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Letter to the Editor

Comparison of extra-fine-particle inhalational corticosteroid add-on therapy with dose-escalation of large-particle inhalational corticosteroid therapy in patients with incompletely controlled asthma

Dear Editor,

Asthma is a chronic inflammatory disease of large and small airways.¹ Persistent allergic airway inflammation in small airways can cause the refractory disturbance of asthma control because conventional therapeutics, including a combination of inhalational corticosteroids (ICS) and long-acting β_2 -agonists (LABAs), have difficulty in reaching those deep areas.

Recently, several fine-particle ICSs possessing a particle mass median aerodynamic diameter (MMAD) of approximately 2 μm and a few aerosols of extra-fine-particle ICSs with an MMAD of 1 μm became available for improvement of peripheral airway function inflammation, hyperresponsiveness, and clinical indices in patients with mild-to-moderate or refractory eosinophilic asthma.^{2–5} However, the benefit of additive therapy with extra-fine-particle ICSs for uncontrolled moderate-to-severe asthma is unclear. Thus, the aim of this study was to determine whether adding an ICS ciclesonide (CIC) (MMAD, 0.9 μm) to the combination drug of an ICS fluticasone propionate (FP) and a LABA salmeterol (SFC) (MMAD, 4.4 μm) improves eosinophilic airway inflammation in not well-controlled moderate-to-severe asthma relative to the effect of increasing the SFC dose.

This study was a 48-week randomized open-label controlled trial conducted in Saitama Medical University Hospital (Supplementary Methods). Adult patients with not well-controlled asthma [Asthma Control Test (ACT) score of <25] who received an ICS (400–1000 μg per day of FP or a corresponding dose of another ICS) with any maintenance therapeutics for ≥ 8 weeks were enrolled (Supplementary Fig. 1). During the run-in period, the eligible participants were asked to change ICS/LABA to SFC 50/250 μg Diskus bid therapy for 4 weeks. Subsequently, subjects who showed an ACT score of <25 initially were randomized to the following two arms: change SFC 50/250 μg bid to SFC 50/500 μg bid therapy (the SFC1000 arm) or added ciclesonide-hydrofluoroalkane (CIC-HFA) 400 $\mu\text{g}/\text{d}$ to SFC 50/250 μg bid therapy (the SFC500 + CIC400 arm). The use of other maintenance therapeutics was allowed without any changes. A salbutamol inhaler and oral corticosteroid were administered to treat asthma exacerbation.

This study was approved by the institutional review board of Saitama Medical University Hospital (approval number: 11–080) and was registered in the UMIN Clinical Trials Registry (UMIN000012189). Written informed consent was obtained from all patients before beginning the study.

At weeks 4, 12, and 48, sputum induction and fractional exhaled nitric oxide (FeNO) concentrations were examined as described previously,⁶ and the ACT score was obtained. Daily peak expiratory flow (PEF) values were recorded in the intervention period. Cells in sputum were counted after separated by centrifugation. The primary efficacy measure was the percentage of eosinophil in sputum at week 48. Measurements at each visiting day were compared with those at week 0 within each intervention arm. Measurements at each visiting day were compared between the two intervention arms. Parametric and nonparametric variables were analyzed by Student's *t*-test or the Mann–Whitney U test, respectively. Categorical variables were analyzed by using χ^2 tests. SPSS version 20.0 (IBM, Armonk, New York, USA) was used for statistical analysis.

Forty-four patients with asthma were enrolled. Finally, 17 in the SFC500 + CIC400 arm and 17 in the SFC1000 arm completed the study (Supplementary Fig. 2). Table 1 presents the characteristics of the subjects. There were no significant differences in any of the indices. Sputum eosinophil ratios were significantly decreased at week 48 in both arms, and the reduction ratio was significantly greater in the SFC500 + CIC400 arm than the ratio in the SFC1000 arm (Fig. 1A). Significant reductions in the eosinophil ratios were observed after week 4 in the SFC500 + CIC400 arm and after week 12 in the SFC1000 arm. FeNO was significantly reduced after week 12 in both groups. The reduction in FeNO at week 48 was significantly greater in the SFC500 + CIC400 arm than in the SFC1000 arm (Fig. 1B). Changes in daily variation in PEF from week 0 sequentially decreased throughout the intervention period in both arms (Fig. 1C), which were significantly greater in the SFC500 + CIC400 arm than in the SFC500 + CIC400 arm at week 48. Significant reduction was observed after week 4 in the SFC500 + CIC400 arm and after week 12 in the SFC1000. Percent of change in V50/V25 from week 0–48 decreased in the SFC500 + CIC400 arm, whereas it increased in the SFC1000 arm (Supplementary Fig. 3). ACT scores were significantly improved after week 12 in both groups, and there was a significant decrease at week 48 in the SFC500 + CIC400 arm relative to that in the SFC1000 arm (Fig. 1D).

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Table 1
Demographics of the subjects.

	SFC1000 (N = 17)	SFC500 + CIC400 (N = 17)	P value
Age, y	53.7 (17.3)	57.5 (16.2)	N. S.
Female/male, n	7/10	6/11	N. S.
Body mass index, kg/m ²	23.0 (3.3)	24.6 (3.3)	N. S.
Smoking history, yes, n (%)	3 (17.6)	4 (23.5)	N. S.
Duration of asthma (y)	7.0 (2.0–12.5)	7.0 (3.5–9.5)	N. S.
ICS dose (μg/d)	400 (400–800)	400 (400–600)	N. S.
LABA, n (%)	17 (100)	17 (100)	N. S.
LTRA, n (%)	14 (82.4)	15 (88.2)	N. S.
Theophylline, n (%)	3 (17.6)	3 (17.6)	N. S.
ACT	22 (15–23)	19 (16–22)	N. S.
FeNO, ppb	44 (20–61)	42 (28–69)	N. S.
Total IgE, IU/L	281 (103–281)	132 (25–132)	N. S.
Blood eosinophil, cell/μL	262 (108–496)	249 (82–568)	N. S.
Sputum eosinophil [†] , %	11.2 (10.4)	13.8 (19.4)	N. S.
Morning peak flow [‡] , L/min	472 (104)	486 (81)	N. S.
Daily variation in peak flow [‡] , L/min	27.8 (13.3)	27.4 (7.3)	N. S.
FEV1, L/min	2.6 (0.8)	2.2 (0.7)	N. S.
FEV1, %predicted	102.7 (22.0)	93.6 (12.2)	N. S.
FEV1/FVC, %	77.7 (12.4)	75.9 (14.4)	N. S.
V50/V25	2.8 (0.3)	3.5 (0.3)	N. S.

Data are expressed as means (SD) unless otherwise indicated. Nonparametric data are expressed as medians (25%–75%). ICS = inhalation corticosteroid (fluticasone), where 2 μg beclomethasone = 2 μg budesonide = 1 μg fluticasone. P values were calculated by using Student's *t*-test for variables with a parametric distribution, the Mann–Whitney U test for nonparametric data, and Fisher's exact test for comparison of proportions.

SFC, salmeterol/fluticasone combination; CIC, ciclesonide; LABA, long-acting β₂-agonist; LTRA, leukotriene receptor antagonist; ACT, asthma control test; FeNO, fraction of exhaled nitric oxide.

Values were compared within the three asthma subgroups. Numbers of two groups: [†]SFC1000 group = 15, SFC500 + CIC400 group = 14; [‡]SFC1000 group = 5, SFC500 + CIC400 group = 6.

In this study, we observed that the combination of SFC500 and CIC400 was superior to SFC1000 in reduction of eosinophilic airway inflammation, improvement of PEF variability and asthma symptoms

in not well-controlled moderate-to-severe asthmatics. These results are in line with those of several studies that demonstrated that extra-fine-particle ICS exhibited a greater reduction of asthma

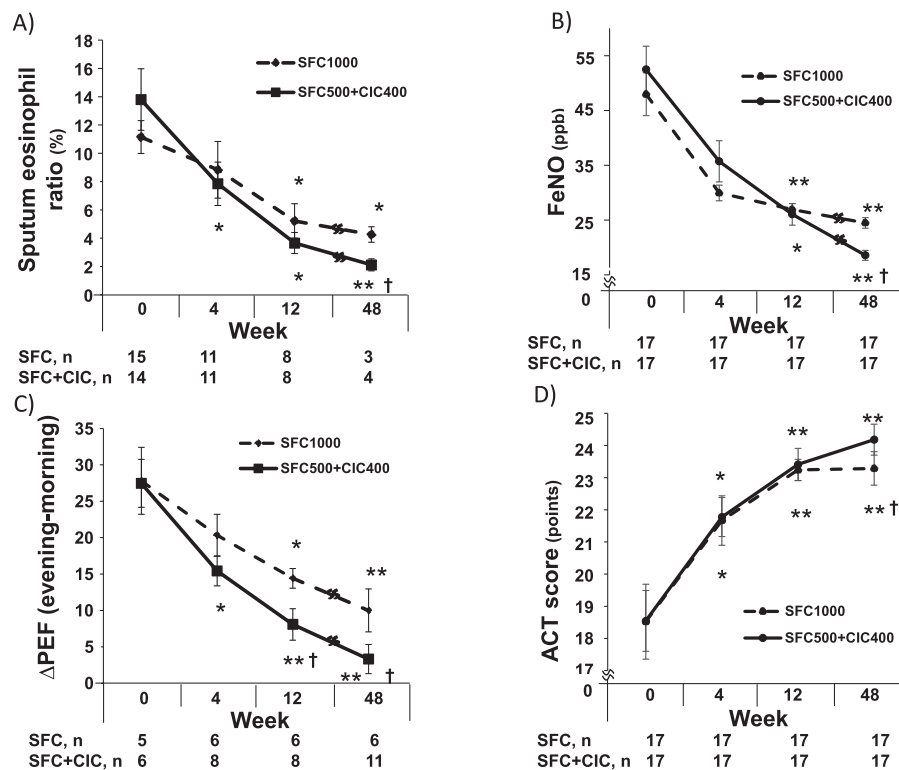


Fig. 1. Effect of add-on ciclesonide (CIC) and dose-escalated salmeterol/fluticasone combination (SFC) on sputum eosinophil ratio, fractional exhaled nitric oxide (FeNO), change in daily variation of peak expiratory flow (PEF), and asthma control test (ACT) score in the treatment period. The SFC1000 arm and SFC500 + CIC400 arm showed significantly decreased (A) sputum eosinophil ratios at week 48 ($p < 0.05$ and $p < 0.01$, respectively), (B) FeNO levels ($p < 0.01$ for both arms), (C) differences between morning and evening PEF ($p < 0.01$ for both arms), and significantly increased (D) ACT score ($p < 0.01$ for both arms). The SFC500 + CIC400 arm improved those four parameters significantly more than did the SFC1000 arm at week 48. P values were calculated by performing Student's *t*-test for nonparametric data or the Mann–Whitney U test for nonparametric data in comparisons of objective values at weeks 4, 12, or 48 with those at week 0 within each treatment arm as well as those at weeks 4, 12, or 48 between the two treatment arms. The results are presented as means $\pm$ SEMs. vs. week 0: * $p < 0.05$, ** $p < 0.01$. vs. SFC1000: † $p < 0.05$. SFC1000, SFC 50/500 μg bid; SFC500 + CIC400, SFC 50/250 μg + CIC 200 μg bid.

exacerbation risk in mild-to-moderate asthmatics than that of fine-particle ICS in real-life practice.^{7,8} Likewise, this study demonstrated that adding extra-fine-particle ICS to standard-size particle ICS/LABA provided. Superior clinical benefits for daily control of asthmatic condition for more severe asthmatics than reported in previous studies for asthmatics, which is important in general practice.

In this study, the addition of CIC400 to SFC500 achieved greater reduction of sputum eosinophil ratios and FeNO than did dose-escalation to SFC1000. A previous study similarly showed that an extra-fine-particle ICS/LABA formulation decreased alveolar nitric oxide concentrations more compared with a particle ICS or standard-size-particle ICS/LABA formulation.⁵ These reductions in eosinophilic inflammation in small airways were likely because extra-fine-particle ICSs exhibit higher lung deposition (50%–60%).⁹ Thus, a high lung-deposition ability of CIC may have helped reduce sputum eosinophil ratios in this study. This better anti-inflammatory effect of CIC may be involved in the improvement in daily variation of PEF and percent of change in V50/25. Our finding is in agreement with that of a previous study showing that a lower dose of extra-fine-particle CIC achieved improvement of FEV1 equivalent to that of a higher dose of standard-size particle FP.¹⁰

There were some study limitations that should be considered. Other beneficial inhalations, for example, Fluticasone Furoate/Vilanterol Trifenatate (FF/VI), may be more suitable for a combination therapy with CIC compared with SFC because FF/VI has a particle size similar to SFC (MMAD, approximately 4.0 µm) and is inhaled once a day. Adverse influence of patients' adherence might be small on clinical benefits for patients in the SFC500 + CIC400 arm, despite the use of two different kinds of inhalation devices because this regimen exhibited better clinical efficiency than the SFC1000 therapy. This study was open-label and had a small sample size, which might have influenced the results. A large-size prospective study is needed to verify the observation study findings.

In conclusion, this study clarified that step-up therapy consisting of addition of extra-fine-particle CIC showed greater benefit in an assessment of clinical asthma control points than that of the addition of standard-size particle SFC. For patients with not well-controlled asthma and persistent eosinophilic airway inflammation, addition of extra-fine-particle ICS may be a better choice than increasing standard-size-particle ICS.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2019.05.008>.

Conflict of interest

The authors have no conflict of interest to declare.

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Supplementary Methods

Study design

We conducted a 48-week randomized open-label controlled trial. Outpatients with asthma treated at Saitama Medical University Hospital between 2012 and 2014 were eligible. The study adhered to the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the institutional review board of Saitama Medical University Hospital (approval number: 11-080). This study was registered in the UMIN Clinical Trials Registry (Registry Identified UMIN000012189). Written informed consent was obtained from all patients before beginning the study.

Patient inclusion and exclusion criteria

The inclusion criteria were age > 20 years; diagnosis of asthma according to the Japanese guideline for adult asthma (E1); had received administration of 400–1000 µg per day of fluticasone propionate or corresponding dose of other inhaled corticosteroids for ≥8 weeks; received administration of long-acting β₂-agonists (LABAs); and an Asthma Control Test (ACT) score ≤25.

The exclusion criteria were concomitant lung disease other than asthma; asthma exacerbation for ≥4 weeks before the beginning of enrollment; pregnancy; and

comorbid diseases, including cancer, severe renal failure, or severe heart failure.

Study schedule

The study schedule is shown in Supplemental Figure 1, and consisted of the run-in period and intervention period of 48 weeks. During the run-in period, the participants who met the eligible criteria were enrolled and switched from ICS and LABAs, which had been received, to salmeterol combination (SFC) 50/250 µg Diskus (dry powder inhaler) bid for 4 weeks. After that, if the enrolled participants had an ACT score <25, they were randomized into the following two groups: 1) escalation of dose for SFC 50/250 µg bid to SFC 50/500 µg bid (the SFC1000 arm), 2) addition of CIC-HFC 200µg bid to SFC 50/250 µg bid (the SFC500 + CIC400 arm). The envelope method was used to perform randomization. Other medications for asthma control, including leukotriene receptor antagonists, or sustained release theophylline, were allowed to be continued during the intervention period. The use of a salbutamol inhaler as required was allowed, and oral corticosteroids for 3 days were given for severe asthma exacerbation defined as worsening of symptoms or a >20% decrease of morning PEF before for > 3 continuous days, required visit to the emergency room, or hospitalization. The participants attended the hospital at Weeks 4, 12, and 48 in the intervention period. Induction sputum was

performed, fractional exhaled nitric oxide levels were measured, and ACT scores were determined at every visit day. The participants were asked to measure their peak expiratory flow every day.

Sputum induction and processing

Induced sputum was collected as described previously (E2, 3). After salbutamol was administered, sterile hypertonic saline (4.5%) from an ultrasonic nebulizer was inhaled.

Sputum was obtained at 5-min intervals for ≤ 20 min. The participants were asked to rinse their mouth with water before each expectoration. Sputum samples were collected into 50-mL polypropylene tubes and stored at 4°C for further processing. Hanks'

balanced salt solution (HBSS; 1 mL) containing 1% dithiothreitol (Sigma, St. Louis, MO, USA) was added to the sputum samples. Then, they were gently vortex-mixed and repeatedly aspirated to make the mixture homogeneous at ambient temperature. The samples were diluted with HBSS to 5 mL and separated by centrifugation at 400 x g for 10 min. Cytospin slides were prepared by using a Cytospin 3 (Shandon, Tokyo, Japan) and were stained with May–Grunwald–Giemsa stain for differential cell counts.

Inflammatory cells in each sample were counted up to >500 cells by an independent investigator. When the squamous epithelial cell count on the Cytospin slides was $\leq 50\%$,

the sample was considered to be adequate for analysis.

Exhaled NO

Exhaled NO levels were measured by using a NIOX MINO (Aerocrine AB, Solna, Sweden) according to the 2005 American Thoracic Society and European Respiratory Society guideline (E4).

Statistical analysis

The primary endpoint was change in the percentage of eosinophils in sputum at week 48. The percentage of eosinophils in sputum, FeNO, daily variability of PEF, and ACT scores were compared between Week 0 and Weeks 4, 12, or 48 within the SFC1000 arm and the SFC500 + CIC400 arm, and the measurements at each visiting week were compared between the two arms. Student's *t*-test was used to analyze parametric variables. The Mann–Whitney U-test was used to analyze nonparametric variables. Categorical variables were tested by using χ^2 tests. Values are described as means $\pm$ standard deviations or medians with 25th–75th percentile ranges. SPSS version 20.0 (IBM, Armonk, New York, USA) was used to analyze data.

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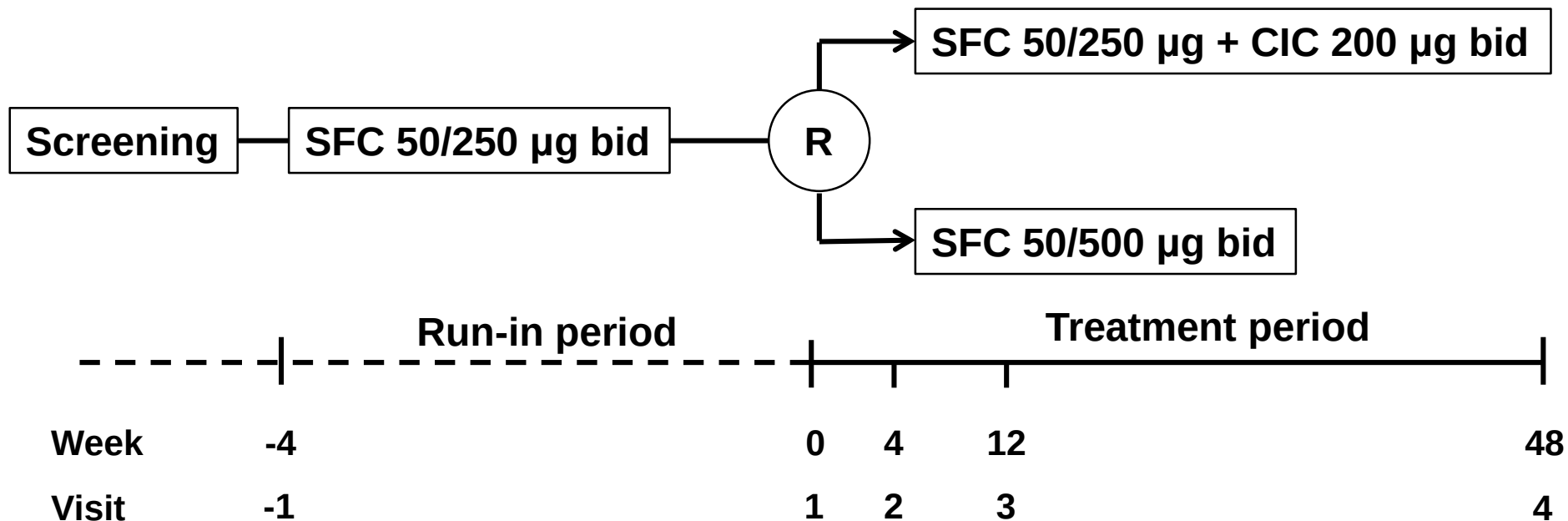
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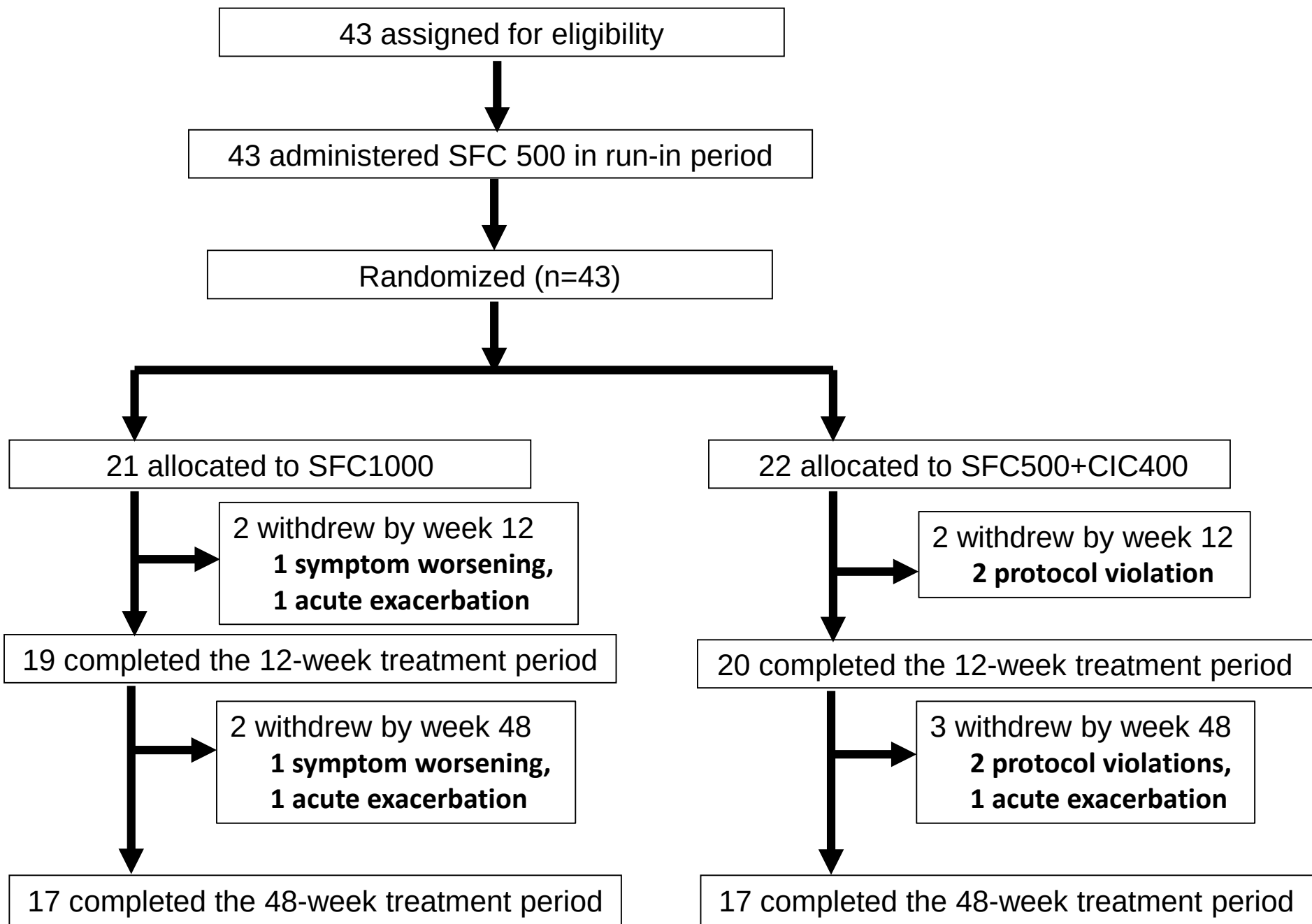
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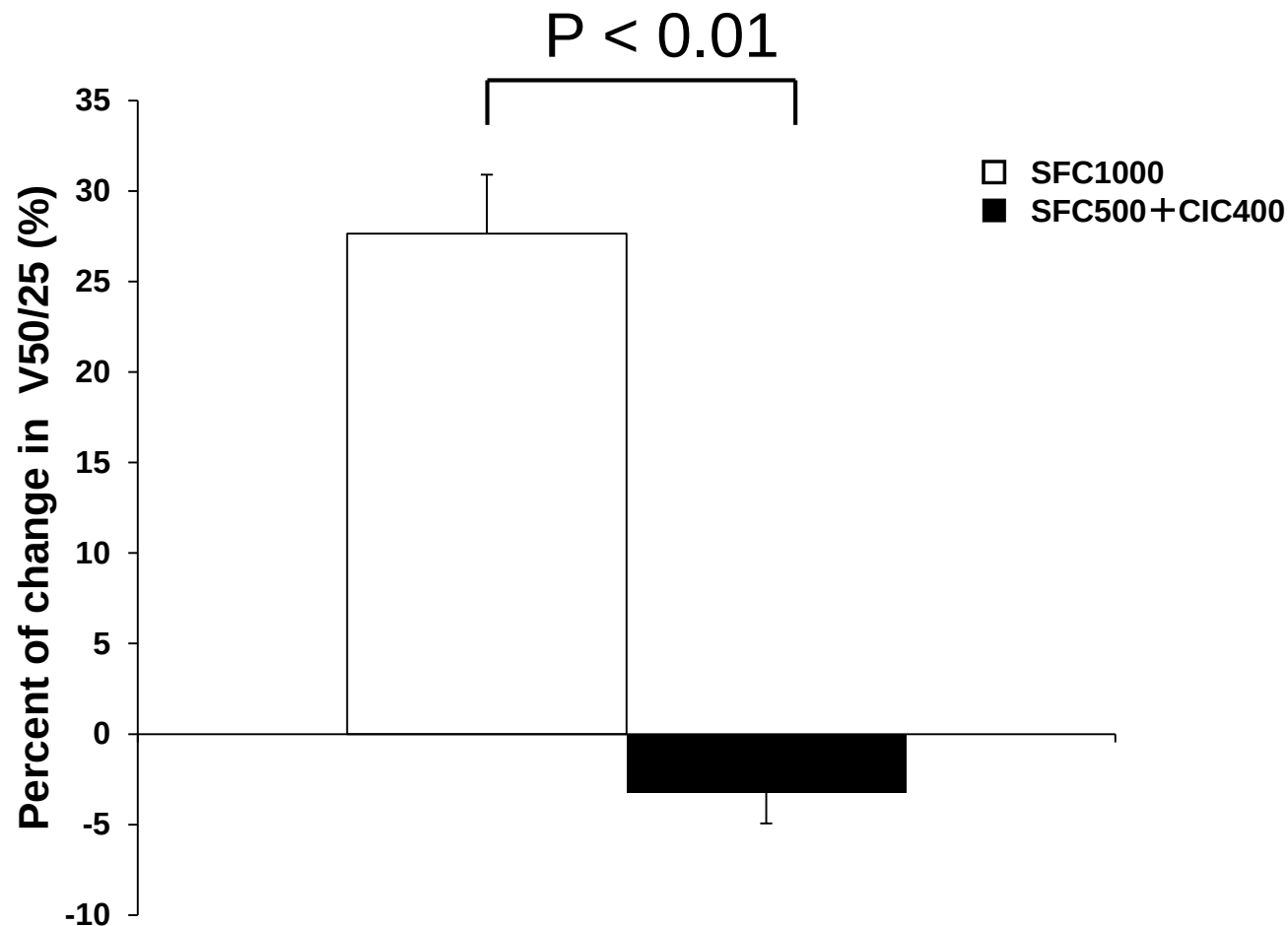


Supplementary Figure 1. Study design.

SFC, salmeterol/fluticasone combination; CIC, ciclesonide; R, randomization



Supplementary Figure 2. Consort flow diagram



Supplementary Figure 3. Percent of change in V50/V25 from the entry to the end of the study in the intervention groups.

Percent of change in V50/V25 from week 0 to 48 are $-3.3 \pm 3.3\%$ in the SFC500+CIC400 arm and $26.7 \pm 1.7\%$ in the SFC1000 arm.