2. SYNOPSIS

Name of Sponsor / Company: Almirall, S.A **Name of Finished Product:** N.A. **Name of Active Ingredients:** Aclidinium bromide/Formoterol fumarate inhalation powder.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Title of Study: A RANDOMISED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE-CONTROLLED STUDY EVALUATING THE EFFICACY, SAFETY AND TOLERABILITY OF TWICE-DAILY ACLIDINIUM BROMIDE /FORMOTEROL FUMARATE COMPARED WITH TWICE-DAILY SALMETEROL/FLUTICASONE PROPIONATE FOR 24-WEEKS TREATMENT IN SYMPTOMATIC PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Investigators:
This study was conducted by 126 investigators in 14 countries: Austria (5), Bulgaria (8), Canada (7), the Czech Republic (6), France (3), Germany (31), Hungary (10), Italy (3), Lithuania (4), the Netherlands (6), Poland (17), South Africa (7), Spain (11) and the United Kingdom (8). A total of 121 investigators randomised patients and 5 investigators (1 investigator in Canada, Germany, and the Netherlands; and 2 investigators in the United Kingdom) did not randomise any patients.

Study centres:
This study was conducted at 140 activated sites. A total of 121 sites randomised patients: 5 sites in Austria, 8 sites in Bulgaria, 6 sites in Canada, 6 sites in the Czech Republic, 3 sites in France, 30 sites in Germany, 10 sites in Hungary, 3 sites in Italy, 4 sites in Lithuania, 5 sites in the Netherlands, 17 sites in Poland, 7 sites in South Africa, 11 sites in Spain and 6 sites in the United Kingdom.

Publication (reference):
None

Studied period (years): Date study initiated (first screening): 11 October 2013 Date study finalised (last patient last visit): 04 August 2014	**Phase of development:** IIIb

Objectives:

- To assess the long term bronchodilator efficacy of Aclidinium bromide/Formoterol fumarate administered twice daily (BID), compared to Salmeterol/Fluticasone propionate (Seretide™ Accuhaler™) in symptomatic COPD patients.
- To compare the benefits of Aclidinium bromide/Formoterol fumarate administered BID, versus twice daily regimen of Seretide™ Accuhaler™ in disease-related health status and COPD symptoms.
- To evaluate the long term safety and tolerability of Aclidinium bromide/Formoterol fumarate, administered BID, compared to twice daily Seretide™ Accuhaler™ in the same target population.

Methodology:
This was a 24-week treatment, randomised, double-blind, double-dummy, active comparator controlled, parallel, multinational and multicentre clinical study.
The study consisted of a Screening Visit (Visit 1) conducted after signing the informed consent form, where medical history, smoking history, physical examination, laboratory, electrocardiogram (ECG) measurement, COPD assessment test (CAT) and COPD severity stage, according to Global Initiative for Chronic Obstructive Lung Disease (GOLD guidelines) were checked. Patients fulfilling inclusion/exclusion criteria at the time of the Screening Visit were entered into a run-in period of 7 to 10 days in order to obtain the patient's baseline data. At the Screening Visit (Visit 1) patients were provided with the electronic diary (e-diary) to collect the use of relief medication and their COPD symptoms twice a day.
During the 24 week double-blind treatment period, patients visited the site to assess clinical efficacy and safety on 4 occasions (from Visit 2 to Visit 5). Additionally, a phone contact was performed between Visit 4 and 5 (18 weeks after first study drug dose administration) in order to assess new or ongoing adverse events (AEs), as well as any concomitant medication administered to treat the mentioned AE. Patients completing the study were those patients who completed Visit 5, even if they did not complete the follow-up contact (2 weeks after Visit 5).

Number of patients (planned and analysed):
Planned: Approximately 1300 patients were planned to be screened in order to achieve a total of 900 randomised patients (450 per treatment group).
Screened: 1125
Randomised: 933
Completed study: 788
Evaluated for safety: 933
Evaluated for efficacy (Intention-to-Treat [ITT] analysis): 931
Evaluated for efficacy (Per-Protocol [PP] analysis): 837

Diagnosis and main criteria for inclusion:
- Male and female patients aged ≥40 years.
- Clinical diagnosis of COPD according to GOLD guidelines 2013, with a post bronchodilator forced expiratory volume in 1 second (FEV_1) <80%, and FEV_1/Forced Vital Capacity (FVC) <70% at Screening Visit (Visit 1).
- Symptomatic patients with a CAT ≥10 at Screening and Randomisation Visit (Visit 1 and 2).
- Current or ex-smokers of ≥10 pack-years.
- No signs of respiratory tract infection or COPD exacerbation within 6 weeks (or 3 months if hospitalisation was required) before the Screening Visit (Visit 1) or during the run-in period.
- No evidence of clinically significant respiratory and/or cardiovascular conditions (myocardial infarction <6 months, hospitalisation for cardiac failure New York Heart Association class III-IV or unstable arrhythmia <12 months before Screening Visit).
- No contraindication to use of anticholinergic drugs (symptomatic prostatic hypertrophy, symptomatic bladder neck obstruction or known narrow-angle glaucoma).
- Patients who were currently or had participated in a pulmonary rehabilitation program within the previous 3 months were excluded.
- Patients treated on a daily basis with triple therapy, long-acting β_2-agonist + long-acting muscarinic antagonist + inhaled corticosteroids (LABA+LAMA+ICS) within 4 weeks prior to the Screening Visit (Visit 1) were excluded.

Name of Sponsor / Company: Almirall, S.A **Name of Finished Product:** N.A. **Name of Active Ingredients:** Aclidinium bromide/Formoterol fumarate inhalation powder.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Test product, dose and mode of administration, batch number, expiry date:
Name: Aclidinium bromide 400 µg/Formoterol fumarate 12 µg
Administration route: Oral inhalation by Genuair® dry powder inhaler
Dosage form: Dry powder
Dose and regimen: 1 puff of 400 µg/12 µg in the morning (08:00 to 10:00) and in the evening (20:00 to 22.00 pm).

Batch numbers:	Expiry date:
F1-L130	Nov 2015
F1-L182	Nov 2015

Duration of treatment:
The planned duration of treatment for this study was 24 weeks

Reference therapy, dose and mode of administration, batch number, expiry date:
Name: Salmeterol 50 µg/Fluticasone propionate 500 µg
Administration route: Oral inhalation by Accuhaler™ dry powder inhaler
Dosage form: Dry powder
Dose and regimen: 1 puff of 50/500 µg in the morning (08:00 to 10:00) and in the evening (20:00 to 22.00).

Batch numbers:	Expiry date:
4759-L145	Sep 2014
4961-L179	Oct 2015

Name: Placebo to Aclidinium bromide/Formoterol fumarate (lactose monohydrate)
Administration route: Oral inhalation by Genuair® dry powder inhaler
Dosage form: Dry powder
Dose and regimen: 1 puff in the morning (08:00 to 10:00) and in the evening (20:00 to 22.00).

Batch numbers:	Expiry date:
139F0367-L129	Nov 2015
139F0367-L181	Nov 2015

Name: Placebo to Salmeterol/Fluticasone propionate (lactose monohydrate)
Administration route: Oral inhalation by Accuhaler™ dry powder inhaler
Dosage form: Dry powder
Dose and regimen: 1 puff in the morning (08:00 to 10:00) and in the evening (20:00 to 22.00).

Batch numbers:	Expiry date:
E009911-0007I001-L146	Sep 2014
E009911-0007I001-L180	Oct 2015

Criteria for evaluation:

Efficacy:
Primary Efficacy variable:
- Peak FEV_1 at Week 24

Secondary Efficacy variable:
- Transition Dyspnoea Index (TDI) focal score at Week 24.

Additional Efficacy variables:

Pulmonary function:
- Morning pre-dose (trough) FEV_1, FVC and Inspiratory Capacity (IC) at all visits. Trough being defined as the mean of the two pre-dose spirometry values.
- FEV_1, FVC and IC by time-point at all visits.
- Normalised area under the curve (AUC) from 0 to 3 hours ($nAUC_{0\text{-}3h/3h}$) FEV_1 and FVC at all visits.
- Peak and time to peak FEV_1 (except Week 24 which is primary) and FVC at all visits.
- Normalised AUC from 0 to 12 hours ($nAUC_{0\text{-}12h/12h}$) FEV_1 and FVC at Week 24 for patients participating in the 12-hour spirometry sub-study.

COPD symptoms:
- TDI focal score and by dimension, and the percentage of patients who achieved a clinically meaningful improvement (≥1 units) in TDI at all visits.
- Early morning and night-time COPD symptoms
- Exacerbations of Chronic Pulmonary Disease Tool (EXACT) – Respiratory Symptoms (E-RS): Total score and by dimension.

Health Related Quality of Life and other assessments:
- CAT: change from baseline, the percentage of patients with ≥2 units improvement, and the percentage of patients with CAT total score <10 at all visits.
- St. George's Respiratory Questionnaire for COPD patients (SGRQ-C): change from baseline and the percentage of patients with clinically meaningful improvements (≥4-units) at all visits.
- EuroQol Dimensional Questionnaire-5D (EQ-5D): Weighted health state index and Visual Analogue Scale (VAS).
- The percentage of patients with ≥1 COPD exacerbation: based on the health care resource utilisation definition and EXACT-PRO.
- Use of relief medication.
- Device preference and satisfaction.
- Willingness to continue using each of the devices.

Safety:
- AEs and serious AEs (SAEs).
- Clinical laboratory parameters.
- Blood pressure (BP).
- 12-lead electrocardiogram (ECG) parameters.

Statistical methods:
The analyses of the primary and secondary efficacy variables; peak FEV_1 and TDI at Week 24, were performed for ITT and PP populations. The analysis on the PP population was the primary analysis when assessing non-inferiority objectives and the analyses on the ITT population was the primary analysis when assessing the switch to superiority. All other efficacy variables were performed on the ITT population. Safety outcomes were analysed on the Safety population.

Non-inferiority of AB400/FF12 compared to S50/FP500 was assessed first for the primary efficacy variable. If non-inferiority was satisfied, then superiority was assessed for the primary efficacy variable. If superiority was satisfied for the primary efficacy variable, then non-inferiority was tested on the main secondary variable.

The primary and secondary efficacy variables; peak FEV_1 and TDI at Week 24, were analysed by means of a mixed model for repeated measures (MMRM) as well as all continuous variables.

Except for data on the number of patients with ≥1 COPD exacerbation, which were analysed using a

logistic regression model, dichotomous variables were analysed by means of logistic random regression models. Preference variables were analysed using a Chi-Square test. A Cox model was performed for time-to-exacerbation.

Safety outcomes (AEs, laboratory parameters, BP, and 12-lead ECG) were summarised by means of descriptive statistics. Additionally, potentially clinically significant changes in the last three safety outcomes were also assessed.

SUMMARY – CONCLUSIONS

Disposition:

A total of 1125 patients were screened, of whom 933 patients were assessed as eligible and were randomised into the study. Overall, 788 (84.5%) of the randomised patients completed the study.

A total of 145 (15.5%) patients were discontinued from the study, mainly due to withdrawal of informed consent by the patient (23 [4.9%] patients in the AB400/FF12 group and 24 [5.2%] patients in the S50/FP500 group); and AEs (22 [4.7%] patients in the AB400/FF12 group and 23 [4.9%] patients in the S50/FP500 group.

Demographic and Baseline Characteristics: The treatment groups were comparable with respect to mean demographic and baseline data.

Efficacy Results:

Primary Efficacy variable: Peak FEV_1 at Week 24

After 24 weeks of treatment, non-inferiority of AB400/FF12 compared to S50/FP500 was satisfied, as the lower bound of the two sided 95% CI for the difference between AB400/FF12 and S50/FP500 was 0.070 L in the PP population; exceeding the non-inferiority limit of -0.055 L.

Following the pre-specified multiplicity approach, the switch from non-inferiority to superiority was tested:

After 24 weeks of treatment, superiority was satisfied as the AB400/FF12 group showed a statistically significantly greater peak FEV_1 compared to the S50/FP500 group in the ITT population; with an adjusted mean difference compared to S50/FP500 of 0.093 L ($p<0.0001$). This result was supported by the sensitivity analysis.

Secondary efficacy variable: Improvement in TDI at Week 24

Non-inferiority of AB400/FF12 compared to S50/FP500 was satisfied, as the lower bound of the 2-sided 95% CI for the difference between AB400/FF12 and S50/FP500 was -0.46 units; exceeding the non-inferiority limit of -0.5 units. No difference between the treatment groups was observed ($p=0.9951$).

Additional efficacy variables: Endpoints based on FEV_1 FVC, and IC

From first dose administration to end of treatment period (24 weeks), the treatment effect on peak FEV_1 and $nAUC_{0\text{-}3h/3h}$ for FEV_1 favouring AB400/FF12 was sustained, with adjusted mean differences compared to S50/FP500 ranging from 0.081 L to 0.093 L for peak FEV_1 (Week 12 and Week 24, respectively), and 0.075 L to 0.090 L for $nAUC_{0\text{-}3h/3h}$ for FEV_1 (Week 12 and Week 24, respectively) ($p<0.0001$ in all cases). The median time to peak FEV_1 was at 2.00 hours post-dose following administration of both treatments. At Day 1 of treatment, the AB400/FF12 group showed statistically significantly greater FEV_1 compared to the S50/FP500 group at all post-dose timepoints; with adjusted mean differences compared to S50/FP500 ranging from 0.060 L to 0.088 L (at 5 minutes and 3 hours post-dose, respectively) ($p<0.0001$ in all cases). Similar results were observed at Weeks 4 to 24. Over

24 weeks of treatment, the AB400/FF12 showed smaller morning trough FEV_1 compared to S50/FP500, with adjusted mean differences compared to S50/FP500 ranging from -0.011 L to -0.014 L (Week 12 and Week 24, respectively) (p>0.05 in all cases). However, these differences were not considered to be clinically meaningful.

Similar results were observed for peak FVC, and $nAUC_{0\text{-}3h/3h}$ for FVC. After 24 weeks of treatment adjusted mean differences compared to S50/FP500 ranged from 0.118 L to 0.168 L (Day 1 and Week 12, respectively) for peak FVC, and 0.134 L to 0.181 L (Day 1 and Week 24, respectively) for $nAUC_{0\text{-}3h/3h}$ for FVC (p<0.0001 in all cases). At Day 1 of treatment, the AB400/FF12 group showed statistically significantly greater FVC compared to the S50/FP500 group at all post-dose timepoints and visits (p<0.0001 in all cases). Over 24 weeks of treatment, adjusted mean differences in morning trough FVC compared to S50/FP500 ranged from 0.033 L to 0.058 L (Week 4 and Week 12, respectively). Results were statistically significant at the 12-week (0.058 L; p=0.0064) and 24-week visits (0.054 L; p=0.0220).

At Day 1 of treatment, the AB400/FF12 group showed a statistically significantly greater IC compared to the S50/FP500 group at 3 hours post-dose; with an adjusted mean difference compared to S50/FP500 of 0.060 L (p= 0.0019). Similar results were observed at Weeks 4, to 24 (p<0.0001 in all cases). There were no differences between the treatment groups in morning pre-dose (trough) IC (p>0.05 in all cases).

During the 12-hour spirometry substudy, after 24 weeks of treatment: the AB400/FF12 group showed a statistically significantly greater FEV_1 compared to the S50/FP500 group at 1 hour and 2 hours post-dose; with adjusted mean differences from the S50/FP500 group at these timepoints of 0.069 L and 0.080 L, respectively (p=0.0208 and 0.0069, respectively); and a greater $nAUC_{0\text{-}12h/12h}$ for FEV_1 with an adjusted mean difference compared to S50/FP500 of 0.013 L (p=0.6430), which was not considered clinically meaningful. After 24 weeks of treatment, the AB400/FF12 group showed greater FVC compared to the S50/FP500 group up to 12 hours post-dose (inclusive); with adjusted mean differences compared to S50/FP500 ranging from 0.024 to 0.212 L (at 8 hours and 2 hours post-dose respectively). The differences were statistically significant up to 6 hours post-dose, with adjusted mean differences compared to S50/FP500 ranging from 0.109 to 0.212 L (6 hours and 2 hours post-dose, respectively) (p=0.0285 and p<0.0001, respectively). At Week 24, the AB400/FF12 group showed a statistically significant greater increase in the adjusted mean $nAUC_{0\text{-}12h/12h}$ for FVC compared to the S50/FP500 group (3.221 L and 3.110 L, respectively), with an adjusted mean difference compared to S50/FP500 of 0.111 L (p=0.0126).

Other additional efficacy variables:

Clinically meaningful improvements (i.e., increases of ≥1.0 unit) in the TDI focal scores were observed for both treatment groups at all post-baseline visits. However, no differences between the treatment groups in the adjusted means were observed for the TDI focal and dimension scores (p>0.05 in all cases).

Clinically meaningful improvements (i.e., decreases of ≥4.0 units) from baseline in the mean SGRQ-C total scores were observed for both treatment groups after 24 weeks of treatment. However, no differences between the treatment groups in the adjusted means for the SGRQ-C total and 3 dimension scores were observed at any post-baseline visits (p>0.05 in all cases).

The improvements in CAT total scores were clinically meaningful (i.e., a decrease of ≥2.0 units) for both treatment groups after 24 weeks of treatment, and no difference between the treatment groups in the adjusted means were observed at any post-baseline visits (p>0.05 in all cases).

There were no significant differences between treatment groups in the use of relief medication (daily, day-time, and night-time relief) after 24 weeks of treatment.

No differences between the treatment groups in the adjusted mean E-RS total and domain scores, and

the early morning and night-time symptom overall and individual scores were observed after 24 weeks of treatment.

There were no significant differences between in the AB400/FF12 and S50/FP500 groups in the percentage of patients with COPD exacerbations during the study (15.8% and 16.6%, respectively).

Overall, the percentage (%) of patients preferring the Genuair® device was approximately 3 times greater than those preferring the Accuhaler™ device, and this was true for all of the attributes assessed; except "feedback to indicate correct inhalation" where approximately twice the percentage of patients preferred the Genuair® device to the Accuhaler™ device ($p<0.0001$ in all cases).

Safety and Tolerability Results:

A total of 933 patients were analysed in the Safety population.

Overall, Aclidinium/Formoterol 400/12 µg BID administered for a period of 24 weeks was well-tolerated, and did not raise any safety concerns in this study.

The most common TEAEs were COPD (exacerbation) (17.5% of patients overall), headache (6.4% of patients overall) and nasopharyngitis (5.8% of patients overall); all of which were reported at similar frequencies between the treatment groups. The majority of TEAEs were either mild or moderate in intensity, with severe TEAEs reported at a slightly higher frequency for the AB400/FF12 group (9.4%) compared with the S50/FP500 group (7.5%).

Serious TEAEs were experienced by 7.3% of patients overall, and frequencies were similar between the treatment groups. Of these, suicidal ideation, thrombosis, and COPD (exacerbation) in the AB400/FF12 group, and gallbladder disorder in the S50/FP500 group were assessed as related to the study drug. During the study, 3 patients in the AB400/FF12 group died from arrhythmogenic right ventricular dysplasia, cerebrovascular accident, and sudden death; and 1 patient in the S50/FP500 group died from cardiac failure. No deaths were considered related to the study drug.

The frequency of TEAEs leading to discontinuation was higher in the S50/FP500 group (7.3% of patients) compared with the AB400/FF12 group (5.4% of patients).

Respiratory events were the most common type of steroid-related event; reported more frequently for the S50/FP500 group (4.5% of patients) compared with the AB400/FF12 group (1.7% of patients). Of these, lower respiratory and lung infections were reported for 4.5% patients in the S50/FP500 group compared with 1.5% patients in the AB400/FF12 group, and pneumonia was reported for 1.9% patients in the S50/FP500 group compared with 0.6% patients in the AB400/FF12 group. A higher frequency of oral candidiasis was reported with S50/FP500 compared to AB400/FF12 group (1.9% compared with no patients, respectively).

Cardiac events and MACE events were reported at a low frequency; for 2.8% and 0.8% of patients overall, respectively, and at similar frequencies between the treatment groups.

No clinically relevant changes from baseline were observed in laboratory, blood pressure, and ECG parameters, and there was no evidence to suggest that the administration of AB400/FF12 leads to any clinically significant trends in these parameters. No QTcB and QTcF changes from baseline >60 msec were observed.

CONCLUSIONS:

- Overall, Aclidinium /Formoterol 400/12 µg provided superior bronchodilation compared to Salmeterol/Fluticasone 50/500 µg in peak FEV_1 (primary endpoint) and demonstrated non-inferiority with regards to the improvement of TDI scores at Week 24 (secondary endpoint).

- Moreover, Aclidinium/Formoterol 400/12 µg provided symptomatic and quality of life improvements (comparable to those provided by Salmeterol/Fluticasone 50/500 µg, and a similar percentage of patients experienced COPD exacerbations over the 6 months treatment period.

- Overall, inhaled doses of Aclidinium bromide 400 µg/Formoterol fumarate 12 µg administered BID for a period of 24 weeks was well tolerated in COPD patients with a similar safety profile compared to Salmeterol/Fluticasone 50/500 µg; with the exception of a lower incidence of fluticasone-related events such as oral candidiasis and lower respiratory tract infections, including pneumonia.

- Administration via the Genuair® inhaler was preferred by a higher percentage of patients for all attributes assessed, in comparison to the Accuhaler™.

DATE OF REPORT:
18 Dec 2014 (Final)