one day.
  c) Fixed Dose Combination (FDC) of formoterol 12 µg + aclidinium bromide 200 µg delivered by Genuair® (GEN), once a day (one puff) for one day.
  d) Formoterol 12 µg delivered by Foradil® Aerolizer® (AER), twice a day (one puff twice a day) for one day.
- To assess the safety, tolerability and effects on lung function after one single day of therapy (one puff once a day, or one puff twice a day) of the above 4 treatments.

**Methodology:**
This was a randomised, four-way crossover, one-day treatment, evaluator-blinded, multicenter clinical trial. Twenty-four moderate to severe COPD patients were included in the study.
At the end of the run-in period, which lasted up to 14 days, and once all entry criteria were met, patients were randomly assigned to one of four possible treatment sequences, according to a Williams' design for crossover trials using a centralised balanced (1:1:1:1) randomisation.

Throughout the experimental phase, patients received at each treatment period one of the four treatments to be tested. The duration of each treatment period was 48 hours. Between two consecutive treatment periods there was a washout of 7 days.
The IMP was administered in the morning or in the morning and in the evening by inhalation and consisted of dry powder contained in the GEN or the AER devices. Placebo was also administered in the evening and consisted of dry powder contained in the GEN device, when applicable for maintaining the blinding.
The IMP administrations were as follows:

a) Formoterol 12 µg delivered by Foradil® AER, once a day (one puff in the morning), and Placebo delivered by GEN, once a day (one puff in the evening) for one day.

b) Formoterol 12 µg delivered by GEN, once a day (one puff in the morning) and Placebo delivered by GEN, once a day (one puff in the evening) for one day.

c) FDC of formoterol 12 µg + aclidinium bromide 200 µg delivered by GEN, once a day (one puff in the morning) and Placebo delivered by GEN, once a day (one puff in the evening) for one day.

d) Formoterol 12 µg delivered by Foradil® AER, twice a day (one puff in the morning and in the evening, respectively) for one day.

During the washout periods, COPD concomitant and COPD rescue medication were permitted. Specific washout periods were defined for each concomitant treatment including rescue medication prior to the next visit. Throughout the treatment periods, only COPD rescue treatment (100 µg/puff of salbutamol pMDI) was allowed. Patients were provided with a paper diary card to record dose and administration time of the concomitant and rescue medication taken.
At least seven days (up to 16 days) after the last IMP administration a follow-up evaluation took place.

**Number of patients (planned and analysed):**

| | |
|---|---|
| Planned: | 24 |
| Screened: | 55 |
| Randomised: | 24 |
| Completed study: | 22 |
| Evaluated for pharmacokinetics: | 24 |
| Evaluated for safety: | 24 |

**Diagnosis and main criteria for inclusion:**

Caucasian male and non-pregnant, non-lactating female patients aged between 40 and 80 years, both inclusive, with stable moderate to severe COPD. No diagnosis of asthma, allergic rhinitis or atopy. Eosinophil count < 600 cells /$mm^3$; no signs of exacerbation within 6 weeks prior to the screening visit; no evidence of clinically significant respiratory and/or cardiovascular conditions or laboratory abnormalities.

**Test product, dose and mode of administration, batch number, expiry date:**

Name: Formoterol
Administration route: Oral inhalation by AER dry powder inhaler (Foradil® via AER)
Dosage form: Dry powder inhalation
Dose and regimen: 1 puff (formoterol 12 µg) once a day
Batch number: MCN 127
Expiry date: 04/2008

Name: Formoterol
Administration route: Oral inhalation by AER dry powder inhaler (Foradil® via AER)
Dosage form: Dry powder inhalation
Dose and regimen: 1 puff (formoterol 12 µg) twice a day
Batch number: MCN 127
Expiry date: 04/2008

Name: Formoterol
Administration route: Oral inhalation by GEN multidose dry powder inhaler
Dosage form: Dry powder inhalation
Dose and regimen: 1 puff (formoterol 12 µg) once a day
Batch number: MCN 127
Expiry date: 04/2008

Name: Formoterol and Aclidinium bromide
Administration route: Oral inhalation by GEN multidose dry powder inhaler
Dosage form: Dry powder inhalation
Dose and regimen: 1 puff (formoterol 12 µg and aclidinium bromide 200 µg) once a day
Batch number: MCN 127
Expiry date: 06/2008

Name: Placebo (used as evening dose for the once-daily treatments)
Administration route: Oral inhalation by GEN multidose dry powder inhaler
Dosage form: Dry powder inhalation
Dose and regimen: 1 puff once a day
Batch number: MCN 127
Expiry date: 06/2008

**Duration of treatment:**

Four days of treatment per patient with in-clinic observation lasting up to one day after the dosing day in each treatment period. Treatments were tested at a frequency of one per week.

**Criteria for evaluation:**

**Pharmacokinetics**

- Depending on the administered treatment, the pharmacokinetic parameters computed for formoterol, aclidinium bromide, LAS34823 (alcohol metabolite) and LAS34850 (acid metabolite) were AUC(0-t), AUC(0-24), AUC(12-36) (only for formoterol 12 µg BID), $C_{max}$, $C_{max}$ (after the administration of the 2nd formoterol dose of the treatment arm formoterol BID) and $t_{max}$. If the terminal phase of the semi-logarithmic concentration-time curve was well observed, $\lambda_z$, $t_{1/2}$, AUC, CL/f and $V_{z/f}$ were estimated.

- Relative bioavailability of formoterol 12 µg delivered by GEN (one puff once a day) versus formoterol 12 µg delivered by AER (one puff once a day).

  $f_{rel}$ (%) = [$AUC_{GEN\ qd}$ / $AUC_{AER\ qd}$] x 100

- Relative bioavailablity of formoterol 12 µg in FDC with aclidinium bromide 200 µg delivered by GEN (one puff once a day) versus formoterol 12 µg alone delivered by GEN (one puff once a day).

  $f_{rel}$ (%) = [$AUC_{12\ \mu g+Aclidinium\ bromide\ GEN\ qd}$ / $AUC_{12\ \mu g\ GEN\ qd}$] x 100

- Relative bioavailability of formoterol 12 µg in FDC with aclidinium bromide 200 µg delivered by GEN (one puff once a day) versus formoterol 12 µg delivered by AER (one puff once a day).

  $f_{rel}$ (%) = [$AUC_{12\ \mu g+Aclidinium\ bromide\ GEN\ qd}$ / $AUC_{12\ \mu g\ AER\ qd}$] x 100

- Relative bioavailability of formoterol 12 µg delivered by GEN (one puff once a day) versus formoterol 12 µg delivered by AER (one puff twice a day).

  $f_{rel}$ (%) = [$AUC(0\text{-}24)_{12\ \mu g\ GEN\ qd}$ / $AUC(12\text{-}36)_{12\ \mu g\ AER\ bid}$] x 100

  $f_{rel}$ (%) = [$C_{max12\ \mu g\ GEN\ qd}$ / $C_{max}(2nd\ dose)_{12\ \mu g\ AER\ bid}$] x 100

- Relative bioavailability of formoterol 12 µg in FDC with aclidinium bromide 200 µg delivered by GEN (one puff once a day) versus formoterol 12 µg delivered by AER (one puff twice a day).

  $f_{rel}$ (%) = [$AUC(0\text{-}24)_{12\ \mu g+Aclidinium\ bromide\ GEN\ qd}$ / $AUC(12\text{-}36)_{12\ \mu g\ AER\ bid}$] x 100

  $f_{rel}$ (%) = [$C_{max12\ \mu g+Aclidinium\ bromide\ GEN\ qd}$ / $C_{max}(2nd\ dose)_{12\ \mu g\ AER\ bid}$] x 100

**Safety and tolerability:**
Adverse events, physical examination, vital signs (blood pressure and pulse rate), 12-lead ECG, 12-lead 24-hour Holter monitoring, laboratory tests (haematology, coagulation, blood chemistry, urinalysis and serology).

**Lung function tests:**
- Normalised $FEV_1$ and FVC area under the curve over 3 h -AUC(0-3)-, 12 h -AUC(0-12)-, 24 h -AUC(0-24)- or 48 h -AUC(0-48)- post-morning dosing interval.
- Normalised $FEV_1$ and FVC area under the curve between 12 and 24 h -AUC(12-24)-, and 12 and 36 h -AUC(12-36)- post- morning dosing interval.
- Change from pre-dose in normalised $FEV_1$ and FVC AUC(0-3), AUC(0-12), AUC(0-24), AUC(0-48), AUC(12-24), AUC(12-36).
- Trough $FEV_1$ and FVC, computed as the mean of the 23 h and 24 h measurements after the morning IMP administration.
- Change from pre-dose in the trough $FEV_1$ and FVC.
- Peak $FEV_1$ and FVC: the maximum $FEV_1$ and FVC value over the first three hours after the morning IMP administration.
- Change from pre-dose in the peak $FEV_1$ and FVC.
- Change from pre-dose in FEV1 and FVC at each time point.

**Statistical methods:**
The analysis of all pharmacokinetic parameters was performed on the Per Protocol (PP) population. The PP population included patients who had data available at least until 24 hours after morning IMP administration in one of the three treatment periods in which the IMP was administered QD, or information obtained at least until 36 hours after morning IMP administration in the treatment period in which the IMP was administered BID. The analysis of all lung function variables was performed on the PP population. All safety outcomes were analysed using the Safety population, which included all patients who received at least one dose of IMP.
Appropriate descriptive analyses were carried out by treatments for pharmacokinetic, safety, tolerability and lung function data.
Trough $FEV_1$ and FVC, change from pre-dose in the trough $FEV_1$ and FVC, peak $FEV_1$ and FVC, and change from pre-dose in the peak $FEV_1$ and FVC, as well as change from pre-dose of each $FEV_1$ and FVC time point assessment were analysed by means of an ANCOVA model for crossover design with sequence, period and treatment as fixed effect factors, patients nested within sequence as random effect factor, and the corresponding pre-dose value for each period as covariate.
Normalised AUCs of $FEV_1$ and FVC were determined by calculating the AUC using the trapezoidal method and then dividing by the corresponding time intervals. The same ANCOVA model stated above was used to analyse the normalised AUCs of $FEV_1$ and FVC, and change from pre-dose in normalised AUCs of $FEV_1$ and FVC.
Adverse events, physical examination, vital signs, 12-lead ECGs, 12-lead 24-hour Holter monitoring and laboratory tests were summarised by appropriate descriptive statistics according to treatments, and individual listings. Changes from pre-dose for vital signs, ECG parameters, and laboratory data were analysed by treatment using descriptive statistics.

**RESULTS**

**Pharmacokinetic Results:**

The following table presents the PK parameters of aclidinium bromide, LAS34823 and LAS34850 found in COPD patients after administration of the FDC of 12/200 µg of formoterol/aclidinium bromide using the GEN device.

| Device | Statistics | $t_{1/2}$ [h] | CL/f [L/h] | Vz/f [L] | $C_{max}$ [pg/mL] | $t_{max}$ [h] | λz [1/h] | AUC(0-t) [pg · h/mL] | AUC(0-24) [pg · h/mL] | AUC [pg · h/mL] |
|---|---|---|---|---|---|---|---|---|---|---|
| Aclidinium bromide | Mean | 1.45 | 5327 | 8833 | 24.2 | 0.233 | 0.64578 | 28.4 | 35.9 | - |
| | SD | 1.28 | 3751 | 4994 | 15.3 | 0.118 | 0.34345 | 25.1 | 30.3 | - |
| | CV | 88.7 | 70.4 | 56.5 | 63.4 | 50.6 | 53.2 | 88.4 | 84.4 | - |
| | Max | 5.75 | 16412 | 22985 | 57.1 | 0.5 | 1.62042 | 118 | 141 | - |
| | Min | 0.428 | 1351 | 3468 | BLQ | 0.08 | 0.12065 | BLQ | BLQ | - |
| | N | 14 | 14 | 14 | 22 | 20 | 14 | 22 | 22 | - |
| LAS 34823 | Mean | 8.32 | 875 | 6569 | 28.5 | 1.35 | 0.13464 | 293 | 269 | 421 |
| | SD | 6.81 | 738 | 3175 | 14.2 | 1.86 | 0.07390 | 312 | 212 | 350 |
| | CV | 81.9 | 84.3 | 48.3 | 49.9 | 138 | 54.9 | 107 | 78.5 | 83.3 |
| | Max | 21.6 | 3300 | 13553 | 51.42 | 8 | 0.24347 | 1215 | 802 | 1039 |
| | Min | 2.85 | 129 | 3785 | BLQ | 0.25 | 0.03206 | BLQ | BLQ | 154 |
| | N | 17 | 17 | 17 | 22 | 20 | 17 | 22 | 22 | 9 |
| LAS 34850 | Mean | 3.84 | 27.8 | 153 | 938 | 3.91 | 0.18498 | 6311 | 7641 | 8149 |
| | SD | 0.65 | 8.43 | 50 | 411 | 1.15 | 0.02912 | 2569 | 3030 | 3170 |
| | CV | 16.8 | 30.4 | 32.6 | 43.8 | 29.4 | 15.7 | 40.7 | 39.7 | 38.9 |
| | Max | 5.48 | 41.4 | 254 | 2118 | 8 | 0.24650 | 13159 | 15244 | 14820 |
| | Min | 2.81 | 13.5 | 65 | 347 | 2 | 0.12646 | 1649 | 1876 | 4836 |
| | N | 18 | 18 | 18 | 22 | 22 | 18 | 22 | 22 | 14 |

BLQ: below the limit of quantification (<5 pg/mL)
- not calculated

Following administration of the FDC 12/200 µg of formoterol/aclidinium by inhalation using the GEN device, the main aclidinium metabolite circulating in plasma was the LAS34850, achieving mean $C_{max}$ and AUC(0-24) values 39-fold and 212-fold higher than those of the unchanged compound, respectively. By contrast, the mean $C_{max}$ found for the LAS34823 was similar to that of unchanged aclidinium, whereas the mean AUC(0-24) was 8-fold higher. Aclidinium peak plasma concentrations were reached early, obtaining $t_{max}$ values between 0.08-0.5 h and a mean value of 0.24 h. By contrast, the mean $t_{max}$ values found for LAS34823 and for LAS34850 were 1.35 h and 3.91 h, respectively.

Aclidinium concentration declined rapidly from plasma, with a mean elimination half-life of 1.45 h. The results obtained for CL/f and Vz/f gave aberrant physiological values suggesting a very low aclidinium bioavailability (f).

The following table shows the PK parameters of formoterol found in COPD patients (excluding Patient No. 18 due to the presence of consistently high plasma levels of formoterol in all treatment periods) after administration of a single dose of 12 µg of formoterol by dry powder inhalation using AER and GEN devices.

| Device | Statistics | $t_{1/2}$ [h] | CL/f [L/h] | Vz/f [L] | $C_{max}$ [pg/mL] | $t_{max}$ [h] | λz [1/h] | AUClast [pg · h/mL] | AUC(0-24) [pg · h/mL] | AUC [pg · h/mL] |
|---|---|---|---|---|---|---|---|---|---|---|
| Aerolizer® | Mean | 4.99 | 303 | 2097 | 7.30 | 0.67 | 0.15108 | 41.0 | 43.7 | 42.9 |
| | SD | 1.85 | 85.9 | 642 | 2.78 | 0.49 | 0.03688 | 27.3 | 16.5 | 13.0 |
| | CV | 37.0 | 28.4 | 30.6 | 38.0 | 72.7 | 24.4 | 66.6 | 37.7 | 30.3 |
| | Max | 10.6 | 514 | 3807 | 17.2 | 2 | 0.21480 | 155 | 98.5 | 74 |
| | Min | 3.23 | 163 | 883 | 3.8 | 0.08 | 0.06541 | 18.7 | 22.5 | 23.3 |
| | N | 21 | 21 | 21 | 23 | 23 | 21 | 23 | 23 | 19 |
| Genuair® | Mean | 5.83 | 348 | 2631 | 5.78 | 0.29 | 0.13725 | 32.8 | 36.2 | 38.9 |
| | SD | 2.37 | 134 | 676 | 2.53 | 0.31 | 0.05041 | 12.2 | 11.7 | 13.5 |
| | CV | 40.7 | 38 | 25.7 | 43.8 | 107 | 36.7 | 37.2 | 32.2 | 34.8 |
| | Max | 11.6 | 673 | 4219 | 11.7 | 1 | 0.25795 | 56.5 | 56.5 | 59.9 |
| | Min | 2.69 | 180 | 1580 | 1.93 | 0.08 | 0.05981 | 14.1 | 15.5 | 17.8 |
| | N | 20 | 20 | 20 | 23 | 23 | 20 | 23 | 23 | 17 |
| Genuair® (FDC) | Mean | 5.72 | 496 | 2979 | 5.66 | 0.37 | 0.15244 | 30.4 | 32.3 | 40.3 |
| | SD | 2.88 | 526 | 1305 | 2.91 | 0.35 | 0.07347 | 16.2 | 15.5 | 17.1 |
| | CV | 50.3 | 106 | 43.8 | 51.4 | 95.6 | 48.2 | 53.4 | 47.9 | 42.4 |
| | Max | 11.3 | 2460 | 7498 | 10.5 | 1 | 0.32802 | 54.5 | 54.5 | 63.6 |
| | Min | 2.11 | 189 | 1604 | 0.938 | 0.08 | 0.06120 | 3.31 | 4.34 | 14.4 |
| | N | 17 | 17 | 17 | 21 | 21 | 17 | 22 | 22 | 13 |

Following inhalation of a single dose of 12 µg of formoterol using Foradil® via AER or GEN devices, alone or in combination with aclidinium bromide, formoterol showed a rapid absorption with individual $t_{max}$ values ranging from 0.08 to 2 h. However, differences in the rate of absorption were observed between the two devices used in the study. Whereas the mean $t_{max}$ obtained by using the AER device (qd) was 0.67 h (40 min) with 10 out of 23 values within the first 15 min, it was 0.29 h (17 min) when administered alone by using the GEN device, with 18 out of 23 values within the first 15 min. Following inhalation of the fixed dose combination 12/200 µg of formoterol/aclidinium by using the GEN device the mean $t_{max}$ value was 0.37 h (22 min) with 13 out of 21 values within the first 15 min. These results could suggest that the GEN device provides a more rapid rate of absorption for formoterol.

The mean ± SD $C_{max}$ value of formoterol obtained in patients who received a single dose of 12 µg via AER was 7.30 ± 2.78 pg/ml, whereas it was 5.78 ± 2.53 pg/ml and 5.66 ± 2.91, respectively, when administered alone or in combination with aclidinium via GEN. Similarly, the mean ± SD AUC(0-24) values, obtaining when administered via AER was 43.7 ± 16.5 pg•h/ml, whereas it was 36.2 ± 11.7 and 32.3 ± 15.5, respectively, when administered alone or in combination with aclidinium via GEN.

Formoterol concentrations declined generally in a bi-exponential manner from plasma with mean ± SD elimination half-lives of 4.99 ± 1.85 h for AER, 5.83 ± 2.37 h for GEN administered alone and 5.72 ± 2.88 h for GEN in combination with aclidinium.

The following table shows the PK parameters of formoterol in COPD patients (excluding Patient No. 18) after administration of 12 µg of formoterol twice daily by inhalation using AER.

| Device | Statistics | 1st dose | | | 2nd dose | | | AUC(0-12) [pg · h/mL] | AUC(0-24) [pg · h/mL] | AUC(12-36) [pg · h/mL] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | $C_{max}$ [pg/mL] | $t_{max}$ [h] | $t_{1/2}$ [h] | $C_{max}$ [pg/mL] | $t_{max}$ [h] | $t_{1/2}$ [h] | | | |
| Aerolizer® | Mean | 6.84 | 0.56 | 4.79 | 8.34 | 0.26 | 8.01 | 35.5 | 83.2 | 69.0 |
| | SD | 2.21 | 0.48 | 1.27 | 3.09 | 0.31 | 2.70 | 10.7 | 26.7 | 24.9 |
| | CV | 32.3 | 86.6 | 26.5 | 37.0 | 118.3 | 33.7 | 30.2 | 32.1 | 36.0 |
| | Max | 13.7 | 2.0 | 7.41 | 15.5 | 1.0 | 15.9 | 61.3 | 164 | 134 |
| | Min | 4.06 | 0.08 | 1.56 | 3.89 | 0.08 | 5.01 | 17.4 | 51.5 | 36.1 |
| | N | 23 | 23 | 23 | 23 | 23 | 22 | 23 | 23 | 23 |

The administration of 12 µg formoterol twice daily by using the AER inhaler resulted in a mean ± SD $C_{max}$ of 6.84 ± 2.21 pg/mL after the first administration, and 8.34 ± 3.09 pg/mL after the second administration.

The systemic exposure (AUC(0-24)) of formoterol following administration with GEN is in general lower than following administration with AER when administered both alone (mean frel = 86.4%, n = 23) or in combination with aclidinium bromide (mean frel = 77.1%, n = 21). The mean bioavailability (AUC(0-24)) of formoterol following GEN administered in combination with aclidinium or alone was similar (mean frel = 94.5%, n=21). These results suggest that the combination with aclidinium has a minimal impact on the rate and extent of formoterol absorption in comparison to the administration alone.

**Safety and Tolerability Results:**

A total of 41 treatment-emergent adverse events (TEAEs) occurred in 13 patients, and a total of 3 non-TEAEs occurred in 2 patients. Most adverse events (AEs) were of mild or moderate intensity.

The lowest number of TEAEs occurred during the treatment FDC Formoterol 12 µg + aclidinium bromide 200 µg GEN (one puff once a day), with 3 TEAEs in 2 out of 22 patients (9.09%), followed by the treatment formoterol 12 µg AER (one puff twice a day), with 8 TEAEs in 3 out of 24 patients (12.5%), the treatment formoterol 12 µg AER (one puff once a day), with 13 TEAEs in 8 out of 24 patients (33.33%), and the treatment formoterol 12 µg GEN (one puff once a day), with 17 TEAEs in 10 out of 24 patients (41.67%).

Overall, the most frequent TEAEs were headache (2 TEAEs in 2 patients under treatment with formoterol 12 µg GEN [one puff once a day], 4 TEAEs in 2 patients under treatment with formoterol 12 µg AER [one puff twice a day] and 4 TEAEs in 4 patients under treatment with formoterol 12 µg AER [one puff once a day], followed by ventricular tachycardia (1 TEAE in 1 patient under treatment with formoterol 12 µg GEN [one puff once a day], 4 TEAEs in 1 patient under treatment with formoterol 12 µg AER [one puff twice a day], and 2 TEAEs in 1 patient under treatment with formoterol 12 µg AER [one puff once a day]).

Altogether, 9 TEAEs were assessed as related to IMP: under treatment with formoterol 12 µg GEN (one puff once a day) 3 TEAEs (headache, cough, and ventricular tachycardia) in 3 patients; under treatment with formoterol 12 µg AER (one puff twice a day) 1 TEAE (headache) in 1 patient; under treatment with formoterol 12 µg AER (one puff once a day) 3 TEAEs (two events of headache and one event of peripheral coldness) in 3 patients, and under treatment with FDC of formoterol 12 µg + aclidinium bromide 200 µg GEN (one puff once a day), 2 TEAEs (two events of dyspnoea) in 1 patient.

One treatment-emergent serious adverse event (SAE), severe gastrointestinal infection, occurred in a patient 9 days after having received treatment with formoterol 12 µg GEN (one puff once a day), and was assessed as not IMP-related.

Two TEAEs of moderate ventricular tachycardia under treatment with formoterol 12 µg AER (one puff once a day), assessed as not related to IMP, led to withdrawal of a patient from the trial. A moderate COPD exacerbation in another patient under treatment with formoterol 12 µg AER (one puff once a day) and assessed as not related to IMP, led to withdrawal of the patient from the trial.

At the end of the study, all patients who experienced AEs had recovered without sequelae and without the need for remedial therapy.

No bronchospasms occurred.

No clinically significant deviations of laboratory values, vital signs, and ECG parameters were observed. Twenty-four hour ECG-Holter monitoring confirmed that the FDC of formoterol 12 µg + aclidinium bromide 200 µg has a cardiac safety profile that is consistent with the background morbidity in the COPD population.

The four treatments were assessed as safe and well tolerated.

**Lung Function Tests Results:**

An improvement of lung function ($FEV_1$ and FVC) was observed under all four treatments.

The below table shows the $FEV_1$ change from pre-dose in the most relevant variables of lung function, distributed by treatment.

| | | Formoterol 12 µg qd (Genuair®) | Formoterol 12 µg bid (Aerolizer®) | Formoterol 12 µg qd (Aerolizer®) | FDC of Formoterol 12 µg + Aclidinium bromide 200 µg qd (Genuair®) |
|---|---|---|---|---|---|
| | | N=24 | N=24 | N=24 | N=22 |
| Change from pre-dose in nAUC(0-12) (L) | LSMean (SE) | 0.259 (0.041) | 0.287 (0.041) | 0.249 (0.041) | 0.296 (0.041) |
| Change from pre-dose in nAUC(0-24) (L) | LSMean (SE) | 0.175 (0.038) | 0.285 (0.037)[a] | 0.173 (0.038) | 0.225 (0.038) |
| Change from pre-dose in nAUC(12-24) (L) | LSMean (SE) | 0.088 (0.039) | 0.281 (0.038)[a] | 0.083 (0.040) | 0.153 (0.040) |

[a]p<0.05 versus each of the other 3 treatments.

nAUC=normalised area under the curve; LSMean = least squares mean. SE= standard error; L = litres.

Data were analysed using the ANCOVA model for crossover design with sequence, period and treatment as fixed effect factors, patients nested within sequence as random effect factor, and the corresponding pre-dose value for each period as covariate.

The combination of aclidinium bromide and formoterol in the FDC GEN (one puff once day) resulted in trends towards an improvement for the normalised $FEV_1$ AUC(0-12), $FEV_1$ AUC(0-24) and $FEV_1$ AUC(12-24) over formoterol 12 µg GEN (one puff once a day) and formoterol 12 µg AER (once puff once a day). However, formoterol administed twice daily via AER was statistically superior to the once daily FDC treatment with respect to the normalised $FEV_1$ AUC(0-24) and $FEV_1$ AUC(12-24) ($p<0.05$ for both variables). No statistically significant differences were observed between the two once-daily monotherapy formoterol arms in any of the variables assessed.
The [LSMean (SE)] $FEV_1$ maximum increase versus pre-dose was observed 3 hours after morning IMP administration, the greatest produced by formoterol 12 µg AER (one puff twice a day) [0.395 (0.050) L], followed by the FDC of formoterol 12 µg + aclidinium bromide 200 µg GEN (one puff once a day) [0.382 (0.051) L], formoterol 12 µg GEN (one puff once a day) [0.360 (0.050) L], and formoterol 12 µg AER (one puff once a day) [0.337 (0.051) L].
After evening IMP administration, formoterol 12 µg AER (one puff twice a day) produced a second $FEV_1$ increase that reached a maximum 2 hours after dosing [0.420 (0.045) L]. In the other treatment arms, placebo was administered in the evening, and a second $FEV_1$ increase was observed, but was of much lower magnitude [between 0.150 (0.046) L for formoterol 12 µg AER –one puff once a day- and 0.245 (0.047) L for the FDC] than the one obtained with the active treatment. However, the second $FEV_1$ increase versus pre-dose was much greater with the fixed dose combination of formoterol 12 µg + aclidinium bromide 200 µg [maximum of 0.245 (0.047) L vs pre-dose] than with formoterol 12 µg GEN [maximum of 0.157 (0.045) L vs pre-dose] and formoterol 12 µg AER [maximum of 0.150 (0.046) L vs pre-dose].

**CONCLUSIONS:**

**DATE OF REPORT:**
15 April 2009