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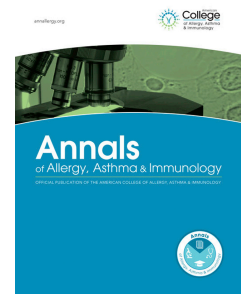
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Conflicts of interest

EDB reports personal fees from AstraZeneca, ALK, Boehringer Ingelheim, Cipla, ICON, Menarini, Novartis, Sanofi/Regeneron, Vectura, and grants to institution from AstraZeneca, Boehringer Ingelheim, Merck, Takeda, GSK, Hoffmann le Roche, Actelion, Chiesi, Sanofi-Aventis, Cephalon, Teva, and Novartis. EDB is a Member of Global Initiative for Asthma Board and Science Committee. WB reports consulting fees from Novartis, Roche, GSK, AstraZeneca, Genentech (and Data Safety Monitoring Board [DSMB], Sanofi-Regeneron, Boehringer Ingelheim, Circassia, Sanofi Genzyme, Teva, 3M, PrEP Biopharm, and Peptinnovate, board membership for Boston Scientific (DSMB) and ICON Clinical Research Limited (Study Oversight Committee), editor fees from Elsevier. SEP has received personal fees from ALK, AstraZeneca and Chiesi. JB has received personal fees from Almirall, AstraZeneca, Chiesi, GSK, Meda, Menarini, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach. MG

and NG are employees of, and hold shares/share options in, GSK; SH (Hollis) is employed as a contingent worker by GSK. XZ and SH have no conflicts to declare.

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Abbreviations List

AE: adverse event

bid: twice daily

CI: confidence interval

FEV₁: forced expiratory volume in 1 second

FP: fluticasone propionate

FP/SAL: fluticasone propionate/salmeterol

GINA: Global Initiative for Asthma

GOAL: Gaining Optimal Asthma control

ICS: inhaled corticosteroid

ITT: intent-to-treat

LABA: long-acting β -adrenoreceptor agonist

OR: odds ratio

PC: partly controlled

PEF: peak expiratory flow

SAL: salmeterol

S: stratum

WC: well controlled

WC/PC: at least partially-controlled asthma (patients with PC asthma plus those with WC asthma)

Introduction

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

In 2004, the Gaining Optimal Asthma control (GOAL) study (SAM40027) demonstrated that most patients with uncontrolled asthma receiving fluticasone propionate in combination with salmeterol (FP/SAL) met guideline-derived criteria for asthma control (based on 1998 Global Initiative for Asthma [GINA] and 1997 National Institutes of Health reports).⁵⁻⁷ Control was achieved more rapidly, and a lower inhaled corticosteroid (ICS) dose, with FP/SAL compared with FP alone.⁵ GOAL was the first clinical study to assess asthma control as its primary endpoint using a composite measure that included peak expiratory flow (PEF), rescue medication use, symptoms, night-time awakenings, exacerbations, emergency visits, and treatment-related adverse events.⁵

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.⁸ It described a composite control measure comprising symptoms, activity limitation, rescue reliever use and forced expiratory volume in 1 second (FEV₁) or PEF.⁹ More recently, a major revision of GINA report in 2014 included the “risk factors” domain, comprising lung function and exacerbations, to make the distinction from current symptom control and identify features that lead to poor future patient outcomes.^{10, 11} Symptom control (daytime symptoms, night-time awakenings due to 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.¹

26 The implication of the revised definitions of asthma symptom control on the findings of the
27 GOAL study are unclear. We report here the results of a post hoc analysis of the GOAL
28 study, to which the revised asthma symptom control definitions, as per GINA 2016,¹²
29 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 FP alone or FP/SAL to achieve asthma control.⁵ 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 prior to screening; patients in stratum 1 (S1) had not used ICS, patients in stratum 2 (S2) had used low-dose ICS (≤ 250 μ g FP daily, ≤ 500 μ g beclomethasone dipropionate daily, ≤ 400 μ g budesonide daily or equivalent)¹² and patients in stratum 3 (S3) had used medium-dose ICS (> 250 – ≤ 500 μ g FP daily, > 500 – ≤ 1000 μ g beclomethasone dipropionate daily, > 400 – ≤ 800 μ g budesonide daily or equivalent).¹²

Patients were randomized (1:1) to FP/SAL (starting dose 100/50 μ g [S1 and S2] or 250/50 μ g [S3] twice daily [bid]) or FP (starting dose 100 μ g [S1 and S2] or 250 μ g [S3] bid).⁵

The study consisted of a dose-escalation phase (Phase I) and fixed-dose treatment phase (Phase II). During Phase I, treatment was “stepped up” every 12 weeks until either “Total Control” (Table 1) was achieved or the highest dose of study drug was reached (FP/SAL 500/50 μ g or FP 500 μ g bid). Phase II was entered either after achieving Total Control or after 12 weeks on the maximum dose of study medication. Patients remained on 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 methodology, including inclusion and exclusion criteria, has been described previously.⁵ Anonymized individual participant data from this study plus the annotated case report form, protocol, reporting and analysis plan, dataset specifications, raw dataset, analysis-ready dataset, and clinical study report are available for research proposals approved by an independent review committee. Proposals should be submitted to www.clinicalstudydatarequest.com. A data access agreement will be required.

Endpoints and assessments (post hoc analysis)

The primary endpoint was the proportion of patients that achieved at least PC asthma (ie, those with PC asthma plus those with WC asthma; WC/PC) in Phase I. 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 endpoints included the proportion of patients with: WC asthma in Phase I; WC/PC and WC asthma by the end of Phase II. Additional secondary endpoints 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 endpoints, not included in the post hoc analysis plan, were the proportion of patients achieving WC/PC and WC asthma by FP dose at the end of Phase I; the maintenance of control in Phase II in patients who had achieved control in Phase I; and the rate of exacerbations (requiring oral corticosteroids, hospitalizations, or emergency visits) during Phase II according to control status during Phase I. 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;⁵ 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 of study drug. Statistical analysis was performed using SAS software v9.4 (SAS Institute Inc., Cary, NC, USA). The statistical methods used followed those in the original analysis of the GOAL study.⁵ 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 FEV₁. 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 who were already controlled at baseline were excluded from these “time to” analyses (in contrast to the original GOAL study⁵ where all patients were included in the time-to-event analyses, with only a small proportion of patients controlled at baseline by design).

To assess the influence of asthma control on subsequent exacerbation rates, irrespective of treatment group, the rate of exacerbations during Phase II was evaluated according to control status during Phase I using a Poisson regression model with an offset term to allow for time on treatment, and adjustment for sex, age and baseline FEV₁, 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 I, and 2890 completed Phase II.⁵ A summary of patient demographics and baseline characteristics has previously been reported.⁵

Achievement of asthma control

In Phase I, a high proportion of patients achieved WC/PC asthma with both FP/SAL and FP, respectively, in S1 (91% [490/539] and 85% [464/544]), S2 (86% [504/583] and 82% [476/577]), and S3 (76% [434/568] and (66% [372/567]) (Figure 1). Significantly higher proportions of patients achieved WC/PC asthma with FP/SAL than FP alone in S1 (OR 1.82 [95% confidence interval [CI] 1.23, 2.71]; $P=.003$) and S3 (OR 1.78 [95% CI 1.35, 2.33]; $P<.001$), but not S2 (OR 1.36 [95% CI 0.97, 1.89]; $P=.072$) (Figure 1; Table 2). A significantly higher proportion of patients in all strata achieved WC asthma with FP/SAL than FP alone (Figure 1; Table 2).

By the end of Phase II, a significantly greater proportion of patients achieved WC/PC asthma (in S1 and S3) and WC asthma (all strata), with FP/SAL versus FP (Table 2). Most patients who achieved control in Phase I were also controlled at the end of Phase II. Across the strata, 82%–85% of patients on FP/SAL and 79%–81% of patients on FP maintained WC/PC asthma in Phase II and 71%–76% and 71%–74%, respectively, maintained WC asthma.

Analysis of time to control

Asthma control was achieved more rapidly with FP/SAL versus FP alone for both WC/PC asthma and WC asthma (all strata $P\leq.027$; eFigure 1).

Achievement of asthma control by week

In S1, the proportion of patients achieving WC/PC asthma increased rapidly during the first 2–3 weeks of study treatment, with a further slow increase in control rate seen until around Week 16, which plateaued thereafter (Figure 2). In S2 and S3, the proportion of patients achieving WC/PC asthma increased more steadily over the first 18–20 weeks of study treatment (Figure 2). The difference between treatments was more noticeable in these strata compared with S1, with higher proportions of patients with WC/PC asthma in the FP/SAL versus FP groups and an earlier plateau in the proportion of patients achieving WC/PC asthma with FP/SAL versus FP.

A steady increase in the proportion of patients with WC asthma was observed over the entire treatment period with both FP and FP/SAL for all strata; but a higher proportion of patients achieved WC asthma in the FP/SAL versus FP groups (Figure 2).

Achievement of asthma control by dose

WC/PC and WC asthma was achieved at a lower dose of FP with FP/SAL compared with FP alone across all three strata (Figure 3, eTable 1).

Failed criteria by overall asthma control status in Phase I

Most patients who achieved PC asthma did not meet criteria for WC asthma on the basis of failing one or two 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 uncontrolled patients, 11% experienced exacerbations; the majority did not achieve asthma control due to failure to meet multiple symptom criteria.

Exacerbation rate during Phase II by Phase I control status

The frequency of exacerbations experienced during Phase II was lower with improved asthma control during Phase I, with mean annual rates of exacerbations in Phase II of 0.31 (95% CI

141 0.27, 0.36) in patients with uncontrolled asthma, 0.16 (95% CI 0.14, 0.18) in patients with PC
142 asthma, and 0.09 (95% CI 0.08, 0.10) in patients with WC asthma during Phase I (Figure 4).

Discussion

The 2014 GINA report details a major revision which reflects the evolved understanding of the need to distinguish between current symptom control and risk prevention.^{10, 11} Further, it is now accepted that occasional symptoms (≤ 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 (or other criteria of uncontrolled asthma) in one of the 8-week assessment periods, and for Well Controlled asthma, which allowed for ≤ 2 days with symptoms per week.⁵

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 FP/SAL and FP alone in achieving the GINA 2016 definitions of asthma symptom control combined with no exacerbations.¹² The analysis revealed a markedly higher proportion of patients achieved control under the GINA 2016 definition relative to the original GOAL study analysis. An additional 18%–32% of patients receiving FP/SAL or FP alone achieved the primary endpoint of WC/PC asthma, across all three strata than with the GOAL primary endpoint of Well Controlled asthma.⁵ Similarly, an additional 14%–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,⁵ and consistent with a number of previous clinical trials,¹³⁻¹⁵ a greater proportion of patients achieved WC asthma with FP/SAL than FP alone, across all levels of permitted baseline therapy. Supporting a further key finding of the GOAL study⁵, in the current post hoc analysis, patients achieved WC asthma at a lower dose of FP with

FP/SAL compared with FP alone. Although clinical benefits were seen across all three strata, there was some suggestion the benefit of adding SAL to FP may increase with increasing asthma severity (from S1 to S3). Moreover, the proportion of patients achieving control plateaued earlier with FP/SAL than with FP alone in S2 and S3 compared with S1. A further common finding between this and the original GOAL analysis was that the clinical benefit in all three strata was sustained, ie, continued in Phase II for most patients who achieved symptom control in Phase I.¹⁶ The frequency of exacerbations was also lower across all control levels in Phase II.

A ceiling effect was apparent, in all strata, with a proportion of patients not achieving WC/PC with either FP/SAL or FP alone. Since nearly all patients in S1 and S2 achieved WC/PC asthma with FP alone, there was little opportunity to detect additional benefit of FP/SAL in these strata. In S3, 49% of patients did not achieve WC asthma 3 months after moving to the highest FP/SAL 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.¹⁷ Asthma control was achieved more rapidly with FP/SAL versus FP alone for both WC/PC asthma and WC asthma in all strata, suggesting a benefit for adding a long-acting β -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 one or two criteria, whereas uncontrolled patients 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 uncontrolled by the original GOAL study criteria.⁵ Given that night-time awakenings are linked to asthma severity and the number of emergency visits,¹⁸ it is important to strive to achieve WC over PC asthma. The

observation that over a third of patients with PC asthma still experience marked night-time symptoms is supported by findings from other studies.¹⁹

Another key difference in the control criteria was the requirement of PEF $\geq 80\%$ predicted 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”,^{5,6} which may have led to a proportion of patients that 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.^{5,20} As long-term PEF monitoring is now only recommended under special circumstances,^{1,10,12} 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 if the dose was to be escalated or not during the conduct of the study, whilst 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 over-interpret these results.

In summary, this post hoc analysis of the GOAL study demonstrated that a markedly higher proportion of patients receiving FP/SAL or FP achieved satisfactory asthma control, according to the GINA 2016 definitions, than in the original GOAL analysis. In agreement with the original analysis, FP/SAL achieved control in more patients and at lower doses of ICS than was achieved with escalating doses of FP 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 a LABA/ICS as the preferred treatment for

217 patients in Steps 3, 4, and 5 of asthma management. This post hoc analysis which focused on
218 efficacy does not affect the risk:benefit analysis of FP/SAL or FP.

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References

1. Global Initiative for Asthma. *Global strategy for asthma management and prevention*. Bethesda: Global Initiative for Asthma (GINA), National Heart, Lung and Blood Institute (NHLBI); 2017.
2. 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.
3. Chipps 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.
4. 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.
5. 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.
6. Global Initiative for Asthma. *Pocket guide for asthma management and prevention*. Bethesda: National Institutes of Health, National Heart, Lung, and Blood Institute; 1998.
7. National Asthma Education and Prevention Program. *Guidelines for the diagnosis and management of asthma: expert panel report 2*. Bethesda: National Institutes of Health, National Heart, Lung, and Blood Institute; 1997.
8. Koshak EA. Classification of asthma according to revised 2006 GINA: evolution from severity to control. *Ann Thorac Med*. 2007;2:45-46.

9. Global Initiative for Asthma. *Global strategy for asthma management and prevention*. Bethesda: Global Initiative for Asthma (GINA), National Heart, Lung and Blood Institute (NHLBI); 2006.
10. 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.
11. Global Initiative for Asthma. *Global strategy for asthma management and prevention*. Bethesda: Global Initiative for Asthma (GINA), National Heart, Lung and Blood Institute (NHLBI); 2015.
12. Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention* 2016.
13. 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.
14. 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.
15. 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.
16. 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.

17. 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.
18. 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.
19. Sanz de Burgoa V, Rejas J, Ojeda P, investigators of the Coste Asma s. Self-perceived Sleep Quality and Quantity in Adults With Asthma: Findings From the CosteAsma Study. *J Investig Allergol Clin Immunol*. 2016;26:256-262.
20. 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.

Figure Legends

Figure 1. Percentage of patients who achieved at least partly controlled (WC/PC) asthma, or well-controlled (WC) asthma, during Phase I (ITT population).

FP, fluticasone propionate; FP/SAL, fluticasone propionate/salmeterol; ITT, intent-to-treat; PC, partly controlled; S, stratum; WC, well controlled.

P-values relate to WC/PC asthma. *P*-values for WC asthma: S1, *P*=.005, S2, *P*<.001; S3, *P*<.001.

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

FP, fluticasone propionate; FP/SAL, fluticasone propionate/salmeterol; ITT, intent-to-treat; PC, partly controlled; S, stratum; WC, well controlled.

Figure 3. Percentage of patients who achieved at least partly controlled (WC/PC) asthma (A), or well-controlled (WC) asthma (B), during Phase I, by FP dose (ITT population).

bid, twice a day; FP, fluticasone propionate; FP/SAL, fluticasone propionate/salmeterol; ITT, intent-to-treat; PC, partly controlled; S, stratum; WC, well controlled.

Figure 4. Mean annual exacerbation rate during Phase II by control status during Phase I (ITT population).

ITT, intent-to-treat. PC, partly controlled; WC, well controlled.

Patients with missing covariates (including baseline FEV₁) are excluded. n=mean number of exacerbations per year from Poisson model. Data are pooled by treatment and strata.

Table 1. Asthma control criteria from original GOAL study and the post hoc analysis (based on GINA 2016 criteria) [5, 12].

	Original GOAL study		Post hoc analysis (GINA 2016)	
	Total Control ^a	Well Controlled	WC	PC
	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/week with a score >1 ^b	≤2 days/week with a score >1 ^b	≤2 days/week with a score >1 ^b
Reliever use	None	≤2 days/week and ≤4 occasions/week	≤2 occasions/week	≤2 occasions/week
Morning PEF	≥80% predicted every day	≥80% predicted every day	Not included in assessment	
Night-time awakenings	None		None	None
Activity limitation	Not included		None	None
Exacerbations	None		None	
Emergency visits	None		Not included	
Treatment-related AEs	No AEs enforcing a change in asthma therapy		Not included	

Assessment period	8 consecutive weeks	Final 4 weeks of assessment period
Requirements to achieve control	Total Control or WC criteria for symptoms ^c and PEF met for ≥ 7 of the 8 weeks; no exacerbations, emergency 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

^aWC included patients with Total Control. ^bSymptom score: 1 was defined as “symptoms for one short period during the day”; overall scale:

0 (none) to 5 (severe). ^cDaytime symptoms, reliever use, night-time awakenings. AE, adverse event; GINA, Global Initiative for Asthma;

GOAL, Gaining Optimal Asthma control; PC, partly controlled; PEF, peak expiratory flow; WC, well controlled.

Table 2. Proportions and odds ratios for patients achieving asthma control during Phase I and Phase II (ITT population)^a

	S1		S2		S3	
	FP	FP/SAL	FP	FP/SAL	FP	FP/SAL
	n=544	n=539	n=577	n=583	n=567	n=568
Phase I						
WC/PC, n (%)	464 (85)	490 (91)	476 (82)	504 (86)	372 (66)	434 (76)
Odds ratio (95% CI) ^b	1.82 (1.23, 2.71); <i>P</i> =.003		1.36 (0.97, 1.89); <i>P</i> =.072		1.78 (1.35, 2.33); <i>P</i> <.001	
WC, n (%)	306 (56)	347 (64)	237 (41)	342 (59)	124 (22)	227 (40)
Odds ratio (95% CI) ^b	1.45 (1.12, 1.88); <i>P</i> =.005		2.16 (1.69, 2.77); <i>P</i> <.001		2.55 (1.94, 3.35); <i>P</i> <.001	
Phase II						
WC/PC, n (%)	477 (88)	505 (94)	503 (87)	517 (89)	425 (75)	470 (83)
Odds ratio (95% CI) ^b	2.23 (1.42, 3.50); <i>P</i> <.001		1.15 (0.79, 1.66); <i>P</i> =.465		1.68 (1.24, 2.27); <i>P</i> <.001	
WC, n (%)	346 (64)	378 (70)	290 (50)	394 (68)	204 (36)	292 (51)
Odds ratio (95% CI) ^b	1.38 (1.06, 1.81); <i>P</i> =.019		2.22 (1.72, 2.86); <i>P</i> <.001		2.06 (1.60, 2.65); <i>P</i> <.001	

^aA total of 38 patients with missing baseline FEV₁ were excluded from the analysis. ^bFP-treated patients used as the reference group.

CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FP, fluticasone propionate; FP/SAL, fluticasone propionate/salmeterol;

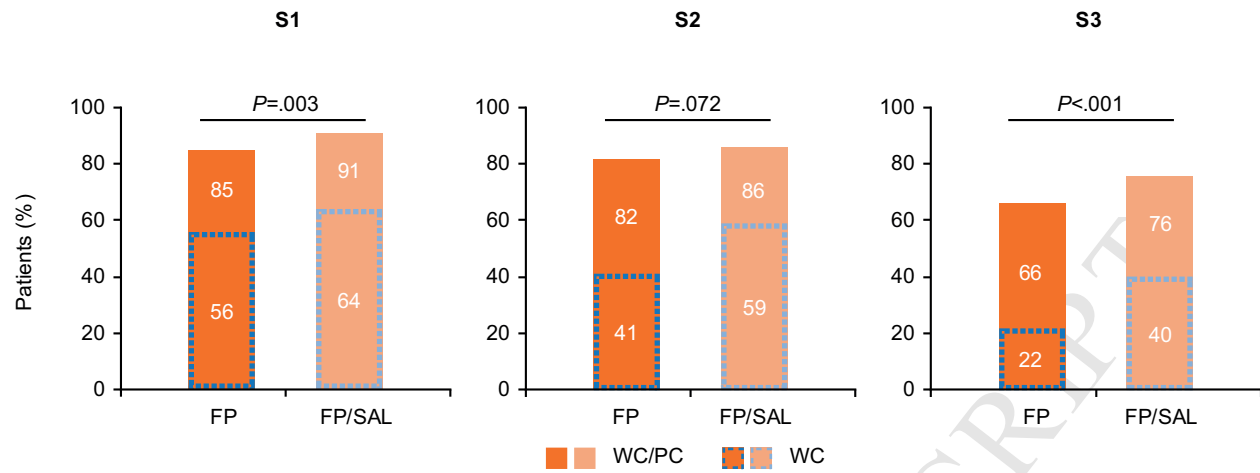
ITT, intent-to-treat; PC, partly controlled; S, stratum; WC, well controlled.

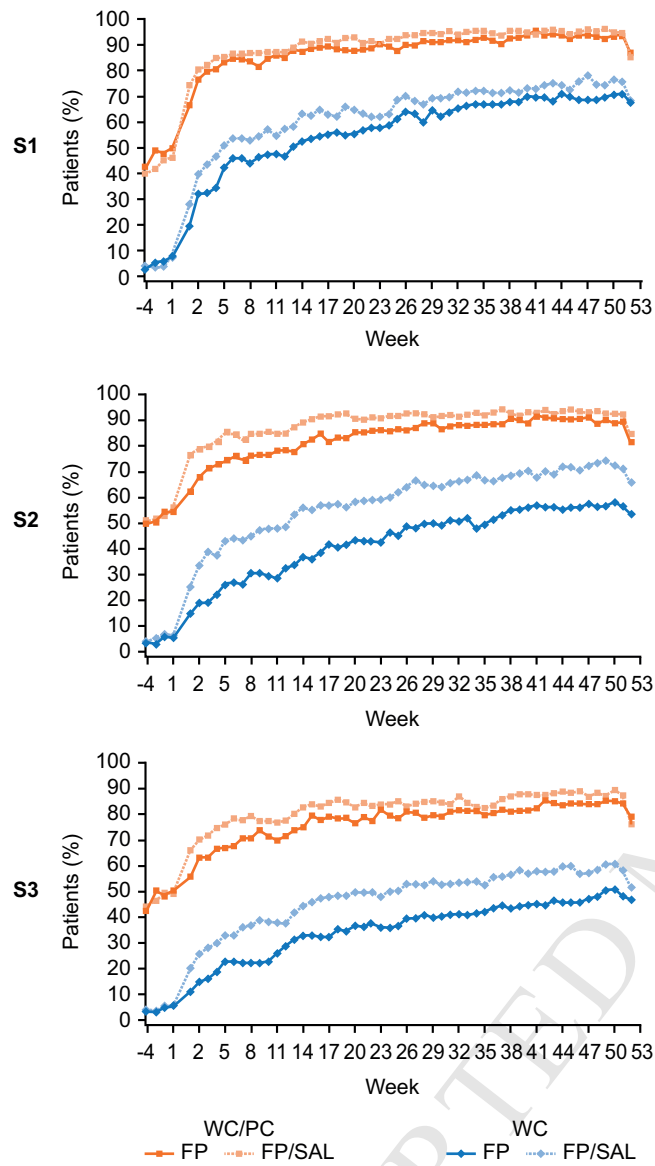
Table 3. Reasons for failing to achieve asthma control according to GINA 2016 criteria (ITT population)^a

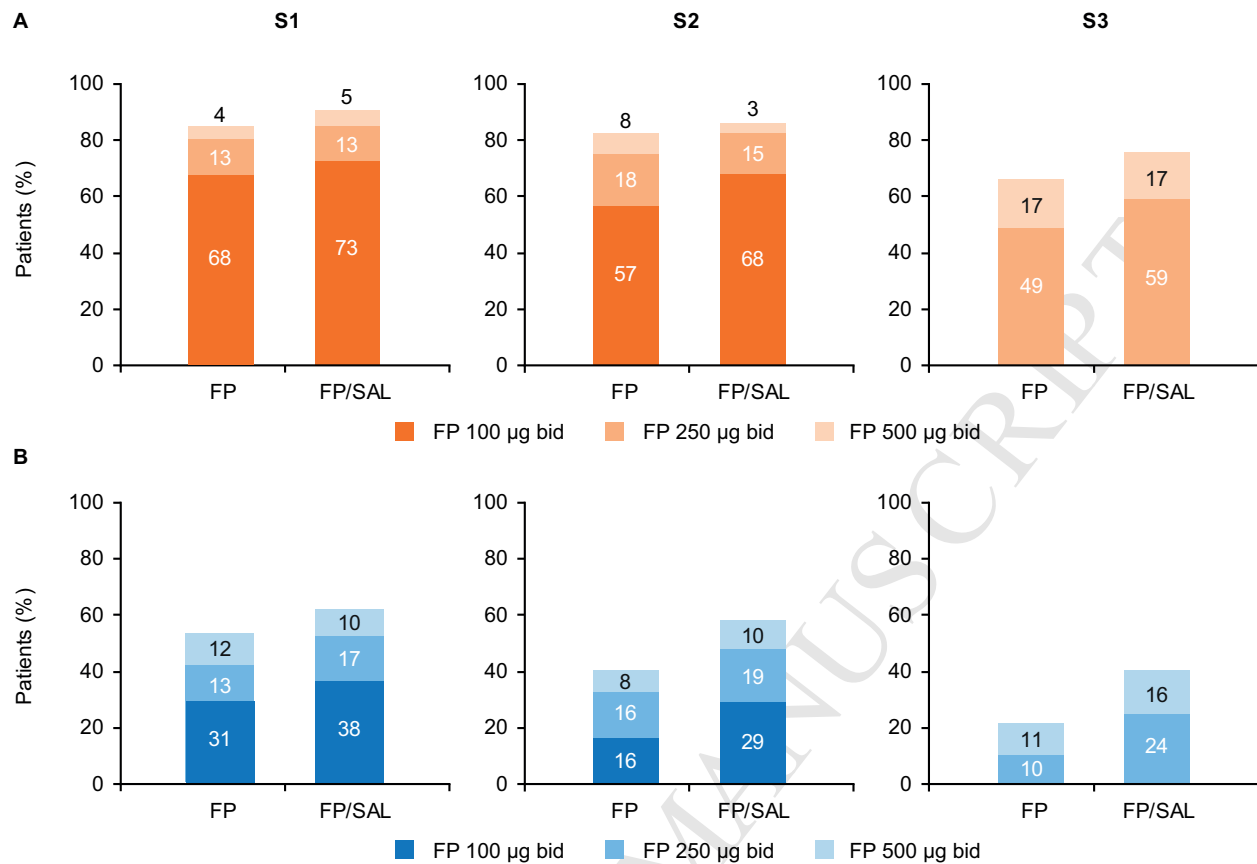
	WC patients, n (%) (n=1583)	PC patients, n (%) (n=1157)	Uncontrolled patients, n (%) (n=474)
Number of criteria failed during the 4-week assessment period			
No criteria failed	1583 (100)	39 ^b (3)	-
One criterion failed	-	486 (42)	-
Two criteria failed	-	601 (52)	-
Three criteria failed	-	31 ^c (3)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

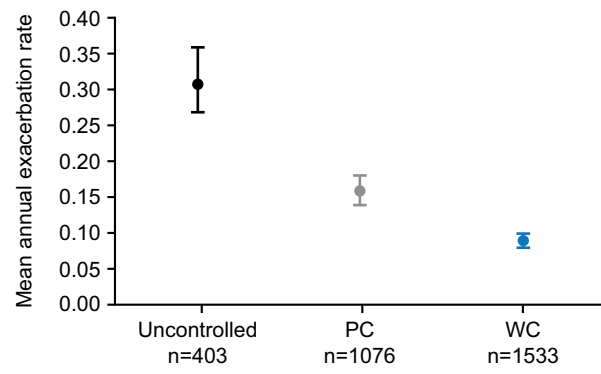
^aFP and FP/SAL groups combined; 164 patients were unevaluable and were not included in WC, PC or uncontrolled categories; 38 patients with missing baseline FEV₁ were also excluded. ^bThese patients could not be classified as WC due to some criteria being unevaluable. ^cThese patients failed 1–2 criteria within each week but failed >2 criteria over the total 4-week assessment period. ^dPercentages 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.

CI, confidence interval; FEV₁, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; ITT, intent-to-treat; PC, partly controlled; WC, well controlled.

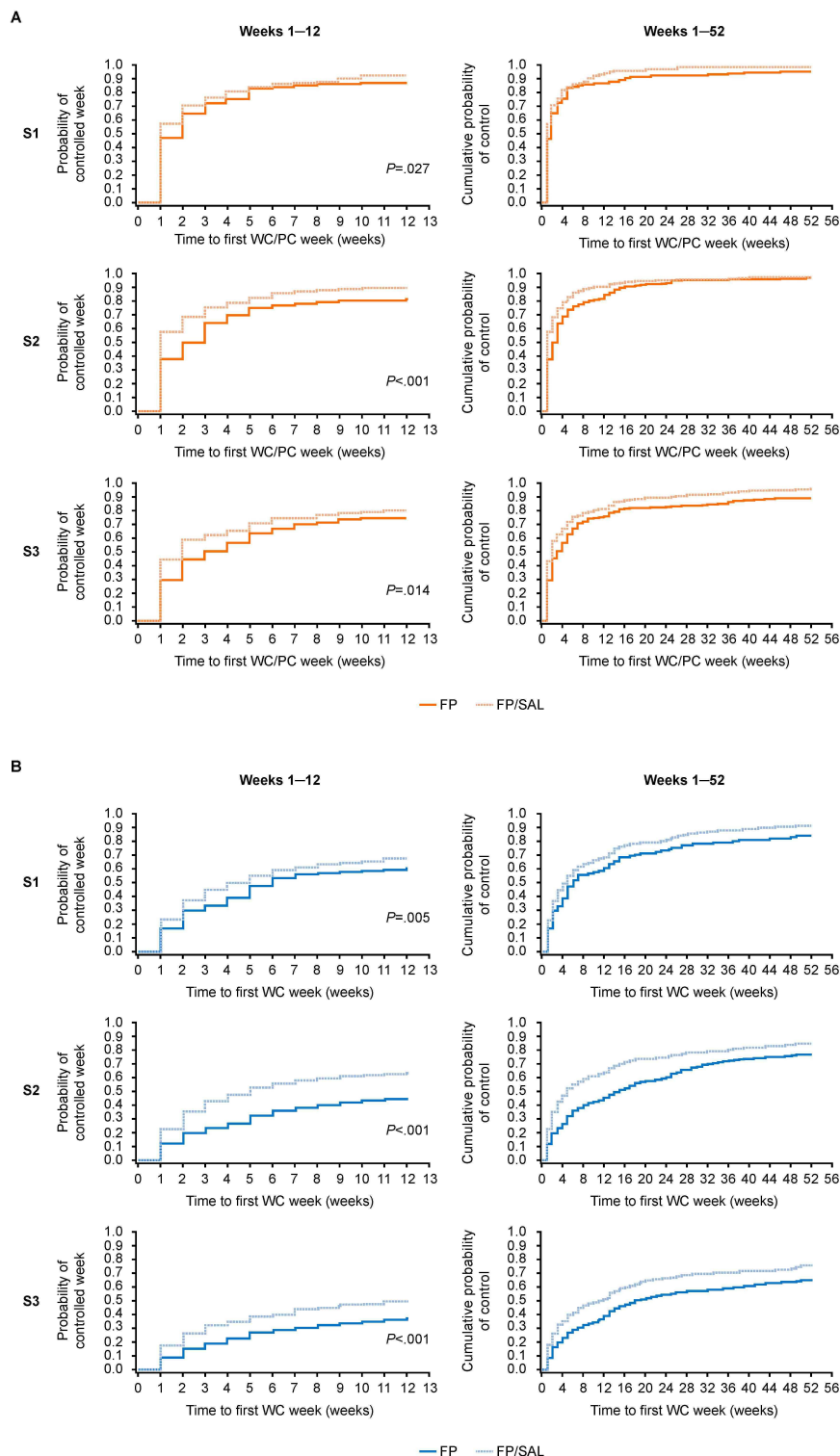








eFigure 1. Inverse Kaplan–Meier plot of time to first individual week of WC/PC asthma (A), or WC asthma (B) over Weeks 1–12 and 1–52 in S1, S2, and S3 (ITT population)



FP, fluticasone propionate; FP/SAL, fluticasone propionate/salmeterol; ITT, intent-to-treat; PC, partly controlled; S, stratum; WC, well controlled. *P*-values were not calculated for the Week 1–52 plots.

eTable 1. Summary and analysis of steroid dose (μg) at which WC/PC or WC asthma was first achieved in Phase I (ITT population)^a.

	S1		S2		S3	
	FP	FP/SAL	FP	FP/SAL	FP	FP/SAL
	n=544	n=539	n=577	n=583	n=567	n=568
WC/PC						
100 μg , n (%)	372 (68)	396 (73)	300 (57)	398 (68)	0 (0)	0 (0)
250 μg , n (%)	68 (13)	69 (13)	101 (18)	88 (15)	278 (49)	337 (59)
500 μg , n (%)	24 (4)	25 (5)	45 (8)	18 (3)	94 (17)	97 (17)
Odds ratio ^b		1.40		1.65		1.61
(95% CI)		(1.07, 1.83)		(1.29, 2.09)		(1.28, 2.03)
<i>P</i> -value		.015		<.001		<.001

WC						
100 µg, n (%)	169 (31)	204 (38)	95 (16)	170 (29)	0 (0)	0 (0)
250 µg, n (%)	73 (13)	90 (17)	93 (16)	111 (19)	59 (10)	137 (24)
500 µg, n (%)	64 (12)	53 (10)	49 (8)	61 (10)	65 (11)	90 (16)
Odds ratio ^b		1.44		2.11		2.60
(95% CI)		(1.15, 1.80)		(1.68, 2.64)		(1.99, 3.39)
<i>P</i> -value		.001		<.001		<.001

CI, confidence interval; FEV₁: forced expiratory flow in 1 second; FP, fluticasone propionate; FP/SAL, fluticasone propionate/salmeterol; ITT, intent-to-treat;

PC, partly controlled; S, stratum; WC, well controlled.

^aPatients with missing baseline FEV₁ are excluded. ^bOdds ratios are derived from a proportional odds logistic regression with FP-treated patients as the reference group.