2. SYNOPSIS

Study centre(s)

This study was conducted in 88 study centres located in 5 countries/regions, out of which 81 study centres were active and recruited subjects: China (50), India (15), Philippines (8), Taiwan (China) (3), and Vietnam (5).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the bronchodilatory effect of AB/FF 400/12 µg compared to individual components and placebo when administered twice daily via inhalation to COPD subjects. • To assess the bronchodilatory effect of AB 400 µg compared to placebo when administered twice daily via inhalation to COPD subjects.	• Change from baseline in 1-hour morning post-dose FEV_1 of AB/FF 400/12 µg compared to AB 400 µg at Week 24. • Change from baseline in morning pre-dose (trough) FEV_1 of AB/FF 400/12 µg compared to FF 12 µg at Week 24. • Change from baseline in trough FEV_1 of AB 400 µg compared to placebo at Week 24.
Secondary	
• To assess the benefits of AB/FF 400/12 µg in COPD symptoms, disease-related health status and COPD exacerbations compared to placebo, when administered BID via inhalation to COPD subjects. • To assess the benefits of AB 400 µg in COPD symptoms, disease-related health status and COPD exacerbations compared to placebo, when administered BID via inhalation to COPD subjects.	• Change from baseline in peak FEV_1 of AB 400 µg compared to placebo at Week 24. • Improvements TDI focal score of AB/FF 400/12 µg compared to placebo at Week 24. • Improvements TDI focal score of AB 400 µg compared to placebo at Week 24. • Change from baseline in SGRQ total score of AB/FF 400/12 µg compared to placebo at Week 24. • Change from baseline in SGRQ total score of AB 400 µg compared to placebo at Week 24.
Safety	
• To evaluate the safety profile of AB/FF 400/12 µg and AB 400 µg in the same subject population.	• Adverse events • Clinical laboratory test • Blood pressure • ECG

The additional efficacy variables for the secondary endpoints have not been included in the synopsis but are available in the clinical study report.

AB = aclidinium bromide; BID = twice daily; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; FEV_1 = forced expiratory volume in 1 second; FF = formoterol fumarate; FVC = forced vital capacity; SGRQ = St. George's Respiratory Questionnaire; TDI = Transition Dyspnoea Index.

Study design

This was a multiple dose, randomised, parallel-group, double-blind, double-dummy, multicentre, and multinational Phase III study to determine the efficacy and safety of aclidinium bromide/formoterol fumarate (AB/FF) 400/12 µg compared to individual components and placebo and AB 400 µg compared with placebo when administered to subjects with stable chronic obstructive pulmonary disease (COPD).

The study consisted of a Screening visit (Visit 1), 24-week treatment period, and a 2-week follow-up period post-treatment. Subjects fulfilling inclusion/exclusion criteria at the time of the Screening entered into a run-in period of 14 ± 3 days prior to randomisation to assess the subject's disease stability.

Subjects who still met the entry criteria at Visit 2 were randomised in a ratio 1:1:1:1 to one of the 4 treatment arms: AB/FF 400/12 µg twice daily (BID), AB 400 µg BID, FF 12 µg BID, and placebo BID. A double-dummy design was adopted in the study to achieve blinding.

After randomisation, subjects were dispensed one medication kit with 4 Genuair® inhalers containing AB/FF 400/12 µg, or AB 400 µg or matching placebo and 4 Turbuhaler® inhalers containing FF 12 µg or matching placebo. At Visit 5, a second kit was dispensed with 4 additional Genuair® and 4 Turbuhaler® inhalers of matching active or placebo inhalers.

Each Genuair® inhaler contained at least 60 doses (and a maximum of 68 doses). Each Turbuhaler® inhaler contained at least 60 doses.

During the treatment period, the subjects visited the sites at Visit 3 (Week 1), Visit 4 (Week 4), Visit 5 (Week 12), Visit 6 (Week 18), and Visit 7 (Week 24) for assessments of clinical efficacy and safety.

A follow-up contact was performed 2 weeks after the last investigational product (IP) administration for both subjects who completed the study treatment and subjects who discontinued from the study (withdrawals), to assess new or ongoing adverse events (AEs), COPD exacerbations, as well as any concomitant medication(s) administered to treat the mentioned AE.

Target population and sample size

The study population consisted of male or non-pregnant, non-lactating female subjects, aged ≥ 40 years, with moderate to severe stable COPD.

The main inclusion criteria to determine subject's eligibility included post-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥ 30% and < 80% of the predicted normal and post-bronchodilator FEV_1/forced vital capacity (FVC) < 70%, current or former smokers, with a smoking history of ≥ 10 pack-years, ability to perform acceptable and repeatable pulmonary

function testing for FEV_1 according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2005 criteria at Visit 1.

Approximately 1515 subjects were planned to be screened in this study (assuming an estimated ineligibility rate of 30%) to have an overall sample size of 1060 subjects randomised to AB/FF 400/12 µg, AB 400 µg, FF 12 µg, or placebo based on a randomisation ratio of 1:1:1:1, which corresponds to 265 subjects per treatment arm.

The sample size was calculated based on previous data, with a sample size of 265 randomised subjects per group, to provide at least 90% power to detect a statistically significant difference at Week 24 of:

- 100 mL between AB/FF 400/12 µg and AB 400 µg in change from baseline at 1-hour morning post-dose FEV_1,
- 65 mL between AB/FF 400/12 µg vs FF 12 µg in change from baseline morning pre-dose (trough) FEV_1,
- 100 mL between AB 400 µg vs placebo in trough FEV_1, and
- 175 mL between AB 400 µg vs placebo in peak FEV_1.

Previous studies on the same drug and for the same spirometric endpoints showed a standard deviation (SD) of 230 mL.

The same sample size provided at least 90% power to detect a statistically significant difference at Week 24 of at least 1-unit between AB/FF 400/12 µg and AB 400 µg vs placebo in Transition dyspnoea index (TDI) focal score, assuming a SD of 3.5-units, and at least 4-unit difference in change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score assuming a SD of 13.5-unit for the same treatment comparisons.

All tests were performed using two-sided tests at 5% significance level.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Investigational product consisted of AB/FF 400/12 µg administered via Genuair®([redacted]), AB 400 µg administered via Genuair® ([redacted]), FF 12 µg administered via Turbuhaler® ([redacted]), placebo to AB/FF 400/12 µg and AB 400 µg administered via Genuair® ([redacted]), and placebo to FF 12 µg administered via Turbuhaler® ([redacted]).

Subjects were instructed to take 1 puff from the Genuair® and 1 puff from the Turbuhaler® in the morning and 1 puff from the Genuair® and 1 puff from the Turbuhaler® in the evening during the 24 weeks of treatment.

Duration of treatment

The study consisted of a 24-week treatment period.

Statistical methods

Statistical analyses:

The analyses of the primary and secondary variables were performed on the intention-to-treat (ITT) and per protocol (PP) analysis sets while all other analyses were performed for the ITT analysis set. Safety outcomes and COPD exacerbations were analysed for the safety analysis set (SAF). Moreover, smoking status and country were used as treatment allocation factors during the randomisation process.

The primary efficacy variables were analysed by means of mixed models for repeated measures (MMRM), adjusted for pre- and post-bronchodilator (salbutamol) FEV_1 at Screening visit, age, and baseline FEV_1 as covariates, and treatment group, country, smoking status, visit, and treatment group-by-visit interaction as fixed effect factors. To assess the robustness to variations of the missing data assumptions underlying the primary analysis on the primary efficacy endpoints, sensitivity analyses were conducted by imputing missing values using multiple imputation methods.

Improvements in TDI focal score and change from baseline in SGRQ total score at Week 24 were analysed by means of MMRM, adjusted by the corresponding baseline value (baseline dyspnoea index [BDI] or SGRQ at baseline) and age as covariates, and treatment group, country, smoking status, visit, and treatment group-by-visit interaction as fixed effect factors.

Additional endpoints like the area under the curve from time 0 to 3 hours for FEV_1, 'FEV_1 (AUC_{0-3})', COPD exacerbations, symptoms based on COPD assessment test (CAT) and exacerbations of chronic pulmonary disease tool (EXACT) - respiratory symptoms (E-RS) questionnaires, and rescue medication were also analysed.

Safety outcomes were summarised by means of descriptive statistics across time by treatment group.

Study population

A total of 1625 subjects were screened into the study; of these, 1066 subjects were randomised to one of the 4 treatment arms (AB/FF 400/12 µg, AB 400 µg, FF 12 µg, and placebo). Four (4) of the 1066 randomised subjects were excluded from the SAF because they did not receive study treatment, 9 subjects (all from study [redacted]) were excluded from the

ITT analysis set due to significant protocol deviations and 192 subjects were excluded from PP analysis set due to important protocol deviations (IPDs). The mean compliance with study treatment was at least 88% for all subjects.

The Asian (100%) study population had a mean age of 65.2 years and included a majority of male (95.8%), normal weight category for BMI (65.3%) subjects with either moderate (48.6%) or severe (51.2%) airflow limitations, category A, B, C, or D COPD (27.2%, 56.7%, 4.6%, and 11.5%, respectively), and no exacerbations in the past year (65.2%). The Asian study population included subjects from China (n=749, 70.3%), India (n=146, 13.7%), Philippines (n=118, 11.1%), Vietnam (n=39, 3.7%), and Taiwan (n=14, 1.3%). The treatment groups were generally comparable with regard to withdrawals from the study, demographics and baseline disease characteristics, and nicotine use/consumption. The concomitant medications used were reasonable in the clinical context. The higher use of inhaled medications for obstructive airway diseases and other inhalants other than the IP that was observed for all on-study concomitant medications compared to the on-treatment concomitant medications might be related to an increase in COPD medication use after IP treatment completion or withdrawal.

This subject population was representative of the target population for the treatment combination under evaluation.

Summary of efficacy results

Primary objectives:

- The primary objective of the study was met with values indicating superior bronchodilation with the AB/FF 400/12 µg combination compared with each of the relevant individual components (monotherapies). Compared with AB 400 µg, AB/FF 400/12 µg statistically significantly increased the change from baseline in 1-hour post-dose FEV_1 at Week 24 by 0.092 L ($p \leq 0.001$). Compared with FF 12 µg, AB/FF 400/12 µg statistically significantly increased the change from baseline in predose (trough) FEV_1 at Week 24 by 0.085 L ($p < 0.001$).
- The second primary objective of the study was met with values indicating superior bronchodilation with the AB 400 µg monotherapy compared with placebo. Treatment with AB 400 µg statistically significantly increased the change from baseline in pre-dose (trough) FEV_1 at Week 24 by 0.134 L ($p < 0.001$).

Secondary objectives:

- The AB 400 µg change from baseline in peak FEV_1 at Week 24 increased by 0.217 L compared with placebo and this difference reached statistical significance ($p < 0.001$).
- The adjusted mean improvement in TDI focal score at Week 24 was higher for AB/FF 400/12 µg (2.9 units) compared with placebo (2.1 units) and this difference reached statistical significance ($p = 0.005$). The adjusted mean improvement at Week 24

was higher for AB 400 µg (2.6 units) compared with placebo (2.1 units) but statistically significance was not achieved (p = 0.132).

- The treatment effect of SGRQ total score at Week 24 for both the AB/FF 400/12 µg and AB 400 µg groups compared with placebo was nominally statistically significant greater (treatment difference of -4.0 units [p = 0.003] and -2.9 units [p = 0.031] respectively).

Results for the additional efficacy variables (endpoints) have not been included in the synopsis but are available in the clinical study report (CSR).

Summary of safety results

- Overall, AB/FF 400/12 µg administered BID for a period of 24 weeks was well tolerated in subjects with moderate to severe COPD.
- The most common treatment-emergent adverse events (TEAEs) were exacerbation of underlying COPD (ranging from 9.8% to 15.9% of subjects) and upper respiratory tract infection (ranging from 8.9 to 11.8% of subjects). In general, the frequency of TEAEs was similar across treatment groups.
- Most of the TEAEs reported were mild or moderate in intensity; subjects who had severe TEAEs were reported in a similar frequency across treatment groups, ranging from 5.3% to 7.6% of subjects.
- Most TEAEs were not considered to be related to treatment by the Investigator. Among the treatment-related TEAEs, dizziness, increased blood creatine phosphokinase, and exacerbation of underlying COPD were reported in ≥ 2 (1.1%) subjects in any treatment group.
- TEAEs with a fatal outcome (death) were reported for 3 subjects, 1 subject in the FF 12 µg group (acute myocardial infarction) and 2 subjects in the placebo group (unknown cause of death and dyspnoea). None of the events were considered to be related to study treatment by the Investigator. Deaths were additionally reported pre-treatment for 1 subject in the AB/FF 400/12 µg group (hepatic cancer) and post-treatment for 1 subject of the FF 12 µg group (unknown cause of death).
- Treatment-emergent serious adverse events (SAEs) were reported in similar incidences across treatment groups, ranging from 7.2% to 9.8%. The most frequent SAE was exacerbation of underlying COPD.
- TEAEs leading to IP discontinuation were reported in low incidences across treatment groups ranging from 1.5% to 2.3%, with exacerbation of underlying COPD as the only TEAE leading to IP discontinuation that occurred in more than 1 subject.
- Cardiovascular and cerebrovascular TEAEs were reported without major differences across treatment groups ranging from 4.2% to 7.1%.
- Eight (8) major adverse cardiovascular events (MACEs) were reported across treatment groups. Two (2) cardiovascular deaths (1 subject each in the FF 12 µg [acute myocardial infarction] and placebo [dyspnoea] groups); 1 non-fatal myocardial infarction (FF 12 µg treatment group [acute myocardial infarction]); 5 non-fatal strokes (2 subjects in the AB 400 µg group [cerebral infarction and basal ganglia haemorrhage], and 3 subjects in the placebo group [2 cerebral infarctions and 1 cerebral haemorrhage]).

- A low percentage of subjects reported anticholinergic events during the study, ranging from 4.9% to 9.7% with highest percentage in the placebo group, and incidences were in general low and similar across treatment groups.
- Events of pneumonia were low and similar across treatment groups.
- A similar percentage of subjects reported β_2-adrenergic events during the study, ranging from 11.7% to 19.0% with the highest percentage in the placebo group. The most common events in the AB/FF 400/12 µg group were cough, dizziness, hypertension, hyperglycaemia, and throat irritation.
- Changes from baseline in clinical laboratory tests, vital signs, and electrocardiogram (ECG) parameters showed no clinically relevant differences among treatment groups. Clinically significant abnormalities were reported similarly across treatment groups.

Conclusions

- AB/FF 400/12 µg provided statistically superior bronchodilation compared to relevant individual components as demonstrated by the analysis of each co-primary endpoints.
- AB 400 µg provided statistically superior bronchodilation compared to placebo as demonstrated by the change from baseline in morning pre-dose (trough) FEV_1 at Week 24 as well as at peak FEV_1 at Week 24.
- Treatment with AB/FF 400/12 µg improved TDI focal score compared with placebo over the 24-week treatment period. An improvement trend was observed for the AB 400 µg compared to placebo at Week 24.
- Treatment with AB/FF 400/12 µg and AB 400 µg improved SGRQ total score compared with placebo over the 24-week treatment period.
- Onset of action of AB/FF 400/12 µg was observed within 5 minutes post-dose administration.
- In general, the effect of AB/FF 400/12 µg on pulmonary function variables (FEV_1, FVC) was sustained over the 24-week treatment period.
- On Day 1 and at Week 24, AB/FF 400/12 µg was nominally statistically superior to placebo for change from baseline in the normalised FEV_1 AUC_{0-3}.
- Treatment with AB/FF 400/12 µg improved CAT scores and was nominally statistically superior to placebo over the 24-week treatment period.
- The proportion of subjects experiencing an HCRU COPD exacerbation of any severity was lowest in the AB/FF 400/12 µg and AB 400 µg groups (10.6% and 8.6%, respectively). Both AB/FF 400/12 µg and AB 400 µg experienced nominally significantly lower adjusted rates of HCRU COPD exacerbations of any severity than placebo (p-values of 0.042 and 0.008 respectively). For moderate-to-severe exacerbations, adjusted rates were nominally significantly lower in the AB 400 µg group compared to placebo (p-value = 0.016) and numerically lower in the AB/FF 400/12 µg group compared to placebo; however, this reduction was not nominally significant.
- Additional evidence of symptomatic improvements associated with the AB/FF 400/12 µg combination relative to placebo was provided by a reduction in rescue medication use and improvement in EXACT-respiratory symptoms (E-RS).

- No new safety concerns were observed from this study. AB/FF 400/12 µg and AB 400 µg were well-tolerated, and the safety findings observed were consistent with the mono-components AB 400 µg and FF 12 µg.