2.SYNOPSIS

Name of Company: Chiesi Farmaceutici S.p.A.	**Individual Study Table Referring to Part of the Dossier**	*(for National Authority Use only)*
Name of Finished Product: Atimos® 12 µg	**Volume:**	
Name of Active Ingredient: Formoterol fumarate dihydrate	**Page:**	

Title of Study: A Single-centre, Double-blind, Double-dummy, Randomised, Crossover Study to investigate the effect of Formoterol HFA-pMDI versus Salmeterol HFA-pMDI on small airways physiological parameters in COPD patients. IMPERIAL Study

Investigators: [redacted], Omar S Usmani

Study Centre(s) :
Airway Disease Section, National Heart and Lung Institute, Imperial College London (Royal Brompton and Harefield NHS Trust Campus), London SW3 6LY, UK.

Publication (reference) : Not published as of date of report finalisation

Studied Period: FPFV: 08/Apr/2011 LPLV: 17/Sep/2012	**Phase of development:** Phase IV

Objectives:

Primary: The primary objective of the study was to evaluate the effect of formoterol compared to salmeterol (HFA-pMDI) on small airways physiological parameters in patients with Chronic Obstructive Pulmonary Disease (COPD) in terms of lung reactance (X5) assessed by impulse oscillometry (IOS) .

Secondary: To further compare the treatment effects on:

- Additional Impulse oscillometry (IOS) parameters: Lung Resistance (R5, R20) and Lung Reactance (X), Lung Impedance (Z) (Z=X+R) Integrated Low-frequency Reactance Area (AX) and Resonant frequency (RF)
- Multiple Breath Nitrogen Washout parameters (MBNW): Sacin (Acinar) and Scond (Conducting) and Vtg (Volume trapped gas) and LCI (lung clearance index)
- Lung function test (LFT) parameters: body plethysmography: specific airway conductance (sGaw), airway resistance (Raw), functional residual capacity (FRC), vital capacity (VC), inspiratory capacity (IC), intra-thoracic gas volume (IGV), total lung capacity (TLC), residual volume (RV) and RV/TLC and Spirometry (FEV_1, FVC, FEF_{25-75}, PEF)
- Multiple expiration flow of Exhaled NO ($MEFE_{NO}$) exchange parameters: airway wall NO flux (JNO), and the steady-state alveolar NO concentration (Calv)

To assess the safety and tolerability, as determined by vital signs of HR and blood pressure and by the reporting of adverse events (AEs) and adverse drug reactions (ADRs).

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Methodology *(Study Design)*:
This was a single-centre, randomised, double-blind, double-dummy, crossover study.
The study plan included a screening visit followed by a 7-14 day run-in period; study treatment Visit 1 followed by a 7-14 day wash-out period; study treatment Visit 2 followed by a 7-14 day wash-out period; study treatment Visit 3. Finally, subjects attended a follow-up non-treatment visit. The run-in period and the wash out period were increased from 7-10 days with Substantial General Amendment number 2.

Number of patients *(planned and analysed)*:
Forty patients planned to be randomised with the aim to obtain 30 patients completing the study. Sixteen patients were randomised and 15 were analysed.

Diagnosis and main criteria for inclusion:
The study was conducted in patients with a clinical diagnosis of COPD, aged 40 years or older.
Inclusion criteria were:

1. Subjects written informed consent obtained prior to any study-related procedures
2. Male and female outpatients, aged ≥ 40 years
3. Patients with a clinical diagnosis of COPD (according to GOLD guidelines)
4. Post bronchodilator (to salbutamol 400 µg inhalation pMDI as per GOLD guidelines) FEV1 between 30% and 80% predicted values (30% ≤ FEV_1 < 80%) documented at screening visit [=Stage 2 and Stage 3 GOLD criteria]
5. Post-bronchodilator (to salbutamol 400 µg inhalation pMDI as per GOLD guidelines) FEV1/FVC < 0.7 (absolute value) documented at screening visit
6. Ability to be trained to use the pMDI device correctly.

Test product, dose and mode of administration, batch number:
Formoterol fumarate 12 µg inhaled via pMDI, using a HFA-134a propellant - (Atimos® 12 µg, Chiesi Farmaceutici S.p.A.). Batches: [redacted], [redacted].

Duration of treatment:
Three single administrations of the test treatment, preceded by a 7 - 14 day run-in with a washout of 7 - 14 days separating the study periods.
• Treatment A: formoterol 12 µg PMDI HFA (Atimos), 1 inhalation; matched placebo to salmeterol, 2 inhalations
• Treatment B: matched placebo to formoterol, 1 inhalation; salmeterol 25 µg PMDI HFA (Serevent™), 2 inhalations
• Treatment C: matched placebo to formoterol, 1 inhalation; matched placebo to salmeterol, 2 inhalations

Reference therapy, dose and mode of administration, batch number:
• Salmeterol xinofoate 25 µg via pMDI, using an HFA-134a propellant - (Serevent, Allen & Hanburys). Batches: [redacted], [redacted].
• Formoterol matched placebo via pMDI, using an HFA-134a propellant. Batches: [redacted].
• Salmeterol matched placebo via pMDI, using an HFA-134a propellant. Batches: [redacted].

Criteria for evaluation:
Primary Efficacy variable:
Lung Reactance (X5) by IOS.

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Secondary variables:
To further compare the treatment effects on:
• Additional Impulse oscillometry (IOS) parameters: Lung Resistance (R5, R20) and Lung Reactance (X), Lung Impedance (Z) (Z=X+R), Integrated Low-frequency Reactance Area (AX) and Resonant frequency (RF).
• Multiple Nitrogen Washout parameters (MBNW): Sacin (Acinar) and Scond (Conducting) and Vtg (Volume trapped gas) and LCI (lung clearance index).
• Lung function test (LFT) parameters: body plethysmography: specific airway conductance (sGaw), airway resistance (Raw), functional residual capacity (FRC), vital capacity (VC), inspiratory capacity (IC), IGV intra-thoracic gas volume (IGV), total lung capacity (TLC), residual volume (RV) and RV/TLC and Spirometry (FEV1, FVC, FEF25-75, PEF).
• Multiple expiration flow of Exhaled NO (MEFENO) exchange parameters: airway wall NO flux, (JNO), and the steady-state alveolar NO concentration (Calv).

Safety Efficacy variables:
• Adverse events, adverse drug reactions were monitored and measured as safety variables throughout all the study period.
• Vital signs (HR and blood pressure) were assessed at screening visit and at treatment-period visits.

Statistical methods:
Descriptive analyses only were carried-out due to the low number of randomised patients.

Summary – Conclusions:
A total of 20 patients provided written informed consent and were screened for enrolment in the study. Of these, 16 patients were randomised into the study. Fifteen patients were dispensed and took study medication, with 1 patient not receiving study medication due to an adverse event. For both the intent-to-treat and the safety populations, 13 patients were treated with formoterol, 13 with salmeterol, and 15 with placebo.

Efficacy Results:
Lung distal reactance (X5) was reduced (less negative) in both formoterol and salmeterol treatment groups indicating a lesser degree of peripheral obstruction. In the formoterol group, X5 was reduced (less negative) at 5 minutes after dosing and remained reduced (less negative) at 6 hours post-dose, returning towards pre-dose values at 8 hours post-dose. In the salmeterol group, X5 was reduced (less negative) at 15 minutes post dose and remained reduced (less negative) to 8 hours post-dose. These changes towards less negative values in the treatment groups indicate a lesser degree of peripheral obstruction which was reached faster in the formoterol group (5 minutes) compared to the salmeterol one (15 minutes), although the duration of the effect seemed to be longer in the salmeterol group compared to formoterol. There was no apparent change in X5 in the placebo group. However, due to the small sample size it is not possible for any conclusions to be made with regard to the statistical significance of these changes.

Exhaled NO measurements during the study were reported as JNO and Calv. In the formoterol group, JNO was increased at 2 hours post-dose and reduced at 8 hours post-dose relative to pre-dose values. Calv was increased at 2 hours post-dose with a further increase at 8 hours post-dose. In the salmeterol group, JNO was increased at 2 hours post-dose, increasing further at 8 hours, while Calv was reduced at both 2 hours and 8 hours post-dose. In the placebo group there was no apparent change in JNO, while Calv was reduced at both 2 hours and 8 hours post-dose.

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However, due to the small sample size it is not possible for any conclusions to be made with regard to the statistical significance of these changes.

Spirometry data and body plethysmography data during the study showed similar changes in the formoterol and salmeterol treatment groups compared to placebo. However, due to the small sample size it is not possible for any conclusions to be made with regard to the statistical significance of these changes. For the same reason it is not possible to draw any conclusions from the impulse oscillometry data.

Safety Results:

The safety population consisted of 15 patients who took at least one dose of study medication. Four doses of study medication were received by 13 patients. Overall, 13 patients were dosed with formoterol and with salmeterol, while 15 patients were dosed with placebo.

The results of the study showed that a total of four Treatment Emergent Adverse Events (TEAEs) were experienced by two patients (13.3%) in the placebo group. There were no TEAEs in the formoterol or salmeterol groups (0%). There were no TEAEs leading to withdrawal from the study. There were no deaths, Adverse Drug Reactions (ADR), Serious Adverse Events (SAE) or Serious Adverse Drug Reactions (SADR) in any treatment group.

The mean values of systolic and diastolic blood pressure showed a slight reduction following dosing in the formoterol and salmeterol treatment groups. This was most marked in the formoterol treatment group, and less so in the salmeterol treatment group. There was no significant change in heart rate in either treatment group. However, the descriptive nature of the analysis makes it difficult to draw any conclusions with regard to statistical and clinical significance for these changes within each group and between groups.

It can be concluded that the safety profile was substantially similar in the two active treatment groups, without any clinically significant changes compared to that of the placebo-treatment group.

Conclusion:

The results of the study suggest that lung distal reactance (X5) was reduced (less negative) in both formoterol and salmeterol treatment groups indicating that the degree of peripheral obstruction was reduced. The descriptive nature of the analysis makes it difficult to draw any conclusions with regard to statistical and clinical significance for these changes within each group and between groups. Similarly, although NO measurements were affected by formoterol and salmeterol treatment, it is not possible to draw any conclusions with regard to statistical and clinical significance for these changes within each group and between groups.

The safety profile was substantially similar in the formoterol and salmeterol treatment groups, and without clinically meaningful differences compared to that of the placebo-treatment group.

Date of report: 21 Dec 2015