

# Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting $\beta$ -agonist inhaler therapy in asthma

Kyle Perrin, MBChB, FRACP,<sup>a,b</sup> Mathew Williams, Dip Ex Sci,<sup>a</sup> Meme Wijesinghe, BSc, MBBS, MRCP,<sup>a,b</sup> Kate James, MBChB,<sup>a,b</sup> Mark Weatherall, MBChB, FRACP,<sup>b,c</sup> and Richard Beasley, MBChB, DSc<sup>a,b,c</sup>

Wellington, New Zealand

**Background:** The inhaled corticosteroid (ICS)/long-acting  $\beta$ -agonist (LABA) combination inhaler has the potential to improve adherence with ICS therapy in asthma.

**Objective:** To determine whether ICS/LABA combination inhaler therapy improves adherence compared with separate inhaler use.

**Methods:** In a 24-week randomized controlled parallel group study, 111 subjects were prescribed 125  $\mu$ g fluticasone dipropionate (FP) and 25  $\mu$ g salmeterol, 2 actuations twice daily through either a combination inhaler or separate inhalers concurrently. Medication use was recorded by covert electronic monitors. The primary outcome variable was adherence during the final 6-week period, defined as the number of doses taken as a percentage of those prescribed.

**Results:** Complete adherence data from the final 6-week period were available for 49 and 54 subjects in the separate and combination groups, respectively. The mean (SD) adherence was 73.7% (36.0) for FP, 76.7% (30.5) for salmeterol, and 82.4% (24.5) for FP/salmeterol. There were no significant differences in adherence between FP/salmeterol and FP (−8.7%; 95% CI, −10.6 to 3.3) and salmeterol (−5.6%; 95% CI, −16.4 to 5.1). There was no significant difference in overuse among the FP, salmeterol, or FP/salmeterol groups. In 2 (4%) of 49 subjects, salmeterol was effectively taken as monotherapy during a 6-week period.

**Conclusion:** In the setting of a randomized controlled trial, use of a combination ICS/LABA inhaler does not markedly increase adherence above that observed with separate inhaler use. LABA monotherapy was observed in a small proportion of patients prescribed ICS and LABA therapy via separate inhalers. (*J Allergy Clin Immunol* 2010;126:505-10.)

**Key words:** Asthma, adherence, compliance, inhaled corticosteroids, long-acting  $\beta$ -agonists

Poor adherence with inhaled corticosteroid (ICS) therapy in asthma is a major factor contributing to poor disease control and is associated with an increased risk of morbidity and mortality.<sup>1-3</sup> Combination metered dose inhalers that include both ICS and a long-acting  $\beta$ -agonist (LABA) represent an asthma treatment with the potential to improve adherence with ICS therapy. First, the addition of a bronchodilator means the patient may obtain a symptomatic benefit and therefore take the medication that also delivers ICS more regularly. Second, it simplifies the medication regimen (compared with an ICS and LABA separately), an approach that has the potential to improve adherence.<sup>4,5</sup> In addition, there are safety concerns regarding the use of LABAs without concomitant ICS therapy in asthma,<sup>6-8</sup> and the use of a combination inhaler ensures that patients cannot take LABAs as monotherapy.

There is epidemiologic evidence to suggest that the use of combination ICS/LABA inhalers improves adherence with ICS therapy.<sup>9-11</sup> In 3 retrospective studies of medication refill persistence, there was a 30% to 73% greater use of ICS therapy when prescribed as a combination inhaler compared with separate inhaler use. However, this method of assessing adherence does not provide data on patterns of actual use, which are inherently difficult to measure directly.<sup>12</sup> Patient diaries are known to be inaccurate,<sup>12-14</sup> and other methods such as canister weighing are poorly reflective of day-to-day patterns of use, overestimating actual adherence.<sup>14,15</sup> The optimal method uses electronic monitors that accurately record the date and time of each dose.<sup>16</sup> Covert electronic monitoring is preferred because patients who are aware of dose recording change their patterns of use.<sup>17</sup> Although there have been a number of studies using electronic monitoring to determine the factors that contribute to adherence with ICS therapy in asthma,<sup>14,18-27</sup> this is the first randomized controlled trial using covert electronic monitoring to assess the effect of combining ICS with LABA therapy in a single inhaler.

## METHODS

### Subjects

Adults in the Wellington region age 16 to 65 years with a diagnosis of asthma were enrolled (Fig 1). Subjects were recruited from existing research volunteer databases, newspaper advertisements, and letters via family doctors. To be included, subjects had to have a diagnosis of asthma and to be currently taking ICS at a stable dose with or without a separate LABA inhaler. Exclusion criteria were a diagnosis of chronic obstructive pulmonary disease, current use of a combination ICS/LABA inhaler, women who were pregnant or lactating, a history of other clinically significant disease, or a significant exacerbation of

From <sup>a</sup>the Medical Research Institute of New Zealand; <sup>b</sup>Wellington Hospital, Capital and Coast District Health Board; and <sup>c</sup>the University of Otago Wellington.

Supported by a research grant from GlaxoSmithKline (GSK study no. SAM106689).

The trial was registered with the Australian New Zealand Clinical Trials Registry, ACTRN12606000508572.

In this article, the term *adherence* has been used rather than *compliance* because of the willing partnership between the clinician and patient in the setting of the research study.

Disclosure of potential conflict of interest: R. Beasley has received a consulting fee and research support from GlaxoSmithKline. The rest of the authors have declared that they have no conflict of interest.

Received for publication March 18, 2010; revised May 31, 2010; accepted for publication June 8, 2010.

Reprint requests: Richard Beasley, Medical Research Institute of New Zealand, Private Bag 7902, Wellington 6242, New Zealand. E-mail: Richard.Beasley@mri.nz.ac.nz. 0091-6749/\$36.00

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doi:10.1016/j.jaci.2010.06.033

**Abbreviations used**

ACQ: Asthma Control Questionnaire  
 FP: Fluticasone propionate  
 ICS: Inhaled corticosteroid  
 LABA: Long-acting  $\beta$ -agonist  
 MDI: Metered-dose inhaler

asthma in the previous month requiring a clinic or hospital attendance. The study (GlaxoSmithKline study number SAM106689) was approved by the Central Regional Ethics Committee, and all subjects gave written informed consent. The trial was registered with the Australian New Zealand Clinical Trials Registry, registration number ACTRN12606000508572.

**Smartinhaler**

The Smartinhaler (Nexus6, Auckland, New Zealand) is a metered-dose inhaler (MDI) casing that contains a battery and electronics to record the date and time of each actuation by way of a microswitch. The casing is designed to be used with standard pressurized MDI canisters, and its accuracy has been independently validated.<sup>28</sup> The Smartinhalers used in the study were red (fluticasone propionate [FP]), green (salmeterol), and purple (FP/salmeterol) depending on which study medication they contained.

**Design**

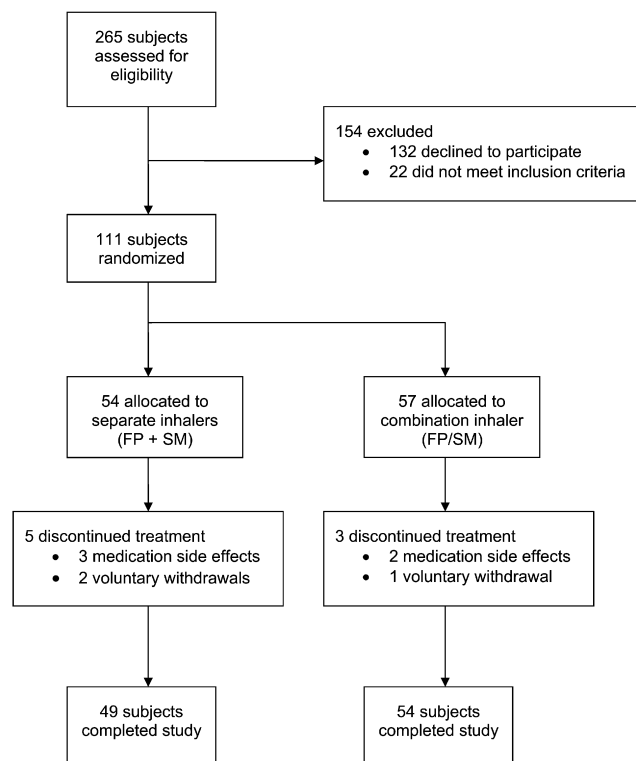
The study was undertaken at the Medical Research Institute of New Zealand and the P3 Research Clinical Trials Unit at Bowen Hospital, Wellington, New Zealand. Subjects were randomized to receive 1 of 2 treatment regimens for a duration of 24 weeks:

- 125  $\mu$ g FP and 25  $\mu$ g salmeterol in a combination Smartinhaler, 2 actuations twice daily
- 125  $\mu$ g FP and 25  $\mu$ g salmeterol in separate Smartinhalers, 2 actuations twice daily

Participants were seen in the clinic on 5 occasions. At the first visit, subjects were randomized and issued the appropriate Smartinhalers, and inhaler technique was checked. Subjects were instructed to take 2 actuations of the study medications twice daily, resulting in a daily dose of 500  $\mu$ g FP and 100  $\mu$ g salmeterol with both regimens. Subjects were advised that the study was designed to compare the efficacy of the 2 regimens but were not informed that adherence would be monitored. They were told that the MDI casing looked different because it was possible to program it with a reminder alarm, but that this function would not be used in this study. The issue of covert monitoring was specifically discussed with the ethics committee because it involved a degree of deception. The committee granted approval on the basis that there was no other way to gather accurate data and the subjects were unlikely to be harmed by this approach. At baseline and at the 4 subsequent clinic visits, FEV<sub>1</sub> was recorded (best of 3 attempts), and the Asthma Control Questionnaire (ACQ) and the Asthma Exacerbation Questionnaire were administered. Information was collected about the need for oral steroids or doctor visits over the previous 6 weeks. At clinic visits, adherence data were uploaded from the Smartinhaler to a computer out of sight of the subjects under the guise of cleaning the MDIs to ensure optimal drug delivery.

The primary hypothesis was that treatment with a combination ICS/LABA MDI would result in increased adherence compared with ICS in a single MDI. The primary outcome variable was adherence during the final (fourth) 6-week period of the study, defined as the number of doses taken as a percentage of those prescribed. Secondary outcome variables included the following:

1. Adherence in the first, second, and third 6-week periods of the study.
2. Percentage of days on which subjects were fully adherent—that is, took 2 doses twice daily—in each 6-week period of the study. This required subjects to take 2 doses twice daily within a 24-hour period, which started at 0300. The 2 doses had



**FIG 1.** The CONSORT figure showing the inclusion of subjects in the clinical trial. *SM*, Salmeterol.

**TABLE I.** Characteristics of subjects

Variable	Single inhalers n = 54	Combination inhaler n = 57
Age (y), mean (SD)	49.2 (11.2)	45.5 (13.8)
FEV <sub>1</sub> (L), mean (SD)	2.51 (0.81)	2.60 (0.75)
FEV <sub>1</sub> % predicted, mean (SD)	79.9 (19.6)	82.3 (18.3)
ACQ, mean (SD)	1.3 (0.7)	1.2 (0.7)
Male, no. (%)	25 (46.2)	25 (43.9)
AEQ score = 0, no. (%)	46 (85.2)	43 (75.4)

AEQ, Asthma Exacerbation Questionnaire.

to be separated by at least 6 hours, and on each occasion the 2 doses had to be more than 2 seconds apart.

3. The proportion of subjects who took >50%, >80%, or >90% of doses prescribed in each 6-week period of the study.
4. Overuse defined as >2 doses taken within a 6-hour period or >4 doses taken within a 24-hour period. In each 6-week period of the study, overuse was expressed as (1) the percentage of days on which overuse occurred, and (2) the mean number of extra doses taken per day.

For all outcome variables, calculations were made after excluding doses falling within a period of dose dumping. Dose dumping was defined as 10 or more actuations within a 3-hour period.

A *post hoc* analysis was undertaken in which the number of patients who had <5% adherence to ICS therapy during a 6-week period was documented and patterns of use compared with LABA therapy reported. Adherence of <5% was considered to represent effective discontinuation of ICS therapy.

**Sample size**

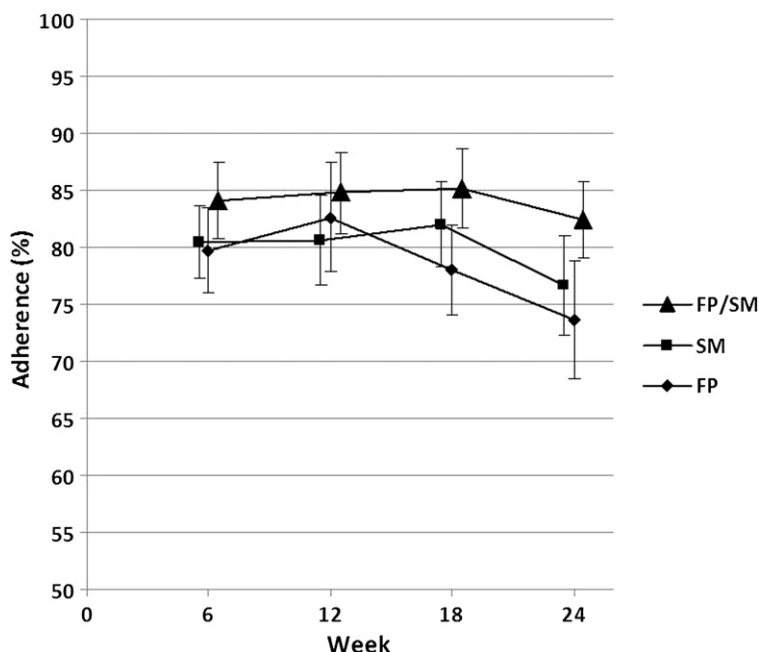
On the basis of a previous similar study,<sup>26</sup> we assumed a mean adherence of approximately 65% with an SD of 18%. If combination therapy could increase adherence to 75%, then at the 5% level of significance and with 80% power,

**TABLE II.** Adherence with therapy between 18 and 24 weeks

Variable	FP (n = 49) Mean (SD)	SM (n = 49) Mean (SD)	FP/SM (n = 54) Mean (SD)	FP minus FP/SM Estimate (95% CI)	SM minus FP/SM Estimate (95% CI)
Adherence (%)	73.7 (36.0)	76.7 (30.5)	82.4 (24.5)	-8.7 (-10.6 to 3.3) <i>P</i> = .15	-5.6 (-16.4 to 5.1) <i>P</i> = .30
Adherent days (%)	49.4 (27.9)	53.3 (29.3)	53.9 (25.3)	-4.5 (-14.9 to 5.9) <i>P</i> = .40	-0.6 (-11.4 to 10.2) <i>P</i> = .91

SM, Salmeterol.

Adherence (%), The number of doses taken as a percentage of those prescribed. Adherent days (%), Percentage of days on which subjects took 2 doses twice daily.



**FIG 2.** Adherence in the four 6-week periods of the study in the subjects prescribed FP/salmeterol (SM; ▲), SM (■), and FP (◆). The symbols show the mean and the error bars the SEM.

50 participants were needed in each arm. Therefore, allowing for a dropout rate of 10%, 110 subjects were recruited. Although information on lung function and symptoms was collected, the study was not powered to assess clinical efficacy.

Randomization was by computer-generated random code supplied by a statistician. The sequence was imbedded in a Microsoft Access Database (Microsoft Corp, Redmond, Wash) by a third party and concealed from the researchers until the time the subject was enrolled and entered into the database.

### Statistical methods

The primary outcome variable, adherence over the final 6 weeks of the trial, expressed as a percentage, was compared by Student *t* test with appropriate CIs. In the secondary analyses for continuous variables, *t* tests were used with appropriate CIs. For the number of subjects who took >50%, >80%, or >90% of the prescribed medication, comparison was by calculation of relative risk together with a  $\chi^2$  test. SAS version 9.1 (SAS Institute Inc, Cary, NC) was used.

### Role of sponsor

The sponsor had no involvement in the study design, collection, analysis, and interpretation of data, writing of the report, or the decision to submit for publication.

### RESULTS

There were 111 subjects (50 male) enrolled in the study, 54 to the separate inhaler group and 57 in the combination inhaler group. The 2 groups were well matched with regard to age, sex,

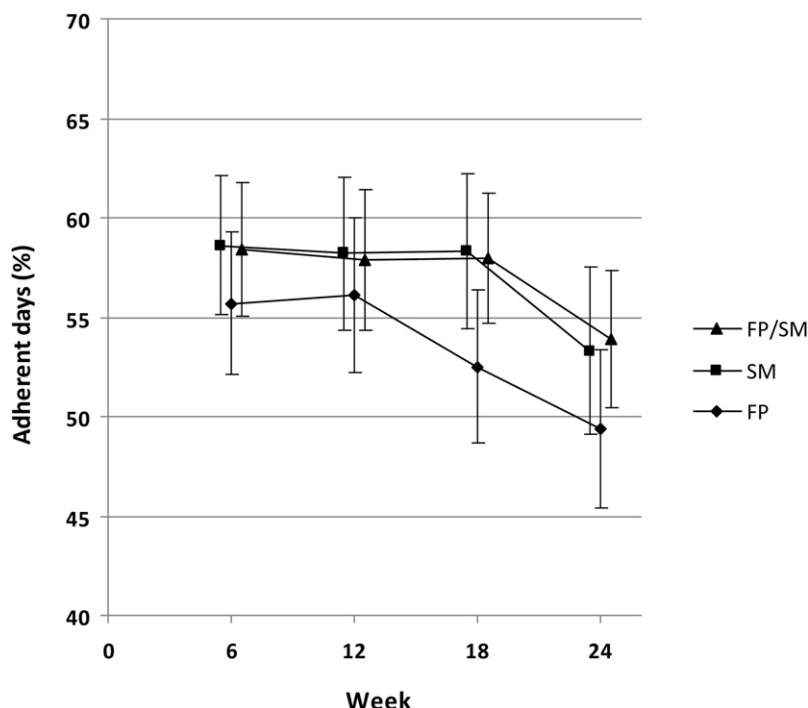
baseline lung function, and asthma control (Table I). After allowing for withdrawals, complete adherence data from the final 6-week study period were available for 49 and 54 subjects in the separate and combination groups, respectively (Fig 1). Eligible participants were recruited and studied between February and October 2007.

### Primary outcomes

During the final 6 weeks of the study, the mean (SD) percent adherence was 73.7% (36.0) for FP, 76.7% (30.5) for salmeterol, and 82.4% (24.5) for FP/salmeterol (Table II). There was no significant difference between FP/salmeterol and FP (-8.7%; 95% CI, -10.6 to 3.3) or FP/salmeterol and salmeterol (-5.6%; 95% CI, -16.4 to 5.1).

### Secondary outcomes

The point estimates for adherence were consistently higher for FP/salmeterol compared with FP or salmeterol in all four 6-week periods; however, the differences were not statistically significant (Fig 2). Likewise, there were no significant differences between the different medications when adherence was expressed as the percentage of days on which subjects were fully adherent, taking the prescribed 2 doses twice daily (Table II). Throughout the



**FIG 3.** Percentage of adherent days in the four 6-week periods of the study in the subjects prescribed FP/salmeterol (SM; ▲), SM (■), and FP (◆). The symbols show the mean and the error bars the SEM.

study, subjects were fully adherent about 4 days per week (Fig 3). The proportion of subjects who took >50%, >80%, or >90% medication as prescribed was not significantly different among the different medications, although the point estimates consistently favored the FP/salmeterol regimen (Table III).

Extra doses of medication were taken on about 1 day per week, with no significant differences among the 3 medications (Table IV). Likewise, when expressed as the mean number of extra doses, there was no significant difference among the 3 medications.

There were eleven 6-week periods in which a total of 6 subjects took <5% of their prescribed FP doses. In 8 of these 6-week periods (3 subjects), adherence with LABA therapy was also <5% (3 as separate inhalers, 5 as combination inhalers). In the other 3 subjects, compliance with ICS therapy was <5%, and adherence with LABA therapy was 6%, 43%, and 51%. This means that 2 (4%) of 49 subjects were effectively taking salmeterol as monotherapy during 1 of the 6-week periods.

There were no significant differences in asthma control (mean [SD], ACQ score, 0.89 [0.84] vs 0.86 [0.73] for separate and combination inhaler groups, respectively; difference, 0.03; 95% CI, -0.27 to 0.33;  $P = .85$ ) or in lung function (mean [SD], FEV<sub>1</sub> 2.70 [0.84] vs 2.69 [0.76] L for separate and combination inhaler groups, respectively; difference, 0.01 L; 95% CI, -0.30 to 0.33;  $P = .93$ ).

## DISCUSSION

This is the first randomized controlled trial in which the effect of a combination ICS/LABA inhaler on adherence with ICS therapy has been directly measured by covert electronic monitors. It has demonstrated that although the point estimates were consistent with greater adherence with FP/salmeterol, there was

**TABLE III.** Proportion of subjects with >50%, >80%, and >90% adherence during the final 6-week period of study

Variable	Single inhaler n/N (%)	Combination inhaler n/N (%)	Relative risk (95% CI)	<i>P</i> value
Adherence >50%				
FP	40/49 (81.6)	51/54 (94.4)	0.86 (0.75-1.0)	.06
SM	40/47 (85.1)	51/54 (94.4)	0.90 (0.79-1.03)	.18
Adherence >80%				
FP	24/49 (50.0)	32/54 (59.3)	0.83 (0.58-1.2)	.33
SM	26/47 (55.3)	32/54 (59.3)	0.93 (0.67-1.3)	.84
Adherence >90%				
FP	18/49 (36.7)	24/54 (44.4)	0.83 (0.51-1.3)	.55
SM	21/47 (44.7)	24/54 (44.4)	1.0 (0.65-1.6)	1.0

SM, Salmeterol.

no significant difference compared with FP and salmeterol prescribed in separate inhalers. Furthermore, there was no evidence of a significant difference in preferential overuse of salmeterol compared with FP in those subjects randomized to separate inhalers. However, LABA monotherapy was observed during a 6-week period of the study in 2 (4%) patients prescribed FP and salmeterol as separate inhalers.

There were a number of methodologic issues considered in the study design that are relevant to the interpretation of the study findings. The first is that in a study of this design, adherence is likely to be higher initially because of participation in the research project.<sup>18,23,26</sup> It was for this reason that the study had a duration of 24 weeks and that for the primary outcome variable, adherence was assessed in the final 6-week period of the study.

The second issue is that subjects were informed the purpose of the study was to compare the efficacy of ICS and LABA therapy when taken as separate or combination inhaler therapy. Subjects

**TABLE IV.** Overuse of therapy between 18 and 24 weeks

Variable	FP (n = 49) Mean (SD)	SM (n = 49) Mean (SD)	FP/SM (n = 54) Mean (SD)	FP minus FP/SM Estimate (95% CI)	SM minus FP/SM Estimate (95% CI)
Overuse days (%)	13.8 (15.7)	15.0 (14.0)	17.7 (13.9)	-3.8 (-9.6 to 2.0) P = .19	-2.7 (-8.2 to 2.8) P = .33
Overuse (mean)	0.34 (0.63)	0.33 (0.36)	0.40 (0.41)	-0.06 (-0.27 to 0.14) P = .55	-0.07 (-0.22 to 0.08) P = .36

SM, Salmeterol.

Overuse defined as >2 doses taken within a 6-hour period or >4 doses taken within a 24-hour period, expressed as the percentage of days on which overuse occurred and the mean number of extra doses taken per day.

were not told that the assessment of adherence was the primary outcome of the study because this had the potential to change patient behavior.<sup>12,17</sup> Ethical approval for this approach was obtained on the basis that there was no other way to collect this information, no harm was anticipated, and the subjects were likely to benefit from participating in this clinical trial. It is possible that some subjects became aware of the adherence monitoring in the study, although only 2 patients specifically questioned the investigators about the ability of the device to record their drug use.

The primary measure of adherence was the number of doses taken as a percentage of the doses prescribed. A number of other measures of adherence were used including the number of adherent days, in which the prescribed 2 doses were taken twice daily, and the proportion of patients who took >50%, >80%, and >90% of doses prescribed as previously defined.<sup>26</sup> Measures of overuse were also used in an attempt to define whether LABA therapy was used in preference to ICS therapy when prescribed as separate inhalers. For all measures, we excluded dose dumping, which is a recognized feature of clinical trials of adherence with ICS therapy.<sup>15,17</sup>

The main finding was that although the point estimates consistently favored greater adherence with FP/salmeterol than with FP alone, the differences did not reach statistical significance. This may relate to the greater variance of adherence and the higher level of adherence for FP than anticipated in the sample size calculations. Although the difference in adherence between FP/salmeterol and FP was 8.7%, close to the anticipated 10% used in the power calculations to signify a clinically relevant difference, the SD was substantially higher at 36% compared with the 18% anticipated on the basis of a previous study from our group.<sup>26</sup> In addition, the mean baseline adherence for FP was 74% rather than 65% as anticipated. In part, this may be a result of the fact that a number of subjects were recruited from previous study databases and therefore may be more familiar with clinical trials and thus more compliant. In addition, patients who know they are in a clinical study are likely to have better adherence than those in a real world setting, even when the adherence monitoring is covert. As a result, the study may have been underpowered to detect small but clinically important differences in compliance.

This finding contrasts with those of 3 large retrospective cohort studies suggesting, in terms of prescription refill, that combination inhalers are associated with considerably greater adherence to ICS than single inhaler therapy, on the order of 30% to 73%.<sup>9-11</sup> This difference may relate to the higher rates of adherence in our subjects, who were well trained, many having previously participated in clinical trials. This suggests that combination ICS/LABA therapy has less effect on adherence in randomized controlled trials than expected from community studies of routine clinical practice.

The other main finding was that the use of separate inhalers did not result in preferential overuse of salmeterol compared with FP. This is consistent with the report of similar rates of prescription refill for ICS and LABA therapy in patients prescribed separate inhalers concurrently.<sup>9</sup> The absence of preferential salmeterol overuse is likely to relate to its prescription as a regular twice-daily medication, together with the availability of a short-acting  $\beta$ -agonist for use as required for symptomatic relief.

The individual subject data were also reviewed to identify whether any subjects had effectively stopped their ICS use but continued with their LABA therapy. This pattern was identified in 2 subjects, 1 in whom adherence with FP in the last 6 weeks of the study was 1% compared with 43% for salmeterol during this period. In the other subject, adherence with FP fell to 2% in the last 6-week period compared with 51% for salmeterol. It is likely that both these subjects had symptomatic asthma, as suggested by the continued salmeterol use. As a result, around 4% of our subjects were effectively taking salmeterol as monotherapy for at least a 6-week period. This proportion is likely to be higher in routine clinical practice, in which adherence with ICS is known to be considerably less than that observed in this study.<sup>3,9-11,14</sup> These findings are of clinical relevance because monotherapy with LABAs in patients with poorly controlled asthma may be associated with an increased risk of mortality.<sup>29-32</sup> This finding would provide support for the recommendation that LABAs are prescribed only as ICS/LABA combination therapy, thereby ensuring that LABA monotherapy cannot occur.<sup>33</sup>

Another observation from our study is that subjects were essentially taking their ICS therapy within the framework of variable dosing. On average, subjects took the prescribed 2 doses twice daily on about 4 days per week, using in excess of this prescribed dose about 1 day per week, and less than this prescribed dose the remaining 2 days per week. Although there may be numerous reasons for such patterns of use, it is likely that subjects vary their use at least in part according to perceived need.

In conclusion, this is the first clinical trial to use a prospective randomized controlled design and covert electronic monitoring to assess adherence with the combination FP/salmeterol inhaler. We did not observe either a marked difference in adherence with FP/salmeterol combination therapy or overuse with salmeterol compared with FP separate inhaler therapy as proposed in the *a priori* hypotheses. However, we did observe a small but potentially important proportion of subjects who effectively took salmeterol monotherapy, with discontinuation of their FP. We propose that further research is urgently required to study patterns of use of separate and combination ICS/LABA therapy, particularly LABAs with different properties including speed of onset and duration of bronchodilator action, and the different regimens including fixed once-daily or twice-daily maintenance dosing,

and according to the maintenance and as-required regimens. We suggest that our study provides further data to support the recommendation that the use of LABAs in asthma be restricted to combination ICS/LABA therapy.

**Clinical implications: In the setting of a randomized controlled trial, combination ICS/LABA therapy does not markedly increase adherence above that observed with separate inhaler use but does prevent LABA monotherapy, which may occur in a small proportion of patients.**

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