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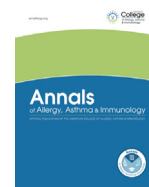
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# Global Initiative for Asthma 2016–derived asthma control with fluticasone propionate and salmeterol

## A Gaining Optimal Asthma Control (GOAL) study reanalysis

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### ABSTRACT

**Background:** In 2004, the landmark Gaining Optimal Asthma Control (GOAL) study demonstrated that most patients can achieve asthma control through sustained treatment and that adding a long-acting  $\beta_2$ -adrenoreceptor agonist to an inhaled corticosteroid (ICS) is more effective than ICS alone in this regard. Definitions of asthma control have since evolved, and the consequent implications for the GOAL study findings are unclear. **Objective:** To evaluate the efficacy of fluticasone propionate and salmeterol and fluticasone propionate alone in achieving and maintaining asthma control, as derived from the Global Initiative for Asthma (GINA) 2016 report. **Methods:** In total, 3416 patients were stratified by prior medication (ICS-naïve [stratum 1], low-dose ICS [stratum 2], or medium-dose ICS [stratum 3]) and randomized to receive fluticasone propionate and salmeterol or fluticasone propionate. The primary end point was the proportion of patients achieving well-controlled or partly controlled asthma; secondary end points included the proportion of patients achieving well-controlled asthma. Control was evaluated during the last 4 weeks of each dose titration. **Results:** In all strata, more patients achieved well-controlled or partly controlled asthma with fluticasone propionate and salmeterol vs fluticasone propionate alone (stratum 1: 91% vs 85%;  $P = .003$ ; stratum 2: 86% vs 82%;  $P = .07$ ; and stratum 3: 76% vs 66%;  $P < .001$ ), as well as patients with well-controlled asthma (stratum 1: 64% vs 56%;  $P = .005$ ; stratum 2: 59% vs 41%;  $P < .001$ ; and stratum 3: 40% vs 22%;  $P < .001$ ). **Conclusion:** A markedly higher proportion of patients with uncontrolled asthma in each stratum achieved control according to GINA 2016 criteria compared with the original study criteria. The proportion of patients achieving control remained greater with fluticasone propionate and salmeterol than with fluticasone propionate alone.

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**Table 1**  
Asthma Control Criteria From the Original GOAL Study and the Post Hoc Analysis (Based on GINA 2016 Criteria)<sup>5,12</sup>

Variable	Original GOAL study		Post hoc analysis (GINA 2016)	
	Total control <sup>a</sup>	WC	WC	PC
Criteria	Pass ALL	Pass at least 2 of 3 shaded and ALL other criteria	Pass ALL	Pass 2–3 of 4 shaded and ALL other criteria
Daytime symptoms	None	≤2 days per week with a score >1 <sup>b</sup>	≤2 days per week with a score >1 <sup>b</sup>	≤2 days per week with a score >1 <sup>b</sup>
Reliever use	None	≤2 days per week and ≤4 occasions per week	≤2 occasions per week	≤2 occasions per week
Morning PEF	≥80% predicted every day	≥80% predicted every day	Not included in assessment	
Night-time awakenings	None	None	None	None
Activity limitation	Not included	None	None	None
Exacerbations	None	None	None	None
Emergency department visits	None	None	Not included	Not included
Treatment-related AEs	No AEs enforcing a change in asthma therapy	None	Not included	Not included
Assessment period	8 Consecutive weeks	Final 4 weeks of assessment period	Final 4 weeks of assessment period	
Requirements to achieve control	Total control or WC criteria for symptoms <sup>c</sup> and PEF met for ≥7 of the 8 weeks; no exacerbations, emergency department visits or treatment-related AEs at any point during the 8 weeks	WC or PC symptoms criteria met in each of the 4 weeks; no exacerbations at any point during the 4 weeks	WC or PC symptoms criteria met in each of the 4 weeks; no exacerbations at any point during the 4 weeks	

Abbreviations: AE, adverse event; GINA, Global Initiative for Asthma; GOAL, Gaining Optimal Asthma Control; PC, partly controlled; PEF, peak expiratory flow; WC, well controlled.

<sup>a</sup>WC included patients with total control.

<sup>b</sup>Symptom score of 1 was defined as symptoms for one short period during the day; overall scale was 0 (none) to 5 (severe).

<sup>c</sup>Daytime symptoms, reliever use, and night-time awakenings.

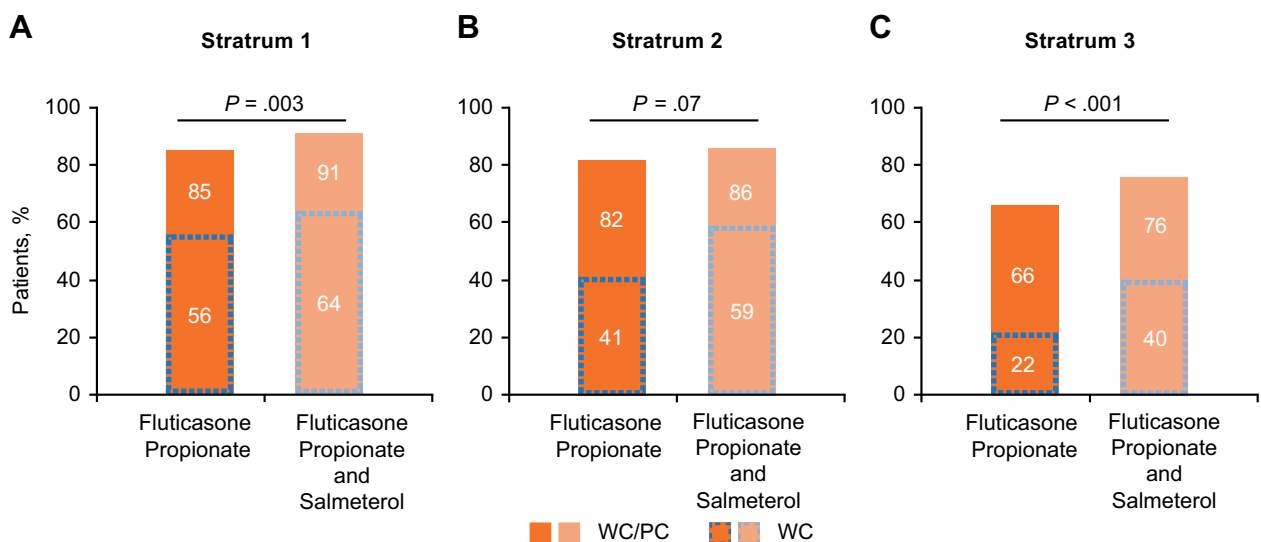
## Introduction

The long-term goals of asthma management are to improve symptom control and reduce the risk of poor outcomes, including exacerbations.<sup>1</sup> For patients, quality of life depends on the overall level of asthma control achieved,<sup>2–4</sup> which may encompass the frequency and severity of a number of asthma measures, including symptoms, lung function, and exacerbations.<sup>5</sup>

In 2004, the Gaining Optimal Asthma Control (GOAL) study (SAM40027) demonstrated that most patients with uncontrolled asthma receiving fluticasone propionate in combination with salmeterol met guideline-derived criteria for asthma control (based on the 1998 Global Initiative for Asthma [GINA] and 1997 National Institutes of Health reports).<sup>5–7</sup> Control was achieved more rapidly, and with a lower inhaled corticosteroid (ICS) dose, with fluticasone propionate and salmeterol compared with fluticasone propionate alone.<sup>5</sup> GOAL was the first clinical study to assess asthma control as its primary end point using a composite measure that included

peak expiratory flow (PEF), rescue medication use, symptoms, night-time awakenings, exacerbations, emergency department visits, and treatment-related adverse events.<sup>5</sup>

Since the GOAL study was performed, the concepts of asthma control have evolved as more evidence has been published. The 2006 GINA report recommended that asthma should be classified by level of control rather than severity.<sup>8</sup> It described a composite control measure that comprised symptoms, activity limitation, rescue reliever use, and forced expiratory volume in 1 second (FEV<sub>1</sub>) or PEF.<sup>9</sup> More recently, a major revision of the GINA report in 2014 included the risk factors domain, which was composed of lung function and exacerbations, to make the distinction from current symptom control and identify features that lead to poor future patient outcomes.<sup>10,11</sup> Symptom control (daytime symptoms, night-time awakenings because of asthma, reliever use, and activity limitation) now relates to the last 4-week period and is categorized as well controlled (WC; the highest level of control), partly controlled (PC), or uncontrolled.<sup>1</sup>



**Figure 1.** Percentage of patients who achieved at least partly controlled (WC/PC) asthma or well-controlled (WC) asthma during phase I (intent-to-treat population). *P* values relate to WC/PC asthma. *P* values for WC asthma are *P* = .005 for stratum 1, *P* < .001 for stratum 2, and *P* < .001 for stratum 3.

**Table 2**  
Proportions and Odds Ratios for Patients Achieving Asthma Control During Phase 1 and Phase 2 (ITT population)<sup>a</sup>

Variable	Stratum 1			Stratum 2			Stratum 3					
	Fluticasone propionate, No. (%) (n = 544)	Fluticasone propionate and salmeterol, No. (%) (n = 539)	OR (95% CI) <sup>b</sup>	P value	Fluticasone propionate, No. (%) (n = 577)	Fluticasone propionate and salmeterol, No. (%) (n = 583)	OR (95% CI) <sup>b</sup>	P value	Fluticasone propionate, No. (%) (n = 567)	Fluticasone propionate and salmeterol, No. (%) (n = 568)	OR (95% CI) <sup>b</sup>	P value
Phase 1												
WC/PC	464 (85)	490 (91)	1.82 (1.23–2.71)	.003	476 (82)	504 (86)	1.36 (0.97–1.89)	-.7	372 (66)	434 (76)	1.78 (1.35–2.33)	<.001
WC	306 (56)	347 (64)	1.45 (1.12–.88)	.005	237 (41)	342 (59)	2.16 (1.69–2.77)	<.001	124 (22)	227 (40)		<.001
Phase 2												
WC/PC	477 (88)	505 (94)	2.23 (1.42–3.50)	<.001	503 (87)	517 (89)	1.15 (0.79–1.66)	.46	425 (75)	470 (83)	1.68 (1.24–2.27)	<.001
WC	346 (64)	378 (70)	1.38 (1.06–1.81)	.02	290 (50)	394 (68)	2.22 (1.72–2.86)	<.001	204 (36)	292 (51)	2.06 (1.60–2.65)	<.001

Abbreviations: OR, odds ratio; PC, partly controlled; WC, well controlled.

<sup>a</sup>A total of 38 patients with missing baseline forced expiratory volume in 1 second data were excluded from the analysis.<sup>b</sup>Fluticasone propionate–treated patients used as the reference group.

The implication of the revised definitions of asthma symptom control on the findings of the GOAL study are unclear. We report here the results of a post hoc analysis of the GOAL study to which the revised asthma symptom control definitions, as per GINA 2016,<sup>12</sup> combined with the absence of exacerbations have been applied.

## Methods

### Study Design and Treatment

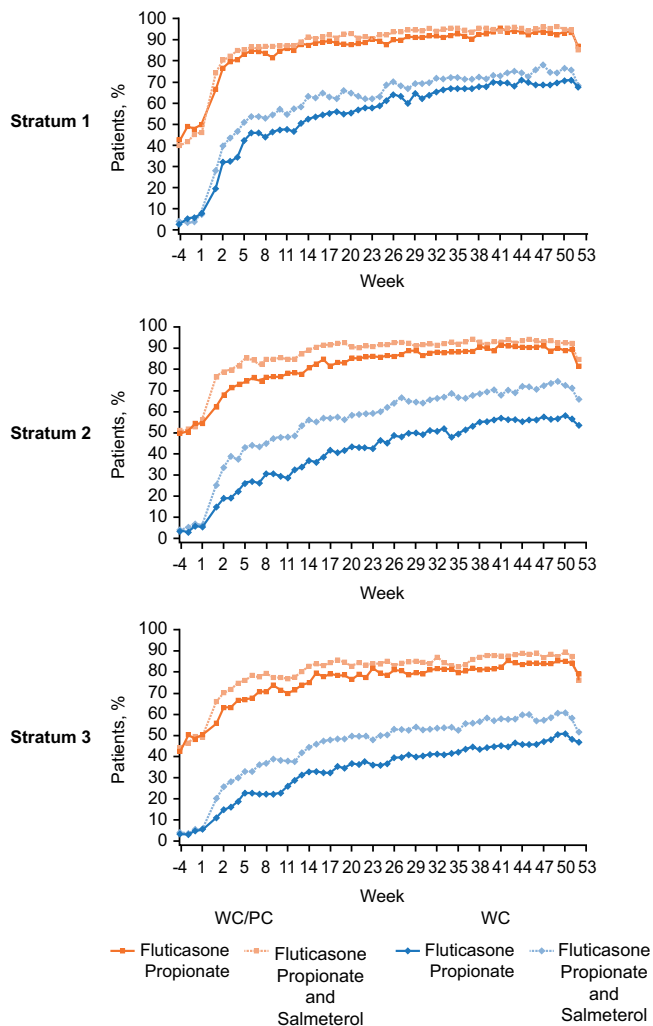
GOAL was a 1-year, randomized, double-blind, parallel-group study to compare the efficacy of an increasing dose of fluticasone propionate alone or fluticasone propionate and salmeterol to achieve asthma control.<sup>5</sup> Patients who did not achieve at least 2 well-controlled weeks in the 4-week run-in period were stratified according to their medication use in the 6 months before screening; patients in stratum 1 had not used ICSs, patients in stratum 2 had used low-dose ICSs ( $\leq 250$   $\mu\text{g}/\text{d}$  of fluticasone propionate,  $\leq 500$   $\mu\text{g}/\text{d}$  of beclomethasone dipropionate,  $\leq 400$   $\mu\text{g}/\text{d}$  of budesonide or equivalent)<sup>12</sup> and patients in stratum 3 had used medium-dose ICSs ( $>250$ – $\leq 500$   $\mu\text{g}/\text{d}$  of fluticasone propionate,  $>500$ – $\leq 1000$   $\mu\text{g}/\text{d}$  of beclomethasone dipropionate,  $>400$ – $\leq 800$   $\mu\text{g}/\text{d}$  of budesonide or equivalent).<sup>12</sup> Patients were randomized (1:1) to receive fluticasone propionate and salmeterol (starting dose, 100/50  $\mu\text{g}$  [strata 1 and 2] or 250/50  $\mu\text{g}$  [stratum 3]) twice daily) or fluticasone propionate (starting dose, 100  $\mu\text{g}$  [strata 1 and 2] or 250  $\mu\text{g}$  [stratum 3]) twice daily.<sup>5</sup>

The study consisted of a dose-escalation phase (phase 1) and fixed-dose treatment phase (phase 2). During phase 1, treatment was stepped up every 12 weeks until either total control (Table 1) was achieved or the highest dose of study drug was reached (500/50  $\mu\text{g}$  of fluticasone propionate and salmeterol or 500  $\mu\text{g}$  of fluticasone propionate twice daily). Phase 2 was entered after achieving total control or after 12 weeks of taking the maximum dose of study medication. Patients continued the dose at which they achieved total control or the maximum dose for the remainder of the 1-year double-blind treatment period. The full methods, including inclusion and exclusion criteria, have been described previously.<sup>5</sup> Anonymized individual participant data from this study plus the annotated case report form, protocol, reporting and analysis plan, data set specifications, raw data set, analysis-ready data set, and clinical study report are available for research proposals approved by an independent review committee. Proposals should be submitted to [www.clinicalstudydatarequest.com](http://www.clinicalstudydatarequest.com). A data access agreement will be required.

### End Points and Assessments (Post Hoc Analysis)

The primary end point was the proportion of patients who achieved at least PC asthma (ie, those with PC asthma plus those with WC asthma [WC/PC]) in phase 1. Patients were considered to have WC or PC asthma if they achieved the corresponding GINA 2016 symptom criteria in each of the final 4 weeks of any dose titration step and experienced no exacerbations during those 4 weeks (Table 1).

Secondary end points included the proportion of patients with WC asthma in phase 1 and WC/PC and WC asthma by the end of phase 2. Additional secondary end points included the time to reach the first week of WC/PC and WC asthma and the proportion of patients achieving WC/PC and WC asthma by week. Exploratory end points, not included in the post hoc analysis plan, were the proportion of patients achieving WC/PC and WC asthma by fluticasone propionate dose at the end of phase 1, the maintenance of control in phase 2 in patients who had achieved control in phase 1, and the rate of exacerbations (requiring oral corticosteroids, hospitalizations, or emergency department visits) during phase 2 according to control status during



**Figure 2.** Cumulative incidence of patients who achieved at least partly controlled (WC/PC) asthma, or well-controlled (WC) asthma by week (intent-to-treat population).

phase 1. Reasons for failure to achieve control according to GINA 2016 criteria were additionally summarized within each control category.

#### Sample Size and Statistical Analysis

Sample size calculations were performed for the original GOAL study<sup>5</sup>; each stratum was individually powered. All analyses were performed in the intent-to-treat (ITT) population, which consisted of all patients who were randomized and received 1 dose or more of study drug.

Statistical analysis was performed using SAS software, version 9.4 (SAS Institute Inc, Cary, North Carolina). The statistical methods used followed those in the original analysis of the GOAL study.<sup>5</sup> The difference between treatments in the proportion of patients achieving control was assessed using logistic regression, adjusting for sex, country, age, treatment group, and baseline pre-bronchodilator FEV<sub>1</sub>. The analysis by dose was performed using proportional odds logistic regression, using the same covariates. The underlying assumption of a constant odds ratio (OR) across strata was assessed using plots of the empirical logits, and no evidence of substantial deviation from this assumption was seen.

Time to achieving the first individual week of WC/PC or PC asthma during the first dose titration step was summarized using Kaplan-Meier plots and compared between treatments using the

log-rank test. Patients were censored at the earliest of 12 weeks or the end of the first dose titration step if they had not yet achieved WC or PC asthma. Patients whose asthma was already controlled at baseline were excluded from these time-to analyses (in contrast to the original GOAL study<sup>5</sup> in which all patients were included in the time-to-event analyses, with only a small proportion of patients having asthma controlled at baseline by design).

To assess the influence of asthma control on subsequent exacerbation rates, irrespective of treatment group, the rate of exacerbation during phase 2 was evaluated according to control status during phase 1 using a Poisson regression model with an offset term to allow for time receiving treatment and adjustment for sex, age, and baseline FEV<sub>1</sub> analyzed for the total study population (all strata and both treatment groups combined).

## Results

### Patient Population

In total, 5068 patients were screened in the GOAL study. All 3416 patients in the ITT population were included in the current post hoc analysis. A total of 3039 patients completed phase 1, and 2890 completed phase 2.<sup>5</sup> A summary of patient demographics and baseline characteristics has previously been reported.<sup>5</sup>

### Achievement of Asthma Control

In phase 1, a high proportion of patients achieved WC/PC asthma with both fluticasone propionate and salmeterol and fluticasone propionate, respectively, in stratum 1 (91% [490/539] and 85% [464/544]), stratum 2 (86% [504/583] and 82% [476/577]), and stratum 3 (76% [434/568] and 66% [372/567]) (Fig 1). Significantly higher proportions of patients achieved WC/PC asthma with fluticasone propionate and salmeterol than fluticasone propionate alone in stratum 1 (odds ratio [OR], 1.82; 95% CI, 1.23-2.71;  $P = .003$ ) and stratum 3 (OR, 1.78; 95% CI, 1.35-2.33;  $P < .001$ ) but not stratum 2 (OR, 1.36; 95% CI, 0.97-1.89;  $P = .07$ ) (Fig 1 and Table 2). A significantly higher proportion of patients in all strata achieved WC asthma with fluticasone propionate and salmeterol than fluticasone propionate alone (Fig 1 and Table 2).

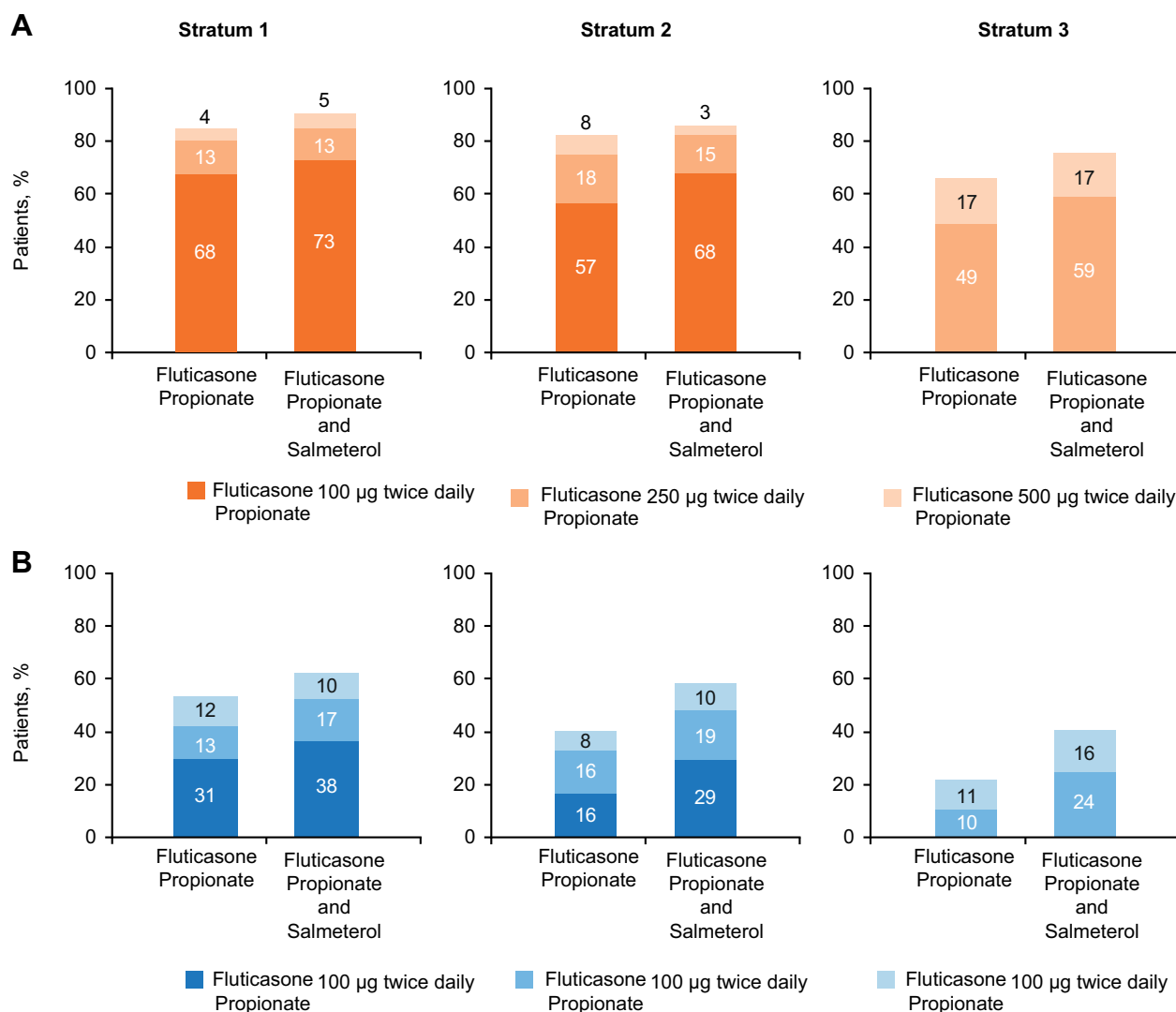
By the end of phase 2, a significantly greater proportion of patients achieved WC/PC asthma (in strata 1 and 3) and WC asthma (all strata) with fluticasone propionate and salmeterol vs fluticasone propionate (Table 2). Most patients who achieved control in phase 1 were also controlled at the end of phase 2. Across the strata, 82% to 85% of patients taking fluticasone propionate and salmeterol and 79% to 81% of patients taking fluticasone propionate maintained WC/PC asthma in phase 2 and 71% to 76% and 71% to 74%, respectively, maintained WC asthma.

### Analysis of Time to Control

Asthma control was achieved more rapidly with fluticasone propionate and salmeterol vs fluticasone propionate alone for both WC/PC asthma and WC asthma (all strata  $P \leq .03$ ) (eFig 1).

### Achievement of Asthma Control by Week

In stratum 1, the proportion of patients achieving WC/PC asthma increased rapidly during the first 2 to 3 weeks of study treatment, with a further slow increase in control rate seen until approximately week 16, which plateaued thereafter (Fig 2). In strata 2 and 3, the proportion of patients achieving WC/PC asthma increased more steadily during the first 18 to 20 weeks of study treatment (Fig 2). The difference between treatments was more noticeable in these strata compared with stratum 1, with a higher proportions of patients with WC/PC asthma in the fluticasone propionate and salmeterol vs fluticasone propionate groups and an earlier plateau



**Figure 3.** Percentage of patients who achieved at least partly controlled (WC/PC) asthma (A) or well-controlled (WC) asthma (B) during phase 1 by fluticasone propionate dose (intent-to-treat population).

in the proportion of patients achieving WC/PC asthma with fluticasone propionate and salmeterol vs fluticasone propionate.

A steady increase in the proportion of patients with WC asthma was observed during the entire treatment period with both fluticasone propionate and fluticasone propionate and salmeterol for all strata; but a higher proportion of patients achieved WC asthma in the fluticasone propionate and salmeterol vs fluticasone propionate groups (Fig 2).

#### Achievement of Asthma Control by Dose

WC/PC and WC asthma was achieved at a lower dose of fluticasone propionate with fluticasone propionate and salmeterol compared with fluticasone propionate alone across all 3 strata (Fig 3 and eTable 1).

#### Failed Criteria by Overall Asthma Control Status in Phase 1

Most patients who achieved PC asthma did not meet criteria for WC asthma on the basis of failing 1 or 2 criteria, most commonly reliever use (Table 3). After daytime symptoms and reliever use, the most common reason for failing to be WC was night-time awakenings. Among patients with uncontrolled asthma, 11% experienced

exacerbations; most did not achieve asthma control because of failure to meet multiple symptom criteria.

#### Exacerbation Rate During Phase 2 by Phase 1 Control Status

The frequency of exacerbations experienced during phase 2 was lower with improved asthma control during phase 1, with mean annual rates of exacerbations in phase 2 of 0.31 (95% CI, 0.27–0.36) in patients with uncontrolled asthma, 0.16 (95% CI, 0.14–0.18) in patients with PC asthma, and 0.09 (95% CI, 0.08–0.10) in patients with WC asthma during phase 1 (Fig 4).

#### Discussion

The 2014 GINA report details a major revision that reflects the evolved understanding of the need to distinguish between current symptom control and risk prevention.<sup>10,11</sup> Furthermore, it is now accepted that occasional symptoms ( $\leq 2$  per week) are common, even in patients whose control is otherwise satisfactory, and should not prompt a step-up in treatment, especially if this might involve addition of another controller medication. This tolerant view of occasional symptoms was implicit in the definition of total control in the original GOAL study design, in that it permitted symptoms

**Table 3**  
Reasons for Failing to Achieve Asthma Control According to GINA 2016 Criteria (Intent-to-Treat Population)<sup>a</sup>

Reason	Patients with WC asthma, No. (%) (n = 1583)	Patients with PC asthma, No. (%) (n = 1157)	Patients with uncontrolled asthma, No. (%) (n = 474)
Criteria failed during the 4-week assessment period			
No criteria failed	1583 (100)	39 <sup>b</sup> (3)	0
One criterion failed	0	486 (42)	0
Two criteria failed	0	601 (52)	0
Three criteria failed	0	31 <sup>c</sup> (3)	268 (57)
Four criteria failed	0	0 (0)	152 (32)
Exacerbation (any number of criteria failed)	0	0	54 (11)
Patients failing each criterion <sup>d</sup>			
Daytime symptoms	0	461 (40)	434 (92)
Night-time awakenings	0	413 (36)	421 (89)
Reliever use	0	799 (69)	454 (96)
Activity limitation	0	108 (9)	253 (53)

Abbreviations: GINA, Global Initiative for Asthma; PC, partly controlled; WC, well controlled.

<sup>a</sup>Fluticasone propionate and fluticasone propionate and salmeterol groups combined; 164 patients were unevaluable and were not included in the WC, PC, or uncontrolled categories; 38 patients with missing baseline forced expiratory volume in 1 second data were also excluded.

<sup>b</sup>These patients could not be classified as having WC asthma because of some criteria being unevaluable.

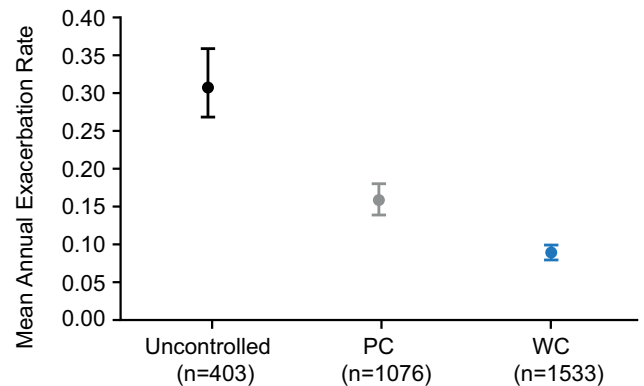
<sup>c</sup>These patients failed 1 to 2 criteria within each week but failed more than 2 criteria during the total 4-week assessment period.

<sup>d</sup>Percentages sum to more than 100% because each patient could fail multiple criteria. Missing or unevaluable criteria are taken into account in the overall assessment of control but are not counted here as failed.

(or other criteria of uncontrolled asthma) in 1 of the 8-week assessment periods, and for WC asthma, which allowed for 2 or more days with symptoms per week.<sup>5</sup>

Given the changes in the definition of asthma control since the GOAL study was conducted, in the current post hoc analysis we sought to evaluate the efficacy of fluticasone propionate and salmeterol and fluticasone propionate alone in achieving the GINA 2016 definitions of asthma symptom control combined with no exacerbations.<sup>12</sup> The analysis revealed that a markedly higher proportion of patients achieved control under the GINA 2016 definition relative to the original GOAL study analysis. An additional 18% to 32% of patients receiving fluticasone propionate and salmeterol or fluticasone propionate alone achieved the primary end point of WC/PC asthma across all 3 strata compared with the GOAL primary end point of WC asthma.<sup>5</sup> Similarly, an additional 14% to 26% of patients achieved the highest level of control of WC asthma compared with total control in the original GOAL analysis. The magnitude of this difference between the analyses is somewhat surprising given that both definitions of symptom control originate from GINA criteria.

In line with the primary analysis<sup>5</sup> and consistent with a number of previous clinical trials,<sup>13–15</sup> a greater proportion of patients achieved WC asthma with fluticasone propionate and salmeterol than



**Figure 4.** Mean annual exacerbation rate during phase 2 by control status during phase 1 (intent-to-treat population). Patients with missing covariates (including baseline forced expiratory volume in 1 second) are excluded. Sample sizes are the mean number of exacerbations per year from the Poisson model. Data are pooled by treatment and strata. PC, partly controlled; WC, well controlled.

fluticasone propionate alone across all levels of permitted baseline therapy. Supporting a further key finding of the GOAL study,<sup>5</sup> in the current post hoc analysis, patients achieved WC asthma at a lower dose of fluticasone propionate with fluticasone propionate and salmeterol compared with fluticasone propionate alone. Although clinical benefits were seen across all 3 strata, there was some suggestion that the benefit of adding salmeterol to fluticasone propionate may increase with increasing asthma severity (from stratum 1 to stratum 3). Moreover, the proportion of patients achieving control plateaued earlier with fluticasone propionate and salmeterol than with fluticasone propionate alone in stratum 2 and stratum 3 compared with stratum 1. A further common finding between this and the original GOAL analysis was that the clinical benefit in all 3 strata was sustained (ie, continued in phase 2 for most patients who achieved symptom control in phase 1).<sup>16</sup> The frequency of exacerbations was also lower across all control levels in phase 2.

A ceiling effect was apparent, in all strata, with a proportion of patients not achieving WC/PC asthma with fluticasone propionate and salmeterol or fluticasone propionate alone. Because nearly all patients in strata 1 and 2 achieved WC/PC asthma with fluticasone propionate alone, there was little opportunity to detect additional benefit of fluticasone propionate and salmeterol in these strata. In stratum 3, 49% of patients did not achieve WC asthma 3 months after moving to the highest fluticasone propionate and salmeterol dosage (ie, by week 36), with no notable further increase in the proportion with WC asthma by the end of the study. Such patients, who fulfill the criteria for the term *severe asthma* (as defined by the American Thoracic Society/European Respiratory Society Severe Asthma Task force), require additional treatments.<sup>17</sup> Asthma control was achieved more rapidly with fluticasone propionate and salmeterol vs fluticasone propionate alone for both WC/PC asthma and WC asthma in all strata, suggesting a benefit for adding a long-acting  $\beta$ -adrenoreceptor agonist (LABA) when the speed of achieving the highest level of control is important.

Most patients with PC asthma failed to meet the definition of WC asthma by only 1 or 2 criteria, whereas patients with uncontrolled asthma typically failed to meet the control definitions on multiple criteria. Of special interest is that 36% of patients meeting the current definition of PC had night-time awakenings and, on this basis, were defined as having uncontrolled asthma by the original GOAL study criteria.<sup>5</sup> Given that night-time awakenings are linked to asthma severity and the number of emergency department visits,<sup>18</sup> it is important to strive to achieve WC over PC asthma. The observation that more than a third of patients with PC asthma still experience marked night-time symptoms is supported by findings from other studies.<sup>19</sup>

Another key difference in the control criteria was the requirement of PEF of 80% predicted or higher in the original GOAL study, a threshold based on a pragmatic interpretation of the 1998 GINA goal of achieving “normal or near-normal lung function,”<sup>5,6</sup> which may have led to a proportion of patients who achieved GINA 2016 WC asthma but not GOAL total control. It was acknowledged that this may have been unduly strict, with many patients achieving considerable clinical benefit despite not achieving normalized lung function and thereby total control.<sup>5,20</sup> Because long-term PEF monitoring is now only recommended under special circumstances,<sup>1,10,12</sup> the GINA 2016 asthma control criteria are likely to be more clinically useful than those used in the GOAL study.

The key limitation of this analysis is that dose escalation was based on the original control criteria of total control. This was used to determine whether the dose was to be escalated or not during the conduct of the study, whereas WC asthma, which is currently suggested as the highest level of control and used in the current analysis, is not as stringent. For these reasons, we have been careful not to overinterpret these results.

In summary, this post hoc analysis of the GOAL study demonstrated that a markedly higher proportion of patients receiving fluticasone propionate and salmeterol or fluticasone propionate alone achieved satisfactory asthma control, according to the GINA 2016 definitions, than in the original GOAL analysis. In agreement with the original analysis, fluticasone propionate and salmeterol achieved control in more patients and at lower doses of ICS than was achieved with escalating doses of fluticasone propionate alone. Moreover, the combination appeared to be of greater advantage in patients with more severe disease. Together these results suggest a higher proportion of patients are adequately treated with LABA-ICS than previously thought and confirm the basis for LABA-ICS as the preferred treatment for patients in steps 3, 4, and 5 of asthma management. This post hoc analysis that focused on efficacy does not affect the risk-benefit analysis of fluticasone propionate and salmeterol or fluticasone propionate alone.

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### Supplementary Data

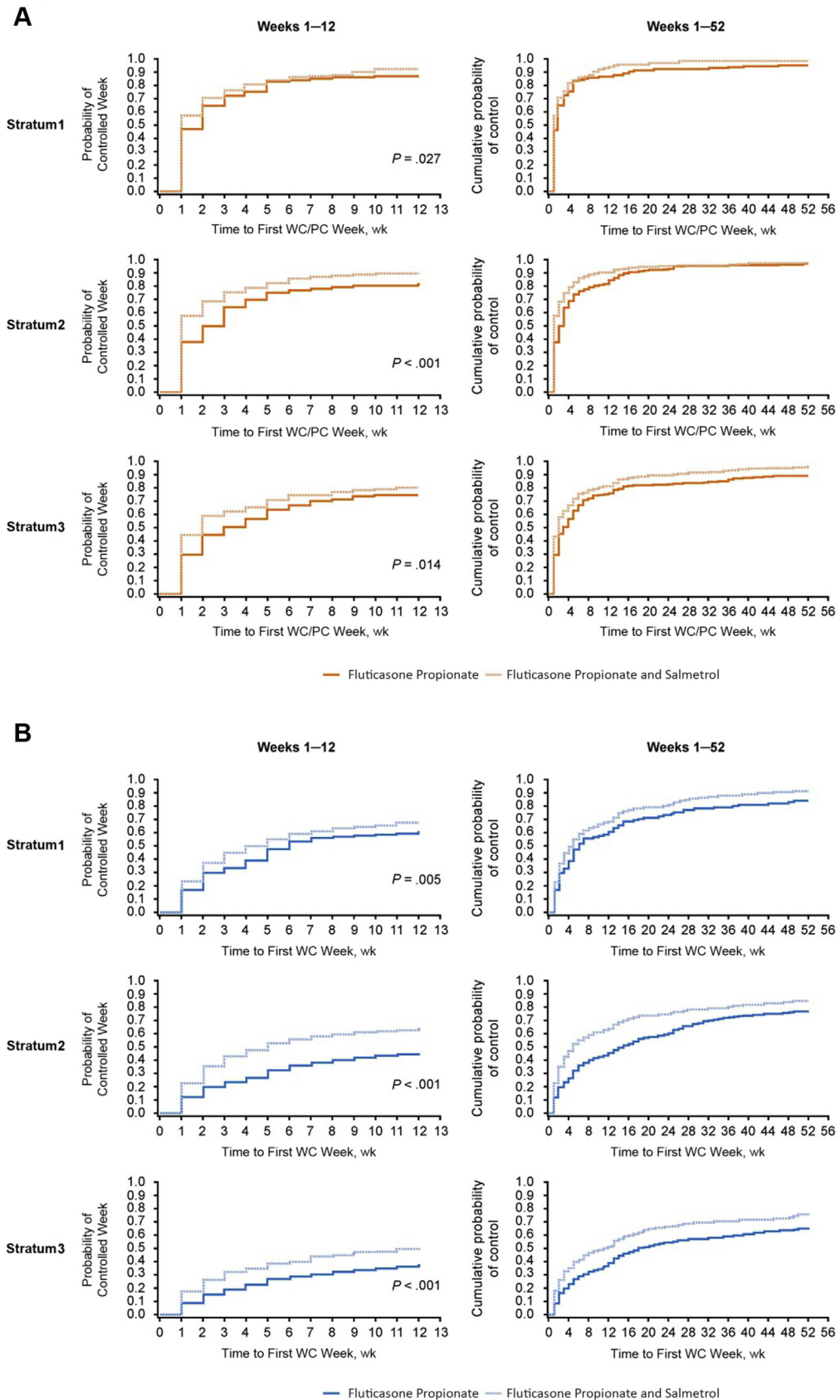
Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.anai.2019.04.018>.

### References

- Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention*. Bethesda, MD: Global Initiative for Asthma, National Heart, Lung and Blood Institute; 2017.
- Chen H, Gould MK, Blanc PD, et al. Asthma control, severity, and quality of life: quantifying the effect of uncontrolled disease. *J Allergy Clin Immunol*. 2007;120:396–402.
- Chippes BE, Zeiger RS, Borish L, et al. Key findings and clinical implications from the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol*. 2012;130:332–342.e310.
- Bateman ED, Bousquet J, Keech ML, Busse WW, Clark TJ, Pedersen SE. The correlation between asthma control and health status: the GOAL study. *Eur Respir J*. 2007;29:56–62.
- Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? the Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med*. 2004;170:836–844.
- Global Initiative for Asthma. *Pocket Guide for Asthma Management and Prevention*. Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute; 1998.
- National Asthma Education and Prevention Program. *Guidelines for the Diagnosis and Management of Asthma: Expert Panel Report 2*. Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute; 1997.
- Koshak EA. Classification of asthma according to revised 2006 GINA: evolution from severity to control. *Ann Thorac Med*. 2007;2:45–46.
- Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention*. Bethesda, MD: Global Initiative for Asthma, National Heart, Lung and Blood Institute; 2006.
- Reddel HK, Bateman ED, Becker A, et al. A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J*. 2015;46:622–639.
- Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention*. Bethesda, MD: Global Initiative for Asthma, National Heart, Lung and Blood Institute; 2015.
- Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention*. Bethesda, MD: Global Initiative for Asthma, National Heart, Lung and Blood Institute; 2016.
- Kavuru M, Melamed J, Gross G, et al. Salmeterol and fluticasone propionate combined in a new powder inhalation device for the treatment of asthma: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol*. 2000;105:1108–1116.
- Renzi PM, Howard LA, Ortega HG, Ahmad FF, Chapman KR. Low-dose fluticasone propionate with and without salmeterol in steroid-naïve patients with mild, uncontrolled asthma. *Respir Med*. 2010;104:510–517.
- Shapiro G, Lumry W, Wolfe J, et al. Combined salmeterol 50 microg and fluticasone propionate 250 microg in the diskus device for the treatment of asthma. *Am J Respir Crit Care Med*. 2000;161:527–534.
- Bateman ED, Bousquet J, Busse WW, et al. Stability of asthma control with regular treatment: an analysis of the Gaining Optimal Asthma Control (GOAL) study. *Allergy*. 2008;63:932–938.
- Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43:343–373.
- Stallberg B, Lisspers K, Hasselgren M, Johansson G, Svardsudd K. Factors related to the level of severity of asthma in primary care. *Respir Med*. 2007;101:2076–2083.
- Sanz de Burgoa V, Rejas J, Ojeda P, Investigators of the CosteAsma Study. Self-perceived sleep quality and quantity in adults with asthma: findings from the CosteAsma Study. *J Investig Allergol Clin Immunol*. 2016;26:256–262.
- Woodcock AA, Bagdonas A, Boonsawat W, et al. Improvement in asthma endpoints when aiming for total control: salmeterol/fluticasone propionate versus fluticasone propionate alone. *Prim Care Respir J*. 2007;16:155–161.



Supplementary Data



**eFigure 1.** Inverse Kaplan–Meier plot of time to first individual week of well-controlled (WC) or partly controlled (PC) asthma (A) or WC asthma (B) during weeks 1 to 12 and 1 to 52 in strata 1, 2, and 3 (intent-to-treat population). *P* values were not calculated for the weeks 1 to 52 plots.

**eTable 1**Summary and Analysis of Steroid Dose at Which WC/PC or WC Asthma Was First Achieved in Phase 1 (Intent-to-Treat Population)<sup>a</sup>

Dose	Stratum 1				Stratum 2				Stratum 3			
	Fluticasone propionate, No. (%) (n = 544)	Fluticasone propionate and salmeterol, No. (%) (n = 539)	OR (95% CI) <sup>b</sup>	P value	Fluticasone propionate, No. (%) (n = 577)	Fluticasone propionate and salmeterol, No. (%) (n = 583)	OR (95% CI) <sup>b</sup>	P value	Fluticasone propionate, No. (%) (n = 567)	Fluticasone propionate and salmeterol, No. (%) (n = 568)	OR (95% CI)	P value
WC/PC												
100 µg	372 (68)	396 (73)	1.40 (1.07-1.83)	.02	300 (57)	398 (68)	1.65 (1.29-2.09)	<.001	0 (0)	0 (0)	1.61 (1.28-2.03)	<.001
250 µg	68 (13)	69 (13)			101 (18)	88 (15)			278 (49)	337 (59)		
500 µg	24 (4)	25 (5)			45 (8)	18 (3)			94 (17)	97 (17)		
WC												
100 µg	169 (31)	204 (38)	1.44 (1.15-1.80)	.001	95 (16)	170 (29)	2.11 (1.68-2.64)	<.001	0 (0)	0 (0)	2.60 (1.99-3.39)	<.001
250 µg	73 (13)	90 (17)			93 (16)	111 (19)			59 (10)	137 (24)		
500 µg	64 (12)	53 (10)			49 (8)	61 (10)			65 (11)	90 (16)		

Abbreviations: OR, odds ratio; PC, partly controlled; WC, well controlled.

<sup>a</sup>Patients with missing baseline forced expiratory volume in 1 second data are excluded.<sup>b</sup>The ORs are derived from a proportional odds logistic regression with fluticasone propionate–treated patients as the reference group.