# Intensified Therapy with Inhaled Corticosteroids and Long-Acting β₂-Agonists at the Onset of Upper Respiratory Tract Infection to Prevent Chronic Obstructive Pulmonary Disease Exacerbations

## A Multicenter, Randomized, Double-Blind, Placebo-controlled Trial

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## ABSTRACT

**Rationale:** The efficacy of intensified combination therapy with inhaled corticosteroids (ICS) and long-acting β₂-agonists (LABA) at the onset of upper respiratory tract infection (URTI) symptoms in chronic obstructive pulmonary disease (COPD) is unknown.

**Objectives:** To evaluate whether intensified combination therapy with ICS/LABA, at the onset of URTI symptoms, decreases the incidence of COPD exacerbation occurring within 21 days of the URTI.

**Methods:** A total of 450 patients with stable, moderate to very severe COPD, were included in this investigator-initiated and -driven, double-blind, randomized, placebo-controlled study. At inclusion, patients were assigned to open-labeled low-maintenance dose ICS/LABA. Each patient was randomized either to intensified-dose ICS/LABA or placebo and instructed to start using this medication only in case of a URTI, at the onset of symptoms, twice daily, for 10 days.

**Measurements and Main Results:** The incidence of any exacerbation following a URTI was not significantly decreased in the ICS/LABA group, as compared with placebo (14.6% vs. 16.2%; hazard ratio, 0.77; 95% confidence interval, 0.46-1.33; $P = 0.321$) but the risk of severe exacerbation was decreased by 72% (hazard ratio, 0.28; 95% confidence interval, 0.11-0.74%; $P = 0.010$). In the stratified analysis, effect size was modified by disease severity, fractional exhaled nitric oxide, and the body mass index-airflow obstruction-dyspnea, and exercise score. Compared with the stable period, evidence of at least one virus was significantly more common at URTI, 10 days after URTI, and at exacerbation.

**Conclusions:** Intensified combination therapy with ICS/LABA for 10 days at URTI onset did not decrease the incidence of any COPD exacerbation but prevented severe exacerbation. Patients with more severe disease had a significant risk reduction for any exacerbation.

Clinical trial registered with www.isrctn.com (ISRCTN45572998).

**KEYWORDS:** treatment for COPD exacerbations; ICS; LABA

**AT A GLANCE COMMENTARY**

**Scientific Knowledge on the Subject:** Exacerbations are significant events in chronic obstructive pulmonary disease, contributing to morbidity, mortality, hospital admission, and health care costs. Viral upper respiratory tract infections are responsible for 40-80% of chronic obstructive pulmonary disease exacerbations, and patients who are affected frequently require hospitalization. Combination therapy with high-dose inhaled corticosteroids and long-acting $\beta_2$-agonists reduces the incidence of acute exacerbations in chronic obstructive pulmonary disease.

**What This Study Adds to the Field:** The short-term increase in the inhaled corticosteroids/long-acting $\beta_2$-agonists dosing at the onset of upper respiratory tract infection symptoms seems to lead to a clinically significant reduction of severe exacerbations in all patients and of any exacerbation in patients with more severe disease and evidence of eosinophilic airway inflammation.

Chronic obstructive pulmonary disease (COPD) is one of the fastest-growing causes of morbidity and mortality (1-4). It is the fourth leading cause of death worldwide, and a further increase in its prevalence and mortality is expected in the coming decades (1). Exacerbations are significant events in COPD, contributing to morbidity, mortality, hospital admission, health care costs, and affecting progression of disease as assessed by the rate of decline in $FEV_1$ (5-8). Thus, new approaches to reduce the burden of these episodes are urgently required (9).

Most exacerbations of COPD are triggered by either bacterial or viral infection or a combination of both (10). A growing body of evidence implicates viral respiratory tract infection as the predominant risk factor associated with exacerbations of COPD and the development of chronic airway disease (11-13). It has been estimated that viral upper respiratory tract infections (URTI) are responsible for 40-80% of COPD exacerbations, and patients who are affected frequently require hospitalization (9, 14-16). However, it is difficult to define precisely the proportion of exacerbations caused by viruses because URTI symptoms often precede COPD exacerbation by days to weeks.

Combination therapy with high-dose inhaled corticosteroids (ICS) and long-acting $\beta_2$-agonists (LABA) reduces the incidence of acute exacerbations in COPD (17). However, high-dose maintenance ICS have been associated with pneumonia (17, 18). Thus, reduction of ICS exposure to the minimum required for preventing exacerbation is a goal in the management of COPD. In asthma, a flexible regimen of ICS and LABA "on-demand" in patients on low-maintenance ICS/LABA significantly reduces steroid exposure while leading to a decrease in asthma exacerbation rate as compared with a fixed regimen of high-maintenance dose ICS/LABA (19).

The primary objective of the present study was to investigate whether intensified combination therapy with ICS/LABA at the onset of URTI could reduce exacerbations in patients with COPD receiving low-maintenance dose ICS/LABA. The secondary objectives were to investigate whether intensified combination therapy with ICS/LABA could 1) reduce hospital admission (i.e., severe exacerbation, within 21 d of an URTI); 2) improve symptom scores, modified Medical Research Council dyspnea scale, and lung function parameters on Day 10 after the onset of an URTI; and 3) reduce exposure to steroids and antibiotics within 21 days of URTI. Primary and secondary outcomes measures were assessed in subgroups of patients according to COPD severity. Some of the results of the present study have been previously reported in the form of an abstract (20).

## METHODS

### Study Design

In the present paper, we present results from the interventional part of the PREVENT (Preventing Viral Exacerbation of Chronic Obstructive Pulmonary Disease in Upper Respiratory Tract Infection) study, which was an investigator-initiated and -driven, multicenter, randomized, double-blind, controlled trial. The study was approved by each of the institutional review boards (EKBB 306/10). All patients provided written informed consent for participation in the study, which was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the guidelines on good clinical practice. Detailed methodology of the study is provided in the online supplement.

### Patients

We enrolled 450 patients with COPD, older than 40 years of age, with a smoking history of at least 10 pack-years; a post-bronchodilator $FEV_1$ less than 80% of the predicted value and a post-bronchodilator ratio of $FEV_1$ to FVC of less than 0.7 (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2-4); and a clinically relevant disease, as defined by a history of at least one exacerbation in the previous 12 months.

**Interventions**

At inclusion, all patients were assigned to open-labeled low-maintenance dose of ICS/LABA (budesonide, 200 µg/formoterol, 6 µg, twice daily), which was continued for the whole duration of the study. Concomitant medication, other than ICS/LABA, including long-acting muscarinic antagonist (LAMA), was left unchanged. In addition, each patient was block-randomized 1:1 to receive the investigational medicinal product (IMP) as an inhaler, containing either intensified dosage of the combination ICS/LABA (budesonide, 400 µg/formoterol, 12 µg) or placebo. Patients were instructed to keep the IMP at home and to start using the IMP only in case of a URTI, at the onset of the symptoms, twice daily, for 10 days. Open-labeled low-maintenance dose of ICS/LABA was continued throughout the study, including the URTI episodes. On Day 10 after each URTI and at each stable visit preceding the expiration of the previously given IMP, patients were randomized once again to a new IMP and reinstructed to keep the IMP at home and use it only in case of another URTI, at the onset of the symptoms.

Therefore, each patient could be randomized several times during the study, depending on the number of URTIs and expiration date of the IMP (*see* Figure E1 in the online supplement). Each URTI episode was treated independently of previous and subsequent URTI episodes and adjusted for clustering within patients.

**Adherence of Patients to Study Interventions**

Patients were instructed at the baseline to recognize the symptoms of URTI, to fulfill the provided questionnaires, to perform the nasopharyngeal and oral swabs, and to start inhaling the medication and contact the study center in case of persistent symptoms of URTI during at least 12 hours. These instructions have been reemphasized at every stable visit, at every patient's contact including telephone contacts every 3 month, and at the postcards that had to be sent by the patient every month reporting the events of URTI/exacerbation to order another maintenance inhaler.

In case of a URTI, all patients included in the study were instructed to be presented for a clinical visit, 10 days after the event. During this visit, patients were asked to bring their IMP along and study physicians checked the number of inhalations made by the patients from the beginning of the event to ensure adherence to treatment. This approach allowed the assessment of the effect of the intervention in the patients that were compliant (per protocol analyses).

**Randomization**

The study physician was responsible to enroll patients. At inclusion and on Day 10 following each new episode of URTI symptoms, the study physician assigned patients to the intervention. Patients were randomly assigned to receive an inhaler containing either the combination corticosteroid/LABA (budesonide, 400 µg/formoterol, 12 µg) or placebo twice a day, according to prespecified computer-generated randomization list and concealed by using the web-based, centralized password-secured website. Each patient was randomized 1:1 to the active substance or placebo using a fixed block size of 6.

**Method of Blinding**

Inhalation devices, containing both medication and placebo, were identical. The study team (coinvestigator, study physician, study nurse) were blinded in regard to allocation of study participants. None of the study investigators had access to the randomization codes. Generator and executors of randomization were separated. Study personnel, after structured training, used a website-based electronic case report form (e-CRF) to input data at the study site. The e-CRF was designed specifically for the PREVENT study by CLIN-IT, Germany, and allowed data entry at all foreseen visits. Formal training on website assess, randomization procedure, and electronic data entry was provided to all study personnel including coinvestigators. Data monitoring was performed through e-CRF and on-site.

***Table 1.*** *Baseline Characteristics of the Patients Included in the Clinical Trial\**

|  | **All Patients** *(n =450)* |
|---|---|
| Age, yr | 66.92 ± 9.37 |
| Male sex, *n* (%) | 304 (67.55) |
| BMI, kg/m$^2$ | 27.19 ± 6.38 |
| Current smoker, *n* (%) | 158(35.11) |
| Pack-years | 52.20 ± 27.73 |
| Duration of COPD, yr | 7.77 ± 1.55 |
| Mean number of exacerbations in the previous year | 1.14 ± 0.88 |
| Supervised rehabilitation in the previous 6 mo, *n* (%) | 142 (31.55) |
| Any LABA, *n* (%) | 356(79.11) |
| Any LAMA, *n* (%) | 297 (66) |
| Any inhaled glucocorticoids, *n* (%) | 326 (72.44) |
| MMRC Dyspnea scale[†] | 1.51 ± 1.00 |
| Total score on the SGRQ[‡] | 37.59 ± 17.92 |
| Score on the CAT[§] | 14.95 ± 6.88 |
| Post-bronchodilator FEV$_1$, L | 1.44 ± 0.54 |
| Post-bronchodilator FEV$_1$, % of predicted value | 54.48 ± 16.85 |
| Post-bronchodilator ratio of FEV$_1$ to FVC, % of predicted value | 45.44 ± 13.34 |
| Post-bronchodilator TLC, % of predicted value | 112.48 ± 21.12 |
| Post-bronchodilator RV, % of predicted value | 151.70 ± 49.00 |
| Post-bronchodilator ratio of RV to TLC, % of predicted value | 51.50 ± 9.75 |
| Reversibility, *n* (%)[‖] | 28 (6.62) |
| Fractional exhaled nitric oxide, ppm | 20.55 ±13.36 |
| Atopy, *n* (%)[¶] | 88 (23.40) |
| Oxygen saturation on room air, % | 94.26 ± 4.29 |
| 6-min-walk distance, m | 379.50 ±111.0 |
| Total score on the BODE** | 2.53 ± 2.04 |
| Potential pathogenic bacteria in the sputum, *n* (%) | 75(16.66) |

*Definition of abbreviations:* BMI = body mass index; BODE = body mass index-airflow obstruction-dyspnea, and exercise; CAT = COPD assessment test; COPD = chronic obstructive pulmonary disease; LABA = long-acting β$_2$-agonist; LAMA = long-acting muscarinic antagonist; MMRC = Modified Medical Research Council; ppm = parts per million; RV= residual volume; SGRQ = St. George's Respiratory Questionnaire for COPD.

*Values are presented as means ± SD, unless specified otherwise.

[†]Score on the MMRC ranges from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.

[‡]Scores on the SGRQ-C range from 0 to 100, with higher scores indicating worse health status; the minimum clinically important difference is 4 points.

[§]CAT ranges from 0 to 40, with higher scores denoting a more severe impact of COPD on a patient's life. The difference between stable and exacerbation patients was five units. No target score represents the best achievable outcome.

[‖]Reversibility was defined as a change in FEV$_1$ ≥ 12% and ≥ 200 ml when comparing prebronchodilator and post-bronchodilator values.

[¶]Atopy was defined by a positive skin prick test for at least 1 of the 16 most common aeroallergens at the inclusion sites, comprising a grass, rye, birch, hazelnut tree, alder, ash tree, ribwort, mugwort, ambrosia, *Dermatophagoides pteronyssinus, Dermatophagoides farinae,* dog hair, cat hair, *Aspergillus fumigatus, Cladosporium, Penicillium* mix.

**Score on the BODE index ranges from 0 to 10, with higher scores indicating a greater risk of death.

**IMP Accountability and Compliance**

IMP was labeled according to the regulatory requirements in all countries conducting the trial. The investigator or designee (i.e., pharmacist) was responsible for ensuring adequate accountability of all used and unused IMP. This included acknowledgment of receipt of each shipment of IMP (quantity and condition) and subject dispensing record and returned or destroyed IMP. Dispensing records documented quantities received from the sponsor and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, and the initial of the person dispensing the IMP. All IMP supplies and associated documentation was periodically reviewed and verified by the study monitor over the course of the study.

Accurate records were maintained for all used and unused IMP dispensed to and returned by each subject. At study initiation, the monitor evaluated the site's standard operating procedure for IMP disposal/destruction to ensure that it complies with good clinical practice requirements.

The sponsor provided IMP budesonide 400 µg/formoterol 12 µg or placebo. On initial receipt of IMP, the investigator and/or site staff acknowledged receipt of the material, indicating shipment content and condition. The study site maintained a dated inventory record of all IMP received and dispensed to subjects along with all IMP returned. IMPs were stored at controlled room temperature (25°C or 77°F).

Throughout the study, 1,314 IMPs were randomized for a total of 408 URTIs. The main reason for having this high number of IMPs issued was that patients were randomized during the stable visits, so that they received and kept the IMP with them at home in case of a URTI. The rationale for doing so despite the greater complexity was that, in case of a URTI, the patients could start treatment immediately at home, without requiring a further visit to the clinic, thus mimicking the procedure that would happen in real practice. In addition to the IMP issued at the baseline visit, some IMPs had to be replaced because of the limited shelf life of the IMP (24 mo from production to use, including delivery, clearing by the authorities, labeling at the site, and so forth). Thus, for some patients the IMP expired during the study and required replacement for a new one at the last stable visit before the expiration date of the IMP. This course of action ensured that, in case of a URTI, the patient would always have a valid IMP at home that could be used immediately but only in case of URTI symptoms.

**Procedures**

In case of URTI, defined as new or increased coryzal symptoms (one or more of runny or blocked nose, postnasal drip, and sneezing) for at least 12 hours, patients were instructed to collect nasopharyngeal and oral swabs and inhale the study medication twice daily, for 10 days, irrespective of symptoms and concomitantly to the low-maintenance dose of ICS/LABA. Nasopharyngeal and oral swabs were collected at the study center at stable visits, 10 days following the onset of URTI and at exacerbation. Patients who were recruited within the first 24 months of the study ($n = 383$) were followed for 36 months, and patients who were recruited within the last 12 months ($n = 67$) were followed for 18 months. COPD exacerbation was defined as mild (requiring medical care and an increased dose of short-acting $\beta_2$-agonists), moderate (requiring either antibiotics and/or parenteral corticosteroids), and severe (requiring hospitalization or resulting in death) (21). Management of COPD exacerbations was left up to the discretion of the treating physician and was not influenced by study personnel. Health status was verified every 6 weeks by consulting the patient's diaries (recording any URTI, exacerbation, and use of steroids and antibiotics) and the healthcare records of all involved providers.

Regular, scheduled interviews were performed every 6 weeks over the telephone and every 6 months on-site throughout the study period.

**Table 2.** *Characteristics of the Patients Developing a URTI**

| | **ICS/LABA** | | | |
| | **All URTI** *(n=408)* | **Group** *(n = 192)* | **Placebo Group** *(n=216)* | **P Value** |
|---|---|---|---|---|
| Age, yr | 65.65 ± 8.80 | 65.53 ± 9.03 | 65.75 ± 8.60 | 0.865 |
| Male sex, *n* (%) | 264 (64.70) | 129 (67.18) | 135 (62.50) | 0.351 |
| Current smoker, *n* (%) | 134 (32.84) | 59 (30.72) | 75 (34.72) | 0.400 |
| Severity of airflow obstruction, *n* (%) | | | | |
| GOLD 1 [†] | 35 (8.66) | 20 (10.47) | 15(7.04) | 0.650 |
| GOLD 2 | 238 (58.91) | 110 (57.59) | 128 (60.09) | |
| GOLD 3 | 107 (26.48) | 49 (25.65) | 58 (27.23) | |
| GOLD 4 | 24 (5.940) | 12 (6.28) | 12 (5.63) | |
| Severity of the disease, *n* (%)[†] | | | | |
| Group A | 68 (16.83) | 30 (15.70) | 38(17.84) | 0.852 |
| Group B | 188 (46.53) | 92 (48.16) | 96 (45.07) | |
| Group C | 13(3.22) | 7 (3.66) | 6 (2.82) | |
| Group D | 135 (33.41) | 62 (32.46) | 73 (34.27) | |
| MMRC Dyspnea Scale, *n* (%)[‡§] | | | | |
| Grade 0 | 100 (24.63) | 48 (25.13) | 52 (24.18) | 0.903 |
| Grade 1 | 155(38.17) | 73 (38.21) | 82 (38.13) | |
| Grade 2 | 102 (25.12) | 50 (26.17) | 52 (24.18) | |
| Grade 3 | 43 (10.59) | 18 (9.424) | 25 (11.62) | |
| Grade 4 | 6 (1.477) | 2 (1.047) | 4 (1.860) | |
| Any LAMA, *n* (%) | 277 (67.89) | 127 (66.14) | 150 (69.44) | 0.524 |
| Reversibility, *n* (%)[‖] | 36 (8.91) | 19 (9.95) | 17 (7.98) | 0.600 |
| Fractional exhaled nitric oxide, ppm | 21.00 ±13.81 | 22.12 ±15.15 | 20.04 ±12.50 | 0.251 |
| Atopy, *n* (%)[¶] | 117(29.17) | 54 (28.72) | 63 (29.57) | 0.912 |
| Contact with cold within 1 wk, *n* (%) | 132 (32.67) | 61 (31.94) | 71 (33.33) | 0.765 |
| Contact with kid within 1 wk, *n* (%) | 84 (20.69) | 39 (20.42) | 45 (20.93) | 0.899 |
| Total score on WURSS-21** | 61.11 ±24.34 | 61.31 ± 22.60 | 60.94 ± 25.86 | 0.973 |
| Viral infection, *n* (%) | 206 (52.68) | 102 (53.96) | 104(51.48) | 0.685 |

*Definition of abbreviations:* GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroids; LABA= long-acting β₂-agonists; LAMA = long-acting muscarinic antagonist; MMRC = Modified Medical Research Council; ppm = parts per million; URTI = upper respiratory tract infection; WURSS-21 = Wisconsin Upper Respiratory Symptom Survey-21.

*A total of 202 patients suffered one or more URTIs (408 URTIs in total) during the study. Chi-square test or Fisher exact test, as applicable, for proportion comparisons and Mann-Whitney *U* test for comparisons of continuous parameters. Characteristics were assessed at the last stable visit before the URTI or at the URTI. Data are presented as means ± SD, unless specified otherwise.

[†]Although all patients had $FEV_1$ <80% at inclusion, some patients were reclassified as GOLD 1 during the trial because of an improvement in $FEV_1$ at a visit at stable state. For four patients, $FEV_1$ measurements at stable visit before the URTI could not be performed.

[‡]The severity of COPD was determined on the basis of the GOLD 2015 staging system, in which group A indicates low risk and low symptom burden, group B low risk and high symptom burden, group C high risk and low symptom burden, and group D high risk and high symptom burden.

[§]Score on the MMRC ranges from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.

[‖]Reversibility was defined as a change in $FEV_1 \geq 12\%$ and $\geq 200$ ml when comparing prebronchodilator and post-bronchodilator values.

[¶]Atopy was defined by a positive skin prick test for at least 1 of the 16 most common aeroallergens at the inclusion sites, comprising a grass, rye, birch, hazelnut tree, alder, ash tree, ribwort, mugwort, ambrosia, *Dermatophagoides pteronyssinus, Dermatophagoides farinae,* dog hair, cat hair, *Aspergillus fumigatus, Cladosporium, Penicillium* mix.

**WURSS-21 ranges from 0 to 140, with higher scores indicating worse cold-specific quality-of-life. The minimal important difference is 10.3.

*Figure 1*. The Consolidated Standards of Reporting Trials flow diagram for the PREVENT (Preventing Viral Exacerbation of Chronic Obstructive Pulmonary Disease in Upper Respiratory Tract Infection) study. ICS = inhaled corticosteroids; IMP = investigational medicinal product; LABA= long-acting $\beta_2$-agonists; URTI = upper respiratory tract infection.
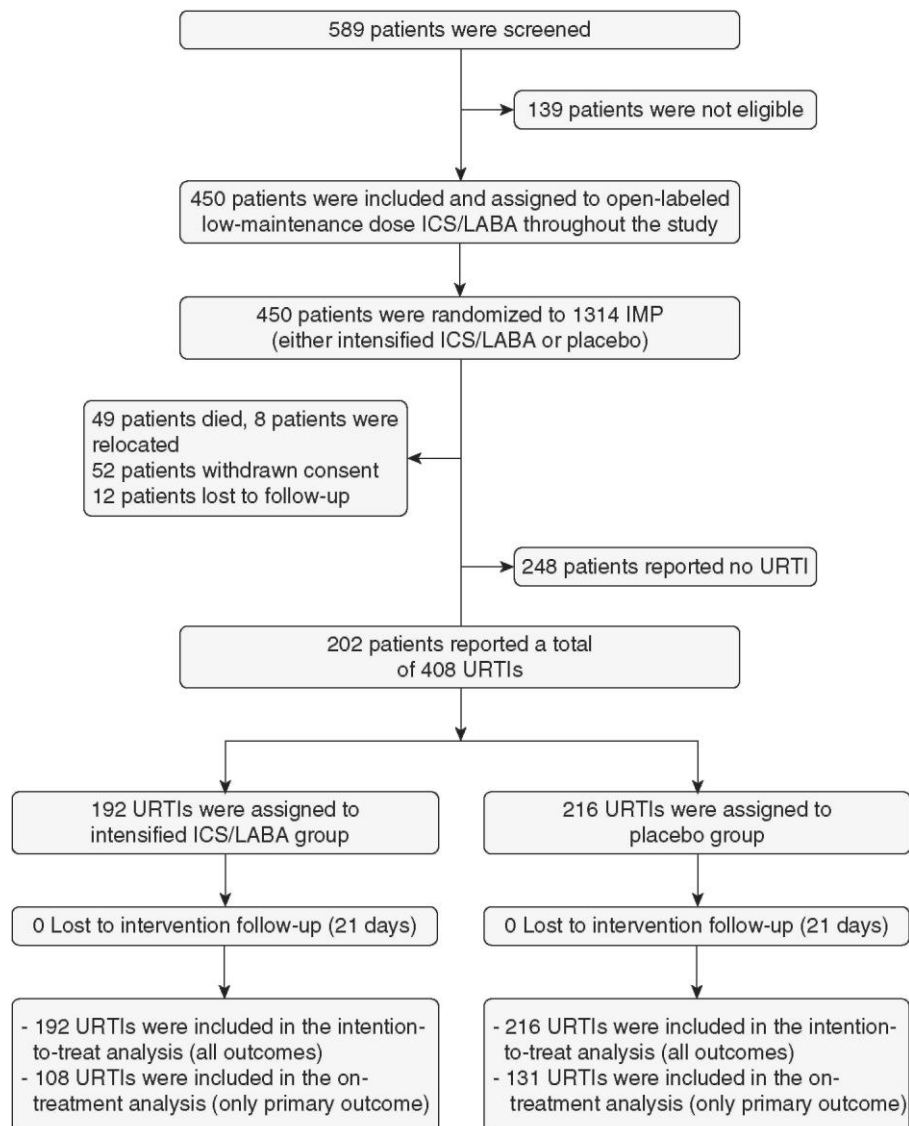
**Primary and Secondary Outcome Measures**

The primary outcome measure was the number of patients that had an exacerbation occurring within 21 days after the onset of a URTI. The secondary outcomes measures were 1) number of patients that required hospital admission of any cause within 21 days after URTI onset; 2) change in symptoms scores and lung function parameters (FVC, $FEV_1$, $FEV_1$/FVC ratio as absolute values and % predicted) on Day 10 after the onset of a URTI; and 3) exposure to steroids and antibiotics within 21 days of URTI.

**Prespecified Subgroup Analysis**

In a second step, primary and secondary outcomes were assessed in subgroups of patients according to COPD severity.

**Sample Size**

The sample size was based on the ability to detect superiority of the ICS/LABA treatment group regarding the incidence of exacerbations given a 43% projected proportion of exacerbation within 21 days after the onset of URTI and a median frequency of URTI symptoms of 1.3 episodes per patient/year (9). Therefore, the overall projected incidence of URTI episodes was 745 for the duration of the study.

A relative risk reduction of 25% (absolute risk reduction of 15%) of the primary endpoint in comparison with placebo was assumed to be clinically meaningful. A total of 310 patients, 155 in each treatment arm, would be needed to detect a difference of 15% in the proportion of patients with exacerbation with 21 days of URTI onset with a power of 80% using a two-sided $P$ equal to 0.05 level test. Considering a 10% loss to follow-up and the possibility of a lower prevalence of URTI among optimally treated patients with COPD, a total of 450 patients were enrolled to ensure an adequate sample size.

**Statistical Analysis**

The detailed methodology used for the analysis of the primary and secondary endpoints is provided in the online supplement. The cumulative probability for any exacerbation and for hospital admission within 21 days after the onset of a URTI was investigated using a Cox proportional hazards regression model for recurrent events and adjusted for clustering within patients. To investigate if there was a carryover effect of a previous treatment or of the time interval between URTI episodes, we performed five different models by introducing different variables in the Cox regression models. The risk ratio of a severe exacerbation within 21 days after a URTI was calculated using a Cox proportional hazards regression model adjusted for clustering within patients.

**Figure 2.** *Hazard ratio and cumulative probability of any exacerbation and of a severe exacerbation between 0 and 21 days after onset of an upper respiratory tract infection (URTI) in the inhaled corticosteroids (ICS)/long-acting β₂-agonists (LABA) and placebo groups. (A) Hazard ratio for any exacerbations and for severe exacerbations in the intensified ICS/LABA group (budesonide 400 μg/formoterol 12 μg) as compared with the placebo group (budesonide 200 μg/formoterol 6 μg). The bars indicate 95% confidence intervals. Cumulative probability for any exacerbation (B) and for severe exacerbation (C) in the ICS/LABA group and the placebo group. To illustrate the time course of exacerbation events after URTIs, the same follow-up time scale for each person was used, with Day 0 at enrollment. For each day of follow-up and for each of the two treatments, the number of prior events and the number of days at risk were cumulated following a URTI under the respective treatment. The cumulative number of respective events was then plotted against the cumulative number of respective days at risk for each of the two treatments. The analyses were performed in the intention-to-treat population that included all patients who underwent randomization and reported a URTI (i.e., only patients who suffered URTIs were at risk). Chronic obstructive pulmonary disease exacerbation was defined as severe if requiring hospitalization or resulting in death. The presented P value is that derived from a Cox proportional hazards regression model for recurrent events and adjusted for clustering within patients. \*A patient could be assigned to a different treatment at onset of different URTIs, which occurred over the time of the study. §Censoring time for patients without an event or previous censoring was 21 days. Numbers in parenthesis are censored patients at a certain time. CI = confidence interval; HR = hazard ratio.*

**B**

Event: any exacerbation
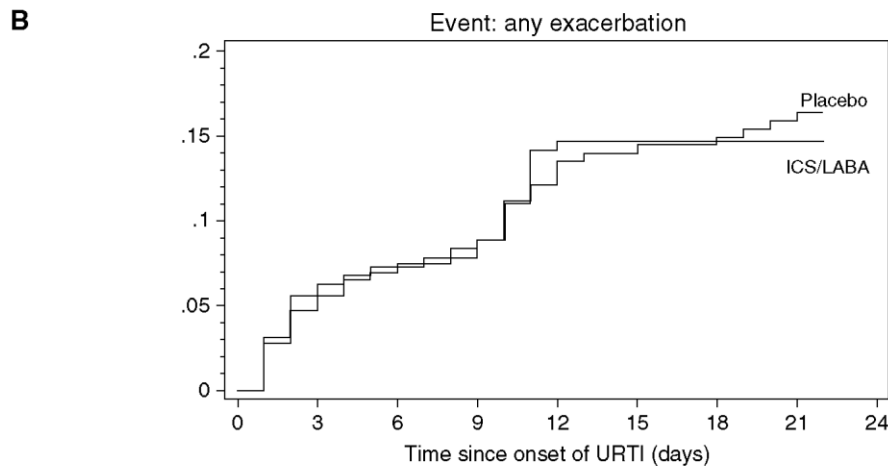
Patients at risk*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 216 | 203(1) | 199 | 195(1) | 184(1) | 180 | 179(2) | 175(1)§ |
| ICS/LABA | 192 | 180 | 177(1) | 173(1) | 162 | 159(3) | 159 | 159§ |

**C**

Event: severe exacerbation
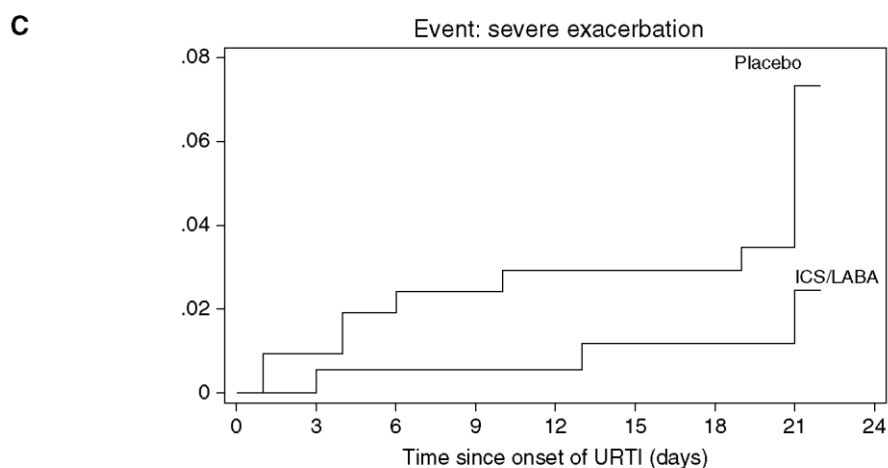
Patients at risk*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 212 | 200(10) | 196(1) | 193(3) | 183(9) | 179(4) | 178(1) | 167(3)§ |
| ICS/LABA | 188 | 176(11) | 173(3) | 170(3) | 159(11) | 156(2) | 156(0) | 153(1)§ |

**RESULTS**

A total of 450 patients were included in the study (Table 1). Of those, 54.7% were using triple therapy (LABA, LAMA, and ICS) and 5% had at least one respiratory virus detected at the time of inclusion. Throughout the study, 1,314 IMPs were randomized; 656 corresponding to intensified ICS/LABA and 658 corresponding to placebo. A total of 408 URTIs were reported; 192 were assigned to the ICS/LABA group and 216 were assigned to the placebo group (Figure 1). A total of 196 exacerbations were observed in 122 patients. From these exacerbations, 26 (13.3%) were mild, 124 (63.3%) were moderate, and 46 (23.5%) were severe. From the 122 patients, 26 patients (21.3%) had URTI-related exacerbations, 74 patients (60.7%) had non-URTI exacerbations, and 22 patients (18.0%) had non-URTI- and URTI-related exacerbations. The time to a URTI-related exacerbation was $6.9 \pm 5.2$ days (mean $\pm$ SD), the median (interquartile range) was 7 (2-11) days, and the range was 1-21.

Disease characteristics at the last stable visit before URTI and at URTI were well balanced between randomized groups (Table 2). Mean follow-up was $712 \pm 338$ days, totaling 877 person-years.

In the intention-to-treat analysis, the proportion of patients developing any exacerbation following a URTI was 14.58% in the ICS/LABA group as compared with 16.20% in the placebo group (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.46-1.28; $P = 0.312$) (Figures 2A and 2B). Similar results were observed in the per protocol analysis (HR, 0.82; 95% CI, 0.36-1.85; $P = 0.626$). Analyses of all other outcomes were performed in the intention-to-treat population.

All hospital admissions occurring within 21 days of a URTI were caused by exacerbation of COPD (i.e., severe exacerbation). The percentage of patients who developed a severe exacerbation of COPD within 21 days of a URTI was significantly lower in the ICS/LABA group (2.1%), as compared with the placebo group (6.6%) (HR, 0.28; 95% CI, 0.11-0.74, representing a 72% lower risk; $P = 0.010$) (Figure 2A). The risk ratio of a severe exacerbation within 21 days after a URTI was 0.32 (95% CI, 0.12-0.87; $P = 0.026$). The cumulative probability for any exacerbation and for severe exacerbation within 21 days after the onset of a URTI is shown in Figures 2B and 2C.

The risk of a COPD exacerbation was always lower and within a certain range for the ICS/LABA group, as compared with the placebo group, despite different previous treatment or different time intervals between URTI events (*see* Table E1).

In the stratified analysis, an effect modification was observed for disease severity, for fractional exhaled nitric oxide ($FE_{NO}$) levels at inclusion, and for the score on the body mass index-airflow obstruction-dyspnea, and exercise (BODE) index. The risk of exacerbation was significantly decreased by 77% in patients with severe airflow limitation ($FEV_1 \leq 50\%$) (HR, 0.23; 95% CI, 0.09-0.61; $P = 0.003$), and by 76% in patients with more severe disease (GOLD C and D) (HR, 0.24; 95% CI, 0.11-0.54; $P < 0.001$), in the ICS/LABA group (Figure 3A). The cumulative risk of any exacerbation developed under URTI according to the disease severity is depicted in Figure 3B.

Among patients with $FE_{NO}$ levels above the median ($\geq 15.5$ parts per million) in the stable state, the exacerbation risk was significantly lower in the LABA/ICS group than in the placebo group (HR, 0.41; 95% CI, 0.18-0.91, representing a 59% lower risk; $P = 0.028$) (Figure 3A). However, when the data were analyzed by quartiles, there was no direct association of the $FE_{NO}$ levels and the effect of ICS/LABA on the exacerbation risk ($P = 0.120$) (Table E2). Among patients with a total BODE score greater than or equal to two points in the stable state, the exacerbation rate was also significantly lower in the LABA/ICS group than in the placebo group (HR, 0.51; 95% CI, 0.27-0.99; $P = 0.046$) (Figure 3A).

The exacerbation risk differed across BODE quartiles and patients categorized in the fourth quartile (BODE score $\geq 3$ points) showed the highest reduction for exacerbation risk in the LABA/ICS group as compared with the placebo group (HR, 0.16; 95% CI, 0.06-0.45, representing an 84% lower risk; $P < 0.001$) (Table E3). The detection of at least one of the 18 respiratory viruses (HR, 0.96; 95% CI, 0.42-2.17; $P = 0.921$) or of rhinovirus (HR, 1.05; 95% CI, 0.26-4.28; $P = 0.941$) did not seem to change the effect of the intervention.

Although URTI symptoms (stuffed or running nose, sniffle, sneeze) significantly improved within 10 days of URTI onset (Table E4), there was a significant increase in lower respiratory symptoms (shortness of breath, cough, sputum) (Table E5), St. George's Respiratory Questionnaire total score, COPD Assessment Test score, modified Medical Research Council score, and a significant deterioration in lung function parameters on Day 10 following URTI compared with the last stable visit (Table E6). The mean deterioration of the St. George's Respiratory Questionnaire on Day 10 following URTI was greater than the reported minimum clinically important difference.

The changes were similar in those developing or not an exacerbation within 21 days of URTI onset.

The changes in symptoms scores and lung function parameters were smaller (i.e., less deterioration) in the ICS/LABA group, as compared with the placebo group (Table E7) and reached statistical significance for the $FEV_1$/FVC ratio in patients with more severe disease (i.e., GOLD C and D; mean difference, 1.78; 95% CI, -0.08 to 3.64 for ICS/LABA; mean difference, -0.91; 95% CI, -2.73 to 1.11 for placebo; $P$ = 0.036) (Table E8).

The exposure to systemic steroids and antibiotics within 21 days of URTI onset was similar in the ICS/LABA and placebo groups (Tables E9-E11). Evidence of at least one respiratory virus was significantly more common at exacerbation (39.0%; $P < 0.001$), at URTI onset (52.7%; $P< 0.001$), and at 10 days following a URTI (15.2%; $P < 0.001$), as compared with the stable period of the disease (5.4%) (Table E12).

**Discussion**

Intensified therapy with ICS/LABA at the onset of URTI, for 10 days, could not decrease significantly the incidence of any exacerbation, as compared with placebo, in patients with COPD already receiving low-maintenance dose ICS/LABA. Nonetheless, this approach significantly reduced the risk of severe exacerbation and of any exacerbation by more than 75% in patients with severe airflow obstruction (GOLD 3-4), and in those with higher risk (GOLD C and D). Patients estimated to have a compromised survival (BODE ≥ 2 points) and those with higher exhaled nitric oxide (suggesting eosinophilic airway inflammation) were also among those in whom the intensified therapy with ICS/LABA was more beneficial in reducing the rate of exacerbations.

Several studies suggest that bronchodilators prevent exacerbations as reviewed by Wedzicha and colleagues (22). It has been suggested that repeated doses of both formoterol and salmeterol induce an effective dose-dependent increase in lung function in patients suffering from COPD exacerbations; however, only formoterol induced a fast onset of action (23). The beneficial effects of corticosteroids in COPD exacerbations have also been widely described. In a randomized placebo-controlled trial, nebulized budesonide was shown to be an alternative to oral prednisolone in the treatment of nonacidotic exacerbations of COPD (24). The same results were also confirmed in a later study including patients that were hospitalized for exacerbations of COPD (25). Etanercept, a tumor necrosis factor-α antagonist, was not more effective than prednisone for treatment of acute exacerbations of COPD and efficacy of prednisone was most apparent in patients with serum eosinophils greater than 2% (26). The combination of ICS/LABA has been considered, however, the cornerstone therapy for severe COPD, mainly because of its ability to decrease exacerbation rate (27, 28). The combination therapy with single inhaler containing budesonide and formoterol has been previously suggested as an alternative to traditional therapy in the treatment of acute exacerbations of COPD (29). It is likely that formoterol, when combined with budesonide, might better influence the control of symptoms in such a pathologic condition.

In a recent proof of concept study, the feasibility and safety of a new strategy that includes early treatment of acute exacerbations of COPD with doubling dose of a combination of ICS/LABA was assessed in 37 outpatients with COPD (30). This strategy was shown to be safe, well-tolerated, and adhered to and resulted in no requirement of systemic corticosteroid in a large proportion of patients presenting with mild-to-moderate worsening of dyspnea. It has also been shown that the combination of budesonide and formoterol can significantly improve spirometry and influence the degree of pulmonary hyperinflation, even after their single dose inhalation (31). Sustained reduction in lung hyperinflation may in turn lessen dyspnea during an exacerbation. However, novel data suggest that withdrawal of ICS in patients on combined bronchodilator therapy with LABA/LAMA does not necessarily increase the exacerbation rate (32) and that the dual bronchodilator regimen might be superior to the combination ICS/LABA in preventing exacerbation (33).

All patients included in our study had a history of previous exacerbations and were assigned to low-maintenance dose of ICS/LABA throughout the study. Such treatment is recommended for patients with COPD with a history of exacerbations in the GOLD guidelines and it represents common practice as shown in large epidemiologic studies (34, 35). Furthermore, higher doses of budesonide/formoterol (320/9 μg, twice daily) than the doses we have used in our study have been used in several randomized control trials, as maintenance therapy for long periods of 6-12 months in large COPD cohorts (36, 37). The data from the present trial suggest that the short-term increase in the ICS/LABA dosage at the onset of URTI symptoms in patients receiving dual therapy with LABA/LAMA, corresponding to 66% of all patients included in the study, did not significantly reduce exacerbation risk. However, the consistent effect among patients with more severe disease, based on lung function impairment, risk of exacerbation, and survival expectancy, confirmed the efficacy of intensified treatment with ICS/LABA in a selected, more severe COPD population.

Most importantly, the results suggest the hypothesis that exacerbation risk could be reduced by an intermittent increase in ICS/LABA dosing at the onset of URTI symptoms. Whether the chronic use of high doses of ICS could be decreased by such an approach remains to be elucidated.

***Figure 3.*** *Exacerbation risk stratified by baseline characteristics and disease severity. (A) Hazard ratio for any exacerbation in the inhaled corticosteroids (ICS)/long-acting $\beta_2$-agonists (LABA) group as compared with the placebo group in the population stratified by baseline characteristics. (B) Cumulative probability for any exacerbation according to airflow obstruction in patients with $FEV_1$ greater than or equal to 50% (Global Initiative for Chronic Obstructive Lung Disease [GOLD] 1 + 2) and $FEV_1$ less than 50% (GOLD 3 + 4), and cumulative probability of any exacerbation according to disease severity in patients categorized as GOLD A + B and GOLD C + D in the ICS/LABA group and the placebo group. The analyses were performed in the intention-to-treat population. The intention-to-treat population included all patients who underwent randomization and reported an upper respiratory tract infection (URTI) (i.e., only patients who suffered URTIs were at risk). The severity of airflow limitation was determined according to the 2011 GOLD recommendations, in which moderate disease is indicated by an $FEV_1$ of 50-79% of the predicted value, severe disease by an $FEV_1$ of 30-49% of the predicted value, and very severe disease by an $FEV_1$ of less than 30% of the predicted value. Although all patients had $FEV_1$ less than 80% at inclusion, some patients were reclassified as GOLD 1 during the trial because of an improvement in $FEV_1$ at a visit at stable state. The severity of chronic obstructive pulmonary disease (COPD) was determined on the basis of the 2015 GOLD staging system, in which group A indicates low risk and low symptom burden, group B low risk and high symptom burden, group C high risk and low symptom burden, and group D high risk and high symptom burden. Characteristics were assessed at the last stable visit before the URTI or at the URTI. Score on the Modified Medical Research Council Dyspnea scale ranges from 0 to 4, with a score of 4*
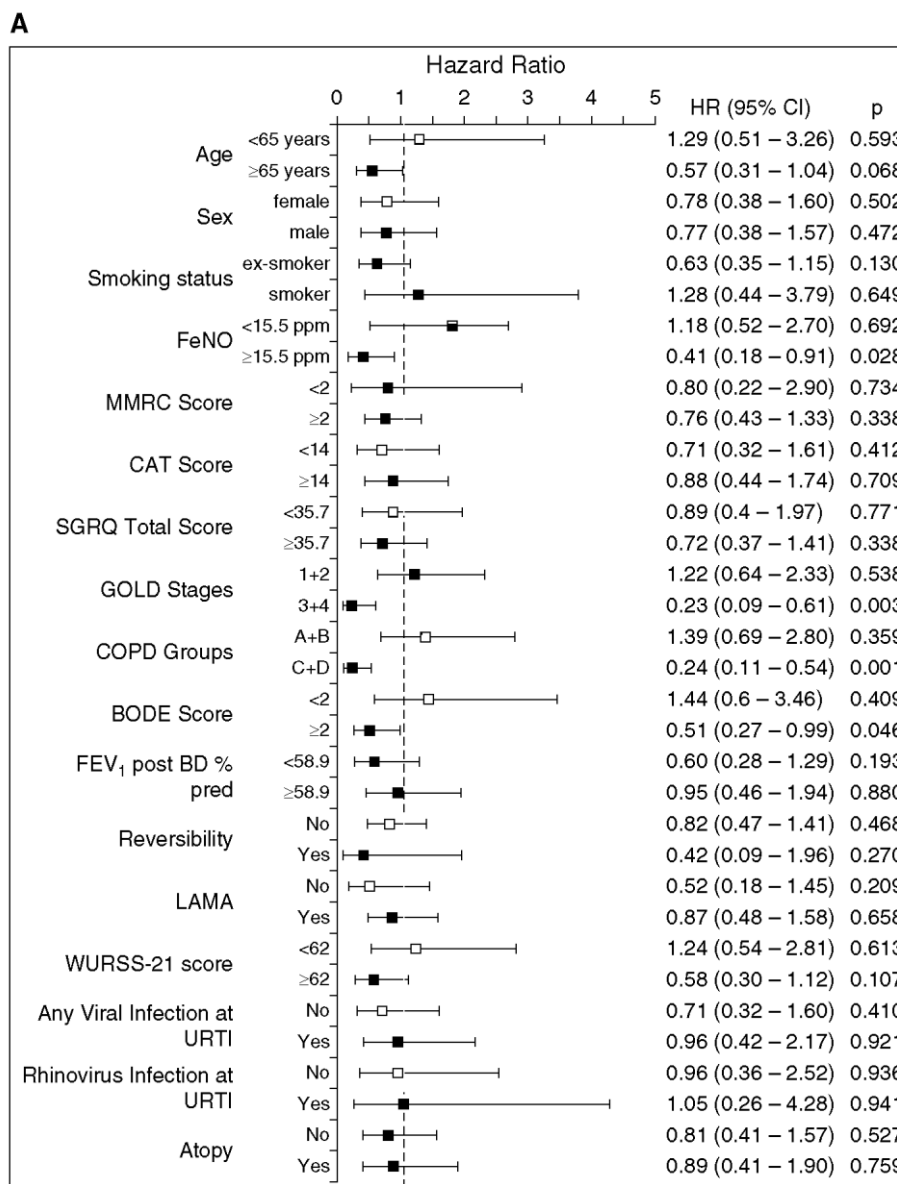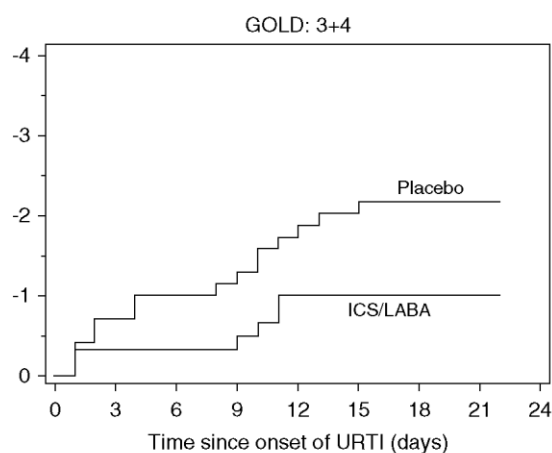
**Figure 3.** *(Continued), indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing. COPD Assessment Test ranges from 0 to 40, with higher scores denoting a more severe impact of COPD on a patient's life. The difference between stable and exacerbation patients was five units. No target score represents the best achievable outcome. Scores on the St. George's Respiratory Questionnaire for COPD range from 0 to 100, with higher scores indicating worse health status; the minimum clinically important difference is 4 points. Score on the body mass index-airflow obstruction-dyspnea, and exercise index ranges from 0 to 10, with higher scores indicating a greater risk of death. Reversibility was defined as a change in $FEV_1$ 5 ≥ 12% and ≥ 200 ml when comparing prebronchodilator and post-bronchodilator values. Wisconsin Upper Respiratory Symptom Survey-21 ranges from 0 to 140, with higher scores indicating worse cold-specific quality-of-life. The minimal important difference is 10.3. Atopy was defined by a positive skin-prick test to any aeroallergen. *A patient could be assigned to a different treatment at onset of different URTIs, which occurred over the time of the study. §Censoring time for patients without an event or previous censoring was 21 days. Numbers in parenthesis are censored patients at a certain time. BD = bronchodilator; BODE = body mass index-airflow obstruction-dyspnea, and exercise; CAT = COPD assessment test; CI = confidence interval; $FE_{NO}$ = fractional exhaled nitric oxide; HR = hazard ratio; LAMA = long-acting muscarinic antagonist; MMRC = Modified Medical Research Council; ppm = parts per million; pred = predicted; SGRQ = St. George's Respiratory Questionnaire for COPD; WURSS-21 = Wisconsin Upper Respiratory Symptom Survey-21.*
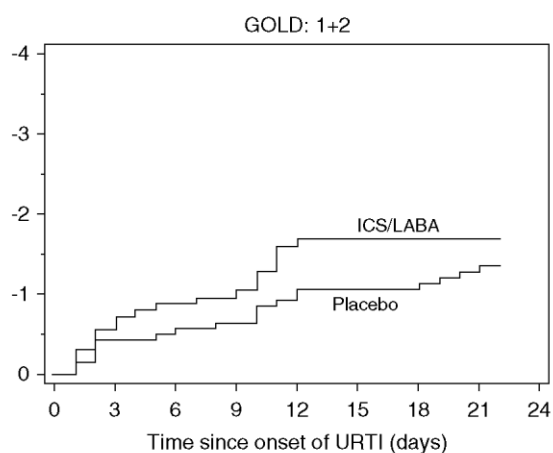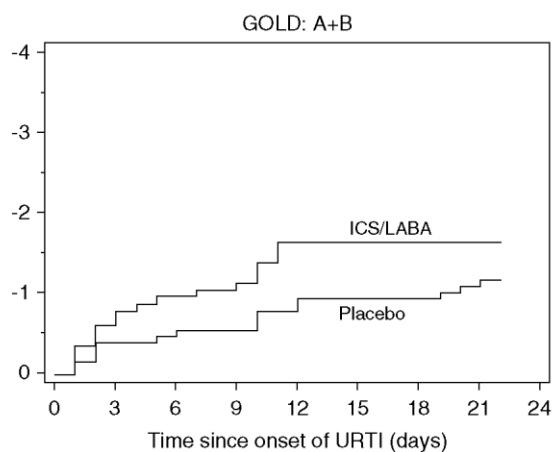


| B GOLD: 1+2 — Patients at risk* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 141 | 135 | 133 | 131(1) | 125 | 124(1) | 123 | 120§ |
| ICS/LABA | 124 | 115 | 111 | 103 | 101(1) | 101 | 101 | 101§ |

| GOLD: 3+4 — Patients at risk* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 70 | 64(1) | 62 | 60 | 55(1) | 52(1) | 52 | 52§ |
| ICS/LABA | 60 | 58 | 57(1) | 56 | 53 | 52(1) | 51(1) | 50(1)§ |

| GOLD: A+B — Patients at risk* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 132 | 127 | 125 | 124 (1) | 119 | 118(1) | 118 | 114§ |
| ICS/LABA | 117 | 108 | 106 | 104 | 98 | 96(1) | 95 | 95§ |

| GOLD: C+D — Patients at risk* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 79 | 72(1) | 70 | 67 | 61(1) | 58(1) | 57 | 57§ |
| ICS/LABA | 69 | 67 | 65(1) | 65 | 60 | 59(1) | 58(1) | 58§ |
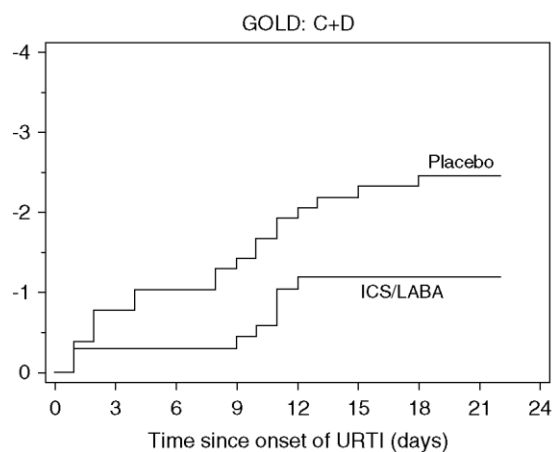
In this trial, we observed that the ICS/LABA regimen had a greater efficacy in reducing exacerbations among patients with higher levels of $FE_{NO}$ at the stable state. Thus, $FE_{NO}$ might be increased in the subgroup of patients with COPD with predominantly eosinophilic airway inflammation, which, in contrast to neutrophilic inflammation, tends to respond to glucocorticoids. As it was published by the American Thoracic Society (38) in chronic inflammatory airway diseases, complementary to conventional tests, such as $FEV_1$ reversibility or provocation tests, that are only indirectly associated with airway inflammation, measurement of $FE_{NO}$ offers added advantages for patient care including, but not limited to, detecting eosinophilic airway inflammation and determining the likelihood of corticosteroid responsiveness. Although most evidence relies on asthma, we decided to investigate this aspect in patients with COPD. Of note, $FE_{NO}$ values among patients with COPD, most receiving ICS before inclusion, were much lower than those observed among patients with asthma and there was no exacerbation risk reduction across $FE_{NO}$ quartiles. Nevertheless, this observation justifies a more detailed evaluation of $FE_{NO}$ as a potential easy and noninvasive marker for ICS response in COPD. Furthermore, it may be of interest to evaluate the association of $FE_{NO}$ and eosinophils in COPD. Our results, however, should be interpreted with caution and we certainly need larger studies to narrow CIs.

We found that there was a significant deterioration of respiratory symptoms, quality of life, and lung function 10 days after the onset of URTI symptoms. This worsening was not restricted to patients fulfilling the European Respiratory Society/American Thoracic Society exacerbation definition criteria, but was also observed in patients who did not require a change in medication or hospitalization because of an increase in COPD symptoms. Consequently, the use of an alternative exacerbation definition (i.e., based on symptoms only) could have evidenced milder events and thus higher rates of exacerbations. It is possible that inclusion of such events could have made it more likely to evidence a superiority of the treatment.

Our results extend previous findings regarding the temporal relationship between URTI symptoms and exacerbations of COPD by rigorously analyzing virus detection at URTI onset, 10 days thereafter, at exacerbation, and at the stable state. A previous report, based on diary recordings, suggested that more than two-thirds of the exacerbations were associated with upper respiratory tract symptoms (39). The importance of colds in COPD exacerbation risk and severity, even in the absence of virus detection, has been recently emphasized (40). Yet, according to an earlier study, there is evidence that exacerbation frequency in COPD is associated with an increased frequency of acquiring the common cold, rather than an increased propensity to exacerbation once a cold has been acquired (9). In this study, exacerbations were assessed using a symptom score, whereas in our study, exacerbations were defined according to the current American Thoracic Society/European Respiratory Society guidelines, as an acute worsening of respiratory symptoms that results in change in therapy. In that study, there was a concomitant onset of the cold and the exacerbation symptoms in most cases, whereas only 13% of the exacerbations were preceded by cold symptoms. These findings are consistent with the 15.4% incidence of exacerbation within 21 days of the onset of coryzal symptoms observed in our study. Hence, coryzal symptoms and exacerbation symptoms usually occurred in parallel, reflecting a simultaneous rather than sequential infection of the upper and lower respiratory tracts in patients with COPD.

Potential limitations of the trial include the relatively small number of patients included and the low number of exacerbations most likely because the diagnosis of exacerbations was restricted to the events fulfilling the criteria suggested by the official European Respiratory Society/American Thoracic Society recommendations (41). It is therefore conceivable that the efficacy of the intensified ICS/LABA therapy in reducing exacerbations could have been underestimated because of a β error, which is typically related to the sample size. Furthermore, the low number of events would prevent refuting the null hypothesis, which is "intensified therapy with ICS/LABA does not reduce exacerbations after URTI." However, the fact that we could demonstrate that intensified combination therapy with ICS/LABA significantly reduced the risk of severe exacerbations in all patients and the risk of any exacerbation in patients with more severe disease, advocates for the adequacy of the sample size. Because of the absence of a gold standard test, the heterogeneity of presentation and severity, and patient-associated factors and comorbidities, the diagnosis of an exacerbation of COPD remains challenging. The uncertainties related to the exacerbation diagnosis are, however, a ubiquitous problem afflicting all COPD studies. The double-blinded, placebo-controlled design of our study is therefore imminent to ensure that the difficulties associated with exacerbation diagnosis are, at most, a nondifferential, measurement error, which tends to bias the results toward the null (e.g., decrease the probability to refute the null hypotheses despite that fact that a difference between the groups is present).

Strengths of the trial include the investigator-initiated and -driven, multicenter, original design; the extensive characterization of the patient population and events, which included body plethysmography; the reasonable exclusion criteria ensuring clinical generalizability; and the extensive, longitudinal data on virus infection, adding up to more than 50,000 individual viral PCRs. Furthermore, because of the study design, patients were able to initiate their treatment at the onset of a URTI without the unnecessary delay of an extra hospital visit.

This procedure replicates the sequence of events plausible in the clinical routine thus ensuring reliability, validity, and transferability of these results beyond the research setting.

In conclusion, we found that intensified combination therapy with ICS/LABA for 10 days at the onset of a URTI failed to significantly prevent exacerbations of COPD. However, this approach significantly reduced the risk of severe exacerbation in all patients and the risk of any exacerbation in patients with more severe disease. These findings have potential implications and applicability for general practitioners, internists, and respiratory physicians, when treating patients with COPD.

Author disclosures are available with the text of this article at www.atsjournals.org.

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