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Efficacy and Safety of Salmeterol/fluticasone Combination Therapy in Infants and Preschool Children with Asthma Insufficiently Controlled by Inhaled Corticosteroids

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Key words
- salmeterol/fluticasone combination
- asthma
- infant
- preschool children
- nighttime sleep disorder score
- long-acting beta-agonist
- inhaled corticosteroid

Abstract

Background: Clinical evidences of inhaled salmeterol/fluticasone propionate combination (SFC) therapy are insufficient in early childhood asthma.

Objectives: To examine the effects of SFC50, a combination product of salmeterol xinafoate (50 µg/day) and fluticasone propionate (100 µg/day), in infants and preschool children with asthma.

Methods: The study was conducted at 31 sites in Japan. 35 patients (6 months to 5 years old) with asthma insufficiently controlled by inhaled corticosteroids (100 µg/day) were initiated to treat with SFC50 twice a day for 12 weeks with pressurized metered dose inhalers. The efficacy of SFC50 was assessed using nighttime sleep disorder score as the primary endpoint and the other efficacy measurements. The safety measurement included the incidences of adverse event (AE).

Results: Mean patient age was 3.1 years, and 94.2% had mild-to-moderate persistent asthma (atopic type: 65.7%). Nighttime sleep disorder scores, assessed by a nighttime sleep diary, significantly decreased after treatment with SFC50 throughout the study period ($p < 0.01$). SFC50 also significantly improved other efficacy outcomes including asthma symptom score, frequency of short-acting beta-agonist treatment, frequency of unscheduled visits to clinic, frequency of exacerbation due to virus infection, asthma control score and patient QOL score ($p < 0.01$). AEs of cold, upper respiratory inflammation and asthmatic attack occurred in each of the 3 patients (8.6%); however, these were not regarded as treatment-related AEs.

Conclusions: SFC50 improved nighttime sleep disorder score and other efficacy outcome measures with no safety concerns. The results suggest that SFC50 treatment is useful to control the mild-to-moderate asthma in infant and preschool-aged children.

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Introduction

Asthma is the most common non-communicable disease among children in the world [1], and is a heterogeneous disorder with a variable course, characterized by episodes of cough, wheezing, shortness of breath, reversible airflow limitation and bronchial hyperresponsiveness [2]. In the United States, 9.6 million children (13.1% of children) under the age of 18 years have been diagnosed with asthma during their lifetime, and 6.7 million of them have been affected by asthma in 2007 [3]. Asthma often begins in early childhood, and preschool-aged children (≤5 years old) with asthma suffer from its symptoms of cough, wheezing and shortness of breath, frequently experiencing daytime fatigue, reduced activity levels, thereby potentially hindering their developmental progress and diminishing social interactions [4]. Therefore, early diagnosis and appropriate management of early childhood asthma are very important medical issues [5, 6]. The National Asthma Education and Prevention Program (NAEPP)/Expert Panel Report (EPR)-3 proposes a stepwise approach towards asthma management in children aged 0–4 years [7]. Fundamental to the NAEPP/EPR-3 treatment paradigm is the categorization of children as having either intermittent or persistent disease. The combination therapy with a medium-dose of inhaled corticosteroid (ICS) and either a long-acting beta-agonist (LABA) or the leukotriene-receptor antagonist (LTRA) montelukast is recommended for the children of 0–4 years old with persistent asthma controlled insufficiently with moderate-dose of ICS therapy (categorized as step 4) [7].

Inhaled salmeterol/fluticasone propionate combination (SFC) treatment is one of the most commonly used combination therapy of ICS and inhaled LABA for the indications of adult and childhood asthma, chronic obstructive pulmonary disease [8], and has been approved at more than 130 countries or regions. However, no published prospective randomized controlled studies have been conducted on the use of combination therapy with ICS plus LABA therapy in early childhood asthma. Additionally, the clinical evidences of inhaled SFC therapy are insufficient in early childhood asthma [6]. Therefore, the accumulation and establishment of clinical evidences for the use of inhaled SFC are needed in the real clinical practices.

In Japan, SFC50, a combination product of inhaled salmeterol xinafoate (50 µg/day) and fluticasone propionate (100 µg/day) has been uniquely approved. We prospectively investigated the effects of SFC50 in infants and preschool children with asthma at 31 medical sites in Japan, based on the real clinical practices data.

Materials and Methods

Study design, patients and treatments

This was an open-label prospective multicenter study conducted at 31 medical sites in Japan from January 2012 to March 2013. Eligible patients were infants and preschool children with asthma aged 6 months to 5 years old, and whose symptoms were insufficiently controlled by the treatment with ICS (100 µg/day), as judged by nighttime awakening occurring one or more times for 4 weeks. Patients who had used SFC or salmeterol prior to enrollment were excluded from the study.

Enrolled patients were initiated to treat with SFC50 twice a day for 12 weeks using the device of pressurized metered dose inhaler (pMDI). During the treatment period, patients visited the clinic or hospital 4 times (Visit 1 [0 week], 2 [4 weeks], 3 [8 weeks] and 4 [12 weeks]) every 4 weeks for assessment of efficacy and safety of SFC50. The dosage of the study drug was not altered during the treatment period. The use of concomitant drugs, such as LTRA was allowed for continuous treatment, as long as the dosage was not changed.

Ethical approval of the study documents was centrally obtained from the Institutional Review Board of the Medical Ethics Committee in Dokkyo Medical University Hospital prior to the beginning of the study. Informed consent was obtained from the parents or the patients of all patients prior to participation in this study.

Efficacy assessment

The primary endpoint was the nighttime sleep disorder score, which was assessed using a nighttime sleep diary [9]. The nighttime sleep disorder score (nighttime awaking score) uses a 4-point scale 0 (never awoke), 1 (rarely awoke), 2 (frequently awoke) and 3 (always awoke). Use of controller, reliever and other drugs, and numbers of doctor visits were recorded every 4 weeks (Visit 1, 2, 3 and 4). Additionally, control levels of early childhood asthma were evaluated with the modified questionnaire sheet of Childhood Asthma Control Test (C-ACT) [10], and the QOL questionnaires for parents [11] were provided at Visit 1 and 4. The secondary endpoints included asthma symptom score, use of short-acting beta-agonist (SABA) including tulobuterol, frequency of unscheduled clinic or hospital visits, frequency of exacerbations associated with virus infection, asthma control score and patient QOL score. Virus infection was defined as having more than 2 symptoms of fever, rhinorrhea or cough as confirmed by a pediatrician. The values for the primary and secondary endpoints were evaluated over the 3-week period prior to each visit.

Safety assessment

The safety of SFC50 treatment was assessed by the incidences of adverse events (AEs), including clinical laboratory values and physical findings at each visit.

Statistical analysis

Changes in the primary and secondary endpoints before and after SFC50 treatment were analyzed statistically using the one-sample Wilcoxon test.

Results

Study patients

Of the 36 enrolled patients, 35 patients were included in the efficacy and safety analysis; one individual was excluded because of no visit to the study site after enrollment. 5 patients discontinued treatment during the study period of 12 weeks. The reasons for discontinuation included emergency hospitalization to a hospital other than the study site (n = 1), protocol violation (n = 1), addition of other medication for asthma/increased dosage of SFC (n = 2), and withdrawal of the study by the patient or patient's own volition (n = 1). 60% of patients were male and the mean age was 3.1 years old. Most of the patients (94.2%) had mild-to-moderate persistent asthma of an atopic type (65.7%) (**Table 1**).

Table 1 Demographic characteristics of the study patients (n = 35).

Characteristics	Data
Age (years)	3.1 ± 1.3
Gender: Male/Female	21 (60.0%)/14 (40.0%)
Height (cm)	91.1 ± 9.9
Body weight (kg)	13.5 ± 2.6
BMI (kg/m^2)	16.3 ± 1.7
Age at asthma onset (years)	1.7 ± 1.1
Asthma duration (months)	17.4 ± 12.9
Severity of asthma	
Mild and persistent	13 (37.1%)
Moderate and persistent	20 (57.1%)
Severe and persistent	1 (2.9%)
Unclear	1 (2.9%)
Type of asthma	
Atopic	23 (65.7%)
Non atopic	11 (31.4%)
Unclear	1 (2.9%)
Concomitant disease	
None	24 (68.6%)
Atopic dermatitis	4 (11.4%)
Allergic rhinitis	3 (8.6%)
Food allergy	3 (8.6%)
Unclear	1 (2.9%)

Data are presented as mean ± standard deviation, or number of the patients (percentage)

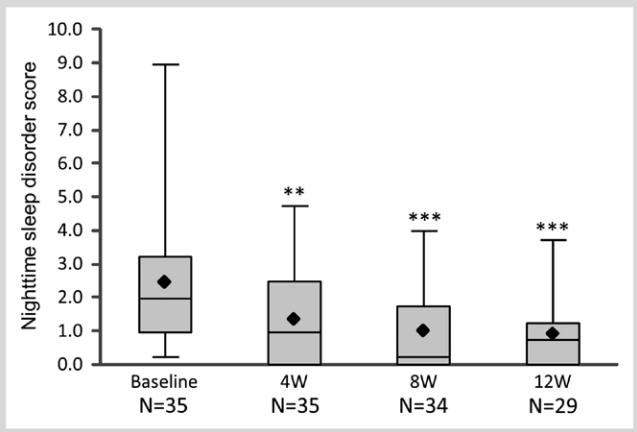

Fig. 1 Changes in nighttime sleep disorder score after SFC50 treatment. Box and whisker plot indicate nighttime sleep disorder score at baseline, weeks 4, 8 and 12. The segments inside the rectangles show the median values, and the whiskers below and above the box show the minimum and maximum values, respectively. The rectangle spans show the first quartile to the third quartile, and the closed squares (♦) represent the mean values. * *: p<0.01, * * *: p<0.001 (vs. baseline values, one-sample Wilcoxon test).

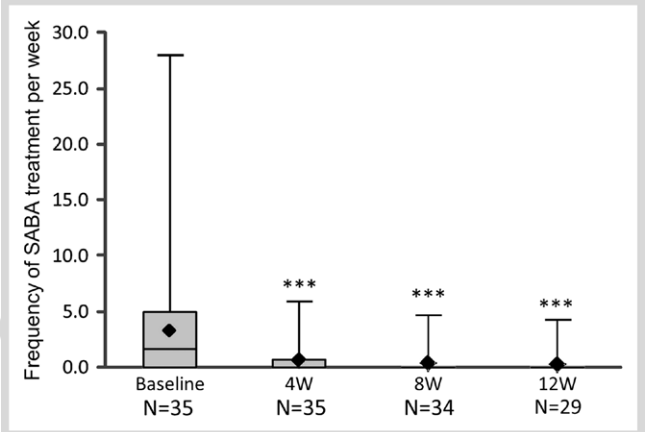

Fig. 3 Changes in frequency of SABA treatment per week after SFC50 treatment. Box and whisker plot indicate SABA used per week at baseline, weeks 4, 8 and 12. The segments inside the rectangles show the median values, and the whiskers below and above the box show the minimum and maximum values, respectively. The rectangle spans show the first quartile to the third quartile, and the closed squares (♦) represent the mean values. * * *: p<0.001 (vs. baseline values, one-sample Wilcoxon test).

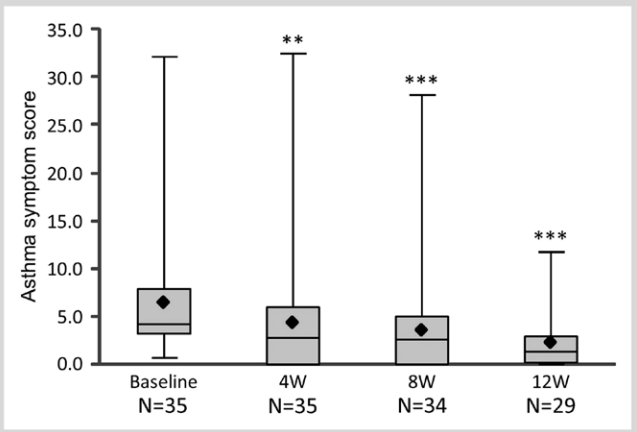

Fig. 2 Changes in asthma symptom score after SFC50 treatment. Box and whisker plot indicate asthma symptom score at baseline, weeks 4, 8 and 12. The segments inside the rectangles show the median values, and the whiskers below and above the box show the minimum and maximum values, respectively. The rectangle spans show the first quartile to the third quartile, and the closed squares (♦) represent the mean values. * *: p<0.01, * * *: p<0.001 (vs. baseline values, one-sample Wilcoxon test).

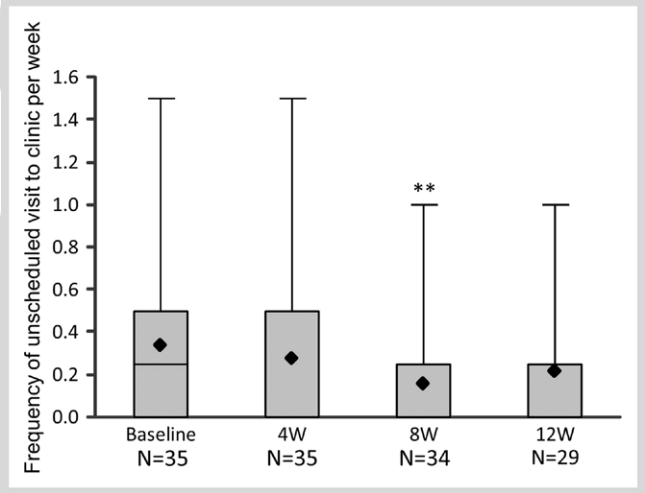

Fig. 4 Changes in frequency of unscheduled visit to clinic per week after SFC50 treatment. Box and whisker plot indicate frequency of unscheduled clinic visit per week at baseline, weeks 4, 8 and 12. The segments inside the rectangles show the median values, and the whiskers below and above the box show the minimum and maximum values, respectively. The rectangle spans show the first quartile to the third quartile, and the closed squares (♦) represent the mean values. * *: p<0.01 (vs. baseline values, one-sample Wilcoxon test).

Nighttime sleep disorder score (primary endpoint)

The median (range) nighttime sleep disorder score at baseline was 2.00 (0.25–9.00) and decreased with duration of SFC50 treatment as shown in **Fig. 1**. Median scores decreased to 1.00 (0–4.75), 0.25 (0–4.00) and 0.75 (0–3.75) at 4, 8 and 12 weeks, respectively. Nighttime sleep disprder scores at each visit were significantly lower than the baseline score (p<0.01).

Other efficacy outcomes

As shown in **Fig. 2**, the median asthma symptom score decreased sequentially from 4.25 (0.75–32.25) at baseline to 1.25 (0–11.75) after 12 weeks of SFC50 treatment. The scores during the treatment period were significantly different from that of baseline (p<0.01). **Fig. 3** shows the frequency of SABA use per week as a rescue drug. The median frequency decreased sequentially from 1.75 (0–28.0) at baseline to 0 (0–4.25) after SFC50 treatment for 12 weeks. The frequencies of use during the treatment period were significantly different compared with baseline value (p<0.001). The frequency of unscheduled clinic visits per week is shown in **Fig. 4**. The median frequency at baseline was 0.25 (0–1.5) and tended to decrease to 0 (0–1.0) at 12 weeks after SFC50 treatment. The median frequency of exacerbations due to virus infection at baseline was 0.25 (0–4.75), and tended to decrease after treatment, with values of 0 (0–2.00), 0.25 (0–3.75) and 0.25 (0–4.00) at 4, 8 and 12 weeks, respectively. The frequency of exacerbations at week 4 and 8 were significantly different compared with baseline values (p<0.01)

(◉ **Fig. 5**). The median asthma control score at baseline was 14.0 (3–23), and improved significantly to 21.0 (0–24) at week 12 ($p<0.001$) (◉ **Fig. 6a**). The median patient QOL score at baseline was 8.0 (0–20), and improved significantly to 2.0 (0–24) at week 12 ($p<0.01$) (◉ **Fig. 6b**).

Safety

Of the 35 patients analyzed, AEs were observed in 3 patients (8.6%) during the study period, including cold (n=1), upper respiratory inflammation (n=1) and asthmatic attack (n=1); however, these symptoms were not regarded as treatment- related AEs.

Discussion

The present study is the first to report on the efficacy and safety of SFC50 in infants and preschool children (aged 6 months to 5 years old) with asthma, because the clinical trials for the marketing authorization of this medication in Japan have been conducted among asthma children aged from 5 to 14 years old [12]. The Global Initiative for Asthma (GINA) regards nighttime symptoms and the degree of sleep disturbance as important indices for the control of asthmatic bronchitis in early childhood [13].

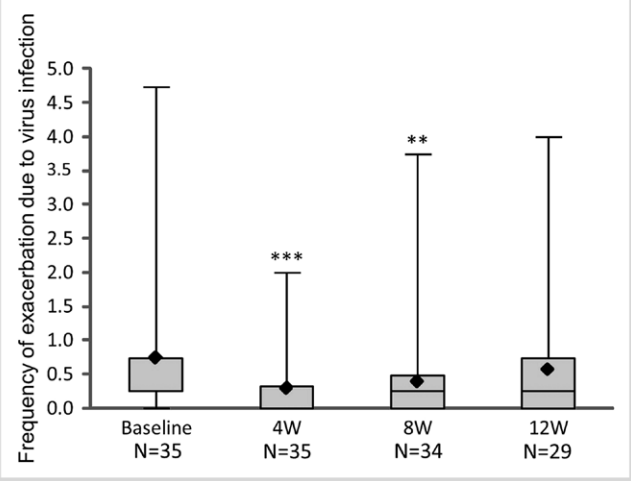

Fig. 5 Changes in frequency of exacerbation due to virus infection after SFC50 treatment. Box and whisker plot indicate frequency of exacerbation due to virus infection. The segments inside the rectangles show the median values, and the whiskers below and above the box show the minimum and maximum values, respectively. The rectangle spans show the first quartile to the third quartile, and the closed squares (◆) represent the mean values. **: $p<0.01$, ***: $p<0.001$ (vs. baseline values, one-sample Wilcoxon test).

Recent guidelines base the diagnosis and assessment of asthma control in infants and children on symptoms such as wheeze, coughing, breathlessness and nighttime awakening [13]. Thus, nighttime asthma symptoms or nighttime awakening is one of the most important indicators of inadequately controlled asthma. In the present study, we used "nighttime sleep disorder score" [9] as the primary endpoint, and the scores significantly decreased from week 4 onwards, compared with before SFC50 treatment. It has been reported that nighttime awakening reduces the QOL not only for patients, but also for their parents [14,15]. Indeed, our previous study showed that the QOL of infants and their patients was lower because of nighttime sleep disturbances [11]. Furthermore, the nighttime awakening score has been reported to be significantly and positively associated with the nighttime asthma symptom score, the daytime asthma symptom score and the number of days with cough [9]. Therefore, SFC50 therapy is useful for the infants and preschool children with asthma as well as for their parents from the view point of improving QOL.

Various endpoints have been used in recent clinical trials to assess efficacy outcomes in early childhood asthma, Busse et al. [16], for instance, reported that omalizumab significantly reduced the number of days with asthma symptoms compared with placebo. In the present study, we used symptom score; frequency of SABA usage, including tulobuterol, as a rescue medication; number of unscheduled clinic visits; incidence of exacerbation due to virus infections; asthma control score and patient QOL score as secondary endpoints. All of these outcome measures improved significantly with SFC50 treatment. In comparison with GINA guidance [13], Japanese guideline for childhood asthma 2014 [17] includes more stringent criteria for maintaining normal respiratory function, with the aim of inducing remission in most cases of early childhood asthma. The Japanese guideline defines mild symptoms and a frequency of beta-agonist treatment of less than once a week but more frequently than once per month as a "partially controlled" asthma. "Poorly controlled" asthma is defined by additional symptoms or restriction of daily life activities. The present study suggests that treatment with SFC50 leads to relatively good control as the symptoms of asthma were reduced significantly, and the frequency of SABA use decreased to less than once per week.

Wheezing with viral infections is thought to be the most common symptom of asthma in infants and preschool children. Linder et al. [18] reported that lower respiratory illness in childhood was associated with human rhinovirus (RV) C infection. It has also been shown that the wheezing caused by RV infection is the most significant predictor of the subsequent development of asthma at the age of 6 years in a high-risk birth cohort [19]. Papi et al. [20] also found that RV-16 infection of the human airway

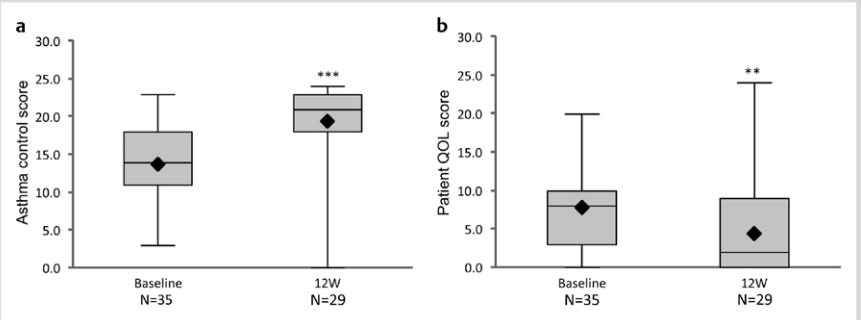

Fig. 6 Changes in asthma control score **a** and patient QOL score **b** after SFC50 treatment. Box and whisker plot indicate asthma control score and patient QOL score, respectively. The segments inside the rectangles show the median values, and the whiskers below and above the box show the minimum and maximum values, respectively. The rectangle spans show the first quartile to the third quartile, and the closed squares (◆) represent the mean values. **: $p<0.01$, ***: $p<0.001$ (vs. baseline values, one-sample Wilcoxon test).

epithelium caused glucocorticoid resistance. Additionally, the prevention of severe respiratory syncytial virus (RSV) infection in infancy was reported to prevent recurrent wheeze in several studies of palivizumab treatment in high-risk pre-term infants [21,22]. In the present study, SFC50 resulted in a significant decrease in the frequency of exacerbations associated with virus infections at 4 and 8 weeks, and may therefore be useful for preventing exacerbation of asthma symptoms caused by virus infections in patients of a young age.

Adverse events observed in the present study included cold, upper respiratory inflammation and asthmatic attack. However, all of these AEs were unrelated to treatment with SFC50. Therefore, these data suggest that SFC50 can be used safely for early childhood asthma patients in the real clinical practices. In addition to these AEs, we also checked the growth (height and body weight) inhibition of the patients as the risk of ICS treatment, but no meaningful difference was observed with standard growth curve. Furthermore, LABA treatment related AEs were cautiously monitored in this study, but no tachysystole, thrill and palpitation were observed. There was no statistically significant difference in blood pressure at baseline and week 12 (data not shown). We also tested the number of eosinophil in the sputum of some study patients, to monitor the airway inflammation as the risk of LABA treatment, but no increase of sputum eosinophil was observed during the study period of 12 weeks.

Limitations of this study included the small number of study patients and short treatment period. Another limitation was study design with no placebo control group, because it was difficult to conduct a placebo-controlled study in infants and preschool children with asthma in light of Japanese medical ethics. It was possible to set the control arm of ICS + LTRA, but the evidences of ICS + LTRA in early childhood asthma are also insufficient, in common with ICS + LABA, especially in the infant populations (study populations in our study). Therefore, we did not set the control arm of ICS + LTRA in our study. Lemanske, et al. [23] have reported that ICS + LABA therapy was significantly more likely to provide the best response than either ICS increasing dose or ICS + LTRA therapy in 182 children (6–17 years of age) with uncontrolled asthma receiving low-dose ICS. This result suggests a high likelihood of the superiority of ICS + LABA to ICS increasing dose or ICS + LTRA even in the earlier childhood asthma including the infant, who were our study populations. There is no control study such as placebo-controlled study, other control drugs-treated study or no-intervention observational study evaluating the nighttime sleep disorder, which was a primary endpoint of this study among early childhood asthma, and we cannot compare the effects of SFC50 with placebo or other control drugs. But we have previously found that nighttime sleep disorder score is significantly associated with the severity of asthma symptoms in the individual 40 early childhood asthma patients treated with ICS or cromolyn sodium nebulized solution [9]. Therefore, we think that guideline-recommended therapy of ICS + LABA [7], SFC50 treatment improved the nighttime sleep disorder by attenuating the severity of asthma symptoms, which were also indicated in the other outcomes such as asthma symptom score or frequency of SABA treatment in this study. We believe that our evidences comparing the symptoms of asthma before and after ICS + LABA treatment in early childhood including infant, are useful in the real clinical practices, because the evidence of medical treatment is insufficient in this populations.

Conclusion

Treatment with SFC50 significantly improved the disturbance of nighttime sleep as the primary endpoint in early childhood asthma patients insufficiently controlled by the ICS only. Treatment was also effective in improving other outcome measures including asthma symptom score, frequency of SABA use, frequency of unscheduled clinic visits, frequency of exacerbations associated with virus infections, asthma control score and patient QOL score. Although AEs were observed in 3 patients (8.6%) during the study period, no AEs related to SFC50 administration were observed. These results suggest that SFC50 is useful for controlling mild-to-moderate asthma in infants and preschool children.

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Declaration of Interest

The authors declare that they have no competing interests, and this study was performed as an investigator initiated study financially supported by the Japan Allergy Foundation.

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