

## Original Article

# A Randomized, Noninferiority Trial Comparing ICS + LABA with ICS + LABA + LAMA in Asthma-COPD Overlap (ACO) Treatment: The ACO Treatment with Optimal Medications (ATOMIC) Study

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**What is already known about this topic?** The inhaled corticosteroid (ICS) + long-acting  $\beta_2$  agonist (LABA) treatment is essential for the initial treatment of asthma and chronic obstructive pulmonary disease (COPD) overlap (ACO) patients with asthma and COPD coexistence, and treatment efficacy with addition of long-acting muscarinic antagonist (LAMA) is unclear.

**What does this article add to our knowledge?** This trial validated the current approach to ACO treatment. It is unclear whether ICS + LABA + LAMA treatment reduces the time to first exacerbation; however, it is obvious that the LAMA add-on treatment improved lung function in ACO.

**How does this study impact current management guidelines?** Similar to current guidelines for treatment with ICS + LABA + LAMA in patients with severe uncontrolled asthma or eosinophilic COPD, ICS + LABA + LAMA treatment may be helpful in patients with ACO.

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The study was conducted between August 2016 and February 2018 in 21 medical centers belonging to the Cohort for Reality and Evolution of Adult Asthma in Korea (COREA). The protocols were approved by the Institutional Review Board

**Abbreviations used**

ACO- Asthma and chronic obstructive pulmonary disease overlap  
 AE- Acute exacerbation  
 COPD- Chronic obstructive pulmonary disease  
 FVC- Forced vital capacity  
 HR- Hazard ratio  
 ICS- Inhaled corticosteroid  
 LABA- Long-acting  $\beta_2$  agonist  
 LAMA- Long-acting muscarinic antagonist

**BACKGROUND:** Current guidelines for the treatment of asthma and chronic obstructive pulmonary disease overlap (ACO) recommend initial treatment using inhaled corticosteroids (ICSs) plus 1 or more bronchodilators.

**OBJECTIVE:** To clarify which therapeutic effect is better between the ICS + long-acting  $\beta_2$  agonist (LABA) and ICS + LABA + long-acting muscarinic antagonist (LAMA) treatment in patients with ACO.

**METHODS:** We conducted a multicenter, 48-week, randomized, noninferiority trial. Patients with ACO were enrolled if they were treated with a moderate to high dose of ICS + LABA. In total, 303 patients were involved in the present trial, with 149 receiving ICS + LABA + LAMA. The primary end point was the time to first exacerbation. Secondary outcomes included changes in FEV<sub>1</sub>, forced vital capacity, FEV<sub>1</sub>/forced vital capacity ratio, asthma control, blood eosinophil count, and fractional exhaled nitric oxide.

**RESULTS:** In the ICS + LABA treatment group, 29 of 154 patients (18.83%) experienced exacerbation, whereas 28 of 149 patients (18.79%) experienced exacerbation in the ICS + LABA + LAMA treatment group. The results of this noninferiority study were ultimately inconclusive (hazard ratio, 1.1; 95% CI, 0.66-1.84). However, the patients treated with the addition of LAMA showed significant improvements in FEV<sub>1</sub> and forced vital capacity ( $P < .001$ ). Asthma control did not improve in either group.

**CONCLUSIONS:** Although this study was unable to conclude that ICS + LABA treatment is not inferior to ICS + LABA + LAMA in terms of exacerbation, it is obvious that the ICS + LABA + LAMA treatment group had improved lung function in ACO. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

**Key words:** Asthma-COPD overlap; ICS; LABA; LAMA; Triple therapy

**INTRODUCTION**

Asthma and chronic obstructive pulmonary disease (COPD) overlap (ACO) is a mixed phenotype of airway disease characterized by both asthma and COPD.<sup>1,2</sup> Asthma and COPD are both heterogeneous diseases; thus, it is often difficult to distinguish between them, especially in elderly patients who smoke.<sup>3</sup> Although clinicians often come across patients with ACO in practice, the phenotype is not well established academically. Many studies have been conducted, but no universally accepted definition of ACO has been established.<sup>4-8</sup> Nevertheless, in a previous study in which ACO was defined on the basis of longitudinal analysis, we showed both that the condition can be defined as a separate disease entity on the basis of the clinical course, and that it is influenced by environmental factors.<sup>9</sup> ACO displays a number of clinical characteristics, such as fixed airway obstruction and airway hyperresponsiveness. In addition, patients with ACO often experience more frequent exacerbations and hospitalizations, as well as a poorer quality of life, than those with asthma or COPD alone.<sup>1,5,7-11</sup> However, it remains unclear whether ACO is a distinct phenotype and its own disease entity, or whether long-standing airway remodeling takes place in patients with ACO.

Many medications used to treat airway disease have been tested in clinical trials involving patients with either asthma or COPD. Most patients with ACO are excluded from such studies; therefore, little research is available to inform clinical treatment guidelines for patients with ACO. As a result, it remains unclear which inhalants should be prescribed to treat this syndrome. For example, patients with ACO show more eosinophilic inflammation, and therefore respond better to inhaled corticosteroids (ICSs), than do patients with only COPD.<sup>12,13</sup> Patients with ACO also present with more severe symptoms than do those with asthma or COPD, and may require long-acting muscarinic antagonist (LAMA) treatment.<sup>14,15</sup>

The Global INitiative for Asthma guidelines recommend initial treatment of ACO with ICS plus long-acting  $\beta_2$  agonist (LABA), because the condition has the characteristics of both asthma and COPD. In some cases, LAMA can be replaced or added instead of LABA.<sup>3</sup>

Using the longitudinal definition of ACO devised in a previous study,<sup>9</sup> we conducted a clinical trial to establish evidence and inform clinical guidelines for the treatment of ACO. In the present study, termed “ACO Treatment with Optimal Medications (ATOMIC),” we hypothesized that the therapeutic effect of ICS + LABA would not be inferior to that of ICS + LABA + LAMA. With these results, we sought to provide data that would guide the management of patients with ACO in clinical practice.

of Asan Medical Center (2016-0729), as well as each participating center. This trial is registered with the Clinical Research Information Service (KCT0002050). The present study was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute funded by the Ministry of Health & Welfare, Republic of Korea (grant no. HC15C1335). Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

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## METHODS

### Study design

The present trial had a multicenter, randomized, open-label, parallel, noninferior study design, and compared treatment with ICS + LABA or ICS + LABA + LAMA in patients with ACO throughout a 48-week study period. The study was conducted between August 2016 and February 2018 in 21 medical centers belonging to the Cohort for Reality and Evolution of Adult Asthma in Korea.<sup>9,16-18</sup> It was performed in accordance with the Declaration of Helsinki, and the protocols were approved by the Institutional Review Board of Asan Medical Center (2016-0729), as well as each participating center. This trial is registered with the Clinical Research Information Service (KCT0002050).

### Patients

Patients included in the present study were adults older than 18 years who had been diagnosed with ACO at least 1 year before recruitment. ACO was defined on the basis of following criteria, as in a previous study<sup>9</sup>: (1) positive response to bronchodilator ( $FEV_1 > 200$  mL, with a 12% increase from baseline) or a positive bronchial provocation test result; (2) prebronchodilator  $FEV_1$ /forced vital capacity (FVC) ratio less than 0.7 at baseline and continuing for at least 3 months despite appropriate therapy. All patients provided written informed consent. In the present trial, patients with ACO with an  $FEV_1$  of more than 30% were administered a moderate to high dose of ICS + LABA.

Patients were excluded if they (1) had a contraindication to treatment using LAMA (ie, severe benign prostatic hyperplasia, glaucoma, or severe renal disease); (2) had heart failure or myocardial infarction within 1 year before recruitment; (3) had an untreated bacterial, fungal, or tuberculosis lung infection; (4) had a tuberculosis-destroyed lung; (5) showed acute exacerbation (AE) at the time of screening; (6) were pregnant or lactating; and (7) were using systemic steroids to treat another disease.

### Randomization and masking

After a 4-week screening period, eligible patients underwent randomization. Patients were randomly assigned to the treatment groups using a 1:1 ratio. The randomization was performed in blocks of 4 per center, with no other stratification applied, while the randomization schedule was generated using a validated system. Patients were assigned to either the ICS + LABA maintaining group or the ICS + LABA + LAMA triple group. Because this was an open-label trial, both clinicians and patients were aware of the type of treatment being received.

### Procedure

The patients attended 7 visits: 1 at the start of the trial (screening), 1 at randomization (baseline), and an additional 5 during the 48-week treatment period (ie, every 3 months other than the first month) (see [Figure E1](#) in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

**Medications.** In the present study, patients were given additional LAMA based on the randomization, while retaining the previously used drugs. If the patients' daily ICS dose using the inhaler was medium or high, their ICS + LABA type was not limited. As a result, different types of ICS + LABA were used for each patient. We used the budesonide equivalent dose to analyze the results. The following drugs were prescribed in the present study: (1) budesonide (320  $\mu$ g) plus formoterol (9  $\mu$ g; 1 dose twice a day) (Symbicort turbuhaler); (2) fluticasone propionate (250  $\mu$ g) plus salmeterol (50

$\mu$ g; 1 dose twice a day) or fluticasone propionate (500  $\mu$ g) plus salmeterol (50  $\mu$ g; 1 dose twice a day) (Seretide diskus); (3) beclomethasone (100  $\mu$ g) plus formoterol (6  $\mu$ g; 2 doses twice a day) (Foster); (4) fluticasone propionate (125  $\mu$ g) plus formoterol (5  $\mu$ g; 2 doses twice a day) or fluticasone propionate (250  $\mu$ g) plus formoterol (10  $\mu$ g; 2 doses twice a day) (Flutiform); (5) fluticasone furoate (200  $\mu$ g) plus vilanterol (25  $\mu$ g; 1 dose every day) (Relva). In Korea, only tiotropium was available to treat patients with asthma; therefore, only tiotropium (Spiriva RespiMat; 2 doses every day) was used as a LAMA in the ICS + LABA + LAMA triple group.

The use of drugs such as methylxanthine or leukotriene receptor antagonists was allowed.

### Outcomes

The primary end point of the study was the time to first exacerbation. AE was defined as the occurrence of 1 or more of the following: (1) emergency room visit; (2) unexpected outpatient visit; (3) inpatient or intensive care unit visit; (4) use of a systemic corticosteroid; (5) a decrease in  $FEV_1$  by more than 20% compared with baseline; (6) rescue medication used more than 8 times per day for 2 consecutive days; (7) nocturnal symptoms for 2 consecutive days; (8) Asthma Control Test score less than 20; (9) clinical judgment of exacerbation. Of these, severe exacerbations were defined on the basis of the first 4 items only.

The secondary outcomes included changes in  $FEV_1$ , FVC, or  $FEV_1$ /FVC ratio at the last visit compared with baseline, as well as changes in Asthma Control Test score, blood eosinophil count, or fractional exhaled nitric oxide compared with baseline.

### Statistical analysis

**Sample size.** In a previous study, Kerstjens et al<sup>19</sup> compared patients with poorly controlled asthma treated with tiotropium plus ICS + LABA with those treated using ICS + LABA alone.<sup>19</sup> They reported that the hazard ratio (HR) was 1 and that the noninferior margin was  $HR = 1.5$ , indicating that the exacerbation rate did not differ significantly between ICS + LABA and ICS + LABA + LAMA. A total of 298 patients, with 149 in each group, were investigated in the present study. The number of subjects was calculated using PASS version 11. A noninferiority log-rank test with an overall sample size of 297 subjects (148 in the reference group and 149 in the treatment group) yielded 80.0% power at a 0.025 significance level to detect an equivalence HR of 1.50, assuming an actual HR that is the equivalence HR of 1.00, and that the reference group hazard rate is 0.7000. The study lasted for 2 time periods, with subject accrual (entry) in the first time period. No subjects dropped out of either the reference group or the treatment group. The proportion switching from the reference group to another group, with a hazard rate equal to that of the treatment group was 0.0. The proportion switching from the treatment group to another group, with a hazard rate equal to that of the reference group, was less than 0.001.

**Analysis.** All statistical analyses were performed using R software (R Project for Statistical Computing, Vienna, Austria; [www.r-project.org](http://www.r-project.org)). The results are presented as mean  $\pm$  SD for continuous variables and as counts of events (%) for categorical variables. The baseline characteristics were compared using *t* tests or Mann-Whitney *U* and Wilcoxon tests for continuous variables, and the  $\chi^2$  or Fisher exact test for categorical variables. To compare the time to first exacerbation between the groups, the HR and 95% CI of the ICS + LABA group were calculated using the ICS + LABA + LAMA group as a reference.

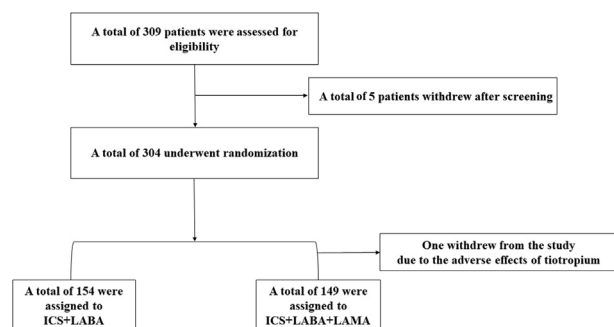


**FIGURE 1.** Screening, randomization, and study enrollment. A total of 303 patients participated in the trial, with 149 in the triple therapy group.

Survival analysis was also performed to show AE between groups. The basic assumption of the log-rank test is that the risk function of the 2 groups is proportional. Because the Kaplan-Meier survival curves of the 2 groups crossed over, no proportional relationship was established. Therefore, we used the modified Peto-Peto's Gehan-Wilcoxon test instead of the log-rank test. In addition, we conducted the Schoenfeld test to determine whether the proportional hazard assumption was correct. The  $P$  value was greater than .05 ( $P = .960$ ), and there was no evidence that the proportional hazard assumption was violated; therefore, HR was used. A paired  $t$  test was performed to evaluate the change in each patient's clinical characteristics after the trial intervention had been applied; the "after intervention" time point was defined as the last visit of each patient. The Wilcoxon signed-rank test was performed when the assumption of normality was violated.

## RESULTS

### Study patients

Of the 309 patients who were screened, 5 were withdrawn because they did not meet the inclusion criteria. One patient was withdrawn later because of an adverse reaction to tiotropium. Ultimately, 303 patients completed the trial, with 149 receiving tiotropium (Figure 1). The baseline characteristics were similar between the study groups (Table I). About half of all patients in both groups were either current or ex-smokers. The mean age, sex, and body mass index of the 2 groups were similar. The mean ICS budesonide equivalent doses were 548.49 mg in the ICS + LABA group and 562.4 mg in the ICS + LABA + LAMA group, corresponding to a medium dose, with no significant difference between the groups. There was no difference between the groups in terms of history of AE or asthma control. The white blood cell count, blood eosinophil count, sputum eosinophil percentage, serum total IgE, fractional exhaled nitric oxide, and lung function was also similar between the groups.

### Primary end point

**Time to first exacerbation.** Among all 303 patients, AE occurred in 57 (18.18%). In the ICS + LABA dual treatment group, 29 patients (29 of 154; 18.83%) experienced exacerbation, whereas 28 (28 of 149; 18.79%) experienced exacerbation in the ICS + LABA + LAMA triple treatment group. There were no significant differences between the groups in this regard (Figure 2, A). The average time until the first exacerbation was  $250.90 \pm$

$157.24$  days for the ICS+LABA group and  $269.30 \pm 146.32$  days for the ICS + LABA + LAMA group ( $P = .248$ ). A subgroup analysis was also performed in patients who had suffered at least 1 exacerbation in the previous year. A total of 52 patients in the ICS + LABA group and 53 patients in the ICS + LABA + LAMA group met this criterion. Of these, 16 patients (30.77%) in the ICS + LABA group and 14 (26.42%) in the ICS + LABA + LAMA group had exacerbations during the trial. In addition, the ICS + LABA group tended to show more exacerbations within the first 3 months, whereas the ICS + LABA + LAMA group showed more exacerbations after 6 months. There was no difference in the rate of exacerbation between the 2 groups (Figure 2, B). The mean blood eosinophil count was more than 300 cells/ $\mu$ L, and patients with low eosinophil count ( $<300$  cells/ $\mu$ L) were reanalyzed separately. Similar to previous results, there was no difference in exacerbation between the groups (see Figure E2, A, in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Using the same method, a comparative analysis of patients treated with a high dose of ICS was performed (Figure E2, B). Using a CI approach in this noninferior trial, with regard to whether the treatment protocol had a significant difference on the primary outcome, it was inconclusive that ICS + LABA is not inferior to ICS + LABA + LAMA (HR, 1.1; 95% CI, 0.658-1.844;  $P = .713$ ; Figure 3). Further analysis of severe exacerbations was also inconclusive (HR, 0.73; 95% CI, 0.350-1.536;  $P = .411$ ; see Figure E3 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

### Secondary end points

**Lung function.** A paired  $t$  test was performed to confirm changes in the patient's clinical characteristics after treatment. Patients were assessed for pulmonary function and symptom score improvement during the trial. Patients in the ICS + LABA group showed no significant improvement in FEV<sub>1</sub> or FVC. However, patients treated using ICS + LABA + LAMA showed significant improvements in FEV<sub>1</sub> and FVC after 1 year (Table II and Figure 4). However, asthma control did not improve in either group (Table II).

### Adverse events

An adverse event was reported in only 1 patient in the ICS + LABA + LAMA group. The patient reported voiding difficulty—a possible side effect of using LAMA. Following the administration of tiotropium, 21 patients with a side effect of upper respiratory tract infection were reported, thereby accounting for the largest proportions. In addition, 2 cases of dry mouth and 2 cases of mild dysuria were observed (see Table E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). No other side effects were reported, and no deaths occurred. All remaining enrolled patients participated according to the study protocol.

## DISCUSSION

The present study was the first large-scale, multicenter, randomized controlled trial designed to determine whether the addition of LAMA is beneficial for the treatment of ACO. As a result, we could not confirm that ICS + LABA treatment in patients with ACO was not inferior to ICS + LABA + LAMA treatment with respect to the time to first exacerbation. However, lung function clearly improved in the ICS + LABA + LAMA triple treatment group, similar to what was reported in the previous study. In particular, the addition of LAMA appeared

**TABLE I.** Baseline characteristics of the patients

| Characteristic                               | Double (ICS + LABA)<br>(N = 154) | Triple (ICS + LABA + LAMA)<br>(N = 149) |
|----------------------------------------------|----------------------------------|-----------------------------------------|
| Age (y)                                      | 61.99 ± 13.69                    | 63.07 ± 11.36                           |
| Female sex, n (%)                            | 67 (43.51)                       | 67 (44.97)                              |
| Body mass index (kg/m <sup>2</sup> )         | 25.01 ± 4.68                     | 24.87 ± 3.71                            |
| Smoking status, n (%)                        |                                  |                                         |
| Never/ex/current                             | 83 (53.90)/51 (33.11)/42 (12.99) | 67 (44.97)/60 (40.27)/22 (14.76)        |
| Mean age of onset (y)                        | 53.19 ± 16.90                    | 55.71 ± 13.83                           |
| Use of maintenance ICS dose*                 | 548.49 ± 548.15                  | 562.4 ± 491.32                          |
| No. of exacerbation (total)                  | 4.29 ± 9.8                       | 3.86 ± 8.18                             |
| Incidence rate of exacerbation               | 1.33 ± 4.01                      | 0.98 ± 3.93                             |
| ACT score                                    | 21.48 ± 3.26                     | 20.97 ± 3.77                            |
| QLQAKA                                       | 68.75 ± 12.21                    | 67.31 ± 11.84                           |
| Blood WBC (× 10 <sup>3</sup> /μL)            | 7.16 ± 2.17                      | 7.76 ± 2.38                             |
| Blood eosinophil (count/μL)                  | 305.51 ± 318.51                  | 397.88 ± 472.39                         |
| Blood total IgE (IU/mL)                      | 317.65 ± 350.41                  | 307.1 ± 376.91                          |
| Sputum eosinophil, %                         | 8.55 ± 16.67                     | 9.67 ± 16.28                            |
| FENO (ppb)                                   | 35.47 ± 23.33                    | 31.21 ± 22.53                           |
| PC20 (mg/mL)                                 | 6.89 ± 6.53                      | 6.31 ± 5.67                             |
| Pulmonary function tests                     |                                  |                                         |
| Prebronchodilator FVC (L)                    | 2.94 ± 0.90                      | 2.89 ± 0.95                             |
| Prebronchodilator FVC (%)                    | 79.07 ± 13.17                    | 78.98 ± 16.17                           |
| Prebronchodilator FEV <sub>1</sub> (L)       | 1.87 ± 0.65                      | 1.79 ± 0.60                             |
| Prebronchodilator FEV <sub>1</sub> (%)       | 67.61 ± 14.17                    | 65.45 ± 13.16                           |
| Prebronchodilator FEV <sub>1</sub> /FVC (%)  | 63.82 ± 10.75                    | 62.76 ± 11.63                           |
| Postbronchodilator FVC (L)                   | 2.91 ± 0.88                      | 2.88 ± 1.00                             |
| Postbronchodilator FVC (%)                   | 82.55 ± 13.63                    | 79.86 ± 19.22                           |
| Postbronchodilator FEV <sub>1</sub> (L)      | 1.80 ± 0.62                      | 1.71 ± 0.52                             |
| Postbronchodilator FEV <sub>1</sub> (%)      | 69.8 ± 14.55                     | 66.4 ± 14.70                            |
| Postbronchodilator FEV <sub>1</sub> /FVC (%) | 62.52 ± 10.92                    | 61.47 ± 11.55                           |

ACT, Asthma Control Test; FENO, fractional exhaled nitric oxide; PC20, provocative concentration of provocholine that results in a 20% drop in FEV<sub>1</sub>; ppb, parts per billion; QLQAKA, Quality of Life Questionnaire for adult Korean Asthmatics; WBC, white blood cell.

\*Budesonide equivalent dose, daily dose (μg).

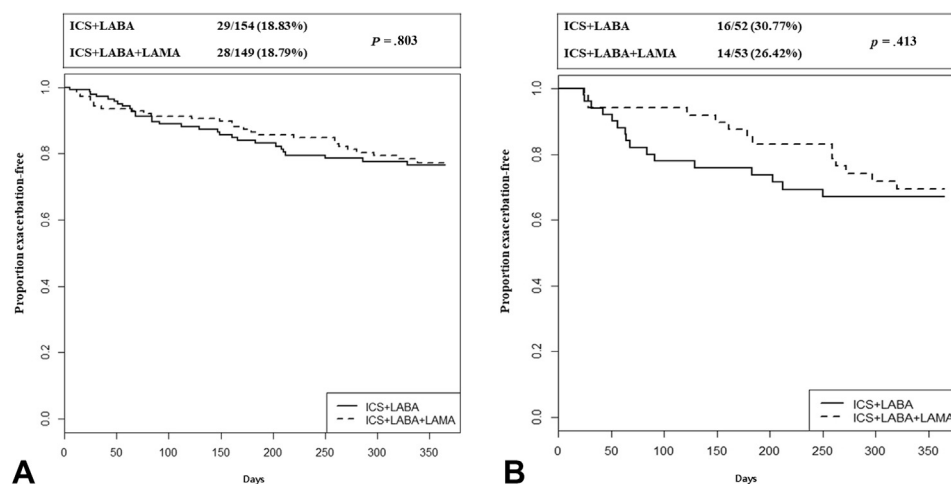


**FIGURE 2.** The description of AEs occurrence over time. **(A)** Comparison of exacerbation among all 303 patients between the ICS + LABA group and the ICS + LABA + LAMA group. Exacerbation events were not significantly different between the groups. **(B)** Comparison involving only those patients who had experienced at least 1 or more exacerbation in the previous year.

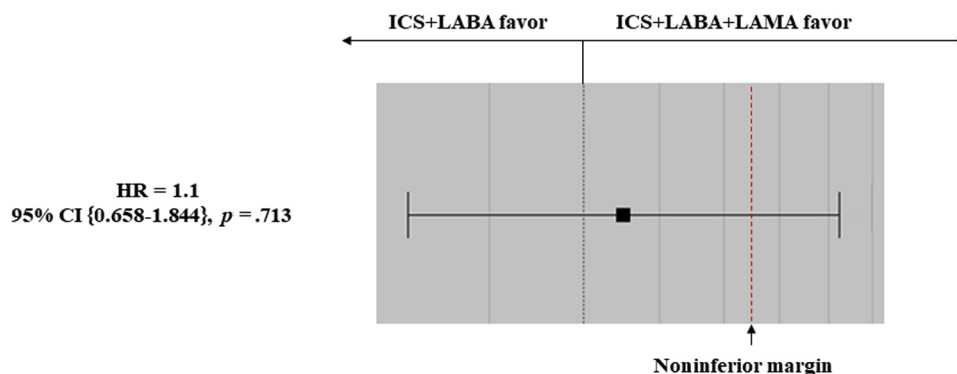


**FIGURE 3.** Treatment differences between the groups for time to first exacerbations. The error bars indicate 2-side 95% CIs. The result shows inconclusive, with HR = 1.1; however, CIs (0.66-1.84) were over the noninferior margin ( $P = .713$ ).

**TABLE II.** Change in clinical characteristics before and after treatment (paired  $t$  test) between the groups

| Characteristic                              | ICS + LABA     |               |           | ICS + LABA + LAMA |               |           |
|---------------------------------------------|----------------|---------------|-----------|-------------------|---------------|-----------|
|                                             | Baseline       | Last visit    | $P$ value | Baseline          | Last visit    | $P$ value |
| Pulmonary function tests                    |                |               |           |                   |               |           |
| Prebronchodilator FVC (L)                   | 2.94 ± 0.90    | 2.94 ± 0.87   | .871      | 2.95 ± 0.95       | 3.07 ± 0.92   | .001      |
| Prebronchodilator FVC (%)                   | 78.92 ± 12.90  | 79.07 ± 12.98 | .838      | 79.43 ± 16.14     | 83.48 ± 15.29 | <.001     |
| Prebronchodilator FEV <sub>1</sub> (L)      | 1.90 ± 0.65    | 1.92 ± 0.64   | .476      | 1.82 ± 0.61       | 1.93 ± 0.62   | .001      |
| Prebronchodilator FEV <sub>1</sub> (%)      | 68.09 ± 13.11  | 69.59 ± 14.11 | .075      | 65.32 ± 12.96     | 70.27 ± 13.80 | <.001     |
| Prebronchodilator FEV <sub>1</sub> /FVC (%) | 64.56 ± 10.44  | 65.14 ± 10.45 | .313      | 62.39 ± 11.34     | 63.24 ± 11.24 | .245      |
| ACT score                                   | 21.68 ± 3.27   | 21.87 ± 3.22  | .595      | 21.02 ± 3.72      | 21.34 ± 3.58  | .358      |
| Characteristic                              | ICS + LABA     |               |           | ICS + LABA + LAMA |               | $P$ value |
| Change in FEV <sub>1</sub> (L)              | 0.017 ± 0.244  |               |           | 0.108 ± 0.352     |               | .023      |
| Change in FVC (L)                           | −0.004 ± 0.270 |               |           | 0.125 ± 0.386     |               | .004      |
| Change in ACT score                         | 0.183 ± 3.768  |               |           | 0.315 ± 3.902     |               | .786      |

ACT, Asthma Control Test.

to slightly delay exacerbations in patients with more than 1 exacerbation in the previous year, but it was not significant. There was no significant improvement in Asthma Control Test score, blood eosinophil count, or fractional exhaled nitric oxide in the triple treatment group.

ACO, characterized by the combination of asthma and COPD, has received much attention recently, despite being known to clinicians for a long time. Similar to asthma and COPD, ACO is very heterogeneous and has not been clearly defined to date.<sup>1</sup> Nevertheless, ACO is common in clinical practice, affecting 15% to 20% of patients with airway disease.<sup>3,5,9,20</sup> It is often referred to as “eosinophilic COPD” or “smokers’ asthma.”<sup>1,21-23</sup> Patients with ACO show higher bronchial hyperresponsiveness than do patients with either COPD or asthma alone, with frequent exacerbation and low symptom control.<sup>1,14,23,24</sup> Nonetheless, because ACO is not yet a clearly defined phenotype, it remains difficult to design a study investigating therapeutic approaches to the condition. Thus, clinical evidence is still lacking.

Treatment of airway diseases such as asthma and COPD center around inhalant therapy, with a stepwise approach based on disease control.<sup>3</sup> Although solid evidence is limited regarding inhalant therapy for patients with ACO, the Global Initiative for Asthma guideline suggests basing treatment on ICS and adding 1 or more bronchodilator, such as LABA or LAMA.<sup>3</sup> Because

ACO is a chronic inflammatory airway disease with fixed airway obstruction, the Global Initiative for Asthma treatment guideline is considered to be especially appropriate. The most important medication for treating asthma is ICS inhalation, whereas the use of LABA alone is prohibited. Meanwhile, COPD treatments center around the use of bronchodilators, such as LABA, LAMA, or a combination of the 2.<sup>1,25</sup> Therefore, it makes sense that the combination of these drugs is suitable for ACO treatment. However, there is little solid evidence to support stepwise treatment by adding LAMA to ICS + LABA therapy for patients with ACO. To date, studies have shown that add-on LAMA therapy is effective for patients with severe uncontrolled asthma, with LAMA therapy leading to decreased exacerbation and FEV<sub>1</sub> improvement.<sup>19</sup> In addition, 1 study has shown that triple therapy with ICS + LABA + LAMA for 12 weeks improves lung function in patients with ACO.<sup>26</sup>

The 2019 Global Initiative for Chronic Obstructive Lung Disease guideline recommends the initial prescription of a dual LABA + LAMA bronchodilator for patients in the Global Initiative for Chronic Obstructive Lung Disease C group, and suggests that ICS should be added only if patients have a blood eosinophil count of greater than or equal to 300 cells/ $\mu$ L, or for those with a blood eosinophil count of greater than or equal to 100 plus 2 or more moderate exacerbations or 1 or more hospitalization.<sup>27</sup> Furthermore, the addition of tiotropium in severe

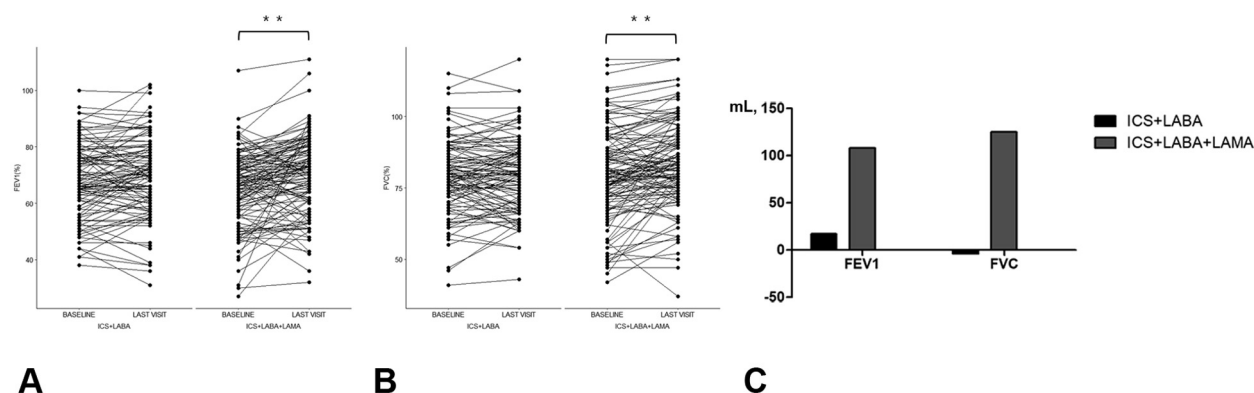


**FIGURE 4.** Individual data for change in pulmonary function (paired *t* test). (A) Change in FEV<sub>1</sub> (%). (B) Change in FVC (%). (C) The mean of change ( $\Delta$ FEV<sub>1</sub>,  $\Delta$ FVC). \*\**P* < .001 between treatment, determined using a paired *t* test.

uncontrolled asthma is strongly recommended on the basis of available evidence.<sup>19</sup> Therefore, in patients with ACO, based on ICS + LABA treatment, the LAMA add-on may be helpful because these patients experience frequent AEs.

Of course, this study has limitations. First, it uses a non-inferiority study design, because it was expected that it would be difficult to recruit patients with ACO to demonstrate superiority results during the limited time. Second, the hazard rate of the reference group was assumed to be 0.7. However, the incidence of AE was much less than expected; specifically, the power was lower than the initial target of 80%. Third, the definition of ACO is still controversial. That being said, we have defined ACO as in previous studies, and believe the recruitment to be highly reliable because multicenter allergy or respiratory specialists enrolled the subjects. Finally, this study was conducted as an open-label study. In an open-label study, it is well known that subject bias can affect the result; therefore, result interpretations require attention. However, the results of this study proved that only relatively objective indicators showed meaningful differences between the groups; hence, it can be judged that these effects were not relatively influenced.

Unfortunately, our study could not reveal the noninferiority comparison between ICS + LABA dual therapy and ICS + LABA + LAMA triple therapy in patients with ACO. Therefore, more studies are needed. For example, the differences in disease control between ICS + LABA and ICS + LABA treatments must be elucidated, and other treatments such as macrolide, roflumilast, and biologics should be evaluated for possible improvement of clinical outcomes.

This trial validated the current approach to ACO treatment. It is not clear whether ICS + LABA + LAMA treatment will reduce the time to first exacerbation, however, it is obvious that the LAMA add-on treatment improved lung function in ACO.

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## ONLINE REPOSITORY

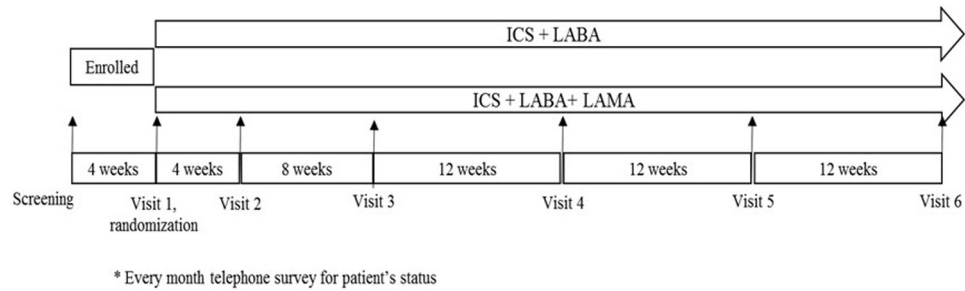


FIGURE E1. Scheme of study design.

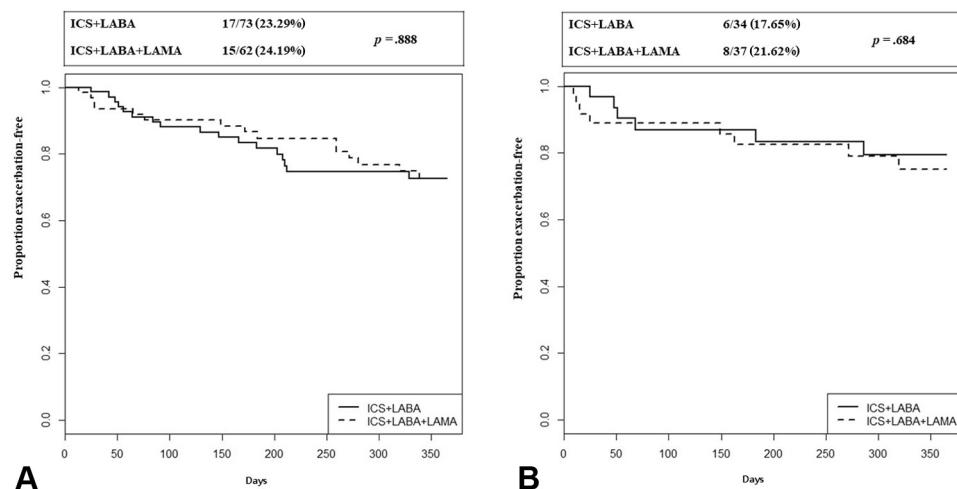


FIGURE E2. The description of acute exacerbations occurrence over time. (A) Subgroup analysis of the comparison of patients with low blood eosinophil count (&lt;300). (B) Subgroup analysis of the comparison of patients with high-dose ICS.

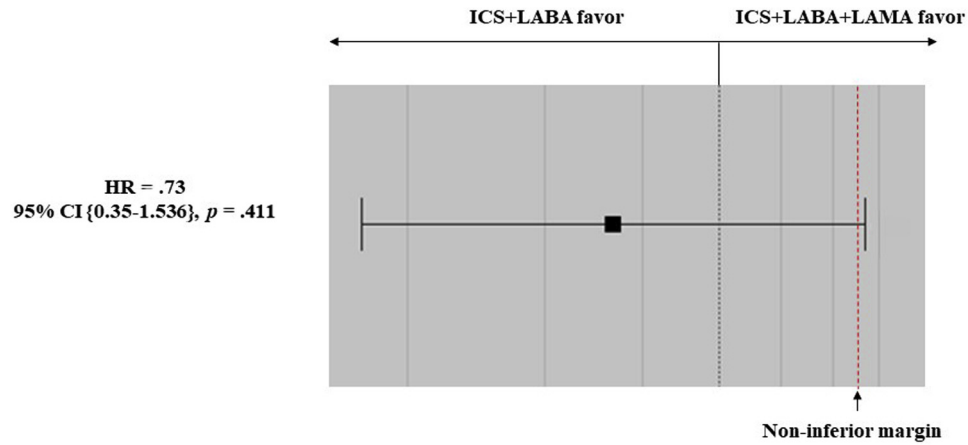


**FIGURE E3.** Treatment differences between the groups for time to first exacerbations. The error bars indicate 2-side 95% CIs. The result shows inconclusive. Only the groups of severe exacerbations were analyzed separately. ICS + LABA treatment reduces the time to first exacerbation, with HR 0.73; however, CIs (0.35-1.54) are over the noninferior margin ( $P = .411$ ).

**TABLE E1.** Summary of side effects reports related to LAMA medication

| Adverse reactions           | n |
|-----------------------------|---|
| Dry mouth                   | 2 |
| Oral pain                   | 1 |
| Upper respiratory infection | 6 |
| Palpitation                 | 1 |
| Dizziness                   | 1 |
| Dysuria, mild               | 2 |
| Dyspnea                     | 2 |
| Itching                     | 1 |
| Arthralgia                  | 2 |
| Pneumonia                   | 3 |