

A twice-daily, fixed-dose combination of acclidinium bromide and formoterol fumarate for the treatment of COPD

Inhaled long-acting β_2 -agonists or long-acting muscarinic antagonists monotherapies are recommended as the first choice of treatment for patients with symptomatic chronic obstructive pulmonary disease. The different but complementary modes of action of these treatments make them suited for use in a fixed-dose combination. Acclidinium bromide 400 μg (a long-acting muscarinic antagonist) twice daily improves patient lung function and health status and reduces breathlessness compared with placebo, and is well tolerated. Combining these effects with the rapid onset of action of formoterol fumarate 12 μg in a twice-daily treatment may provide 24-h relief from chronic obstructive pulmonary disease symptoms. This review discusses the acclidinium/formoterol 400/12 μg combination clinical trial data to date.

Keywords: acclidinium bromide • bronchodilation • combination • COPD • formoterol fumarate • symptoms

Combining long-acting bronchodilators with complementary mechanisms of action to treat patients with chronic obstructive pulmonary disease (COPD) has the potential to improve lung function and symptom management compared with monotherapy treatment [1]. There are currently two classes of long-acting bronchodilators: long-acting β_2 -agonists (LABAs) and long-acting muscarinic antagonists (LAMAs). LABAs are thought to primarily act on prejunctional β_2 -adrenoreceptors to induce G protein-coupled change in intracellular messenger systems and to directly trigger airway smooth muscle relaxation and bronchodilation [2,3]. LAMAs block the muscarinic receptors targeted by acetylcholine, thereby reducing acetylcholine binding and amplifying the bronchodilation induced by the LABA [3].

Studies combining LABAs and LAMAs using a free combination with separate inhalers have demonstrated improved bronchodilation and reduced rescue medication use in patients with COPD compared with monotherapy [4–7]. A dual bronchodilator combination therapy administered using one

inhaler could add further benefit by simplifying treatment regimens, which may improve patient adherence and thereby ultimately reduce healthcare costs [8–10]. Indeed, three fixed-dose combinations of a LABA and LAMA, one administered twice daily, and two administered once daily, have already been approved for use in patients with COPD (twice-daily acclidinium/formoterol [Duaklir[®] Genuair[™]/Pressair^{®a}] [11], once-daily indacaterol/glycopyrronium [Ultibro[®] Breezhaler[®]] [12] and once-daily umeclidinium/vilanterol [Anoro[®] Ellipta[®]] [13,14]), and treatment with a LABA/LAMA combination is now recommended as an alternative choice for patients with moderate to severe COPD [1]. Factors that will impact on the decision to use an alternative treatment may include disease severity, frequency of exacerbations and treatment costs.

Acclidinium bromide

In two randomized studies, monotherapy treatment with the LAMA, acclidinium bromide 400 μg twice daily, provided clinically meaningful improvements in key COPD end

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points, such as lung function (forced expiratory volume in 1 s [FEV₁]), versus tiotropium and placebo, while being well tolerated. [15,16] Other studies have shown significant improvements in lung function end points versus placebo [17–20]. Treatment with acclidinium has also been found to improve health status, exercise endurance and night-time symptoms in patients with COPD [20–22]. Acclidinium bromide 400 µg twice daily was approved for maintenance treatment of COPD in the USA in July 2012 and in the EU in September 2012 [23,24].

Formoterol fumarate

Formoterol fumarate is a well-established LABA that has been used to treat COPD for a number of years [2,25]. It has been shown to improve lung function, COPD symptoms, health-related quality of life and exacerbations while having an acceptable safety profile [2,25]. Moreover, it has a rapid onset of action (1–3 min) with a sustained effect of approximately 12 h that makes it particularly attractive for use in combination therapy [26,27].

Acclidinium/formoterol 400/12 µg combination

Following the completion of two successful Phase III trials [27,28], dual bronchodilation with acclidinium bromide 400 µg/formoterol fumarate 12 µg has recently been approved as a maintenance treatment to relieve symptoms in adult patients with COPD [11]. It has a twice-daily dosing regimen and is delivered via a multidose dry powder inhaler device named Genuair™/Pressair®a [3,29,30].

The purpose of this review is to summarize and discuss the published data from studies of the acclidinium/formoterol combination with a focus on clinical trial data.

Pharmacokinetic data

Studies assessing the pharmacokinetic profile of the acclidinium/formoterol 400/12 µg combination concluded that the monotherapies were combinable [31], and terminal elimination half-lives ($t_{1/2}$) for acclidinium and formoterol have been shown to be approximately 5 and 8 h, respectively [31].

Clinical trials

Two pivotal Phase III studies have been conducted, comparing the approved acclidinium/formoterol 400/12 µg dose with acclidinium 400 µg monotherapy, formoterol 12 µg monotherapy and placebo: ACLidinium bromide/FORMoterol fumarate in the treatment of moderate-to-severe COPD (ACLIFORM; NCT01437397) (Figure 1A) [28] and Acclidinium/formoterol fuma-

rate combination for investiGative use in the treatment of moderate-to-severe COPD (AUGMENT; NCT01437397) (Figure 1B) [27]. These were 24-week, randomized, double-blind, parallel-group studies that recruited 1729 (ACLIFORM) and 1692 (AUGMENT) patients. Inclusion and exclusion criteria were identical in both studies and they shared the same coprimary end points of change from baseline to week 24 in 1-h morning postdose FEV₁ versus acclidinium and change from baseline to week 24 in morning predose (trough) FEV₁ versus formoterol [27,28]. A 28-week extension to AUGMENT, examining long-term efficacy and safety, included 921 patients from the core study [32].

The two core studies comprised 3398 patients in total and the patient demographics were comparable with the general COPD population; most were male Caucasians in their early 60s with COPD of moderate severity [27,28].

Lung function

In both studies, 1-h morning postdose FEV₁ changes were significantly greater with the acclidinium/formoterol 400/12 µg combination at all time points versus acclidinium and placebo (Figure 2A & B). Similarly, trough FEV₁ changes were significantly greater with acclidinium/formoterol 400/12 µg versus formoterol and placebo at all time points (Figure 2C & D). In addition, the acclidinium/formoterol 400/12 µg combination was numerically better than acclidinium for trough FEV₁ (Figure 2C & D), although this did not reach statistical significance. Improvements versus placebo were maintained for up to 52 weeks in the AUGMENT extension [32].

COPD symptoms

The acclidinium/formoterol 400/12 µg combination resulted in clinically and statistically significant improvements in transition dyspnea index (TDI) focal score versus placebo at week 24 in both ACLIFORM and AUGMENT (Figure 3) [27,28]. Witek and Mahler [33] defined the minimum clinically important difference for TDI focal score as a ≥1-unit change versus baseline and this was achieved throughout AUGMENT for the acclidinium/formoterol combination [32]. Similarly, in the AUGMENT extension study, acclidinium/formoterol 400/12 µg significantly improved TDI focal score from baseline at all visits versus placebo [32]. In the individual studies, while treatment with acclidinium/formoterol resulted in numerically greater improvements in TDI focal scores compared with either monotherapy, improvements were not statistically significant. This indicates that combining acclidinium with formoterol may not be entirely additive. Indeed, it would suggest that there is

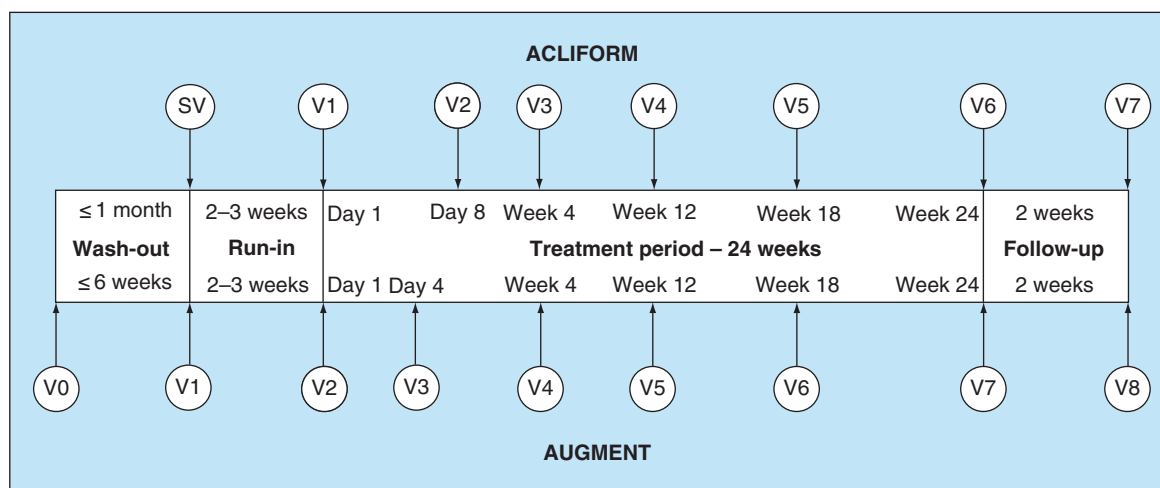


Figure 1. Study design for the two pivotal Phase III studies of acclidinium/formoterol fixed-dose combination twice daily, ACLIFORM and AUGMENT.

SV: Screening visit; V: Visit.

some overlap in function and one possible explanation could be the difference in the timing of the effects of the component drugs, in other words, the rapid effect of formoterol [2,30,34] quickly reduces breathlessness and, as the effect of this drug diminishes, the slower onset but sustained effect of acclidinium maintains the reduced level of breathlessness [19,20].

Both ACLIFORM and AUGMENT showed statistically significant improvements in overall EXAcerbations of Chronic pulmonary disease Tool (EXACT)-respiratory symptoms scores with acclidinium/formoterol 400/12 µg compared with placebo [27,28]. In ACLIFORM, acclidinium/formoterol 400/12 µg also demonstrated improvements in change from baseline in night-time symptoms (as measured by the night-time symptoms of COPD Instrument score) and early-morning symptoms (as measured by early morning symptoms COPD instrument score), although not all comparisons reached statistical significance [28]. In AUGMENT, treatment with the acclidinium/formoterol combination resulted in significant improvements in overall night-time symptom severity versus placebo at all time points, versus acclidinium at weeks 4, 12 and 18, and versus formoterol at weeks 4 and 18 [27]. Furthermore, overall early-morning COPD symptom severity was significantly improved for acclidinium/formoterol 400/12 µg compared with placebo and acclidinium at all time points, but only at weeks 12 and 18 compared with formoterol [27].

Taken together, the combined results from the early morning symptoms COPD instrument and night-time symptoms of COPD instrument questionnaires suggest that twice-daily treatment with acclidinium/formoterol 400/12 µg has the potential to provide 24-h control

of symptoms. It has been suggested that improving 24-h symptoms may improve lung function, quality of life and exacerbation frequency, while reducing the emergence of cardiovascular disease, cognitive effects, depression and mortality [35].

Health status

The St. George's Respiratory Questionnaire (SGRQ) is designed to measure health status in patients with asthma and COPD and has been shown to correlate with symptoms such as breathlessness more closely than lung function tests [36,37]. Improvements from baseline were observed in SGRQ total score for ACLIFORM, but the difference versus placebo was not statistically significant. This was thought to be the result of a large and mostly unexplained placebo response. In contrast, in AUGMENT, improvements in SGRQ total score exceeded the minimum clinically important difference of four units, as defined by Jones *et al.* [38], for the acclidinium/formoterol combination and acclidinium alone compared with placebo [27].

Exacerbations

Exacerbations can be identified either by increased clinical visits and treatments ('reported' exacerbations, identified by investigator/physician intervention through healthcare resource utilization [HCRU]), or by increases in patient-recorded symptoms ('unreported' exacerbations, identified from patient-recorded symptom diaries using the EXACT). Measuring both HCRU exacerbations and EXACT events ensures both reported and unreported exacerbations are captured and a more complete understanding of exacerbation rate is obtained. In a prespecified pooled

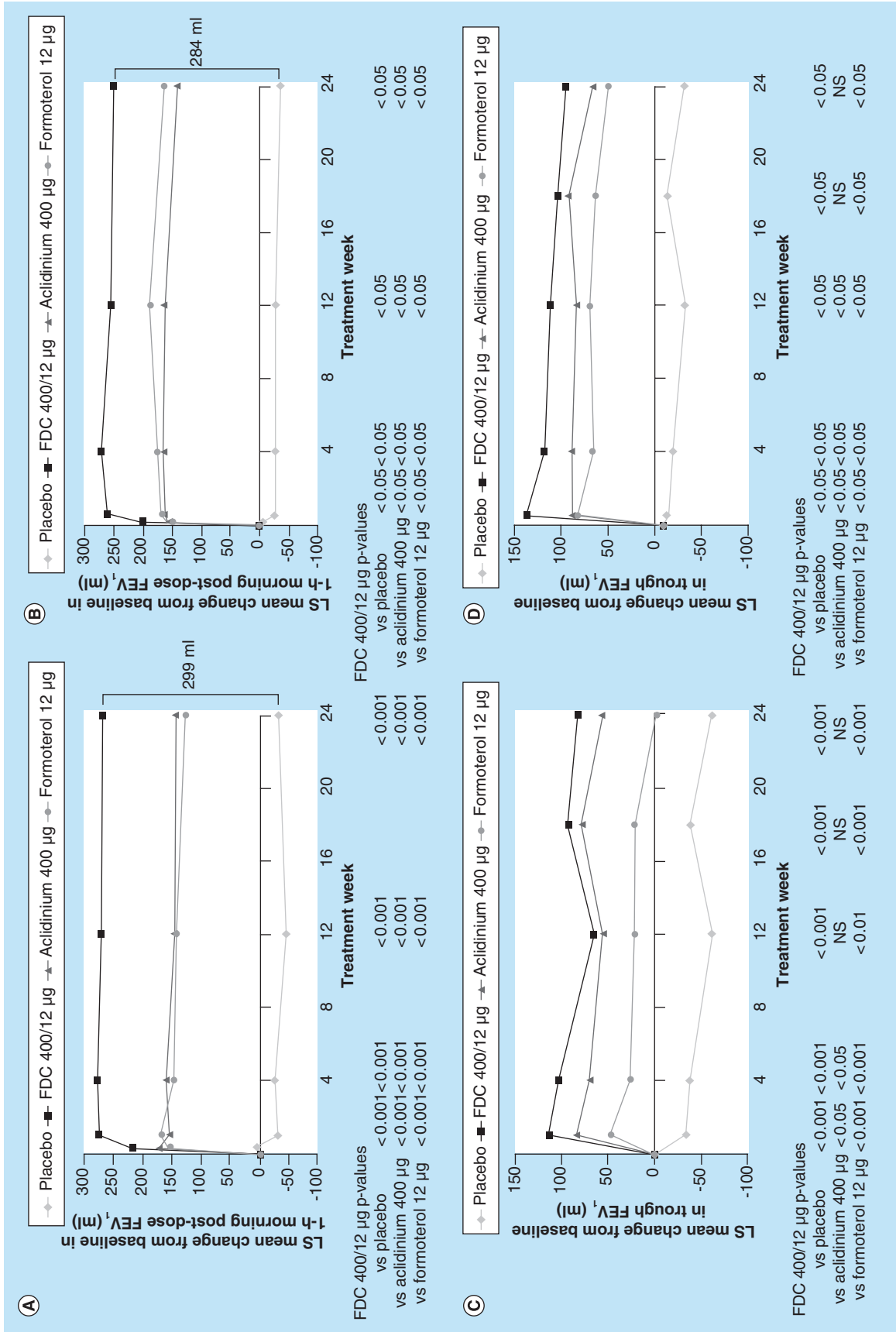


Figure 2. Changes from baseline in bronchodilation over time. LS mean changes from baseline in 1-h morning postdose FEV₁ over time in (A) ACLIFORM, and (B) AUGMENT, and morning predose (trough) FEV₁ over time in (C) ACLIFORM and (D) AUGMENT [27,28]. Data are presented as least squares means for the intent-to-treat population. FDC: Acclidinium/formoterol fixed-dose combination; FEV₁: Forced expiratory volume in 1 s; LS: Least squares; NS: Not significant. Adapted with permission from Singh et al. *BMC Pulm. Med.* 14, 178 (2014) and D'Urzo et al. *Respir. Res.* 15, 123 (2014), both published by BioMed Central [27,28].

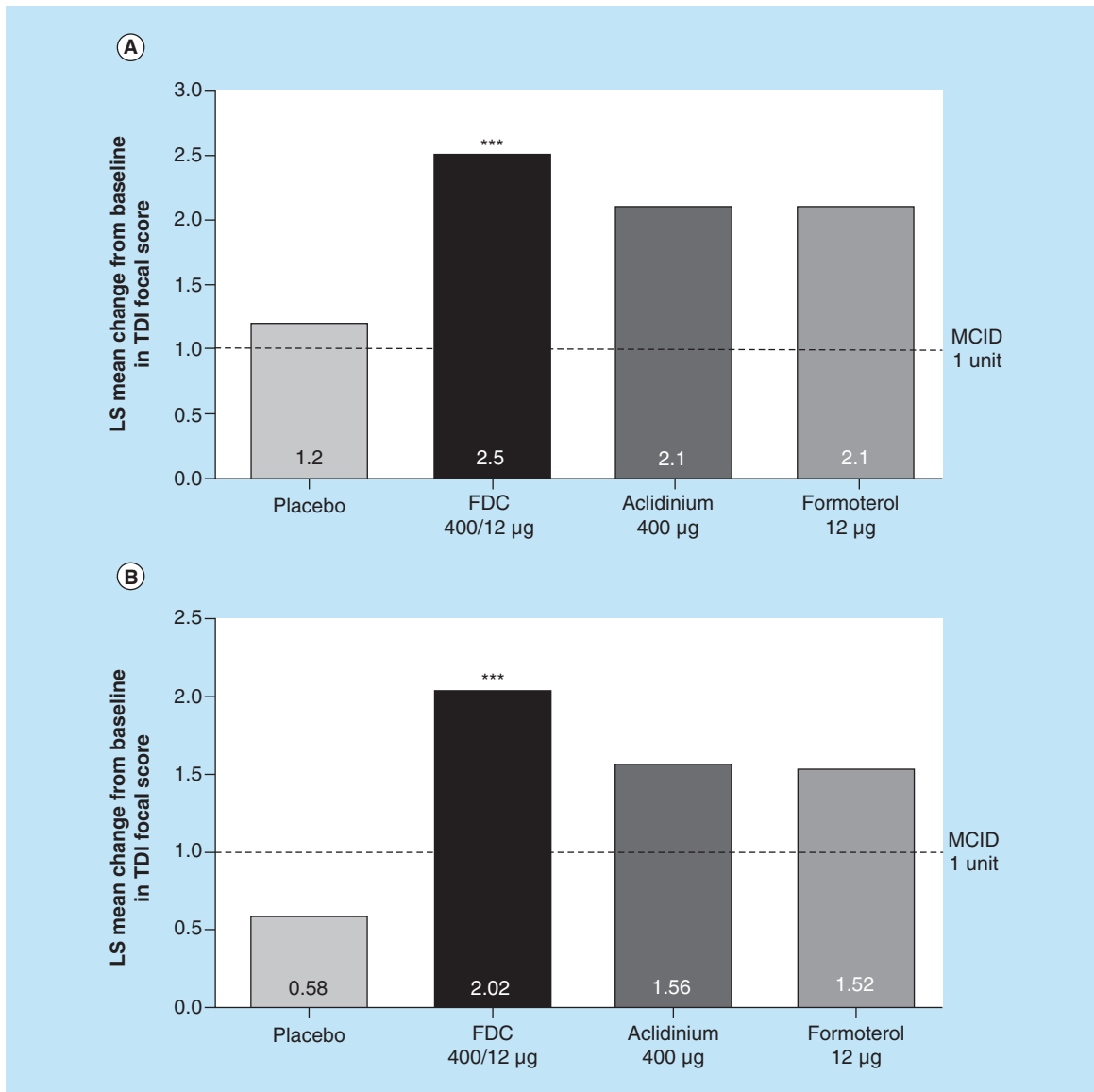


Figure 3. Improvement in transition dyspnea index focal score at 24 weeks. Improvement in TDI focal score at 24 weeks (ITT population) in (A) ACLIFORM and (B) AUGMENT [27,28]. Data are presented as least squares means for the intent-to-treat population *** $p \leq 0.001$ versus placebo.

FDC: Acclidinium/formoterol fixed-dose combination; FEV₁: Forced expiratory volume in 1 s; MCID: Minimum clinically important difference; TDI: Transition dyspnea index; LS: Least squares.

Adapted with permission from Singh *et al. BMC Pulm Med.* 14, 178 (2014) and D'Urzo *et al. Respir Res.* 15, 123 (2014), both published by BioMed Central [27,28].

analysis of ACLIFORM and AUGMENT, the rate of moderate-to-severe HCRU exacerbations was low in all treatment arms. This may reflect the absence of any requirement for patients to have experienced prior exacerbation in each of the study protocols. Despite this, in a pooled analysis of ACLIFORM and AUGMENT, acclidinium/formoterol 400/12 µg significantly reduced moderate-to-severe HCRU exacerbations by 29% compared with placebo [39]. In addition, there was a 22% reduction in EXACT events compared with placebo [39].

Safety & tolerability

The pooled analysis of ACLIFORM and AUGMENT showed that adverse event (AE) frequency was comparable across groups (Table 1) [40]. The most common AEs reported were COPD exacerbation, nasopharyngitis and headache, and these occurred at similar rates across treatment groups and placebo [40]. Of these, headache is a known potential consequence of treatment with a β_2 -adrenergic agent, in other words, a LABA; others include cough, muscle spasms and hypertension [40]. Similarly, treatment with a LAMA

Table 1. Number (%) of patients with adverse events occurring in $\geq 3\%$ of patients in any acclidinium/formoterol fixed-dose combination treatment group (by preferred term; pooled placebo-controlled population) and major adverse cardiac event, cardiovascular, and cerebrovascular adverse events of special interest pooled from ACLIFORM and AUGMENT[†].

n, (%)	Placebo BID (n = 526)	FDC 400/12 μg BID (n = 720)	Acclidinium 400 μg BID (n = 722)	Formoterol 12 μg BID (n = 716)
AEs occurring in $\geq 3\%$ of patients:				
– Greater than or equal to 1 AE [‡]	327 (62.2)	449 (62.4)	452 (62.6)	470 (65.6)
– COPD exacerbation [§]	109 (20.7)	123 (17.1)	142 (19.7)	154 (21.5)
– Nasopharyngitis	33 (6.3)	57 (7.9)	50 (6.9)	58 (8.1)
– Headache	29 (5.5)	49 (6.8)	50 (6.9)	56 (7.8)
– Back pain	23 (4.4)	32 (4.4)	29 (4.0)	34 (4.7)
– UTI	19 (3.6)	30 (4.2)	22 (3.0)	21 (2.9)
– Cough	17 (3.2)	25 (3.5)	23 (3.2)	18 (2.5)
– URTI	15 (2.9)	23 (3.2)	27 (3.7)	26 (3.6)
– Sinusitis	13 (2.5)	16 (2.2)	19 (2.6)	14 (2.0)
– Nausea	12 (2.3)	13 (1.8)	22 (3.0)	16 (2.2)
MACE:				
– Any MACE	4 (0.8)	6 (0.8)	5 (0.7)	7 (1.0)
– CV death	1 (0.2)	2 (0.3)	1 (0.1)	2 (0.3)
– Nonfatal MI	1 (0.2)	4 (0.6)	2 (0.3)	4 (0.6)
– Nonfatal stroke	2 (0.4)	0	2 (0.3)	1 (0.1)
CV events of special interest by SMQ:				
– Any cardiac disorder [¶]	29 (5.5)	31 (4.3)	42 (5.8)	34 (4.7)
– Ischemic heart disease	10 (1.9)	5 (0.7)	10 (1.4)	7 (1.0)
– MI	2 (0.4)	4 (0.6)	5 (0.7)	4 (0.6)
– Other ischemic heart disease	8 (1.5)	2 (0.3)	6 (0.8)	4 (0.6)
– Tachyarrhythmias [#]	10 (1.9)	19 (2.6)	21 (2.9)	15 (2.1)
– Cardiac failure	2 (0.4)	1 (0.1)	5 (0.7)	4 (0.6)
– Bradycardia	1 (0.2)	0	4 (0.6)	0
– Conduction defects	3 (0.6)	11 (1.5)	8 (1.1)	12 (1.7)
CBV events:				
– Any event	3 (0.6)	2 (0.3)	4 (0.6)	1 (0.1)

[†]Data taken from [40,42].
[‡]AEs occurring after the first dose of treatment and up to 30 days following the last dose.
[§]Listed as 'COPD' as a preferred term.
[¶]Includes heart rate increase (data are treatment-emergent AEs by system organ class).
[#]Includes the following preferred terms: tachycardia, heart rate increase and palpitation.
 AE: Adverse event; BID: Twice daily; CBV: Cerebrovascular; COPD: Chronic obstructive pulmonary disease; CV: Cardiovascular; FDC: Acclidinium/formoterol fixed-dose combination; MACE: Major adverse cardiac event; MI: Myocardial infarction; SMQ: Standardized MedDRA queries; URTI: Upper respiratory tract infection; UTI: Urinary tract infection.

can be associated with anticholinergic-related side effects, such as oropharyngeal pain and dry mouth [40]. In ACLIFORM, AEs associated with anticholinergic or β_2 -adrenergic activity generally occurred in less than 3% of patients in any treatment group [28]. Similarly, in AUGMENT, only urinary tract infection, which was listed in this study as both an anticholinergic and β_2 -adrenergic event, occurred in more

than 2% of patients in any treatment group [27]. In the AUGMENT extension study, acclidinium/formoterol 400/12 μg was well tolerated for up to 1 year and demonstrated a similar safety profile to both monotherapies and placebo [41]. Overall, no additive safety effect was observed when combining the two monotherapies [42]. For special populations, such as renally or hepatically impaired patients, since no dosage adjust-

ments are needed for either acclidinium or formoterol monotherapies, no dosage adjustment is warranted for the acclidinium/formoterol combination [31].

There has been an ongoing debate as to whether or not LAMAs are associated with cardiovascular (CV) AEs [43] and one meta-analysis found CV concerns related to tiotropium use, in particular [44]; however, this was not seen in a 4-year trial of tiotropium versus placebo (UPLIFT trial [45]) and the US FDA have closed this debate without adding warnings for either LAMAs in general or tiotropium specifically [46]. A pooled analysis of CV and cerebrovascular AEs in ACLIFORM and AUGMENT revealed that the frequency of these events in the acclidinium/formoterol 400/12 µg treatment group was either lower than or comparable with placebo (Table 1) [42]. Furthermore, 24-h Holter monitoring in ACLIFORM and AUGMENT showed no evidence that acclidinium/formoterol increased ECG abnormalities compared with placebo [27,28].

Therapeutic positioning

With the introduction of the new fixed-dose combinations of LAMA and LABA to the market, a positioning of these agents in the guidelines is expected in the near future. Currently, according to GOLD, the combination of a LAMA and LABA should be considered as an alternative treatment choice in all patients categorized as low risk, more symptoms (patient group B); high risk, less symptoms (patient group C) or high risk, more symptoms (patient group D) [1]. This gives prescribers the possibility to use this additive bronchodilation in symptomatic patients (patient groups B & D) as well as in the frequent exacerbations group (patient groups C & D).

Discussion

The shared coprimary end points of ACLIFORM and AUGMENT were chosen to test the individual contributions of the component therapies, in other words, the ability of formoterol to induce rapid-onset bronchodilation (1-h postdose FEV₁ change from baseline) [2,30,34] and the sustained bronchodilation over 24 h with twice-daily acclidinium (trough FEV₁ changes from baseline) [19,20].

In both studies, acclidinium/formoterol fixed-dose combination twice daily met both coprimary end points and significantly improved pulmonary function after 24 weeks compared with either monotherapy or placebo without a cumulative increase in the risk of AEs in patients with moderate-to-severe COPD. This outcome reflected the US FDA guidance regarding fixed-dose combinations, which states that each component of the combination must contribute to the claimed effects [47].

Both Phase III studies found that the acclidinium/formoterol combination significantly improved breathlessness compared with placebo, and while there was a numerical improvement compared with monotherapies, this was not statistically significant. This indicates that the benefits of the combination are not entirely additive for the two components; however, this may reflect the rapid onset of action and sustained benefits of formoterol and acclidinium, respectively.

Early-morning and night-time symptoms affect many patients with COPD and can be impactful, particularly with regards to patient sleep quality and quality of life [3,35,48]. The early-morning and night-time symptom questionnaire results in ACLIFORM and AUGMENT demonstrated improvements in night-time and early-morning symptoms, suggesting that acclidinium/formoterol may offer control of COPD symptoms over the 24-h period. How influential the twice-daily dosing regimen of the combination is in offering this benefit is unclear, but it is possible that the flexibility of the second dose may confer symptomatic benefits that are not offered by once-daily treatments. Head-to-head studies, and studies measuring the night-time bronchodilatory potency of this fixed-dose combination with full serial spirometry, would be required in order to understand the influence of dosing regimen on response to dual bronchodilation.

A surprisingly large and unexpected placebo effect was seen in the health status evaluation in ACLIFORM, whereas the placebo effect in AUGMENT was as expected for the SGRQ tool. Interestingly, a similarly high placebo effect was observed in the SHINE study (total score change of -6.39 from baseline for placebo), which investigated the LAMA/LABA combination of indacaterol/glycopyrronium [49], suggesting that a placebo effect may be a recurrent issue in COPD studies. Further analysis of ACLIFORM and AUGMENT revealed that the majority of patients in ACLIFORM were randomized during winter/spring and treatment continued into the spring/summer period when exacerbation rates are lower, resulting in a notable improvement in health status [28]. However, *post hoc* analysis did not reveal any factor that may have contributed to the observed placebo response in ACLIFORM.

The rate of HCRU exacerbations in the pooled analysis of ACLIFORM and AUGMENT was lower than expected, despite prior exacerbation not being an inclusion criterion for either study. One potential reason could be the use of a single inhaler to administer the treatments. Simplifying the treatment regimen this way may have led to improved patient adher-

ence and compliance, and consequently, a reduction in exacerbation rates. Studies comparing the use of multiple inhalers with single inhalers in patient populations enriched for exacerbations are needed to investigate this theory. Despite the low rate of HCRU exacerbations, there was a statistically significant reduction with the acclidinium/formoterol combination compared with placebo for both HCRU exacerbations and EXACT events.

Conclusion

In summary, acclidinium/formoterol 400/12 µg is the first twice-daily dual bronchodilator to be approved for the treatment of symptomatic patients with stable COPD, and offers clinicians another treatment option for their patients with COPD.

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Executive summary

- Combining the different but complementary effects of long-acting β_2 -agonists and long-acting muscarinic antagonists as an alternative treatment option for patients with chronic obstructive pulmonary disease (COPD) has the potential to improve lung function without impacting safety outcomes.
- Acclidinium/formoterol 400/12 µg improves lung function and symptoms compared with monotherapies and placebo.
- In addition, acclidinium/formoterol 400/12 µg significantly improves breathlessness compared with placebo.
- Improvements in morning and night-time symptoms indicate that a twice-daily dosing strategy with the acclidinium/formoterol combination could offer 24-h relief of COPD symptoms in patients with moderate-to-severe COPD.

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