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Efficacy and safety of acclidinium/ formoterol *versus* salmeterol/fluticasone: a phase 3 COPD study

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ABSTRACT The efficacy and safety of twice-daily acclidinium bromide/formoterol fumarate was compared with that of salmeterol/fluticasone propionate in patients with stable, moderate-to-severe chronic obstructive pulmonary disease (COPD).

AFFIRM COPD (Acclidinium and Formoterol Findings in Respiratory Medicine COPD) was a 24-week, double-blind, double-dummy, active-controlled study. Patients were randomised (1:1) to acclidinium/formoterol 400/12 µg twice-daily *via* Genuair/Pressair or salmeterol/fluticasone 50/500 µg twice-daily *via* Accuhaler. The primary end-point was peak forced expiratory volume in 1 s (FEV₁) at week 24. Other end-points included Transition Dyspnoea Index (TDI) focal score at week 24, TDI and St George's Respiratory Questionnaire (SGRQ) responders, COPD Assessment Test and SGRQ scores, assessment of COPD symptoms and exacerbations, use of reliever medication, and device preference. Adverse events were monitored throughout.

In total, 933 patients were eligible (mean age 63.4 years, 65.1% male). Acclidinium/formoterol was superior to salmeterol/fluticasone in peak FEV₁ and noninferior in TDI. Health status and reduction in exacerbation risk were similar in both groups. While both treatments were well tolerated, pneumonia occurred less frequently with acclidinium/formoterol than salmeterol/fluticasone.

In stable COPD, acclidinium/formoterol significantly improved bronchodilation *versus* salmeterol/fluticasone, with equivalent benefits in symptom control and reduction in exacerbation risk. Both treatments were well tolerated and treatment-related adverse events were less common with acclidinium/formoterol.



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Introduction

The combination of a long-acting β_2 -agonist (LABA) and a long-acting muscarinic antagonist (LAMA) is one of the treatment options recommended in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report for patients with chronic obstructive pulmonary disease (COPD) classified in groups B, C and D [1]. LABAs and LAMAs relax smooth airway muscle by different, complementary mechanisms: LABAs stimulate airway smooth muscle relaxation and decrease acetylcholine release, whereas LAMAs block the interaction of acetylcholine on muscarinic receptors [2]. When used in combination, LABAs and LAMAs can achieve greater bronchodilation than either agent alone [3, 4].

The combination of the LABA salmeterol and the inhaled corticosteroid (ICS) fluticasone propionate is a well-established treatment for the management of COPD [5]. However, ICS use has been associated with increased risk of certain adverse events, including an increased incidence of pneumonia [6]. Whilst treatment with an ICS has been shown to have benefits for patients at high risk of exacerbations, for many patients, combination treatment with a LABA and a LAMA may be an alternative therapeutic option [1, 7].

A twice-daily dual bronchodilator combining the LAMA aclidinium bromide and the LABA formoterol fumarate has been approved in Europe as a maintenance treatment to relieve symptoms in patients with COPD [8]. Two phase 3 studies demonstrated that in patients with moderate-to-severe COPD, aclidinium/formoterol significantly improved 1-h morning post-dose forced expiratory volume in 1 s (FEV₁) over 24 weeks *versus* both placebo and the monotherapy components, as well as trough FEV₁, compared with placebo [9, 10]. These studies also demonstrated that aclidinium/formoterol significantly improved symptoms of COPD and dyspnoea *versus* placebo [9, 10]. Furthermore, a pre-planned, pooled analysis of the two studies demonstrated significant improvements in dyspnoea with aclidinium/formoterol compared with both monotherapies and placebo, and a reduction in exacerbations compared with placebo [11]. The safety profile of the aclidinium/formoterol combination was comparable with those of the monotherapies [9, 10].

Here, we report the results of the AFFIRM COPD (Acclidinium and Formoterol Findings in Respiratory Medicine COPD) study, which evaluated the efficacy and tolerability of aclidinium/formoterol 400/12 μ g twice daily compared with salmeterol/fluticasone 50/500 μ g twice daily over 24 weeks in symptomatic patients with stable, moderate-to-severe COPD. The primary aim of the study was to demonstrate the superiority of aclidinium/formoterol *versus* salmeterol/fluticasone in terms of peak FEV₁; secondary objectives included comparison of dyspnoea, symptoms and health status between the two therapies.

Methods

Study design

AFFIRM was a randomised, double-blind, double-dummy, active-controlled, multicentre, phase 3b study conducted at 140 centres in 14 countries (www.ClinicalTrials.gov identifier number NCT01908140) between October 11, 2013, and August 4, 2014.

Following screening and a 7–10-day run-in period, patients with stable, moderate-to-severe COPD were randomised 1:1 to 24 weeks of double-blind treatment with aclidinium/formoterol 400/12 μ g twice daily *via* Genuair/Pressair (AstraZeneca group of companies; for use within the USA as Pressair and Genuair within all other licensed territories) or salmeterol/fluticasone 50/500 μ g twice daily *via* Accuhaler (GlaxoSmithKline, Stevenage, UK). There was no pre-treatment washout period and baseline values for all study end-points were reflective of patients receiving pre-study COPD medication. Patients in the aclidinium/formoterol group also received placebo *via* Accuhaler and the salmeterol/fluticasone group received placebo *via* Genuair/Pressair. Study visits were conducted as shown in figure 1. Randomisation was stratified by prior ICS use (yes or no) and exacerbations in the previous 12 months (none, or one or more).

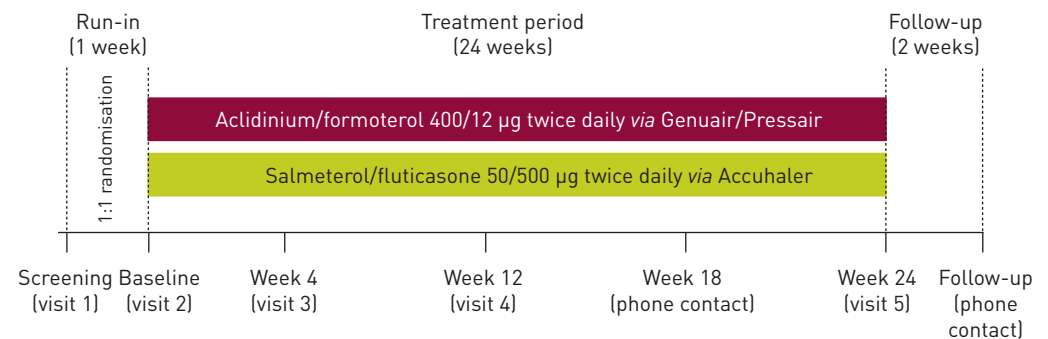


FIGURE 1 Study design.

Study population

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation/Good Clinical Practice Guidelines and local regulations. The protocol was approved by the regulatory authority for each participating country and an independent ethics committee at each centre. Patients gave written informed consent.

Patients ≥ 40 years of age with a smoking history ≥ 10 pack-years and diagnosed with moderate-to-severe COPD (GOLD 2013 criteria: post-bronchodilator FEV₁/forced vital capacity $< 70\%$ and FEV₁ $< 80\%$ predicted) were eligible [1]. All patients were symptomatic with a COPD Assessment Test (CAT) score ≥ 10 at the screening and baseline visits. Exclusion criteria included respiratory tract infection or COPD exacerbation within 6 weeks of screening or during run-in, pulmonary rehabilitation within 3 months, or use of triple therapy (LAMA/LABA/ICS) within 4 weeks of the screening visit. Patients discontinued all bronchodilator and ICS medication the night before the randomisation visit (visit 2). Salbutamol rescue medication was permitted.

End-points

The primary efficacy end-point was peak FEV₁ at week 24 (defined as maximum FEV₁ from 0 to 3 h after the morning dose) for acclidinium/formoterol 400/12 μg *versus* salmeterol/fluticasone 50/500 μg . The secondary efficacy end-point was the Transition Dyspnoea Index (TDI) focal score at week 24. Additional end-points included morning pre-dose (trough) FEV₁ and normalised FEV₁ area under the curve from 0 to 3 h post-dose (AUC_{0-3 h/3 h}), the percentage of patients achieving the minimum clinically important difference (MCID) in TDI (≥ 1 -unit improvement) and St George's Respiratory Questionnaire (SGRQ) score (≥ 4 -unit decrease), change from baseline in CAT score, SGRQ score, Evaluating Respiratory Symptoms in COPD score (E-RS:COPD) (the instrument formerly known as EXACT-RS (Exacerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms)), night-time and early-morning symptom scores, number of patients experiencing at least one COPD exacerbation, change from baseline in relief medication use, and device preference.

Assessments

Spirometry was performed pre-dose and up to 3 h post-dose. Dyspnoea was assessed using the baseline dyspnoea index, with changes measured using the TDI. Health status was assessed using SGRQ and CAT. Exacerbations were identified based on the healthcare resource utilisation (HCRU) criteria (increase in symptoms for two or more consecutive days that required medical intervention such as increasing usual COPD medication, treatment with antibiotics and/or systemic corticosteroids, or hospitalisation) and using EXACT, a 14-item diary was completed every night. COPD symptoms (daytime, night-time and early morning) and reliever medication use were recorded in an electronic diary. The E-RS:COPD tool was used to assess daytime symptoms [12, 13]; night-time and early-morning symptoms were assessed using a multi-item questionnaire completed every morning [14–16]. Device preference was assessed by questionnaire at the end of the treatment period. Patients recorded which device they preferred (Genuair, Accuhaler or no preference) and scored their willingness to continue using each device on a scale of 0–100.

Safety and tolerability assessments involved the recording of adverse events (including cardiac, cerebrovascular and serious adverse events (SAEs)), laboratory tests, blood pressure measurements and 12-lead ECGs. Adverse events commonly associated with the use of ICS, anticholinergic or adrenergic drugs, as defined by the Medical Dictionary for Regulatory Activities (MedDRA), were subject to separate analyses.

Statistical analysis

Data were analysed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). A sample size of 900 randomised patients (allowing for a 10% dropout rate) was estimated to provide 90% power to detect a significant difference of -55 mL (noninferiority limit) and 86% power to detect a significant difference of 60 mL (superiority limit) between acclidinium/formoterol and salmeterol/fluticasone in peak FEV₁ at week 24 (SD 280 mL), and 81% power to detect a significant difference of -0.5 (noninferiority limit) between acclidinium/formoterol and salmeterol/fluticasone in TDI at week 24 (SD 3.0).

To control for multiplicity, a predefined order was applied for the analysis of the primary and secondary end-points, with progression dependent on satisfying the previous criterion: 1) noninferiority of peak FEV₁ at week 24 for acclidinium/formoterol *versus* salmeterol/fluticasone; 2) superiority of acclidinium/formoterol over salmeterol/fluticasone in peak FEV₁; and 3) noninferiority of TDI at week 24 for acclidinium/formoterol *versus* salmeterol/fluticasone. Noninferiority analyses were performed in the per protocol population; all other efficacy analyses, including the subanalyses, were performed on the intent-to-treat (ITT) population (patients with a baseline FEV₁ assessment and who took one or more

doses of study medication) [17]. Safety outcomes were assessed in the safety population (patients who received one or more doses of study medication).

Pulmonary function variables, COPD symptoms, TDI focal score, SGRQ total score, CAT total score and relief medication use were analysed using a mixed model for repeated measures (MMRM) (covariates: age, baseline value; fixed-effect factors: treatment group, ICS use, prior exacerbation, sex, smoking status, visit and treatment group-by-visit interaction). The MMRM for FEV₁ was additionally adjusted by screening pre- and post-bronchodilator FEV₁. A logistic random effects model was used to analyse numbers of patients achieving the MCID in TDI, SGRQ and CAT (covariates: age, corresponding baseline values; factors: treatment, sex, smoking status, ICS use and prior exacerbation), or patients experiencing one or more exacerbations (covariates: age and baseline COPD severity (moderate *versus* severe/very severe); factors: treatment, sex, smoking status, ICS use and prior exacerbation). Treatment effects and treatment differences were estimated by least squares means along with their standard errors and 95% confidence intervals. Device preference was analysed using a Chi-squared test. Safety outcomes were analysed descriptively.

Results

In total, 933 patients were included in the safety population; 788 (84.5%) patients completed the study (figure 2). When stratified by prior ICS use, 357 (38.3%) patients were ICS users and 576 (61.7%) patients were non-ICS users. A total of 931 (99.8%) patients were included in the ITT population and the per protocol population comprised 837 (89.7%) patients (figure 2). Demographics and baseline characteristics were similar between groups (table 1).

Peak FEV₁

Peak FEV₁ (primary efficacy end-point) was significantly greater with acclidinium/formoterol *versus* salmeterol/fluticasone at week 24, with significant differences observed after the first dose on day 1 and at all intervening time-points (all $p < 0.0001$) (figure 3). Noninferiority of acclidinium/formoterol *versus* salmeterol/

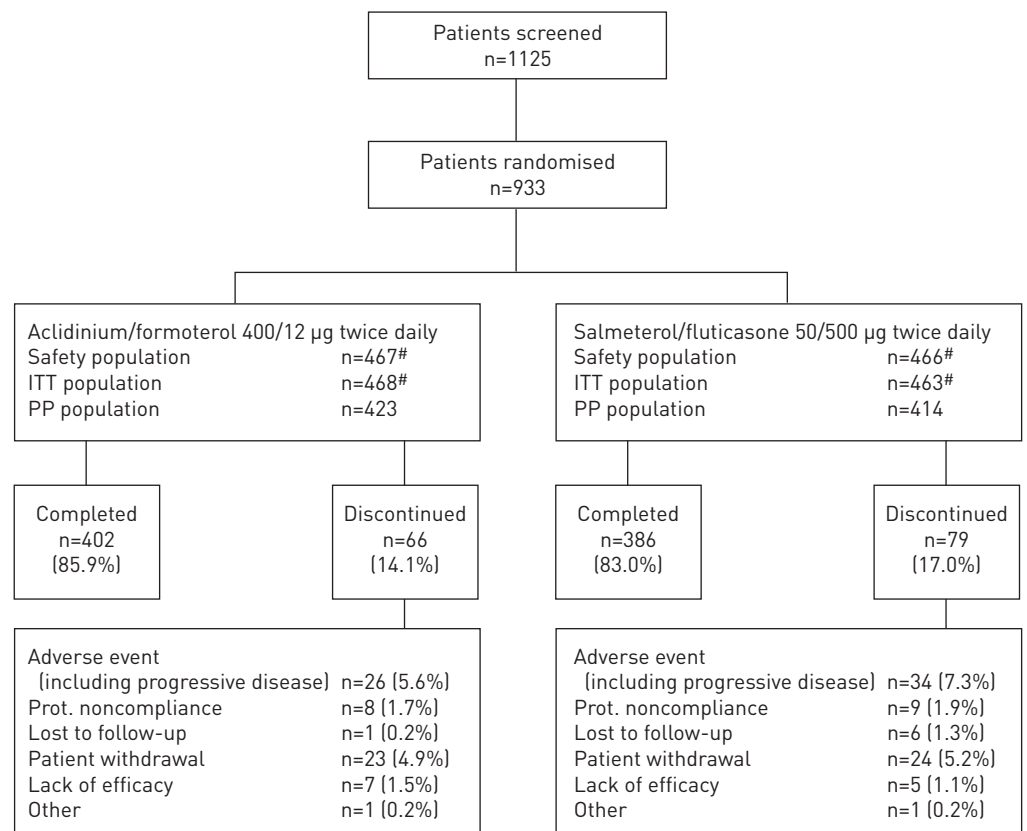


FIGURE 2 Patient disposition. ITT: intent-to-treat; PP: per protocol; Prot.: protocol. #: two patients randomised to acclidinium/formoterol 400/12 µg twice daily received salmeterol/fluticasone 50/500 µg twice daily; one patient randomised to salmeterol/fluticasone 50/500 µg twice daily received acclidinium/formoterol 400/12 µg twice daily. Efficacy data for these patients were analysed according to randomisation; safety data were analysed according to received treatment.

TABLE 1 Patient demographics and baseline characteristics (safety population)

	Acclidinium/formoterol 400/12 µg twice daily	Salmeterol/fluticasone 50/500 µg twice daily
Patients	467	466
Age years	63.5±8.1	63.3±7.5
Males	65.7%	64.4%
Caucasians	443 (94.9%)	437 (93.8%)
GOLD classification		
B	264 (56.5%)	255 (55.2%) [§]
D	203 (43.5%)	207 (44.8%)
Smoking consumption pack-years	41.6±23.1	42.6±20.1
≥1 exacerbation in previous year	147 (31.5%)	152 (32.6%)
Exacerbations in previous year	0.42±0.76	0.44±0.79
Prior COPD medication		
LABA	56 (12.0%)	51 (10.9%)
LAMA	78 (16.7%)	84 (18.0%)
LABA/LAMA	93 (19.9%)	86 (18.5%)
ICS	27 (5.8%)	46 (9.9%)
LABA/ICS [#]	140 (30.0%)	129 (27.7%)
LABA/LAMA/ICS	9 (1.9%)	7 (1.5%)
FEV₁[¶] L	1.388±0.510	1.378±0.522
Post-bronchodilator FEV₁^{¶,*} % predicted	53.3±14.4	53.2±14.8
Bronchial reversibility %	11.3±12.3	12.3±13.0
BDI focal score[¶]	6.4±2.0	6.3±2.0
CAT total score[¶]	18.6±5.6	18.4±5.4
SGRQ total score[¶]	49.9±17.8	49.4±16.8

Data are presented as mean±SD unless otherwise stated. GOLD: Global Initiative for Chronic Obstructive Lung Disease; COPD: chronic obstructive pulmonary disease; LABA: long-acting β₂-agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid; FEV₁: forced expiratory volume in 1 s; BDI: baseline dyspnoea index; CAT: COPD Assessment Test; SGRQ: St George's Respiratory Questionnaire. #: fixed and free; ¶: data reported for intent-to-treat population (aclidinium/formoterol, n=468; salmeterol/fluticasone, n=466); *: data recorded at screening visit; §: data missing for four patients in the salmeterol/fluticasone group.

fluticasone in peak FEV₁ at week 24 was demonstrated, as the lower bound of the 95% confidence interval (70–131 mL) was greater than the predefined –55 mL noninferiority limit. In addition, the mean increase in peak FEV₁ at week 24 was 93 mL greater with aclidinium/formoterol than with salmeterol/fluticasone, thereby demonstrating superiority (p<0.0001, ITT population). Improvements in peak FEV₁ were significantly greater with aclidinium/formoterol *versus* salmeterol/fluticasone regardless of prior ICS use or incidence of exacerbations in the previous 12 months. Mean treatment differences were larger in patients with prior ICS use (122 mL) *versus* no prior ICS (76 mL) and for patients who had experienced exacerbations within 12 months (113 mL) *versus* those who had not (84 mL) (all analyses, p≤0.0001).

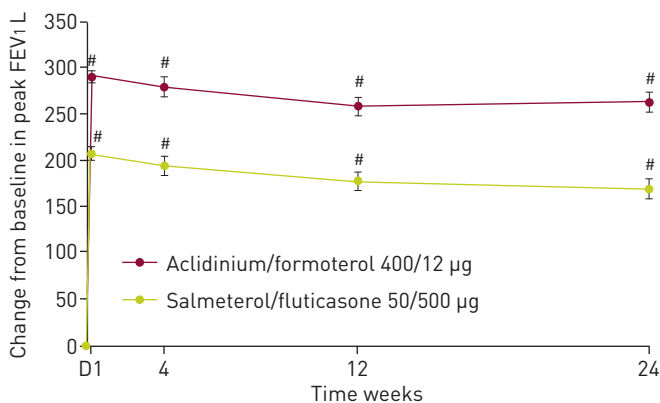


FIGURE 3 Change from baseline in peak forced expiratory volume in 1 s (FEV₁) (intent-to-treat population) by visit over 24 weeks. Data are presented as least-squares mean±SE. D: day. #: p<0.0001 for aclidinium/formoterol *versus* salmeterol/fluticasone.

Dyspnoea

Acclidinium/formoterol and salmeterol/fluticasone resulted in similar, clinically relevant improvements in mean TDI focal score at week 24 and at all previous visits (figure 4). Noninferiority of acclidinium/formoterol *versus* salmeterol/fluticasone was demonstrated at week 24 (95% CI -0.46 – 0.46), as well as at week 4 (95% CI -0.34 – 0.40) and week 12 (95% CI -0.43 – 0.39). At week 24, 55.6% of patients in the acclidinium/formoterol group and 54.5% in the salmeterol/fluticasone group achieved improvements in TDI greater than the MCID (≥ 1 unit). There were no significant differences in TDI scores between treatments when analysing data stratified by prior ICS use or previous exacerbations within 12 months.

Health-related quality of life

Both acclidinium/formoterol and salmeterol/fluticasone achieved clinically relevant changes from baseline in CAT total scores (≥ 2 units) at week 24. There were no significant differences between groups in CAT total score at any study visit (figure 5).

Mean improvements in SGRQ total scores at week 24 were similar following treatment with acclidinium/formoterol or salmeterol/fluticasone (-4.7 and -5.7 , respectively; $p=0.27$). At week 24, 52.6% of patients in the acclidinium/formoterol group and 55.8% in the salmeterol/fluticasone group achieved improvements from baseline in SGRQ total scores greater than the MCID (≥ 4 units).

Exacerbations

There were no significant differences in the incidence of exacerbations between the acclidinium/formoterol and salmeterol/fluticasone groups. Over 24 weeks, 74 (15.8%) patients in the acclidinium/formoterol arm experienced one or more HCRU-defined exacerbation compared with 77 (16.6%) in the salmeterol/fluticasone group. 70 patients in each group experienced one or more moderate or severe HCRU-defined exacerbation during the study period (OR 1.0, $p=0.9805$). In the acclidinium/formoterol group, 177 (37.8%) patients experienced one or more EXACT-defined event, compared with 183 (39.5%) patients in the salmeterol/fluticasone group (OR 0.94, $p=0.6243$).

Other end-points

There were no significant differences in trough FEV₁ between the acclidinium/formoterol and salmeterol/fluticasone treatment arms at week 24 (1.405 *versus* 1.419 L, respectively; $p=0.3635$). Normalised FEV₁ AUC_{0-3 h/3 h} was significantly greater with acclidinium/formoterol than with salmeterol/fluticasone at week 24 (1.577 *versus* 1.487 L, respectively; $p<0.0001$).

Daytime symptoms, measured using the E-RS:COPD tool, did not differ between the two treatment groups at week 24, with 1.0-point (acclidinium/formoterol) and 0.9-point (salmeterol/fluticasone) improvements from baseline. Early-morning symptom total scores were stable over the course of the study, with no significant difference between groups at week 24. Night-time symptom total scores were the same in both groups at week 24, with a 0.2-point reduction from baseline (2.1 at baseline; 1.9 at week 24). There was no significant difference between groups in the use of relief medication (both 0.9 puffs per day at week 24).

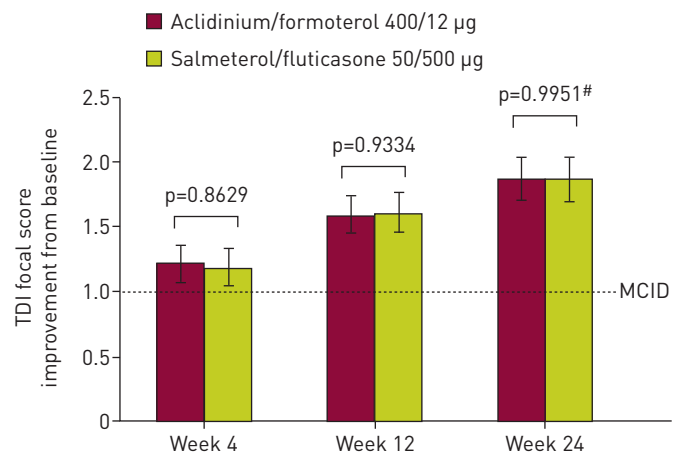


FIGURE 4 Transition Dyspnoea Index (TDI) focal score improvement from baseline to week 24 (per protocol population). Data are presented as least-squares mean \pm SE. MCID: minimum clinically important difference. #: demonstrates noninferiority of acclidinium/formoterol *versus* salmeterol/fluticasone.

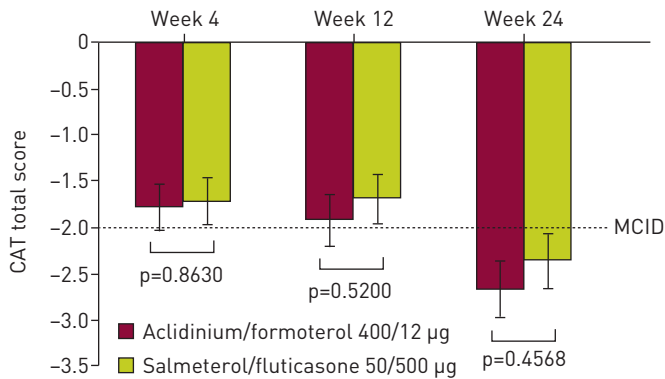


FIGURE 5 COPD Assessment Test (CAT) total scores. Change from baseline to week 24 on treatment with acclidinium/formoterol or salmeterol/fluticasone (intent-to-treat population). Data are presented as least-squares mean \pm SE. COPD: chronic obstructive pulmonary disease; MCID: minimum clinically important difference.

Patient preference

Overall, a significantly greater proportion of patients preferred Genuair (73.7%) than Accuhaler (26.3%) ($p < 0.0001$), with similar proportions of patients preferring Genuair over Accuhaler for each of the device attributes assessed (all $p < 0.0001$). The willingness of patients to continue using each device was greater for Genuair (78.6%) than Accuhaler (64.3%) ($p < 0.0001$).

Safety and tolerability

The incidence of adverse events and SAEs was similar between treatment groups (table 2). The most common adverse events were exacerbation of COPD (17.5%), headache (6.4%) and nasopharyngitis (5.8%), with similar proportions reported in each treatment group (table 2). Treatment-related adverse events were reported by 7.9% of patients in the salmeterol/fluticasone arm (most common: dyspnoea ($n=7$, 1.5%), oral candidiasis ($n=7$, 1.5%) and COPD exacerbation ($n=4$, 0.9%)) and by 5.6% of acclidinium/formoterol-treated patients (most common: product taste abnormal ($n=6$, 1.3%), dyspnoea ($n=4$, 0.9%) and COPD exacerbation ($n=4$, 0.9%)). Adverse events leading to study discontinuation were more frequent with salmeterol/fluticasone than with acclidinium/formoterol. There were four fatal adverse events: three in the acclidinium/formoterol group (arrhythmogenic right ventricular dysplasia, cerebrovascular accident and sudden death) and one with salmeterol/fluticasone (cardiac failure). None was considered to be related to study medication.

Adverse events related to ICS use, as defined by MedDRA, were more common in patients receiving salmeterol/fluticasone than patients receiving acclidinium/formoterol (table 2). Pneumonia was reported in three patients (0.6%) in the acclidinium/formoterol group and nine (1.9%) in the salmeterol/fluticasone group (pneumonia diagnosis was not required to be verified by chest radiography according to the protocol; however, it was radiologically confirmed in one patient in the acclidinium/formoterol treatment group and in one patient in the salmeterol/fluticasone treatment group). 10 (2.1%) patients experienced oral/oropharyngeal candidiasis in the salmeterol/fluticasone group. No patients in the acclidinium/formoterol group experienced either condition. No clinically relevant differences in anticholinergic-related adverse events were reported between groups, with the exception of events associated with inhaled drug administration more generally (dysphonia, pharyngitis and oropharyngeal pain), which were reported slightly more frequently with salmeterol/fluticasone than with acclidinium/formoterol (table 2). The incidence of β_2 -agonist effects was similar with acclidinium/formoterol and salmeterol/fluticasone (table 2).

The incidence of cardiac events was similar in both treatment groups (table 2). The incidence of major adverse cardiovascular events, including cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, was low and comparable between the treatment groups. No clinically significant differences were observed between treatment groups in clinical laboratory tests, vital signs or ECGs.

Discussion

In patients with stable COPD, acclidinium/formoterol demonstrated superiority over salmeterol/fluticasone in peak FEV₁ at week 24 and at all study visits. Acclidinium/formoterol was noninferior to salmeterol/fluticasone in terms of TDI, with both treatments exhibiting equivalent benefits on breathlessness. Acclidinium/formoterol resulted in significantly greater normalised FEV₁ AUC_{0-3 h/3 h} than with salmeterol/fluticasone, whilst improvements in trough FEV₁ and health status were comparable between the two treatment groups. Similarly, exacerbation rates were similar in both treatment groups. While both treatments were well tolerated, ICS-related adverse events occurred more frequently with salmeterol/fluticasone than with acclidinium/formoterol.

TABLE 2 Incidence of adverse events (AEs), cardiac AEs and cerebrovascular AEs in the safety population

	Acclidinium/formoterol 400/12 µg twice daily	Salmeterol/fluticasone 50/500 µg twice daily
Patients	467	466
≥1 AE	235 (50.3%)	265 (56.9%)
≥1 SAE	35 (7.5%)	33 (7.1%)
AEs reported for ≥2% of patients		
COPD exacerbation	80 (17.1%)	83 (17.8%)
Headache	28 (6.0%)	32 (6.9%)
Nasopharyngitis	26 (5.6%)	28 (6.0%)
AEs leading to study discontinuation[#]	26 (5.6%)	34 (7.3%)
ICS-related AEs of interest[¶]		
Any event	20 (4.3%)	50 (10.7%)
Lower respiratory and lung infections	7 (1.5%)	21 (4.5%)
Bronchitis	5 (1.1%)	6 (1.3%)
Pneumonia	3 (0.6%)	9 (1.9%)
Anticholinergic-related AEs[¶]		
Any event	17 (3.6%)	44 (9.4%)
Oropharyngeal pain	6 (1.3%)	9 (1.9%)
Pharyngitis	0	9 (1.9%)
Dysphonia	2 (0.4%)	6 (1.3%)
β₂-agonist-related AEs[¶]		
Any event	69 (14.8%)	76 (16.3%)
Headache	28 (6.0%)	32 (6.9%)
Hypertension	12 (2.6%)	10 (2.1%)
Muscle spasms	7 (1.5%)	11 (2.4%)
Any cardiac event	15 (3.2%)	15 (3.2%)
Serious cardiac events	4 (0.9%)	2 (0.4%)
Cerebrovascular events	2 (0.4%)	2 (0.4%)
Serious cerebrovascular events	2 (0.4%)	2 (0.4%)
MACE composite[*]	4 (0.9%)	3 (0.6%)

SAE: serious adverse event; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; MACE: major adverse cardiovascular events. [#]: includes patients who withdrew due to disease progression after reporting this as an AE; [¶]: data reported for all events plus the three most common events; ^{*}: including cardiovascular death, nonfatal myocardial infarction and nonfatal stroke.

These results are similar to those of other clinical trials comparing LABA/LAMA combinations with salmeterol/fluticasone. Significant improvements in lung function have been reported for indacaterol/glycopyrronium (the ILLUMINATE and LANTERN studies) and umeclidinium/vilanterol over salmeterol/fluticasone [18–20]. An MCID for FEV₁ of 100 mL is generally used for comparisons *versus* placebo; therefore, the mean improvement of 93 mL for acclidinium/formoterol *versus* salmeterol/fluticasone approaches this threshold value and would be expected to be of clinical significance. Similar to AFFIRM, improvements in dyspnoea with umeclidinium/vilanterol were found to be comparable with those with salmeterol/fluticasone [20]. In LANTERN, improvements in TDI were comparable between indacaterol/glycopyrronium and salmeterol/fluticasone, whereas in ILLUMINATE, indacaterol/glycopyrronium provided significantly greater improvements [18, 19].

The comparable exacerbation reduction with both acclidinium/formoterol and salmeterol/fluticasone is also mirrored in studies of other LAMA/LABA combinations *versus* salmeterol/fluticasone [18, 20]. However, the LANTERN study demonstrated a 31% reduction in moderate or severe exacerbations with indacaterol/glycopyrronium compared with salmeterol/fluticasone [19]. Taken together, these data suggest that dual bronchodilation may offer a similar degree of protection from exacerbations as salmeterol/fluticasone in the populations studied. However, it is important to note that the populations differed between studies, potentially masking differences in efficacy. For example, patients with prior exacerbations were specifically excluded from ILLUMINATE and the umeclidinium/vilanterol studies, while the LANTERN study permitted up to one exacerbation in the previous 12 months; in contrast, AFFIRM included patients with multiple prior exacerbations [18–20].

AFFIRM is the first study comparing a LABA/LAMA and LABA/ICS to include both CAT and SGRQ to assess health status. As expected, based on validation studies, the results from each tool were in close

agreement, thereby providing further support for the GOLD guidance, which recommends the use of CAT for routine clinical practice rather than the more complex SGRQ [1, 21]. A further strength of this study was that symptomatic patients were identified according to CAT total score at baseline and this has been demonstrated as correlating well with the validated modified Medical Research Council tool [22]. The improvements demonstrated for CAT, SGRQ and other symptom scores were comparable between acclidinium/formoterol and salmeterol/fluticasone, suggesting that the greater improvements in bronchodilation observed for acclidinium/formoterol did not correlate with symptom outcomes. This is in agreement with results for umeclidinium/vilanterol and indacaterol/glycopyrronium *versus* salmeterol/fluticasone [18–20]. One possible explanation is that the tools used may lack the sensitivity to detect differences between effective active treatment groups [20].

There are noteworthy differences between AFFIRM and previous studies, which mean the population in this study may be more closely matched to real-world patients with COPD. Primarily, AFFIRM enrolled only symptomatic patients with a CAT score ≥ 10 . Indeed, the dropout rate in AFFIRM was much higher than estimated *a priori*, which was likely due to the inclusion of patients, who, by definition, had worse health status than in similar studies. Similarly, baseline disease severity and risk of future exacerbations were categorised in AFFIRM using GOLD B ("low risk, more symptoms") or D ("high risk, more symptoms") by performing a combined assessment of symptoms, breathlessness, spirometry and risk of exacerbations. In contrast, patients in the umeclidinium/vilanterol and indacaterol/glycopyrronium studies were classified as GOLD II or III, solely by assessing spirometry [18–20]. Crucially, AFFIRM included a more severe and less reversible COPD population than ILLUMINATE, which may have had an impact on the response to symptom outcomes and expected rate of exacerbations [18]. Another difference is that ILLUMINATE and LANTERN included a 7-day washout period prior to initiation of study therapy [18], whereas there was no washout period in AFFIRM.

A potential limitation of AFFIRM may be that patients who did not qualify for ICS treatment based on prior exacerbation history were included in the ICS/LABA arm. However, in clinical practice, it is common for patients to be treated with an ICS regardless of exacerbation history, and this is supported by the fact that around one-third of patients were receiving ICS prior to the study. Another potential limitation is that patients receiving triple therapy prior to screening were excluded to ensure their condition was not destabilised on randomisation. However, AFFIRM was designed before the results of the WISDOM trial were available; it is now known that many patients on triple therapy can be withdrawn from ICS therapy without dramatically altering their disease state [23]. Although 37% of patients in the acclidinium/formoterol group had previously been using an ICS, no increase in exacerbations was seen in this treatment group. It should be noted that the treatment strategy used in AFFIRM differed from that used in the WISDOM trial [23], which adds further support for safe withdrawal of ICS. A further limitation of the AFFIRM study, and indeed all of the aforementioned trials, is their short duration; longer-term trials are warranted to detect differences in exacerbations.

As has been observed previously for LAMA/LABA combinations *versus* a LABA/ICS [18, 19], the incidence of pneumonia was found to be lower with acclidinium/formoterol than with salmeterol/fluticasone, and discontinuations due to adverse events were higher with salmeterol/fluticasone than acclidinium/formoterol. As expected, other ICS-related adverse events were more common with salmeterol/fluticasone than with acclidinium/formoterol and there were no differences in adrenergic-related events. Although adverse events nominally defined as being anticholinergic-related were more common in the salmeterol/fluticasone group than with acclidinium/formoterol, these differences were likely related to inhaled therapies in general and were not considered to be clinically relevant.

The results for AFFIRM show that combined therapy with acclidinium/formoterol demonstrated superiority over salmeterol/fluticasone in peak FEV₁. Improvements in dyspnoea and symptom control were comparable between treatment groups and although the study was not powered for exacerbations, exacerbation rates were similar in both groups. While both treatments were well tolerated, ICS-related adverse events were less common with acclidinium/formoterol. These findings support the GOLD recommendations for LAMA/LABA use in patients with symptomatic COPD [1] and demonstrate that acclidinium/formoterol is an effective treatment for these patients.

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