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A Randomized Phase IV Study of the Effect of Aclidinium on Symptoms Including Cough in COPD

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To the editor:

Cough and sputum production are very common and troublesome symptoms for patients with chronic obstructive pulmonary disease (COPD) (1) and are associated with lung function decline, increased exacerbation risk, and poor prognosis (2-4). To date, no clinical studies that have investigated the effect of treatment with a long-acting muscarinic antagonist (LAMA) on cough as a primary or secondary endpoint. Aclidinium is a LAMA approved as a twice-daily maintenance bronchodilator treatment for patients with COPD (5). This study assessed the efficacy of aclidinium on symptoms, including cough, in patients with moderate COPD. This was a phase IV, double-blind, placebo-controlled, parallel-group study (NCT02375724), in 30 centers across five European countries between March 23, 2015 and November 17, 2015. Patients were randomized 1:1 to receive aclidinium 400 µg or placebo twice daily, administered via a multidose, dry-powder inhaler (Genuair™/Pressair®a). The study comprised a 1- to 2-week run-in period followed by an 8-week treatment period. Patients were aged ≥40 years with moderate COPD (post-bronchodilator forced expiratory volume in 1 second (FEV₁) ≥50% and <80% predicted; FEV₁/forced vital capacity <70%). The primary endpoint was change from baseline in Evaluating-Respiratory Symptoms in COPD (E-RS:COPD™) total score over 8 weeks (minimal clinically important difference [MCID], 2.0)(6). Secondary efficacy endpoints were change from baseline in E-RS cough and sputum domain score over 8 weeks (MCID, 0.7)(6) and change from baseline in Leicester Cough Questionnaire (LCQ; MCID, 1.3)(7), at Week 8. Exploratory endpoints included change from baseline in COPD Assessment Test (CAT) score (MCID, 2.0)(8), cough severity visual analogue scale (VAS) score, E-RS total score and E-RS cough and sputum domain score at Weeks 4 and 8, and E-RS breathlessness (MCID, 0.1) and chest domain scores (MCID, 0.7)(6) at Weeks 4, 8, and over 8 weeks. A post hoc analysis stratified patients by baseline cough severity (VAS; >30 mm, more severe; ≤30 mm, less
severe) to assess impact of aclidinium on cough-related endpoints. All patients provided written informed consent; study protocols and amendments were approved by local ethics committees. The primary endpoint was analyzed using a mixed model for repeated measures. Overall, 269 patients were randomized; 135 received aclidinium and 134 received placebo. At baseline, 60% of patients were male, 64% were current smokers, mean age was 62 years, with mean post-bronchodilator FEV₁ 64.2% predicted. Mean baseline E-RS breathlessness, cough and sputum, and chest domain scores were 6.0, 3.7, and 2.9, respectively, and total E-RS was 12.5. Baseline CAT and LCQ scores were 19.4 and 14.5, respectively. Significant improvements in E-RS total score were observed with aclidinium versus placebo (Figure 1). Aclidinium significantly improved E-RS cough and sputum domain scores versus placebo at Week 8 but not at Week 4 or over 8 weeks (Table 1). For E-RS breathlessness domain score, aclidinium provided statistically significant improvements versus placebo at all time points (Table 1). Changes in LCQ total score for aclidinium versus placebo were not statistically significant at any time point (Table 1). Improvements in CAT and E-RS chest domain scores were numerical only (Table 1), as were changes in cough severity (VAS; Week 4, -0.7; Week 8, -1.1; over 8 Weeks, -0.9). In total, 264 patients were stratified by cough severity (more severe, 123 patients; less severe, 141 patients). In patients with more severe cough, significant improvements were observed in E-RS total score at Week 4, and cough and sputum domain scores at each time point (Table 1). Numerical differences versus placebo were observed in LCQ, and E-RS breathlessness and chest domains scores, at Weeks 4 or 8, in patients with more severe cough. Statistically significant improvements were seen for more severe cough patients versus placebo in CAT score at Weeks 4 and 8 (Table 1). No significant differences were observed for any outcome in patients with less severe cough. Overall, aclidinium significantly improved a range of daily COPD symptoms (including cough and sputum) versus placebo. Improvements in quality of life measures LCQ and CAT
did not reach statistical significance for aclidinium versus placebo in the total patient population. Baseline LCQ values in the total population suggested that the impact of symptoms on quality of life was minimal, possibly due to the number of patients with mild cough. Safety outcomes were consistent with those previously reported (9). Post hoc analyses showed that for patients with more severe cough, aclidinium provided greater improvements versus placebo in E-RS cough and sputum domain scores and CAT score. These patients had higher baseline CAT and E-RS total and domain scores than patients with less severe cough, and a mean LCQ of 12.7, indicating prominent cough symptoms. In contrast to the total population, when patients were stratified by cough severity there was a numerical trend towards improvement in LCQ in patients with more severe cough, versus less severe cough. This suggests baseline cough severity could be an important symptomatic marker for treatment response and VAS score may reflect some mechanisms driving cough and sputum production in COPD and specifically those most responsive to aclidinium treatment (10).

One limitation was that this study was powered for E-RS total score and E-RS cough and sputum domain, but not for CAT or LCQ scores. As quality of life instruments LCQ and CAT are designed to capture impact of a condition rather than severity, these tools may not be as sensitive to symptom changes as those specifically designed for symptom severity, such as E-RS. Additionally, only patients with moderate COPD were included, therefore further studies in a more severe COPD population would be beneficial.

In this study, which was one of the first studies to assess the effect of a LAMA on cough outcomes in patients with COPD, aclidinium 400 µg significantly improved a range of daily symptoms, including cough, in symptomatic patients with moderate COPD compared with placebo. Additionally, a subgroup of patients with more severe cough symptoms gained a distinct and early benefit from aclidinium in a number of cough-related endpoints. Therefore,
routine evaluation of cough symptoms in addition to breathlessness, may result in more effective treatment management in patients with moderate COPD.

**Endnotes**

a Registered trademark of AstraZeneca group of companies; for use within the USA as Pressair® and as Genuair™ within all other licensed territories.

b The E-RS™ is owned by Evidera. Permission to use this instrument may be obtained from Evidera (exactpro@evidera.com).

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Competing interests

JAS has received consultancy fees and grant funding from AstraZeneca. LM has received speaker and consultancy fees from Almirall and AstraZeneca. AHM has received fees for lecturing from Almirall and AstraZeneca and has received grant funding from AstraZeneca. SSB has received consultancy fees from Almirall. JAW has received research grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Johnson and Johnson and Novartis and has received meeting expenses from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Novartis. MN is an employee of Menarini Farmaceutica Internazionale s.r.l., Florence, Italy. AZ is an employee of Laboratorios Menarini, S.A. Badalona, Spain. RS, BS, and DJ are employees of AstraZeneca.
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Figure 1. Change from baseline in E-RS total score for aclidinium 400 µg versus placebo (intent-to-treat population).

Data are least squares mean ± standard error.

E-RS = Evaluating-Respiratory Symptoms in COPD (E-RS:COPD™).

*P < 0.05 vs. placebo
Table 1. Summary of efficacy for aclidinium versus placebo (intent-to-treat population)

| Change from baseline | Time point | Any VAS | Baseline cough VAS >30 mm (more severe) | Baseline cough VAS ≤30 mm (less severe) |
|----------------------|------------|---------|----------------------------------------|----------------------------------------|
| E-RS total score     | Week 4     | -0.9 (0.4) * | -1.3 (0.6) * | -0.6 (0.6) |
|                      | Week 8     | -1.1 (0.6) * | -1.2 (0.8) | -1.1 (0.8) |
|                      | Over 8 weeks | -1.0 (0.5) * | -1.2 (0.7) | -0.8 (0.6) |
| E-RS cough and sputum domain | Week 4     | -0.1 (0.1) | -0.3 (0.2) * | 0.1 (0.2) |
|                      | Week 8     | -0.3 (0.2) * | -0.5 (0.2) * | -0.2 (0.2) |
|                      | Over 8 weeks | -0.2 (0.1) | -0.4 (0.2) * | -0.1 (0.2) |
| LCQ                  | Week 4     | 0.1 (0.3) | 0.6 (0.4) | -0.1 (0.4) |
|                      | Week 8     | -0.1 (0.3) | 0.4 (0.4) | -0.4 (0.4) |
| CAT total score      | Week 4     | -0.7 (0.6) | -2.2 (0.8) * | 0.5 (0.8) |
|                      | Week 8     | -0.6 (0.6) | -2.3 (0.9) * | 1.0 (0.9) |
| E-RS breathlessness domain | Week 4     | -0.6 (0.2) * | -0.7 (0.3) | -0.5 (0.3) |
|                      | Week 8     | -0.6 (0.3) * | -0.5 (0.4) | -0.7 (0.4) |
|                      | Over 8 weeks | -0.6 (0.3) * | -0.6 (0.4) | -0.6 (0.4) |
| E-RS chest symptoms domain | Week 4     | -0.2 (0.1) | -0.3 (0.2) | -0.2 (0.2) |
|                      | Week 8     | -0.2 (0.2) | -0.2 (0.2) | -0.2 (0.2) |
|                      | Over 8 weeks | -0.2 (0.1) | -0.3 (0.2) | -0.2 (0.2) |

Data are least-squares mean change from baseline for aclidinium 400 µg vs placebo (± standard error).

Analyzed using a mixed model for repeated measures (covariates: baseline, and age; factors: treatment group, sex, smoking status, visit, and treatment-by-visit interaction.

*Treatment difference was greater than the minimal clinically important difference (8).

Definition of abbreviations: CAT = COPD Assessment Test; E-RS = Evaluating-Respiratory Symptoms in COPD (E-RS:COPD™); LCQ = Leicester Cough Questionnaire; VAS = visual analog scale.

* P<0.05