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ORIGINAL ARTICLE

Airways Disease

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The efficacy and safety of fluticasone/salmeterol compared to fluticasone in children younger than four years of age

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Abstract

Background: Fluticasone propionate 50 μg/salmeterol xinafoate 25 μg (FP/SAL) is widely used in adults and children with asthma, but there is sparse information on its use in very young children.

Methods: This was a randomized, double-blind, multicentre, controlled trial conducted in children aged 8 months to 4 years. During a 2-week run-in period, they all received FP twice daily. At randomization, they commenced FP/SAL or FP twice daily for 8 weeks. All were then given FP/SAL only, in a 16-week open-label study continuation. Medications were inhaled through an AeroChamber Plus with attached face mask. The primary end-point was mean change in total asthma symptom scores from baseline to the last 7 days of the double-blind period. Analyses were undertaken in all children randomized to treatment and who received at least one dose of study medication.

Results: Three hundred children were randomized 1:1 to receive FP/SAL or FP. Mean change from baseline in total asthma symptom scores was −3.97 for FP/SAL and −3.01 with FP. The between-group difference was not statistically significant ($P = 0.21$; 95% confidence interval: −2.47, 0.54). No new safety signals were seen with FP/SAL.

Conclusion: This is the first randomized, double-blind study of this size to evaluate FP/SAL in very young children with asthma. FP/SAL did not show superior efficacy to FP; no clear add-on effect of SAL was demonstrated. No clinically significant differences in safety were noted with FP/SAL usage.

KEYWORDS
asthma, child, combination therapy, double-blind, fluticasone propionate, randomized, salbutamol, salmeterol

These data were presented at the 54th Annual Meeting of Japanese Society of Pediatric Allergy and Clinical Immunology, Tochigi, Japan, 19 November 2017.

To request access to patient-level data and documents for this study, please submit an enquiry via www.clinicalstudydatarequest.com.

Study registration: ClinicalTrials.gov: NCT02113436

1 | INTRODUCTION

Worldwide, asthma is very common in children and is one of the leading causes of hospitalization, particularly in very young children.[1,2] Diagnosis and treatment in this age group is difficult for many reasons.[3-5]

The combination of ICS and a long-acting beta-2-agonist (LABA) is widely used as maintenance therapy for children and adults with asthma in Japan and worldwide. In very young children, there are few clinical studies, but from the available data, no new safety concerns were noted.[6-8]

International and Japanese asthma guidelines recommend studies are needed to establish the safety of ICS/LABA in these very young children.

Concerns about the safety of LABAs have resulted in global large-scale safety studies at the request of the US Food and Drug Administration, which have enrolled children, 4 years and older.[9] The VESTRI study included 6208 children with asthma aged 4-11 years and showed FP/SAL and FP had similar safety profiles.[10] The AUSTRI study enrolled over 11 500 participants with asthma, aged 12 years and older, and showed the same combination therapy had a similar risk of serious asthma-related events, but a lower exacerbation rate to that of FP alone.[11]

FP (50 μg)/SAL (25 μg) is approved as Adoair in Japan for treating adults and children with asthma (the patient information leaflet indicates safety has not been established in children aged 4 years or younger).[12] In most other countries, it is licensed for patients aged 4 years and above.

We report the efficacy and safety outcomes from the first large-scale, randomized, double-blind study to be conducted in Japan in children, aged up to 4 years with asthma.

2 | METHODS

2.1 | Participants

We enrolled Japanese children aged 6 months to 4 years, with bronchial asthma diagnosed according to JPGL2012 [JSPACI 2012],[13] for whom the rationale was documented and ICS/LABA was considered necessary by their physician. They had total asthma symptom scores of ≥6 during the last 7 days of run-in, with daily asthma symptom scores ≥1 on ≥3 of those 7 days. For further details, see Online Repository: Inclusion/exclusion criteria.

2.2 | Study design and treatment

This was a phase 4, stratified, controlled, double-blind, parallel-group study with an open-label uncontrolled extension period conducted from May 2014 to October 2016 in 70 paediatric centres in Japan.

The study had four time-periods (Figure 1). During the run-in, all children aged 2 years and above received inhaled FP 50 μg, 1 or 2 puffs, twice daily (100 or 200 μg/day) according to the judgement of the investigator; those younger than 2 years were limited to one puff twice daily (100 μg/day). After run-in, the children received the same number of inhalations as during the run-in period. During the open-label period, all children started with the same number of actuations as during the double-blind period; after that, the investigator could vary the number of inhalations if thought necessary for all children including those younger than 2 years, 1 or 2 inhalations, twice daily (100 or 200 μg/day as FP), which are the approved dosages for Japanese children. During follow-up, children received care as the investigator felt appropriate.

Salbutamol (Sultanol Inhaler 100 μg) was provided for symptom relief. All study medications were given through the AeroChamber Plus with attached face mask.

We complied with the Declaration of Helsinki, the International Conference on Harmonization and Good Clinical Practice Guidelines. We obtained Independent Ethics Committee approval from each centre and written consent from each child's parent/legal guardian. Further details of study design and treatment are given in the Online Repository: Withdrawal criteria, Study medication, Concomitant medications and non-drug therapies and Table S1.

2.3 | Measurements

The primary efficacy end-point was the mean change in total asthma symptom scores from baseline to the last 7 days of the double-blind period. These scores were recorded in the patient diary, once each morning and once each evening by the child's parent/legal guardian. Scores were selected on a 4-point scale from 0 (no asthma symptoms) to 3 (severe asthma symptoms).[14,15]

Secondary end-points were as follows: mean changes from baseline in daytime and night-time asthma symptom scores, frequency of asthma exacerbations, Japanese Paediatric Asthma Control (JPAC) scores and use of rescue medication over 24 hours.

Japanese Paediatric Asthma Control scores were selected using a 4-point scale from 0 to 3 for each of 6 questions answered by each child's parent/legal guardian. We used a modified version of JPAC to account for the younger age range.[16-18]

The compliance of study drugs was evaluated from what the parents recorded in the patient diary throughout the study periods.

The study protocol was amended after commencing the study to modify the inclusion criteria, to define more clearly our definition of an asthma exacerbation, to include all concomitant medications and clarify withdrawal criteria. The amendment also provided greater clarify to the study conduct and ensured the study criteria were better aligned to global clinical asthma practice.

Adverse events (AEs) and serious AEs (SAEs) were recorded.

Other safety parameters included vital signs, 12-lead electrocardiography (ECG), clinical chemistry, haematology and plasma cortisol measurements. For further details, see Online Repository: Measurements and Table S2.

2.4 | Statistical analyses

To provide 80% power to detect a 30% difference in clinical improvement between FP/SAL and FP, 123 children per group were needed. Assuming 20% enrolled would not be included in the final analysis, we increased this to 148 children per group. A 30% improvement is

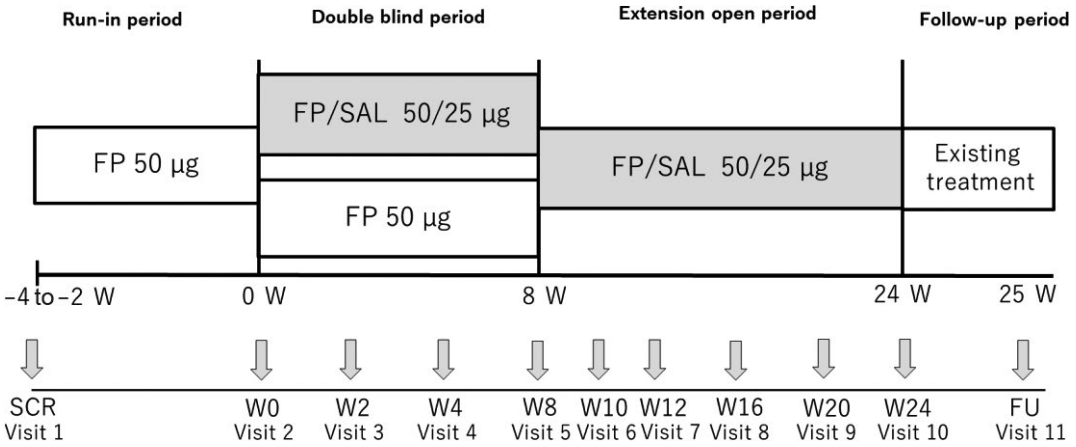

FIGURE 1 The duration of the study was 27 weeks. During the run-in, all children aged ≥2 years received inhaled FP 50 μg, 1 or 2 puffs twice daily (100 or 200 μg/day) according to the judgment of the investigator; those <2 years were limited to 1 puff twice daily (100 μg/day). After run-in, subjects were randomised (1:1) to receive either FP/SAL 50/25 μg or FP 50 μg, during the 8-week double-blind period. All children then received FP/SAL during the open-label extension period, commencing on the same number of inhalations they received during the double-blind period. FP: fluticasone propionate; FU: follow-up; SAL: salmeterol xinafoate; SCR: screening; W: week

equivalent to a change in symptom scores of 1.8 points. A 5% level of significance and standard deviation (SD) was used.

The intent-to-treat (ITT) population comprised all children receiving at least one dose of study medication.

The primary and secondary end-points were analysed using analysis of covariance adjusted for the covariates of baseline total asthma symptom score, sex, age group, number of daily inhalations and treatment groups.

We calculated the proportion of study participants who experienced asthma exacerbations and performed logistic regression analysis, adjusting for covariates.

Subgroup analyses were performed in the two age groups and for the differing number of inhalations depending on age.

All analyses were performed using SAS version 9.4 and S-Plus version 8.2. Randomization was in accordance with a validated computer-generated central randomization schedule (RandAll; GSK, Japan). For further details, see Online Repository: Statistical analyses.

3 | RESULTS

Enrolment and completion of participants is shown in Figure 2.

Demographics and baseline characteristics were comparable across treatment groups (Table 1) and between subgroups. In each

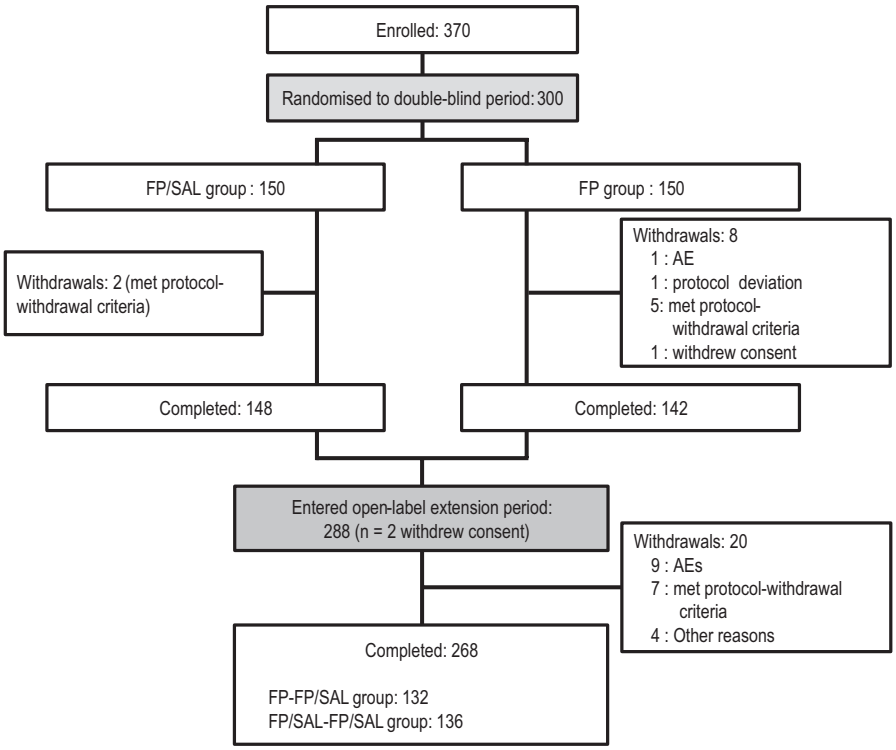

FIGURE 2 Study enrolment flow chart

TABLE 1 Demographics and baseline characteristics (intent-to-treat population)

	FP/SAL N = 150	FP N = 150
Sex, n (%)		
Female	55 (37)	60 (40)
Male	95 (63)	90 (60)
Age		
Mean (SD), y	2.9 (1.12)	2.7 (1.14)
<2 y, n (%)	25 (17)	26 (17)
≥2 y, n (%)	125 (83)	124 (83)
Severity of asthma, n (%)[a]		
Intermittent	0	0
Mild persistent	15 (10)	8 (5)
Moderate persistent	73 (49)	72 (48)
Severe persistent	62 (41)	69 (46)
Most severe persistent	0	1 (<1)
Duration of asthma, n (%)		
<6 mo	21 (14)	24 (16)
6 mo to <1 y	32 (21)	26 (17)
1 y to <2 y	49 (33)	46 (31)
2 y to <3 y	31 (21)	37 (25)
3 y to <4 y	15 (10)	16 (11)
≥4 y	2 (1)	1 (<1)
Mean asthma symptom scores (SD)	11.5 (4.57)	11.4 (4.57)
Asthma symptom scores groups, n (%)		
<6	0	1 (<1)
6 to <10	60 (40)	64 (43)
≥10	90 (60)	85 (57)
Mean JPAC scores (SD)	13.3 (2.85)	12.8 (3.33)
Pre-screening asthma medications, n (%)		
SABA	22 (15)	16 (11)
Anti-allergic other than leukotriene-receptor antagonist	19 (13)	15 (10)
ICS	120 (80)	125 (83)
ICS alone[b]	97 (81)	91 (73)
ICS + LABA[c]	23 (19)	34 (27)
Sustained release theophylline	4 (3)	2 (1)
Leukotriene-receptor antagonists	122 (81)	127 (85)

FP, fluticasone propionate; ICS, inhaled corticosteroid; JPAC, Japanese Pediatric Asthma Control Program; LABA, long-acting beta-2-agonist; SABA, short-acting beta-2-agonist; SD, standard deviation; SAL, salmeterol xinafoate

[a]Based on clinician's judgement (referring to Japanese Pediatric Guideline 2012).

[b]Percentages calculated using the number of children who used ICS as the denominator.

[c]Totals for ICS + SAL, ICS + formoterol and ICS + LABA (patch, oral or inhaler).

treatment group, boys predominated. Those aged 2 years and older had moderate or severe persistent asthma and had baseline asthma symptom scores of ≥10 points. For all treatment groups, the mean treatment compliance was high (≥95%) in both study periods.

3.1 | Total asthma symptom scores (double-blind period)

Least squares (LS) mean change from baseline in the total asthma symptom scores (daytime plus night-time) showed improvement in both FP/SAL and FP groups, with mean changes of −3.97 points (FP/SAL) and −3.01 (FP), but there was no statistically significant difference (P = 0.21; Table 2).

Assessment by age (younger than 2 years or 2 years and above) and by the number of daily inhalations (2 or 4/day) for those aged 2 years and above showed a similar trend between the subgroups. For further details and open-label period outcomes; see Online Repository: Subgroup analyses : Asthma symptom scores (Table S3, S4 and S5).

3.2 | Total asthma symptom scores over time

Total asthma symptom scores decreased from baseline in both groups in the double-blind period. Reductions were also seen during the open-label period (Figure 3).

3.3 | Other efficacy outcomes (double-blind period)

3.3.1 | Asthma exacerbations

Exacerbation frequency was lower in the FP/SAL group, four children (3%) compared with eight children (5%) in the FP group. Odds ratio was 0.47 (95% CI, 0.14, 1.60). For the open-label period outcomes; see Online Repository.

3.3.2 | JPAC scores

Mean change from baseline was greater in the FP/SAL group (0.4 points) than the FP group (−0.3 points), P = 0.04. For the open-label period outcomes; see Online Repository.

TABLE 2 Mean change from baseline in total asthma symptom scores (daytime plus night-time) over the last 7 days of the double-blind period (intent-to-treat population)

	FP/SAL N = 150	FP N = 150
Number of children evaluated, n	148	142
LS mean (standard error)	−3.97 (0.534)	−3.01 (0.545)
LS mean difference versus FP	−0.97	
95% confidence interval	(−2.47, 0.54)	
P-value	0.21	

FP, fluticasone propionate; LS, least squares; SAL, salmeterol xinafoate

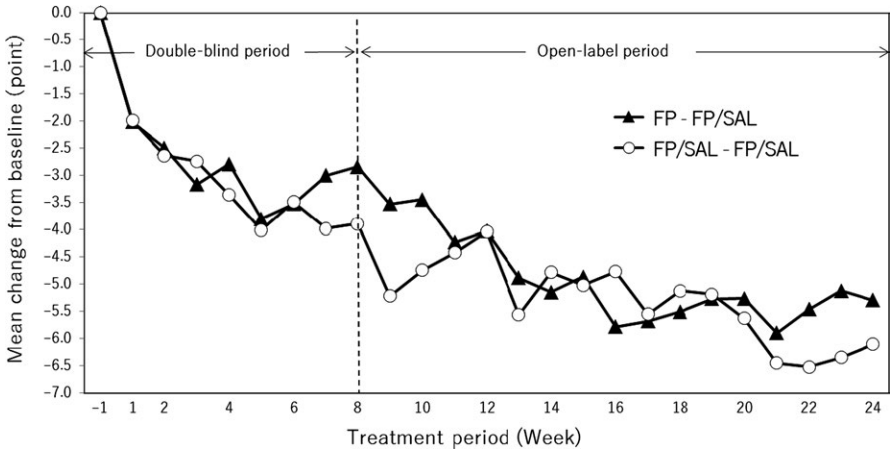

FIGURE 3 Mean change from baseline over time in weekly total (daytime plus night-time) asthma symptom scores in the double-blind and open-label extension periods

3.3.3 | Rescue medication use

There was little change from baseline in daily rescue medication use and percentage of rescue-free days with no statistically significant difference ($P = 0.34$ [95% CI, −0.20, 0.07] and $P = 0.39$ [−3.3, 8.6], respectively) between both groups. The LS mean (standard error [SE]) changes from baseline were 0.01 (0.047) doses (FP/SAL group) versus 0.07 (0.048) doses (FP group) and −0.3% (2.11; FP/SAL group) versus −2.9% (2.16; FP group), respectively. For the open-label period outcomes; see Online Repository.

3.4 | Safety

3.4.1 | Double-blind period

Incidence of AEs was virtually identical between the FP/SAL (74%) and FP (73%) groups (Table 3).

The incidence of AEs was not associated with age (young than 2 or 2 years and above) or number of inhalations (2 or 4 /day). Incidence of drug-related AEs (FP, 1 child, stomatitis) and SAEs (FP/SAL, <1%; FP, 3%) was very low; no SAEs were considered by the investigators to be drug-related.

3.4.2 | Open-label period

Incidence of AEs in the open-label period (FP/SAL total group) was 91%, and 93% in the double-blind + open-label period (FP/SAL-FP/SAL group; Table 3). The most common AEs were similar to those in the double-blind period.

Incidence of drug-related AEs in the total FP/SAL group was low (two children, decreased plasma cortisol). No SAEs were deemed drug-related.

A similar incidence of AEs was seen between weeks 0-8 (74%), weeks 8-16 (76%) and after week 16 (78%) in those children who received FP/SAL during the double-blind and open-label periods.

3.4.3 | Follow-up period

Incidence of AEs after the double-blind period was low, one child receiving FP/SAL had a lower plasma cortisol and two receiving FP had conjunctivitis, otitis media and rhinitis; none was serious and all were considered unrelated to study medications.

Incidence of AEs was 28% (81 children) after the open-label period. Four children showed lower plasma cortisol levels, possibly related to the FP medicine component but of no clinical relevance.

There were no deaths in this study.

3.4.4 | Other safety parameters

No clinically relevant changes from baseline were noted for any other safety parameter. Mild QTc prolongation was noted in two children but not considered clinically relevant and not related to the study drug. Both events were reported at the beginning of the open-label period (5-10 minutes post-dose with FP/SAL at Visit 5). One subject returned to normal at Visit 8, and the other discontinued the study drug due to the event.

4 | DISCUSSION

Very young children with asthma are clinically challenging. Whilst FP/SAL combination therapy is unlicensed in this age group in most countries, clinicians do prescribe its use in an off-label manner.[19] This is the first large-scale study attempting to evaluate its efficacy and safety under 4 years of age.

FP/SAL improved the total asthma symptom scores but did not show more benefit than FP alone during the 8-week double-blind period. Statistically significant treatment differences were seen for some secondary outcomes such as exacerbations and FP/SAL showed better JPAC scores.

Why did FP/SAL combination treatment not show greater improvement than FP alone? Asthma symptoms are more intermittent, particularly in very young children. Between exacerbations, the very

TABLE 3 Summary of on-treatment adverse events reported during the double-blind and open-label periods (intent-to-treat population)

	Double-blind (8 weeks)		Open-label (16 weeks)	Double-blind + Open-label (24 weeks)
	FP/SAL N = 150	FP N = 150	FP/SAL total[b] N = 288	FP/SAL-FP/SAL[b] N = 150
Overall safety summary, n (%)				
Any AEs	111 (74)	110 (73)	262 (91)	139 (93)
AEs related to study drug	0	1 (<1)	2 (<1)	2 (1)
Stomatitis	0	1 (<1)	0	0
Decreased plasma cortisol	0	0	2 (<1)	2 (1)
AEs leading to permanent discontinuation of study drug	0	4 (3)	13 (5)	7 (5)
Asthma[a]	0	4 (3)	8 (3)	Not analysed
AEs of special interest[a]	18 (12)	22 (15)	95 (33)	62 (41)
Asthma	4 (3)	13 (9)	35 (12)	26 (17)
Urticaria	5 (3)	2 (1)	10 (3)	8 (5)
Eczema	2 (1)	2 (1)	12 (4)	9 (6)
Conjunctivitis allergic	3 (2)	1 (<1)	9 (3)	8 (5)
Pneumonia	2 (1)	1 (<1)	12 (4)	7 (5)
Any SAEs[c]	1 (<1)	5 (3)	20 (7)	11 (7)
Bronchitis	1 (<1)	0	1 (<1)	1 (<1)
Asthma	0	4 (3)	8 (3)	5 (3)
Upper respiratory tract infection	0	1 (<1)	0	0
Pneumonia	0	0	7 (2)	4 (3)
Gastroenteritis	0	1 (<1)	1 (<1)	1 (<1)
SAEs related to study drug	0	0	0	0
Fatal SAEs	0	0	0	0
SOC/PT AEs (reported by eight or more children out of total number during double-blind and open-label periods), n (%)				
Infections and infestations	87 (58)	87 (58)	220 (76)	125 (83)
Upper respiratory tract infection	**28 (19)**	**18 (12)**	**56 (19)**	**44 (29)**
Nasopharyngitis	**18 (12)**	**24 (16)**	**68 (24)**	**40 (27)**
Bronchitis	**15 (10)**	13 (9)	**43 (15)**	**27 (18)**
Gastroenteritis	11 (7)	14 (9)	**44 (15)**	**30 (20)**
Pharyngitis	11 (7)	9 (6)	**39 (14)**	**26 (17)**
Hand-foot-and-mouth disease	9 (6)	4 (3)	9 (3)	**15 (10)**
Influenza	3 (2)	4 (3)	**38 (13)**	**24 (16)**
Sinusitis	3 (2)	4 (3)	20 (7)	13 (9)
Molluscum contagiosum	1 (<1)	3 (2)	8 (3)	7 (5)
Conjunctivitis	3 (2)	0	10 (3)	10 (7)
Otitis media	3 (2)	4 (3)	17 (6)	10 (7)
Impetigo	5 (3)	3 (2)	7 (2)	10 (7)
Pneumonia	2 (1)	1 (<1)	12 (4)	7 (5)
Tonsillitis	0	1 (<1)	11 (4)	2 (1)
Respiratory, thoracic and mediastinal disorders	22 (15)	33 (22)	78 (27)	51 (34)
Upper respiratory tract inflammation	10 (7)	**18 (12)**	**34 (12)**	**17 (11)**
Asthma	4 (3)	13 (9)	**35 (12)**	**26 (17)**
Gastrointestinal disorders	15 (10)	10 (7)	47 (16)	36 (24)
Diarrhoea	5 (3)	1 (<1)	14 (5)	11 (7)

(Continues)

TABLE 3 (Continued)

	Double-blind (8 weeks)		Open-label (16 weeks)	Double-blind + Open-label (24 weeks)
	FP/SAL N = 150	FP N = 150	FP/SAL total[b] N = 288	FP/SAL-FP/SAL[b] N = 150
Constipation	1 (<1)	0	11 (4)	6 (4)
Vomiting	2 (1)	4 (3)	11 (4)	5 (3)
Skin and subcutaneous tissue disorders	14 (9)	12 (8)	53 (18)	38 (25)
Eczema	2 (1)	2 (1)	12 (4)	9 (6)
Urticaria	5 (3)	2 (1)	10 (3)	8 (5)
General disorders and administration site conditions	6 (4)	7 (5)	12 (4)	12 (8)
Pyrexia	6 (4)	7 (5)	10 (3)	10 (7)
Eye disorders	4 (3)	2 (1)	19 (7)	16 (11)
Conjunctivitis allergic	3 (2)	1 (<1)	9 (3)	8 (5)

Those events in bold text were the most frequently reported AEs in each treatment group (>10% as PT).
AE, adverse event; FP/SAL, fluticasone propionate/salmeterol xinafoate; FP, fluticasone propionate; SAE, serious adverse event; SOC, system organ class; PT, preferred term
[a]All AEs of special interest experienced by ≥8 participants in any treatment group.
[b]During the open-label period, where all participants received FP/SAL, the FP-FP/SAL group were those children who received FP in the double-blind period and FP/SAL in the open-label period; the FP/SAL-FP/SAL group included those children who received FP/SAL in both the double-blind and open-label periods. The total FP/SAL group included FP/SAL data from the open-label period only.
[c]All other SAEs reported in FP/SAL total and FP/SAL-FP/SAL groups were reported by <1% of participants.

young children may be clinically very well-making medicine comparisons more difficult to evaluate. Although beta-2-receptors are present throughout the respiratory tract from very early in life, Lenney and Milner showed that when treating very young children recovering from an acute wheezing episode, those below 12 months old could show reverse bronchoconstriction once again confusing responses in the very young.[20] We have less knowledge about the airway pathophysiology in very young wheezing children and the true diagnosis of allergic asthma is very difficult to make. Saglani et al in the UK showed that subepithelial membrane thickening is present in wheezing children with a diagnosis of asthma by the age of 3 years.[21]

The mean change from group baseline in JPAC scores (secondary end-point) was statistically significantly different, with a greater improvement in the FP/SAL group. JPAC is a tool to evaluate asthma severity and asthma control, but the minimal clinically important difference has not been established. This result suggests, however, the control of asthma possibly improved more when using the ICS/LABA combination. During the open-label period, further reductions in the total asthma symptom scores were seen with FP/SAL together with improvements in other secondary end-points.

No clinically significant differences were noted in the safety profile between the FP/SAL and FP groups during the 8-week double-blind period. No new safety signals were identified with FP/SAL in the 16-week open-label extension period. Drug-related lower plasma cortisol was reported in six children during the open-label and follow-up periods. Systemic effects are known with any ICS, particularly at high doses prescribed for long periods. When FP (100 μg twice daily) was given to young children aged 12-47 months, with persistent asthma, no decreased cortisol levels were reported.[22] In our study, plasma cortisol shifted from the normal to low values in some children, but most returned to the normal range when repeated.

Asthma in very young children is difficult to diagnose and manage. The use of lung function tests in this age group is not possible in primary care and unavailable in many secondary care centres. We, therefore, entirely rely on clinical assessments, but in very young children, the intermittent nature of their symptoms makes it difficult to differentiate between treatments. Problems with cooperation, inhalation technique, adherence to therapy and our lack of scientific understanding in this very young patient population add to this complexity making consistency of medication administration problematic for parents/legal guardians and healthcare professionals.

The data in this study are of value because they are the first to be published when managing these challenging children. Such data are needed because asthma control is poor compared to that in older children with many more hospital admissions in the very young.[23-26] We believe it is important to collect and report such data, as uncontrolled asthma in young children may well have an impact on future lung growth and respiratory health throughout childhood and into adult life.

Our study offers new clinical efficacy and safety information for those treating very young children with problematic asthma.

5 | CONCLUSION

This is the first randomized, double-blind study with significant numbers of young children evaluating FP/SAL in children up to 4 years of age. We could not confirm a statistically significant effect of FP/SLM

over FP. Although we conducted the study in Japanese children, we believe the results are applicable globally and provide information to others managing this condition, one of the commonest seen in most countries worldwide.

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CONFLICTS OF INTEREST

Authors SY, TT and MI did not receive any personal payments from GSK, but their institutions received research grants from GSK. WL, RT and TH are GSK employees and shareholders. TS is a GSK KK employee and does not hold GSK shares. KH and SK are GSK KK employees and hold GSK shares. None of the authors has been involved in other activities that may have influenced the study findings.

AUTHOR CONTRIBUTION

SY, TT and MI participated in the study as investigators. WL contributed to reviewing the data and on interpretation. RT and TH contributed to study design, reviewing the data and interpretation. HK and ST contributed to study concept, management, implementation, data analysis and interpretation. SK contributed to study management, implementation, data analysis and interpretation. All authors have been involved with developing the manuscript and approving it for publication.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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