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Aclidinium bromide in fixed-dose combination with formoterol fumarate in the management of COPD: an update on the evidence base

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Abstract: Aclidinium bromide/formoterol fumarate (AB/FF) 400/12 µg is a twice-daily long-acting muscarinic receptor antagonist and long-acting β_2 agonist (LAMA/LABA) dual-bronchodilator maintenance therapy used to relieve symptoms and reduce future risk of exacerbations in adults with chronic obstructive pulmonary disease (COPD). To date, there have been several clinical studies and *post hoc* analyses of AB/FF, assessing treatment outcomes in patients with moderate-to-severe COPD. These studies have looked at a range of outcomes, including lung function parameters, patient-reported symptom scores, quality-of-life measures assessing impaired health and perceived well-being, and the frequency, duration, and severity of exacerbations. In light of the major 2017 revision to the Global initiative for chronic Obstructive Lung Disease (GOLD) recommendations, and the subsequent updates, we present an update on the latest evidence supporting the efficacy and safety of AB/FF. This review discusses the clinical relevance of the improvements in lung function, symptoms, quality of life, and exacerbations in patients with COPD reported in the phase III and IV trials of AB/FF. Given the current concerns over unnecessary inhaled corticosteroid (ICS) use in COPD, we also touch briefly on the use of blood eosinophils as a biomarker for identifying those patients with COPD already using LAMA/LABA therapy for whom the addition of ICS might be of benefit.

Keywords: aclidinium, bronchodilators, COPD, formoterol, long-acting muscarinic antagonist, long-acting β_2-agonist, maintenance treatment

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Introduction

Dual-bronchodilator therapy combining a long-acting muscarinic receptor antagonist (LAMA) and a long-acting β_2 agonist (LABA) has become foundational in chronic obstructive pulmonary disease (COPD) treatment.[1] The complementary mechanisms by which LAMAs and LABAs work may be responsible for the additive efficacy and superior bronchodilation seen with LAMA/LABA combinations compared with single bronchodilators and the relatively low side-effect profile.[2–4]

A number of fixed-dose LAMA/LABA combinations are currently available for the treatment of COPD, depending on geographical region: aclidinium bromide/formoterol fumarate;[5] glycopyrrolate/formoterol fumarate;[6] glycopyrronium bromide/indacaterol maleate;[7] tiotropium bromide/olodaterol hydrochloride;[8,9] umeclidinium bromide/vilanterol trifenatate,[10,11] plus single-inhaler triple therapies consisting of a fixed-dose combination of a LAMA, a LABA, and an inhaled corticosteroid (ICS) are also now available.[12,13]

The discovery, development, and pharmacology of LAMA aclidinium bromide (AB), alone or in combination with the LABA, formoterol fumarate (FF), have been reviewed recently.[14] Here,

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we will focus on summarizing the latest clinical evidence supporting the use of AB/FF in the treatment of COPD, particularly in light of the GOLD recommendations.

ACLIFORM COPD and AUGMENT COPD were large pivotal phase III studies that provided a clear demonstration of the efficacy and safety of AB/FF 400/12 μg, a twice-daily (BID) maintenance bronchodilator treatment to relieve symptoms and reduce future risk of exacerbations in adult patients with COPD.[5,15–17] Table 1 contains a summary of the publications reporting the main studies and analyses of AB/FF 400/12 μg, including the population recruited, number of patients enrolled, duration, and study primary endpoint(s). The pivotal studies compared AB/FF 400/12 μg and AB/FF 400/6 μg with placebo, and AB and FF monotherapies in patients with moderate-to-severe COPD, and provided the evidence base for the licensing of the AB/FF 400/12 μg dose.[15,16] A further preplanned, pooled analysis of ACLIFORM and AUGMENT reported the effects of AB/FF 400/12 μg on symptoms of COPD and exacerbations,[17] and several *post hoc* studies provided additional insights into the benefits of AB/FF treatment (Table 1).[18–20] ACTIVATE built upon the results of these studies and investigated the effect of AB/FF on lung hyperinflation, exercise capacity, and physical activity,[21] and AFFIRM COPD provided a direct comparison with the LABA/ICS salmeterol/fluticasone (SAL/FLU) 50/500 μg,[22] a drug combination long used in the treatment of COPD. In addition to the evidence provided by the efficacy studies, the safety and tolerability of AB/FF were examined in the AUGMENT safety extension study,[23] and a long-term, active-control study of AB/FF 400/12 μg *versus* FF 12 μg.[24]

Based on both scientific evidence and expert opinion, the Global initiative for chronic Obstructive Lung Disease (GOLD) program was established in 1998 to provide recommendations on the diagnosis, assessment, treatment, and prevention of COPD.[1] The introduction of the ABCD assessment tool in the 2011 GOLD strategy signaled a change in the traditional spirometry-only-led approach to diagnosis and treatment, and emphasized the importance of symptom burden and exacerbation history in diagnosis and treatment of COPD.[25] The fourth major revision in 2017 was considered a refinement of the ABCD assessment tool.[26] The revised GOLD recommendations aimed for a clearer, more cohesive approach to assessment and treatment of patients with COPD,[25] moving away from treatment driven by degree of airway obstruction and proposed treatment regimens based solely on assessment of symptoms and exacerbation risk.[25] The 1–4 Spirometric Grade remains part of the baseline assessment of COPD,[26] but while forced expiratory volume in 1 s (FEV_1) remains a useful prognostic marker at a population level, it is not a good determinant of therapeutic options.[25] The refined ABCD assessment tool stratifies patients into four phenotypic groups based on exacerbation history and modified Medical Research Council (mMRC) dyspnea scale or COPD Assessment Test (CAT) score, independent of spirometric assessment, and can be summarized as:[1,25,26]

- GOLD group A: low symptom burden, low exacerbation risk;
- GOLD group B: high symptom burden, low exacerbation risk;
- GOLD group C: low symptom burden, high exacerbation risk;
- GOLD group D: high symptom burden, high exacerbation risk.

With respect to maintenance therapy in COPD, the GOLD 2017 major update of the recommendations emphasized the key role of LAMA/LABA therapy, such as AB/FF, in the treatment of COPD and reducing unnecessary ICS use.[26] Furthermore, the latest recommendations advise pharmacologic treatment to be individualized and guided by the severity of symptoms, risk of future exacerbations, side effects, comorbidities, drug availability and cost, and the patient's response, preference, and ability to use various drug delivery devices.[1,25] This emphasis remains in the most recent GOLD 2019 report.[1] To enable effective personalization of treatment, it is important to understand the characteristics and evidence for each therapy.[27] In this article, we provide an update on the latest evidence supporting the efficacy and safety of AB/FF.

Clinical efficacy of aclidinium bromide/formoterol fumarate combination therapy

FEV_1

While GOLD recommendations and clinical practice focus on preventing symptoms and exacerbations, there has previously been a strong focus on the more easily measured lung function parameters.[25] Lung function parameters, such as

Table 1. Summary of AB/FF publications.

Study name (ClinicalTrials.gov identifier)	Authors	Analysis	Population	Patients*	Duration (weeks)	Treatment arms	Primary endpoint(s)
AUGMENT (NCT01437397)	D'Urzo *et al.*[15]	Efficacy and safety of AB/FF	⩾40 years with moderate-to-severe COPD, with no COPD exacerbation within 6 weeks of screening	1668	24	AB/FF 400/12 μg AB/FF 400/6 μg AB 400 μg FF 12 μg Placebo	Change from baseline in 1 h postdose FEV_1 at week 24 (AB/FF *versus* AB) Change from baseline in morning predose (trough) FEV_1 at week 24 (AB/FF *versus* FF)
ACLIFORM (NCT01462942)	Singh *et al.*[16]	Efficacy and safety of AB/FF	⩾40 years with moderate-to-severe COPD, with no COPD exacerbation within 6 weeks of screening	1726	24	AB/FF 400/12 μg AB/FF 400/6 μg AB 400 μg FF 12 μg Placebo	Change from baseline in 1 h morning postdose FEV_1 at week 24 (AB/FF *versus* AB) Change from baseline in morning predose (trough) FEV_1 at week 24 (AB/FF *versus* FF)
AUGMENT & ACLIFORM Pooled (NCT01437397 & NCT01462942)	Bateman *et al.*[17]	Preplanned, pooled data on symptoms and exacerbations for AB/FF	⩾40 years with moderate-to-severe COPD, with no COPD exacerbation within 6 weeks of screening	3394	24	AB/FF 400/12 μg AB/FF 400/6 μg** AB 400 μg FF 12 μg Placebo	As above
	Miravitlles *et al.*[18]	Efficacy of AB/FF stratified by symptom burden: more symptomatic patients' E-RS Total score ⩾ 10 or BDI total score < 7; less symptomatic patients' E-RS Total score < 10 or BDI total score ⩾ 7					
	D'Urzo *et al.*[20]	Lung function outcomes for AB/FF stratified by ICS use					
	Singh *et al.*[19]	Efficacy of AB/FF on first CID and sustained CID events					

(Continued)

Table 1. (Continued)

Study name (ClinicalTrials.gov identifier)	Authors	Analysis	Population	Patients*	Duration (weeks)	Treatment arms	Primary endpoint(s)
1-year safety study (NCT01437540)	Donohue *et al.*[24]	Long-term safety, tolerability, and efficacy of AB/FF	⩾40 years with moderate-to-severe COPD, with no COPD exacerbation within 6 weeks of screening	581	52	AB/FF 400/12 μg FF 12 μg	Long-term safety and tolerability of AB/FF
AFFIRM (NCT01908140)	Vogelmeier *et al.*[22]	Efficacy and safety of AB/FF *versus* LABA/ICS	Symptomatic patients (CAT score ⩾ 10) ⩾40 years with stable, moderate-to-severe COPD, with no COPD exacerbation within 6 weeks of screening	931	24	AB/FF 400/12 μg SAL/FLU 50/500 μg	Maximum FEV_1 from 0 to 3 h after morning dose (peak FEV_1) at week 24 (AB/FF *versus* SAL/FLU)
1-year AUGMENT extension study (NCT01572792)	D'Urzo *et al.*[23]	Long-term efficacy, safety, and tolerability of AB/FF	⩾40 years with moderate-to-severe COPD, with no COPD exacerbation within 6 weeks of screening	918[$] 1669[$$]	52	AB/FF 400/12 μg AB/FF 400/6 μg AB 400 μg FF 12 μg Placebo	Safety of AB/FF over 1 year
ACTIVATE (NCT02424344)	Watz *et al.*[21]	Effect of AB/FF on lung hyperinflation, exercise capacity, and physical activity	⩾40 years with moderate-to-severe COPD, with no COPD exacerbation within 6 weeks of screening	267	8	AB/FF 400/12 μg Placebo	Change from baseline in trough FRC at week 4 (AB/FF *versus* placebo)

*ITT population unless otherwise stated.
**400/6 μg data are not reported in these analyses.
[$]Extension safety population.
[$$]Combined safety population.
AB, aclidinium bromide; BDI, Baseline Dyspnea Index; CAT, COPD Assessment Test; CID, clinically important deterioration; COPD, chronic obstructive pulmonary disease; E-RS, Evaluating-Respiratory Symptoms; FEV_1, forced expiratory volume in 1 s; FF, formoterol fumarate; FLU, fluticasone propionate; FRC, forced residual capacity; ICS, inhaled corticosteroid; ITT, intent to treat; LABA, long-acting β_2 agonist; SAL, salmeterol.

FEV_1, are still considered valuable in predicting outcomes such as mortality and hospitalizations at a population level,[25] and remain an important regulatory endpoint.

A number of studies have shown that treatment with AB/FF improves 1 h postdose FEV_1 from baseline by around 284–299 ml *versus* placebo,[15,16] 82–139 ml *versus* FF,[15,16] and 108–125 ml *versus* AB.[15,16] Treatment with AB/FF led to improvements in trough FEV_1 by approximately 129–209 ml *versus* placebo,[15,16,21] which is greater than the minimal clinically important difference (MCID) of ⩾100 ml,[28] the construct used to determine whether an intervention provides a minimum level of perceived benefit.[29] While it did not quite meet the definition of clinically relevant, AB/FF treatment also led to improvements in trough FEV_1 *versus* FF (45–85 ml).[15,16,24] In the year-long extension study of AUGMENT, AB/FF maintained the improvements in 1 h postdose FEV_1 *versus* placebo and both monotherapies, but not in trough FEV_1.[23]

Compared with SAL/FLU 50/500 μg (a LABA/ICS), AB/FF demonstrated similar improvements in trough FEV_1 and superior improvements in peak FEV_1.[22] Additionally, regardless of concomitant ICS use, postdose FEV_1 and trough FEV_1 significantly improved with AB/FF compared with placebo and FF.[20]

Overall, AB/FF has been shown to provide clinically relevant, sustained improvements in lung function in patients with moderate-to-severe COPD *versus* placebo and monocomponents.

Symptoms

The updated GOLD strategy continues to emphasize the importance of symptom reduction as a priority in the treatment of patients with COPD.[1] Indeed, dyspnea is generally regarded as the cardinal symptom of COPD.[1] In an observational study of over 700 patients, around 59% reported dyspnea of mMRC grade ⩾ 2, which indicated at least a moderate impact of breathlessness on daily activities.[30] Dyspnea can lead patients to become less active, which in turn leads to further deterioration.[31] Consequently, both daytime and night-time dyspnea are considered to be predictive of future mortality risk,[32–34] and may be a better predictor of 5-year survival than lung function.[33] Patients with COPD treated with AB/FF reported a reduced Transition Dyspnea Index (TDI) focal score of approximately 1.32–2.33 units *versus* placebo,[17,23] which was considered clinically relevant (MCID ⩾ 1).[35] AB/FF also reduced TDI by 0.47–0.63 units *versus* FF, and by 0.39–0.44 units *versus* AB, although this did not reach the MCID.[17] In addition, the improvements in dyspnea have been demonstrated as statistically non-inferior to SAL/FLU treatment.[22]

In clinical studies, respiratory symptoms, including dyspnea, can be evaluated using the Evaluating-Respiratory Symptoms (E-RS) in COPD tool (E-RS™ COPD; formerly EXAcerbations of Chronic pulmonary disease Tool (EXACT™)-Respiratory Symptoms), a validated daily diary comprising 11 items (E-RS Total score divided into three domains: Breathlessness, Cough and sputum, and Chest symptoms; E-RS™ is owned by Evidera; permission to use this instrument may be obtained from Evidera [exactpro@evidera.com]).[36] ACLIFORM and AUGMENT showed AB/FF improved E-RS Total score *versus* placebo (−1.2 units) and both monotherapies (both −0.6 units),[17] although the improvements seen in the 52-week AUGMENT extension study (−0.8, −0.2, and −0.1 units for AB/FF *versus* placebo, AB, and FF, respectively) did not reach statistical significance.[23] AB/FF improved E-RS Total score by approximately the same amount as the LABA/ICS SAL/FLU (AB/FF −1.0 units and SAL/FLU −0.9 units).[22]

AB/FF has also demonstrated improvements in both early-morning and night-time symptom overall scores and their individual domain scores (cough, wheezing, shortness of breath, and difficulty bringing up phlegm) *versus* placebo, and early-morning and night-time symptom overall score *versus* both monotherapies.[17]

The body of evidence further supports AB/FF as a beneficial treatment for patients with COPD, particularly for those patients classified in GOLD groups B and D, who experience high levels of dyspnea and symptom burden.[1]

Health-related quality of life

Health-related quality-of-life tools measure the extent to which disease affects the patient's day-to-day life. The St. George's Respiratory Questionnaire (SGRQ) is a 50-item patient-reported outcome

(PRO) measure consisting of three sections (symptoms, activity, and impact) that assesses impaired health and perceived well-being in COPD.[37] AUGMENT found that patients receiving AB/FF reported improvements in SGRQ total score compared with placebo that exceeded the MCID ⩾ 4 units (4.4 units).[15,38] However, due to unexpectedly large improvements observed with placebo, similar improvements observed with AB/FF in ACLIFORM were not statistically significant.[16] During the AUGMENT extension study, AB/FF maintained the significant improvement in SGRQ *versus* placebo to week 38 (3.02 units), which just fell short of the MCID.[23] At the end of the 24-week AFFIRM study, over 52% of patients achieved reductions of ⩾4 units in SGRQ score *versus* baseline,[22] at week 24 of AUGMENT and ACLIFORM, 58.2% and 55.3% of patients achieved the MCID, respectively,[15,16] and at week 52 of the AUGMENT extension study, 57.8% of patients achieved the MCID.[23]

CAT score is a shorter 8-item PRO that also assesses change in health status in patients with COPD.[39] After 24 weeks of treatment in the AFFIRM study, AB/FF led to clinically relevant improvements in change from baseline in CAT score that were similar to those observed with SAL/FLU (reduction of approximately 2.7 and 2.4 units for AB/FF and SAL/FLU, respectively).[22] These improvements were greater than the MCID (⩾2 units).[40]

In summary, the evidence suggests that AB/FF is beneficial in improving quality of life of patients with COPD.

Lung hyperinflation, exercise capacity, and physical activity

Hyperinflation can occur when parenchymal destruction and airway dysfunction (small airway inflammation and potentially increased airway smooth muscle tone) lead to expiratory flow limitation, incomplete lung emptying, and air trapping.[41] Thus, the volume of gas in a patient's lungs is increased compared with their predicted value.[41] Hyperinflation appears to develop early in COPD and seems to be mechanistically linked to exertional dyspnea.[42] Activity-related dyspnea can lead to activity avoidance, physical deconditioning, and reduced quality of life.[41–43] Consequently, GOLD recommends that increased physical activity should be a key component for all patients in the management of COPD.[1]

Prior to the publication of the ACTIVATE study, an 8-week study investigating the effect of AB/FF on lung function, exercise capacity, and physical activity, there was a paucity of data on the effect of AB/FF on hyperinflation.[21] However, encouraging results were seen with AB 400 μg monotherapy in exercise and hyperinflation endpoints, such as exercise endurance time, trough and postdose functional residual capacity (FRC), residual volume (RV) and specific airway conductance (sGaw), and steps/day.[44] In ACTIVATE, AB/FF improved hyperinflation, exercise tolerance, and physical activity *versus* placebo in patients with moderate-to-severe COPD.[21] While AB/FF demonstrated a reduction in the primary endpoint (trough FRC *versus* placebo), this did not reach statistical significance.[21] However, AB/FF did demonstrate significant improvements in predose forced vital capacity and sGaw, and postdose FRC, RV, inspiratory capacity, and sGaw, as well as an increase in exercise endurance time by nearly 1 min and an increase of 731 steps/day compared with placebo at week 4.[21] Additionally, there were fewer patients considered inactive (<6000 steps/day) in the AB/FF treatment arm compared with the placebo treatment arm.[21]

ACTIVATE also showed that patients treated with AB/FF described less difficulty with physical activity compared with placebo, as measured by the Daily PROactive Physical Activity in COPD questionnaire, an electronic, 7-item, daily-recall PRO tool developed to measure physical activity experience (amount and difficulty).[21,45] These improvements provide new insight into the concept of physical activity experience and suggest that increasing physical activity is not an unpleasant, burdensome experience for patients receiving bronchodilator therapy.[21]

ACTIVATE provides evidence that AB/FF pharmacotherapy not only improves hyperinflation, a key cause of activity avoidance and physical deconditioning,[43] but can also aid and support patients to increase their activity levels.

Exacerbations

In patients with COPD, exacerbations lead to increased lung function decline,[46] morbidity, mortality, and poor health status.[47] As such, prevention of exacerbations remains a key goal of COPD treatment in the updated GOLD recommendations.[1,25] As history of exacerbations is currently

the best predictor of future exacerbations,[48] reduction is of particular importance to GOLD groups C and D patients, who report at least two exacerbations (or at least one exacerbation leading to hospitalization) in the last year.[1]

In the AB/FF clinical trial program, exacerbations were additional/exploratory endpoints and were recorded using two different tools: healthcare resource utilization (HCRU) exacerbations, which uses the degree of therapeutic intervention required to treat the event as a means to define severity, and the EXACT, which is a PRO diary designed to count and characterize the frequency, severity, and duration of exacerbations.[49] Depending on the measure used, the pooled analysis of AUGMENT and ACLIFORM showed that AB/FF reduced exacerbation rates *versus* placebo by 22% (any severity) and by around 29% (moderate-to-severe severity),[17] and increased the time to first exacerbation *versus* placebo by 21–28% (any severity) and by around 30% (moderate-to-severe severity).[17] In addition, although reductions in the rate of moderate or severe exacerbations did not reach significance *versus* placebo in the AUGMENT safety extension study,[23] or *versus* FF in the safety study,[24] there was a statistically significant 29% reduction in the risk of exacerbation for AB/FF *versus* placebo.[23] Compared with the LABA/ICS SAL/FLU in the AFFIRM study, patients treated with AB/FF reported similar HCRU and EXACT exacerbation rates (over 24 weeks, 15.8% and 16.6% experienced at least one HCRU exacerbation for AB/FF and SAL/FLU, respectively; and 37.8% and 39.5% experienced at least one EXACT exacerbation for AB/FF and SAL/FLU, respectively).[22] AFFIRM showed in a population not enriched for exacerbations, but also not excluding patients who had previously experienced them, that a LAMA/LABA may be at least as good as LABA/ICS for preventing exacerbations.

Clinically important deterioration

In a *post hoc* pooled analysis of ACLIFORM and AUGMENT, a composite endpoint that measured worsening of the key clinical features of COPD was used to investigate the concept of clinically important deterioration (CID).[19] CID was defined as the occurrence of a moderate/severe exacerbation and/or the worsening from baseline in at least one of the following: FEV_1 $\geqslant$100 ml, TDI focal score $\geqslant$ 1 unit, or SGRQ total score $\geqslant$ 4 units, and was considered sustained if the deterioration was maintained at all subsequent visits, or in the event of any moderate/severe exacerbation.[19] In this pooled analysis, AB/FF significantly reduced the risk of a first CID event *versus* placebo, AB, and FF, and reduced the risk of a sustained CID event *versus* placebo and FF.[19] When considering the individual CID components, AB/FF led to a significant reduction in risk of first and sustained trough FEV_1 CID, TDI CID, and moderate/severe exacerbation CID compared with treatment with placebo.[19] Additionally, there was a significant reduction in the risk of a first SGRQ CID with AB/FF *versus* placebo, FF, and AB, as well as a significant reduction in the risk of a sustained SGRQ CID with AB/FF *versus* placebo.[19]

Overall, this CID analysis concluded that AB/FF appears to provide superior airway stability, and as such, patients experience fewer deteriorations in lung function, health status, dyspnea, and fewer exacerbations compared with placebo or monocomponents.[19]

Symptom status

A further *post hoc* analysis of symptom burden in ACLIFORM and AUGMENT evaluated the efficacy of AB/FF *versus* placebo, AB, and FF in patients defined as less or more symptomatic by both E-RS score $<$10 or $\geqslant$10, and Baseline Dyspnea Index score $\geqslant$7 or $<$7.[18] The analysis found that regardless of symptom burden, AB/FF led to improvements in 1 h postdose FEV_1 *versus* placebo and both monotherapies, and in trough FEV_1 *versus* placebo.[18] In more symptomatic patients, significant improvements in trough FEV_1 were observed compared with both monotherapies, and in less symptomatic patients, significant improvements in trough FEV_1 were observed for AB/FF compared with FF.[18] While improvements in trough FEV_1 *versus* placebo were greater than the MCID in both groups of patients, improvements were between 20–40 ml greater in more symptomatic patients compared with those with fewer symptoms.[18]

Treatment with AB/FF provides improvement in dyspnea compared with placebo, based on TDI focal score, regardless of symptom burden.[18] Patients with greater symptom burden reported improvements in E-RS Total score with AB/FF *versus* placebo and monotherapies, in early-morning symptom severity compared with placebo and

AB, and in night-time symptom severity with AB/FF compared with placebo.[18] In addition, in more symptomatic patients, AB/FF reduced exacerbation rates by 34% *versus* placebo.[18] There was no clear improvement in E-RS Total score, night-time symptom score, or exacerbation rate for patients with fewer COPD symptoms, but patients with fewer symptoms did experience reductions in early-morning symptom overall score with AB/FF *versus* AB and *versus* placebo.[18]

Device handling

The updated GOLD strategy emphasized the importance of patient inhaler preference and proper education on correct device use.[25] This emphasis relates to the relationship between poor symptom control in COPD and unsatisfactory inhaler use,[50] and the role that multiple inhalers,[51] and a lack of education on inhaler technique can play.[50,52]

AB/FF is delivered using the Genuair™/Pressair® inhaler (registered trademarks of the AstraZeneca group of companies; for use within the USA as Pressair® and Genuair™ within all other licensed territories) an easy-to-use, multidose, breath-actuated dry-powder inhaler, with visual and acoustic feedback and safety mechanisms, which does not require inhalation–actuation coordination.[53] To indicate adequate inspiratory flow, an audible click is heard, and once inhalation is complete, the control window turns red.[53] While there has been some concern that patients with poor lung function and/or frailty may be unable to generate adequate inspiratory flow to disperse the dry powder throughout their lungs, data show that patients with moderate-to-severe COPD are able to achieve sufficient inspiratory airflow to inhale the full dose (peak inspiratory flow rate $\geqslant$ 45 l/min).[54] In addition, patient preference and satisfaction have been shown to be higher with Genuair compared with HandiHaler®,[55] Breezhaler®,[56] and Respimat®,[57,58] with the majority of patients rating the Genuair inhaler as 'easy' or 'very easy' to use.[53]

Safety and tolerability of aclidinium bromide/formoterol fumarate

Aclidinium is a rapidly hydrolyzed anticholinergic with a long duration of action and a low, transient systemic exposure.[59–61] Neither aclidinium nor formoterol require dose adjustment for patients with impaired renal or hepatic function.[5,62] Furthermore, AB/FF reported no significant safety or tolerability findings in either of the two pivotal phase III studies,[15,16] ACTIVATE[21] or AFFIRM,[22] and this was maintained over the long term.[23,24] The most common adverse reactions reported by patients receiving AB/FF were nasopharyngitis and headache,[5] which are considered common to all LAMA/LABA combinations.[6–11] Compared with LABA/ICS SAL/FLU in the AFFIRM study, pneumonia was reported in a higher percentage of patients taking SAL/FLU (1.9%) than AB/FF (0.6%), and 2.1% of patients experienced oral/oropharyngeal candidiasis in the SAL/FLU group compared with none in the AB/FF group.[22] The pooled analysis of six phase III studies also showed that there was no increased cardiovascular or cerebrovascular risk with aclidinium bromide *versus* placebo in patients with moderate-to-severe COPD.[63]

Discussion

The major revision of the GOLD recommendations in 2017, and the subsequent updates, created a simpler pathway for clinical management of COPD.[1,26] The 2019 GOLD recommendations more clearly define initial therapy and follow-up treatment, and have introduced biomarker-directed therapy for the first time.[1] Using simple tools that are easily applied in clinical settings, and basing treatment on accurate, comprehensive classification of COPD (symptoms and exacerbation risk separate from lung function), the aim is for a more cohesive, individualized approach to treatment.[1]

Part of this is the increasing emphasis on the role of LAMA/LABA dual-bronchodilator treatment. LAMA/LABA dual therapy is now recommended as initial treatment for group D patients who have a particularly high symptom burden (CAT $>$ 20) in addition to a higher exacerbation risk, and for group B patients with severe breathlessness.[1] Furthermore, if any patients find their response to the initial treatment plan is unsatisfactory, the GOLD guidelines recommend two follow-up treatment pathways based on the predominant treatable trait of the patient's COPD (i.e. dyspnea or exacerbations); LAMA/LABA treatment is a key component of both follow-up pathways.[1] This is a far simpler recommendation than the previous report.

This review has explored the evidence that AB/FF demonstrates a rapid onset of action[15,16,60,64]

and consistent improvements in lung function, symptom management, and exacerbation reduction *versus* placebo and monotherapies, all with no significant safety or tolerability findings,[15–18,21–24] and with potentially few cost implications *versus* monotherapies.[65] This growing evidence base is well matched to the patient needs and treatment options outlined in the updated 2019 GOLD Report. In addition, *post hoc* analysis showed that AB/FF provided lung function benefits *versus* monotherapies regardless of symptom burden[18] or concomitant ICS use.[20] Furthermore, the twice-daily administration of AB/FF may also have the potential for better night-time symptom management and 24 h symptom control for some patients than once-daily therapies, and some patients may prefer the twice-daily regimen.

With the change to the GOLD recommendations, the emphasis on reducing unnecessary ICS use, and the data discussed here showing that AB/FF provides consistent, clinically relevant improvements in lung function, symptoms, quality of life, and exacerbations in patients with COPD without an obviously high risk of exacerbations, it is becoming increasingly clear that fewer patients require an ICS to control their COPD. As recommended by GOLD, initiating LAMA/LABA combination therapy for group D patients with a high symptom burden, in addition to a high exacerbation risk, is a rational approach to treatment in the absence of a specific indication that the patient will respond well to ICS treatment.[1] Identifying biomarkers that would help guide treatment is an important goal. One emerging biomarker for predicting ICS response in COPD is blood eosinophil count, which has become part of the GOLD 2019 treatment recommendations algorithm.[1] Several studies and *post hoc* analyses of other LAMA/LABA combinations and ICS/LAMA/LABA triple combinations have looked at eosinophils as a biomarker to predict the likelihood of a beneficial response to ICS treatment.[66–69] These analyses have yielded some promising results,[66–69] showing a continuous relationship between blood eosinophil counts and ICS response.[70] Although the data appear to be encouraging, the full picture is far from complete,[71] and while data on eosinophil counts in AB/FF trials have yet to be explored, pooling of currently available data may help further elucidate the role of eosinophils as a biomarker to guide treatment decisions in COPD.

As recommended by GOLD, treatment of COPD should be individualized to patients' needs, and should be guided by the severity of symptoms, the risk of exacerbations, the side-effect profile of the treatment, and drug availability and cost.[1,25,26] A systematic review and meta-analysis, together with data from the AFFIRM study, suggest that in patients with stable COPD, LAMA/LABA is at least as efficacious as LABA/ICS but with fewer side effects.[22,72] In general, LAMA/LABA treatment is recommended for any patients whose COPD is not adequately controlled with a single bronchodilator.[1] ICS therapy should therefore be reserved as the initial treatment option for patients who are identified as being likely to have a beneficial response to ICS treatment, and as follow-up treatment for patients requiring further treatment to control exacerbations.[1] For those patients for whom ICS therapy does not appear to be efficacious, other therapies targeting exacerbation reduction should be considered. Currently, research is continuing to investigate ways to identify which patients with COPD are most likely to respond well to LABA/ICS treatment.[73]

In light of the current GOLD recommendations and the phase III and IV studies that have demonstrated consistent lung function improvements, reductions in dyspnea, early-morning and night-time symptoms, and quality-of-life scores with AB/FF *versus* placebo and monotherapies, AB/FF 400/12 μg BID should be considered an effective treatment option for patients with moderate-to-severe COPD.

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References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.6-FINAL-08Nov2018-wms.pdf (2019, accessed 3 December 2018).
2. Cazzola M and Molimard M. The scientific rationale for combining long-acting beta2-agonists and muscarinic antagonists in COPD. *Pulm Pharmacol Ther* 2010; 23: 257–267.
3. Montuschi P, Macagno F, Valente S, *et al.* Inhaled muscarinic acetylcholine receptor antagonists for treatment of COPD. *Curr Med Chem* 2012; 20: 1464–1476.
4. Montuschi P and Ciabattoni G. Bronchodilating drugs for chronic obstructive pulmonary disease: current status and future trends. *J Med Chem* 2015; 58: 4131–4164.
5. AstraZeneca PLC. Duaklir® Genuair™ summary of product characteristics. http://www.medicines.org.uk/emc/medicine/29652 (2018, accessed 22 June 2018).
6. AstraZeneca PLC. Bevespi® Aerosphere®. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208294s000lbl.pdf (2016, accessed 10 November 2017).
7. Novartis International AG. Ultibro® Breezhaler® summary of product characteristics. http://www.medicines.org.uk/emc/medicine/29533 (2015, accessed 18 August 2016).
8. Boehringer Ingelheim GmbH. Spiolto® Respimat® summary of product characteristics. https://www.medicines.org.uk/emc/medicine/30495 (2015, accessed 18 August 2016).
9. Boehringer Ingelheim GmbH. Stiolto™ Respimat®. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206756Orig1s000lbl.pdf (2015, accessed 14 November 2017).
10. GlaxoSmithKline PLC. Anoro® Ellipta® summary of product characteristics. https://www.medicines.org.uk/emc/medicine/28949/ (2015, accessed 18 August 2016).
11. GlaxoSmithKline PLC. Anoro® Ellipta®. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203975s000lbl.pdf (2013, accessed 28 January 2015).
12. GlaxoSmithKline PLC. Trelegy® Ellipta®. https://www.medicines.org.uk/emc/product/8666 (2017, accessed 2 January 2019).
13. Chiesi Limited. Trimbow®. https://www.medicines.org.uk/emc/product/761 (2017, accessed 2 January 2019).
14. Malerba M, Radaeli A, Santini G, *et al.* The discovery and development of aclidinium

bromide for the treatment of chronic obstructive pulmonary disease. *Expert Opin Drug Discov* 2018; 13: 563–577.

15. D'Urzo AD, Rennard SI, Kerwin EM, *et al*. Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study. *Respir Res* 2014; 15: 123.
16. Singh D, Jones PW, Bateman ED, *et al*. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. *BMC Pulm Med* 2014; 14: 178.
17. Bateman ED, Chapman KR, Singh D, *et al*. Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomised studies (ACLIFORM and AUGMENT). *Respir Res* 2015; 16: 92.
18. Miravitlles M, Chapman KR, Chuecos F, *et al*. The efficacy of aclidinium/formoterol on lung function and symptoms in patients with COPD categorized by symptom status: a pooled analysis. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 2041–2053.
19. Singh D, D'Urzo AD, Chuecos F, *et al*. Reduction in clinically important deterioration in chronic obstructive pulmonary disease with aclidinium/formoterol. *Respir Res* 2017; 18: 106.
20. D'Urzo A, Singh D and Garcia Gil E. Use of concomitant inhaled corticosteroids: pooled data from two phase III studies of aclidinium plus formoterol in COPD. *NPJ Prim Care Respir Med* 2017; 27: 13.
21. Watz H, Troosters T, Beeh KM, *et al*. ACTIVATE: the effect of aclidinium/formoterol on hyperinflation, exercise capacity, and physical activity in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 2545–2558.
22. Vogelmeier C, Paggiaro PL, Dorca J, *et al*. Efficacy and safety of aclidinium/formoterol versus salmeterol/fluticasone: a phase 3 COPD study. *Eur Respir J* 2016; 48: 1030–1039.
23. D'Urzo A, Rennard S, Kerwin E, *et al*. A randomised double-blind, placebo-controlled, long-term extension study of the efficacy, safety and tolerability of fixed-dose combinations of aclidinium/formoterol or monotherapy in the treatment of chronic obstructive pulmonary disease. *Respir Med* 2017; 125: 39–48.
24. Donohue JF, Soong W, Wu X, *et al*. Long-term safety of aclidinium bromide/formoterol fumarate fixed-dose combination: results of a randomized 1-year trial in patients with COPD. *Respir Med* 2016; 116: 41–48.
25. Vogelmeier CF, Criner GJ, Martinez FJ, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. *Eur Respir J* 2017; 49: 1700214.
26. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/ (2017, accessed 3 January 2017).
27. Montuschi P, Malerba M, Santini G, *et al*. Pharmacological treatment of chronic obstructive pulmonary disease: from evidence-based medicine to phenotyping. *Drug Discov Today* 2014; 19: 1928–1935.
28. Donohue JF. Minimal clinically important differences in COPD lung function. *COPD* 2005; 2: 111–124.
29. Jones PW, Beeh KM, Chapman KR, *et al*. Minimal clinically important differences in pharmacological trials. *Am J Respir Crit Care Med* 2014; 189: 250–255.
30. Miravitlles M, Worth H, Soler Cataluña JJ, *et al*. Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. *Respir Res* 2014; 15: 122.
31. Reardon JZ, Lareau SC and ZuWallack R. Functional status and quality of life in chronic obstructive pulmonary disease. *Am J Med* 2006; 119: 32–37.
32. Esteban C, Quintana JM, Aburto M, *et al*. Predictors of mortality in patients with stable COPD. *J Gen Intern Med* 2008; 23: 1829–1834.
33. Nishimura K, Izumi T, Tsukino M, *et al*. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002; 121: 1434–1440.
34. Lange P, Marott JL, Vestbo J, *et al*. Prevalence of night-time dyspnoea in COPD and its implications for prognosis. *Eur Respir J* 2014; 43: 1590–1598.
35. Mahler DA and Witek TJ Jr. The MCID of the transition dyspnea index is a total score of one unit. *COPD* 2005; 2: 99–103.

36. Leidy NK, Sexton CC, Jones PW, *et al.* Measuring respiratory symptoms in clinical trials of COPD: reliability and validity of a daily diary. *Thorax* 2014; 69: 443–449.

37. Jones PW, Quirk FH and Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med* 1991; 85(Suppl. B): 25–31.

38. Jones PW. St George's Respiratory Questionnaire: MCID. *COPD* 2005; 2: 75–79.

39. Jones PW, Harding G, Berry P, *et al.* Development and first validation of the COPD assessment test. *Eur Respir J* 2009; 34: 648–654.

40. Kon SSC, Canavan JL, Jones SE, *et al.* Minimum clinically important difference for the COPD assessment test: a prospective analysis. *Lancet Respir Med* 2014; 2: 195–203.

41. O'Donnell DE and Laveneziana P. The clinical importance of dynamic lung hyperinflation in COPD. *COPD* 2006; 3: 219–232.

42. Rossi A, Aisanov Z, Avdeev S, *et al.* Mechanisms, assessment and therapeutic implications of lung hyperinflation in COPD. *Respir Med* 2015; 109: 785–802.

43. Thomas M, Decramer M and O'Donnell DE. No room to breathe: the importance of lung hyperinflation in COPD. *Prim Care Respir J* 2013; 22: 101–111.

44. Beeh KM, Watz H, Puente-Maestu L, *et al.* Aclidinium improves exercise endurance, dyspnea, lung hyperinflation, and physical activity in patients with COPD: a randomized, placebo-controlled, crossover trial. *BMC Pulm Med* 2014; 14: 209.

45. Gimeno-Santos E, Raste Y, Demeyer H, *et al.* The PROactive instruments to measure physical activity in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2015; 46: 988–1000.

46. Donaldson GC, Seemungal TA, Bhowmik A, *et al.* Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57: 847–852.

47. Seemungal TA, Donaldson GC, Paul EA, *et al.* Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1418–1422.

48. Hurst JR, Vestbo J, Anzueto A, *et al.* Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; 363: 1128–1138.

49. Leidy NK, Wilcox TK, Jones PW, *et al.* Development of the EXAcerbations of Chronic obstructive pulmonary disease Tool (EXACT): a patient-reported outcome (PRO) measure. *Value Health* 2010; 13: 965–975.

50. Melani AS, Bonavia M, Cilenti V, *et al.* Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med* 2011; 105: 930–938.

51. Yu AP, Guérin A, De Leon DP, *et al.* Clinical and economic outcomes of multiple versus single long-acting inhalers in COPD. *Respir Med* 2011; 105: 1861–1871.

52. Lewis A, Torvinen S, Dekhuijzen PN, *et al.* The economic burden of asthma and chronic obstructive pulmonary disease and the impact of poor inhalation technique with commonly prescribed dry powder inhalers in three European countries. *BMC Health Serv Res* 2016; 16: 251.

53. Chrystyn H and Niederlaender C. The Genuair® inhaler: a novel, multidose dry powder inhaler. *Int J Clin Pract* 2012; 66: 309–317.

54. Magnussen H, Watz H, Zimmermann I, *et al.* Peak inspiratory flow through the Genuair® inhaler in patients with moderate or severe COPD. *Respir Med* 2009; 103: 1832–1837.

55. van der Palen J, Ginko T, Kroker A, *et al.* Preference, satisfaction and errors with two dry powder inhalers in patients with COPD. *Expert Opin Drug Deliv* 2013; 10: 1023–1031.

56. Pascual S, Feimer J, De SA, *et al.* Preference, satisfaction and critical errors with Genuair and Breezhaler inhalers in patients with COPD: a randomised, cross-over, multicentre study. *NPJ Prim Care Respir Med* 2015; 25: 15018.

57. Ohbayashi H, Kudo S and Ishikawa M. Inhaler operability and patient satisfaction regarding Genuair and Respimat inhalers for chronic obstructive pulmonary disease: a randomized crossover study. *Pulm Ther* 2017; 3: 173–185.

58. Dal Negro RW and Povero M. Acceptability and preference of three inhalation devices assessed by the Handling Questionnaire in asthma and COPD patients. *Multidiscip Respir Med* 2015; 11: 7.

59. Sentellas S, Ramos I, Albertí J, *et al.* Aclidinium bromide, a new, long-acting, inhaled muscarinic antagonist: in vitro plasma inactivation and pharmacological activity of its main metabolites. *Eur J Pharm Sci* 2010; 39: 283–290.

60. Gavaldà A, Miralpeix M, Ramos I, *et al.* Characterization of aclidinium bromide, a novel inhaled muscarinic antagonist, with long duration of action and a favorable pharmacological profile. *J Pharmacol Exp Ther* 2009; 331: 740–751.

61. Prat M, Fernández D, Buil MA, *et al*. Discovery of novel quaternary ammonium derivatives of (3R)-quinuclidinol esters as potent and long-acting muscarinic antagonists with potential for minimal systemic exposure after inhaled administration: identification of (3R)-3-{[hydroxy(di-2-thienyl)acetyl]oxy}-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2 .2]octane bromide (aclidinium bromide). *J Med Chem* 2009; 52: 5076–5092.
62. Schmid K, Pascual S, Garcia Gil E, *et al*. Pharmacokinetics and safety of aclidinium bromide, a muscarinic antagonist, in adults with normal or impaired renal function: a phase I, open-label, single-dose clinical trial. *Clin Ther* 2010; 32: 1798–1812.
63. Chapman KR, Beck E, Alcaide D, *et al*. Overall and cardiovascular safety of aclidinium bromide in patients with COPD: a pooled analysis of six phase III, placebo-controlled, randomized studies. *Chronic Obstr Pulm Dis* 2015; 3: 435–445.
64. Cheer SM and Scott LJ. Formoterol: a review of its use in chronic obstructive pulmonary disease. *Am J Respir Med* 2002; 1: 285–300.
65. Ramos M, Haughney J, Henry N, *et al*. Cost versus utility of aclidinium bromide 400 μg plus formoterol fumarate dihydrate 12 μg compared to aclidinium bromide 400 μg alone in the management of moderate-to-severe COPD. *Clinicoecon Outcomes Res* 2016; 8: 445–456.
66. Roche N, Chapman KR, Vogelmeier CF, *et al*. Blood eosinophils and response to maintenance chronic obstructive pulmonary disease treatment. Data from the FLAME trial. *Am J Respir Crit Care Med* 2017; 195: 1189–1197.
67. Lipson DA, Barnhart F, Brealey N, *et al*. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med* 2018; 378: 1671–1680.
68. Watz H, Tetzlaff K, Wouters EF, *et al*. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir Med* 2016; 4: 390–398.
69. Wedzicha JA, Price D, Mezzi K, *et al*. QVA149 compared with salmeterol/fluticasone (SFC) on exacerbations and its correlation with baseline blood eosinophils: a pooled analysis of LANTERN and ILLUMINATE. *Eur Respir J* 2015; 46: PA1005; DOI: 10.1183/13993003.congress-2015.PA1005
70. Brusselle G, Pavord ID, Landis S, *et al*. Blood eosinophil levels as a biomarker in COPD. *Respir Med* 2018; 138: 21–31.
71. Singh D. Predicting corticosteroid response in chronic obstructive pulmonary disease. Blood eosinophils gain momentum. *Am J Respir Crit Care Med* 2017; 196: 1098–1100.
72. Rodrigo GJ, Price D, Anzueto A, *et al*. LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 907–922.
73. Montuschi P, Malerba M, Macis G, *et al*. Triple inhaled therapy for chronic obstructive pulmonary disease. *Drug Discov Today* 2016; 21: 1820–1827.
74. Battisti WP, Wager E, Baltzer L, *et al*. Good publication practice for communicating company-sponsored medical research: GPP3. *Ann Intern Med* 2015;163: 461–464.

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