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Randomized Trial of Once-Daily Fluticasone Furoate in Children with Inadequately Controlled Asthma

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Objective To evaluate the dose-response, efficacy, and safety of fluticasone furoate (FF; 25 μg, 50 μg, and 100 μg), administered once daily in the evening during a 12-week treatment period to children with inadequately controlled asthma.

Study design This was a Phase IIb, multicenter, stratified, randomized, double-blind, double-dummy, parallel-group, placebo- and active-controlled study in children aged 5-11 years with inadequately controlled asthma. The study comprised a 4-week run-in period, 12-week treatment period, and 1-week follow-up period. Children were randomized to receive either placebo once daily, fluticasone propionate (FP) 100 μg twice daily, FF 25 μg, FF 50 μg, or FF 100 μg each once daily in the evening. Primary endpoint was the mean change from baseline in daily morning peak expiratory flow (PEF) averaged over weeks 1-12. Adverse events (AEs) also were investigated.

Results In total, 593 children were included in the intent-to-treat population. The difference vs placebo in change from baseline daily morning PEF averaged over weeks 1-12 was statistically significant for the FF 25, FF 50, FF 100, and FP 100 groups (18.6 L/min, 19.5 L/min, 12.5 L/min, and 14.0 L/min, respectively; $P < .001$ for all). The incidence of AEs was greater in the FF groups (32%-36%) than in the placebo group (29%); the most frequent AE was cough.

Conclusion FF and FP resulted in significant improvements in morning PEF compared with placebo, suggesting that they are effective treatments for children with inadequately controlled asthma. All treatments were well tolerated; no new safety concerns were identified. *(J Pediatr 2016;178:246-53).*

Trial registration ClinicalTrials.gov: NCT01563029.

Inhaled corticosteroids (ICS) are considered the most effective anti-inflammatory treatments for all severities of persistent asthma.[1-4] National and international guidelines advocate the use of ICS for reducing asthma symptoms and the risk of exacerbations in children aged 5-11 years with persistent asthma.[1-3] Despite effective treatment being available, however, many children with asthma remain uncontrolled. The Global Initiative for Asthma guidelines define uncontrolled asthma as having ≥3 of the following in the previous 4 weeks: daytime asthma symptoms >2 times per week; any night waking due to asthma; the need for reliever for symptoms >2 times per week; or any activity limitation due to asthma.[2] Low adherence has been proposed as a potential contributing factor to uncontrolled asthma in children.[5,6] In addition, adherence to medications including ICS primarily has been shown to decline as the number of doses per day increases,[7,8] including in children with asthma.[9]

AUC_{0-24}	Area under the plasma-concentration curve over 0-24 hours
AE	Adverse event
cACT	childhood Asthma Control Test
FEV_1	Forced expiratory volume in 1 second
FF	Fluticasone furoate
FP	Fluticasone propionate
ICS	Inhaled corticosteroid
ITT	Intent-to-treat
LOCF	Last observation carried forward
MMRM	Mixed modeling repeated measures
PAQLQ(S)	Standardised Paediatric Asthma Quality of Life Questionnaire
PEF	Peak expiratory flow
PK	Pharmacokinetic
PP	Per-protocol
SABA	Short-acting $beta_2$-agonist
UC	Urinary cortisol
VI	Vilanterol

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Fluticasone furoate (FF), delivered via the ELLIPTA inhaler (GlaxoSmithKline, Hertfordshire, United Kingdom), is a novel ICS that has been approved as a once-daily treatment of asthma in adult and adolescent patients in the US.[10] The purpose of this study was to evaluate the dose-response, efficacy, and safety of 3 doses of FF (25 μg, 50 μg, and 100 μg) administered once daily in the evening during a 12-week treatment period to children aged 5-11 years with inadequately controlled asthma. Fluticasone propionate (FP) 100 μg was used as an active comparator.

Methods

This was a Phase IIb, multicenter, stratified, randomized, double-blind, double-dummy, parallel-group, placebo- and active-controlled study (with rescue medication) in children aged 5-11 years with inadequately controlled asthma (ClinicalTrials.gov: NCT01563029 [106855]). The study consisted of a 4-week run-in period, 12-week treatment period, and 1-week follow-up period. During the run-in, children continued taking their current asthma medication. All children were provided with albuterol/salbutamol as needed for the relief of asthma symptoms.

The original primary endpoint was change from baseline in predose evening peak expiratory flow (PEF) at week 12, with missing data for this endpoint assessment imputed by the use of last observation carried forward (LOCF). This was changed to the change from baseline in daily predose morning PEF averaged over weeks 1-12 to use all available PEF data during the treatment period, thereby requiring no imputation of missing data. The endpoint also was changed for consistency with the analysis of PEF in the adult FF/vilanterol (VI) program.[11,12] This change of endpoint was made at the time of writing the reporting and analysis plan, before we unblinded the database, and was approved by the European Medicines Agency Paediatric Committee.

Eligible children were aged 5-11 years, had symptoms of asthma at least 6 months before screening, and had been receiving short-acting beta$_2$-agonist (SABA) alone, SABA with a leukotriene modifying agent, or SABA with low-dose ICS (≤250 μg FP) for ≥4 weeks before screening. Children also had prebronchodilator PEF of 60%-90% of their best postbronchodilator value, and, for those able to perform the maneuver, demonstrated a ≥12% reversibility of forced expiratory volume in 1 second (FEV_1) within ~10-40 minutes following 2-4 inhalations of albuterol/salbutamol. Excluded children had a history of life-threatening asthma; change in asthma medication within 4 weeks of screening; an asthma exacerbation (defined as a deterioration of asthma either requiring the use of systemic corticosteroids for ≥3 days, or a depot corticosteroid injection ≤3 months before screening, or hospitalization or emergency department visit for asthma ≤6 months before screening); concurrent respiratory disease; or any other clinically significant medical condition.

At the end of the run-in period, children eligible for randomization had a prebronchodilator PEF of 60%-90% of their best postbronchodilator value; symptoms of asthma (a score of ≥1 on the daytime or nighttime asthma symptom scores reported on the eDiary); and/or daily use of albuterol/salbutamol on ≥3 of the last 7 consecutive days of the run-in period. In addition, eligible children complied with the run-in medication on ≥4 of the last 7 consecutive days of the run-in period and completed all questions on the eDiary on ≥4 of the 7 days during the screening period. Children excluded from randomization had a change in asthma medication since screening; an asthma exacerbation between screening and randomization; or concurrent respiratory disease or any other clinically significant medical condition.

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the relevant ethics committee or institutional review board at each investigational center. Written informed consent was obtained from 2 parents/legal guardians. If applicable, the child had to be able and willing to give assent to take part in the study according to the local requirements. The investigator was accountable for determining a child's capacity to assent.

Treatment and Assessments

Children were assigned randomly 1:1:1:1:1 to receive either placebo via the ELLIPTA inhaler, FP 100 μg twice daily via the DISKUS inhaler (GlaxoSmithKline), or FF 25 μg, FF 50 μg, or FF 100 μg each once daily in the evening via the ELLIPTA inhaler. In addition, each received placebo twice daily via the DISKUS inhaler, except for children in the FP 100 μg group, who received placebo once daily via the ELLIPTA inhaler. Randomization was stratified by previous ICS therapy. Morning and evening PEF were measured daily by the use of an eDiary with a peak flow meter. FEV_1 was measured in a subset of children in the evening at clinic visits via an electronic spirometer, at screening, randomization, and weeks 2, 4, 8, and 12.

Endpoints

The primary endpoint was the mean change from baseline in daily predose morning PEF averaged over weeks 1-12. Secondary efficacy endpoints were change from baseline in: (1) evening study visit trough FEV_1 at the end of the treatment period (using LOCF for imputation of missing postbaseline FEV_1 values); (2) percentage of rescue-free and symptom-free days averaged over the treatment period; (3) daily predose evening PEF averaged during the treatment period; (4) morning and evening PEF over the last 7 days of the treatment period; and (5) number of withdrawals due to lack of efficacy during the treatment period. Withdrawal because of a lack of efficacy was defined as reaching the PEF stability limit, use of albuterol/salbutamol, experiencing a clinical asthma exacerbation, or worsening of asthma (defined as requiring treatment other than study medication or use of rescue albuterol/salbutamol, including nebulization). Other endpoints included change from baseline in the childhood Asthma Control Test (cACT) score at week 12 and change from baseline in the Standardised Paediatric Asthma Quality of Life Questionnaire, or PAQLQ(S),[13] score at week 12.

Pharmacokinetics (PK) blood samples were collected predose and 20-40 minutes postdose at week 12. Plasma samples were

analyzed for FF by mass spectrometry. The lower limit of quantification was 10 pg/mL. The PK variables, maximum concentration, and area under the plasma-concentration curve over 0-24 hours (AUC_{0-24}) were assessed with PK analysis of the plasma concentration-time data.

Safety and tolerability endpoints included: (1) the incidence of adverse events (AEs) over weeks 1-12; (2) 24-hour urinary cortisol (UC) excretion at baseline and week 12; (3) laboratory assessments at screening and week 12 or early withdrawal; (4) incidence of severe asthma exacerbations throughout the treatment period; and (5) vital signs at randomization and at weeks 2, 4, 8, and 12, or early withdrawal.

Statistical Analysis

With 575 children (115 children per treatment group) the study had 90% power assuming a difference of 12 L/min in morning PEF in the gatekeeper comparison between the average of the greater 2 FF doses (FF 100 μg and FF 50 μg) and placebo, an SD of 28 L/min, and significance declared at the 2-sided 5% level. The study also had 90% power assuming a 12 L/min difference in morning PEF in the comparisons between any active dose and placebo. To account for multiplicity across treatment comparisons for the primary endpoint, comparisons of each FF dose with placebo followed a step-down closed testing procedure.

Provided the test of the average of the 2 greater FF doses vs placebo was statistically significant, inference could be made on comparisons of FF 100 μg vs placebo and FF 50 μg vs placebo. Similarly, if both of these comparisons were statistically significant, inference could then be made on the comparison of FF 25 μg vs placebo with no further multiplicity adjustment. For all efficacy and safety endpoints, the FP 100 μg group was compared with placebo to provide a positive control of relative efficacy.

The intent-to-treat (ITT) population comprised all children randomized to treatment who received ≥1 study medication. The per-protocol (PP) population comprised all children in the ITT population without any full protocol deviations. The UC population consisted of children whose urine samples had no confounding factors that would have affected the interpretation of UC results. Finally, the PK population consisted of children in the ITT population for whom a PK sample was analyzed for FF. The population PK analysis included concentration-time data from the current study combined with data from 2 previous studies.[14,15]

The primary efficacy endpoint was analyzed with an analysis of covariance model, allowing for the effects due to baseline morning PEF, region, sex, actual prescreening ICS use, age, and treatment group on the ITT and PP populations. Because missing data were not imputed in this analysis, 5 sensitivity analyses examined the impact of missing data: 1 mixed modeling repeated measures (MMRM) analysis and 4 multiple imputation sensitivity analyses. The MMRM analysis accounted for effects due to baseline morning PEF, region, sex, age, week, and treatment group, including week-by-treatment and week-by-baseline interaction terms. The other 4 imputation sensitivity analyses used a Missing at Random approach, a Copy Increment from Reference approach, a Jump to Reference approach, and a Copy Reference approach. All sensitivity analyses examined an average treatment effect across the treatment period. Three further supporting analyses were performed on the primary endpoint: dose-response models, Bayesian analyses with noninformative priors, and a MMRM model presenting estimates from each week.

Statistical analyses for secondary endpoints were performed with ANCOVA models with effects due to baseline, region, sex, age, and treatment group. For the secondary endpoint of evening trough FEV_1, an MMRM, and a Bayesian analysis also were performed. The MMRM analysis was as per the primary endpoint. The Bayesian analysis examined the posterior probability distribution of the treatment differences of each active treatment against placebo. For trough FEV_1 and morning and evening PEF at the endpoint, missing data were imputed by use of the LOCF. Programming was performed with SAS, version 9.1.3 (SAS Institute, Inc, Cary, North Carolina) or later. Evaluation of percent predicted FEV_1 values at baseline were not prespecified in the protocol and are reported as post hoc analyses.

Results

A total of 1540 children were screened, 596 children were randomized with 593 (99.5%) children included in the ITT population (**Figure 1**; available at www.jpeds.com). The study period, from the first screening to the last visit, was from March 2012 to September 2014. Demographics were generally similar between treatment groups (**Table I**). There was a lower proportion of children aged 5-7 years in the FF 50 μg treatment group (26%) compared with the other treatment groups (41%-47%). A total of 172 (29%) children withdrew during the study (**Figure 1**), primarily due to lack of efficacy; the latter was greater in the placebo group (35%) than in the FF groups (14%-19%) and the FP group (16%).

Primary Endpoint

The adjusted treatment differences in the mean change from baseline in daily predose morning PEF vs placebo were 18.6 L/min, 19.5 L/min, and 12.5 L/min for the FF 25 μg, FF 50 μg, and FF 100 μg groups, respectively (**Table II** and **Figure 2**; **Figure 2** available at www.jpeds.com). In accordance with the step-down closed testing procedure, all treatment differences vs placebo were statistically significant ($P < .001$; **Table II**). The analysis of the primary endpoint using the PP population plus all sensitivity and supporting analyses using the ITT population supported the findings of the primary analysis. There was no apparent FF dose-ordering. The adjusted treatment difference in the mean change from baseline in morning PEF for FP 100 μg vs placebo also was statistically significant (14.0 L/min; $P < .001$; **Table II**). When stratified by prescreening ICS use, mean changes from baseline in morning PEF were greater for the active treatment groups than placebo for children with prescreening ICS use and without (**Table II**). Changes were similar regardless of prescreening ICS use.

Table I. Summary of demographic characteristics and baseline characteristics

	Number (%) subjects					
	Placebo, N = 119	FF 25 OD, N = 118	FF 50 OD, N = 120	FF 100 OD, N = 118	FP 100 BD, N = 118	Total N = 593
Sex, n (%)						
Female	49 (41)	41 (35)	46 (38)	48 (41)	39 (33)	223 (38)
Male	70 (59)	77 (65)	74 (62)	70 (59)	79 (67)	370 (62)
Age, y						
Mean (SD)	8.0 (1.9)	7.9 (2.1)	8.4 (1.6)	7.8 (2.0)	7.9 (1.9)	8.0 (1.9)
Age group, n (%)						
5-7 y	49 (41)	48 (41)	31 (26)	55 (47)	51 (43)	234 (39)
8-11 y	70 (59)	70 (59)	89 (74)	63 (53)	67 (57)	359 (61)
Race, n (%)						
White	48 (40)	57 (48)	51 (43)	52 (44)	43 (36)	251 (42)
White and American Indian or Alaskan Native	33 (28)	33 (28)	39 (33)	38 (32)	40 (34)	183 (31)
American Indian or Alaskan Native	24 (20)	17 (14)	16 (13)	17 (14)	21 (18)	95 (16)
African American or African heritage	4 (3)	4 (3)	7 (6)	8 (7)	7 (6)	30 (5)
Asian	8 (7)	7 (6)	6 (5)	2 (2)	7 (6)	30 (5)
Other	10 (8)	7 (6)	7 (6)	3 (3)	7 (6)	34 (6)
Ethnicity, n (%)						
Hispanic/Latino	64 (54)	55 (47)	57 (48)	60 (51)	65 (55)	301 (51)
Not Hispanic/Latino	55 (46)	63 (53)	63 (53)	58 (49)	53 (45)	292 (49)
Duration of asthma, n (%)						
<1 y	8 (7)	5 (4)	9 (8)	6 (5)	7 (6)	35 (6)
≥1 to <2 y	15 (13)	22 (19)	14 (12)	14 (12)	15 (13)	80 (13)
≥2 to <5 y	44 (37)	40 (34)	45 (38)	53 (45)	49 (42)	231 (39)
≥5 to <10 y	49 (41)	49 (42)	50 (42)	44 (37)	45 (38)	237 (40)
≥10 y	3 (3)	2 (2)	2 (2)	1 (<1)	2 (2)	10 (2)
Baseline lung function test results						
Mean prebronchodilator PEF (SD), L/min	192.5 (67.1)	193.3 (60.8)	198.1 (54.0)	180.4 (59.8)	182.9 (57.2)	189.5 (60.1)
Mean percentage of pre- to postbronchodilator PEF (SD), %	79.4 (8.4)	79.3 (7.9)	78.5 (8.0)	77.9 (8.8)	79.0 (8.0)	78.8 (8.2)
Baseline FEV_1, L (SD)	1.39 (0.46)	1.44 (0.40)	1.44 (0.42)	1.31 (0.41)	1.33 (0.45)	1.38 (0.43)
Prebronchodilator FEV_1, % predicted*						
n	114	104	115	108	111	552
Mean (SD)	84.4 (19.7)	84.8 (17.6)	84.1 (17.2)	82.1 (17.7)	82.5 (18.9)	83.6 (18.2)
Baseline patient-reported outcomes						
Mean cACT score (SD)	17.8 (3.9)	18.4 (4.2)	17.7 (4.1)	17.4 (4.0)	18.0 (4.3)	-

BD, twice daily; *OD*, once daily.
*% predicted FEV_1 data are post hoc analyses.

Secondary Endpoints

The analysis of change from baseline in trough FEV_1 at week 12 (LOCF) included 508 children (86%) in the ITT population who provided technically acceptable FEV_1 data[16] both at baseline and at least 1 postbaseline visit. There was a statistically significant adjusted treatment difference in the change from baseline in trough FEV_1 at week 12 (LOCF) for the FF 25 μg group compared with placebo (126 mL, $P < .001$) but not for the other treatment comparisons (**Table II**). The results of the MMRM analysis supported the findings of the ITT analysis; however, in a post hoc analysis including only children with acceptable FEV_1 measurements, all treatment groups demonstrated numerically greater changes from baseline vs placebo (**Table III**; available at www.jpeds.com). A further post hoc analysis of FEV_1 data by age subgroup was performed because of statistically significant interactions between treatment and age in the MMRM analysis. The change from baseline in trough FEV_1 for children aged 5-7 years was similar for all groups, including placebo (**Table III**). However, in children aged 8-11 years, the change from baseline in trough FEV_1 was greater than placebo for all active treatment groups (**Table III**).

During the treatment period, notable differences from baseline in percentage of rescue-free days were observed for all FF groups compared with placebo. These differences were statistically significant in the FF 50 μg and FF 100 μg groups (9.8%, $P = .023$ and 12.2%, $P = .004$, respectively), and equated to an additional 0.7 and 0.9 rescue-free days per week, respectively (**Table II**). For symptom-free days, small increases were observed in all groups including placebo and so statistically significant differences vs placebo were not reached in any treatment group (**Table II**).

For all secondary PEF endpoints, FF treatment led to statistically significant improvements compared with placebo (except for change from baseline in evening PEF at week 12 [LOCF] for the FF 100 μg group, $P = .266$), although no dose ordering was observed (**Table II**). The proportion of withdrawals due to lack of efficacy over weeks 1-12 were statistically significantly lower in all FF groups (14%-19%) and the FP 100 μg group (16%) compared with placebo (35%; **Table II**).

Other Endpoints

Improvements from baseline to week 12 were observed for both cACT score and total PAQLQ(S) score in all active treatment groups and placebo (**Table II**). Adjusted treatment differences vs placebo were not statistically significant with FF for change in baseline cACT score or total PAQLQ(S) score analyses (**Table II**).

Table II. Primary, secondary, and other endpoints

	Placebo, n = 119	FF 25 OD, n = 118	FF 50 OD, n = 120	FF 100 OD, n = 118	FP 100 BD, n = 118
Primary endpoint					
Mean change from baseline in daily morning PEF (L/min), weeks 1-12					
n	119	117	118	118	117
LS mean	198.9	217.5	218.4	211.3	212.9
LS mean change (SE)	3.3 (2.6)	21.9 (2.7)	22.8 (2.7)	15.8 (2.6)	17.3 (2.6)
Treatment vs placebo					
Difference, L/min		18.6	19.5	12.5	14.0
95% CI		11.3, 26.0	12.1, 26.9	5.1, 19.8	6.7, 21.4
P value		<.001	<.001	<.001	<.001
Mean change from baseline in daily morning PEF (L/min), weeks 1-12 by prescreening ICS use					
Prescreening ICS used					
n	65	62	65	62	63
Mean (SD)	1.2 (33.6)	21.3 (25.4)	22.3 (37.0)	15.5 (25.2)	20.5 (29.13)
No prescreening ICS used					
n	54	55	53	56	54
Mean (SD)	4.3 (23.6)	16.1 (38.7)	24.2 (32.8)	19.1 (32.1)	17.7 (26.0)
Secondary endpoints					
Change from baseline in evening trough FEV_1, week 12 (LOCF)					
n	102	96	112	96	102
LS mean, L	1.524	1.650	1.545	1.557	1.587
LS mean change, mL (SE)	128 (26)	254 (27)	150 (25)	162 (27)	192 (26)
Treatment vs placebo					
Difference, mL		126	22	33	64
95% CI		51, 201	–50, 94	–41, 108	–10, 137
P value		<.001	.551	.379	.089
Change from baseline in percentage of rescue-free days, weeks 1-12					
n	119	117	118	118	117
LS mean change (SE)	16.5 (3.0)	24.9 (3.0)	26.3 (3.0)	28.7 (3.0)	22.7 (3.0)
Treatment vs placebo					
Difference		8.4	9.8	12.2	6.2
95% CI		0.0, 16.9	1.3, 18.2	3.8, 20.5	–2.1, 14.6
P value		.050	.023	.004	.143
Change from baseline in percentage of symptom-free days, weeks 1-12					
n	119	117	119	118	117
LS mean change (SE)	19.0 (2.9)	21.0 (2.9)	24.7 (2.9)	22.9 (2.9)	22.0 (2.9)
Treatment vs placebo					
Difference		2.1	5.8	3.9	3.0
95% CI		–6.1, 10.2	–2.3, 13.9	–4.1, 12.0	–5.0, 11.1
P value		.619	.161	.340	.459
Change from baseline in evening PEF (L/min), weeks 1-12					
n	119	117	119	118	117
LS mean	210.3	221.5	223.7	218.7	218.3
LS mean change (SE)	5.1 (2.8)	16.3 (2.8)	18.5 (2.8)	13.5 (2.8)	13.1 (2.8)
Treatment vs placebo					
Difference, L/min		11.2	13.4	8.4	8.0
95% CI		3.4, 19.0	5.7, 21.1	0.7, 16.1	0.3, 15.7
P value		.005	<.001	.033	.042
Change from baseline in morning PEF (L/min), week 12 (LOCF)					
n	119	117	118	118	117
LS mean	198.3	218.9	216.1	209.8	214.9
LS mean change (SE)	2.7 (3.8)	23.3 (3.9)	20.6 (3.8)	14.2 (3.8)	19.3 (3.8)
Treatment vs placebo					
Difference, L/min		20.6	17.9	11.5	16.7
95% CI		10.0, 31.3	7.2, 28.6	0.9, 22.1	6.0, 27.3
P value		<.001	.001	.033	.002
Change from baseline in evening PEF (L/min), week 12 (LOCF)					
n	119	117	118	118	117
LS mean	210.3	221.5	223.4	216.2	216.5
LS mean change (SE)	5.0 (3.8)	16.2 (3.8)	18.2 (3.8)	11.0 (3.8)	11.3 (3.8)
Treatment vs placebo					
Difference, L/min		11.2	13.1	5.9	6.2
95% CI		0.7, 21.7	2.6, 23.6	–4.5, 16.3	–4.2, 16.6
P value		.037	.014	.266	.242
Number of withdrawals due to lack of efficacy throughout the 12-wk treatment period n (%)	42 (35)	16 (14)	23 (19)	21 (18)	19 (16)
Treatment vs placebo					
P value		<.001	.006	.003	<.001

(*continued*)

Table II. Continued

	Placebo, n = 119	FF 25 OD, n = 118	FF 50 OD, n = 120	FF 100 OD, n = 118	FP 100 BD, n = 118
Other endpoints					
Change from baseline in cACT score, week 12					
n	70	97	89	84	89
LS mean change (SE)	3.7 (0.4)	4.0 (0.3)	4.4 (0.4)	3.5 (0.4)	4.1 (0.3)
Treatment vs placebo					
Difference		0.2	0.7	−0.2	0.3
95% CI		−0.8, 1.3	−0.4, 1.7	−1.3, 0.8	−0.7, 1.4
P value		.637	.198	.696	.518
Change from baseline in total PAQLQ(S) score, week 12					
n	52	61	71	57	64
LS mean change (SE)	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	1.0 (0.1)	1.1 (0.1)
Treatment vs placebo					
Difference		0.1	0.1	0.2	0.3
95% CI		−0.2, 0.4	−0.1, 0.4	−0.1, 0.5	0.0, 0.6
P value		.423	.349	.112	.036

LS, least squares.

Pharmacokinetics

Concentration-time data for FF from this study were merged with data from 2 previous studies in children aged 5-11 years with FF 100 μg once daily alone[14,15] or in combination with VI.[15] The resulting population PK dataset comprised 306 children. The predicted mean FF maximum concentration (95% CI) for children in the current study was 5.7 pg/mL (5.1-6.4), 11.6 pg/mL (10.6-12.7), and 22.4 pg/mL (19.9-25.3) for the FF 25 μg, FF 50 μg, and FF 100 μg groups, respectively. The predicted mean FF $AUC_{0\text{-}24}$ (95% CI) for children in the current study was 47 pg.h/mL (41-54), 98 pg.h/mL (87-110), and 196 pg.h/mL (167-230) for the FF 25 μg, FF 50 μg, and FF 100 μg groups, respectively.

Safety

The incidence of AEs was slightly greater in the FF groups (32%-36%) than in the placebo group (29%), but there was no apparent dose-ordering (**Table IV**). The most frequent AE was cough (**Table IV**). Four children experienced 4 AEs considered to be related to study treatment. These were pharyngitis and cough, reported for 1 child each in the placebo group; 1 child with cough in the FF 25 μg group; and 1 child with stomatitis in the FF 100 μg group (**Table IV**). Two on-treatment nonfatal serious AEs were reported; 1 event of syncope (FF 50 μg group) and 1 event of hepatitis A (FF 100 μg group) (**Table IV**). Neither was considered to be related to study treatment. Asthma exacerbations were experienced by 12 children

Table IV. Most frequent (≥3% in any treatment group) on-treatment AEs by preferred term (ITT population)

	Number (%) subjects				
AEs	Placebo, n = 119	FF 25 OD, n = 118	FF 50 OD, n = 120	FF 100 OD, n = 118	FP 100 BD, n = 118
Children with any AE	35 (29)	43 (36)	38 (32)	39 (33)	36 (31)
Children with most frequent events	28 (24)	30 (25)	25 (21)	31 (26)	26 (22)
Cough	6 (5)	7 (6)	1 (<1)	10 (8)	5 (4)
Nasopharyngitis	4 (3)	9 (8)	4 (3)	3 (3)	4 (3)
Rhinorrhea	2 (2)	6 (5)	1 (<1)	6 (5)	5 (4)
Pharyngitis	4 (3)	2 (2)	7 (6)	5 (4)	1 (<1)
Headache	2 (2)	2 (2)	2 (2)	7 (6)	4 (3)
Oropharyngeal pain	1 (<1)	6 (5)	2 (2)	2 (2)	4 (3)
Bronchitis	1 (<1)	2 (2)	4 (3)	2 (2)	2 (2)
Upper respiratory tract infection	3 (3)	1 (<1)	0 (0)	4 (3)	3 (3)
Pyrexia	0 (0)	4 (3)	1 (<1)	2 (2)	1 (<1)
Body temperature increased	0 (0)	3 (3)	0 (0)	0 (0)	4 (3)
Rhinitis	3 (3)	1 (<1)	1 (<1)	0 (0)	2 (2)
Tonsillitis	3 (3)	1 (<1)	2 (2)	1 (<1)	0 (0)
Viral infection	2 (2)	0 (0)	3 (3)	1 (<1)	1 (<1)
Dyspnea	3 (3)	0 (0)	0 (0)	1 (<1)	0 (0)
Respiratory tract infection	0 (0)	3 (3)	0 (0)	0 (0)	1 (<1)
Children with treatment-related AEs	2 (2)	1 (<1)	0	1 (<1)	0
Cough	1 (<1)	1 (<1)	0	0	0
Stomatitis	0	0	0	1 (<1)	0
Pharyngitis	1 (<1)	0	0	0	0
Children with treatment-related serious AEs	0	0	0	0	0
Children with nonfatal serious AEs					
Syncope	0	0	1 (<1)	0	0
Hepatitis A	0	0	0	1 (<1)	0

during the treatment period (7 [6%] children in the placebo group, 2 [2%] children in each of the FF 25 μg and FF 50 μg groups, and 1 [1%] in the FF 100 μg group). None of these children were hospitalized, but all were withdrawn from the study. Vital signs at baseline and changes from baseline at all recorded time points were similar between treatment groups.

In the UC population, 1 child had a 24-hour UC excretion at week 12 of 1054.4 nmol/24 hour (**Figure 3**; available at www.jpeds.com). The child had not received any additional glucocorticoids, and findings of the clinical examination of the child were unremarkable. As such, this value was considered an outlier because of technical error and not included in the primary analysis of 24-hour urinary excretion (**Figure 3** and **Table V**; **Table V** available at www.jpeds.com). The analyses with the outlier removed were not prespecified in the protocol and are reported as post hoc analyses. Adjusted ratio to baseline values for 24-hour UC excretion were 1.07 (n = 54) for placebo, 0.95-1.00 (n = 72-75) for the FF treatment groups, and 0.96 (n = 73) for the FP group. Treatment ratios to placebo were 0.89, 0.94, and 0.90, for the FF 25 μg, FF 50 μg, and FF 100 μg groups, respectively, and there were no statistical differences between any of the FF groups and placebo.

Laboratory assessments were within the normal range at screening and week 12 except for serum carbon dioxide content values, which were below the normal range for the majority of children across all treatment groups both at baseline and at week 12 (56%-72%).

Discussion

In this study, all active treatments (FF and FP) resulted in clinically and statistically significant improvements in the mean change from baseline in morning PEF compared with placebo; however, there was no apparent dose-ordering effect in the FF treatment groups. The doses of FF used in our study were based on data from a dose-ranging study in adults and adolescents[17] and a repeat-dose study in children.[14] The lack of dose-ordered response was consistent with the findings of other studies that assessed lung function response to ICS both in adult patients[18] and children.[19]

Although spirometry is a robust measure of lung function and can be performed in young children given encouragement and suitable conditions, in clinical practice this requires experienced specialist staff and cooperation from both the parent and child. Therefore, PEF was chosen as the primary endpoint because it is easier for children to perform than FEV_1.[20] Compared with other studies of ICS in children, the treatment differences in mean change from baseline in morning PEF reported here (12.5-19.5 L/min) show a similar level of improvement. For example, in a randomized trial of FP 50 μg and FP 100 μg in children aged 4-11 years, the mean change from baseline in morning PEF ranged from 48 L/min to 51 L/min compared with 22 L/min in the placebo group ($P \leq .05$).[21] Furthermore, in a randomized trial in children, the approved ICS beclomethasone dipropionate 160 μg/d resulted in a mean change from baseline in morning PEF of 30.8 L/min compared with 9.2 L/min in the placebo group ($P \leq .01$).[22]

The PEF results in our study demonstrate a positive treatment effect on lung function; however, the effect on FEV_1 is less clear. Although FF treatment resulted in an increase from baseline of between 150 mL and 254 mL at week 12, this was not significantly different from placebo for the 50 μg and 100 μg FF groups, mainly because of the pronounced placebo response. The increase in FEV_1 vs placebo was notably greater for the FF 25 μg treatment than the other FF doses and the FP 100 μg treatment. The reason for this is unclear, but because all 3 FF doses were effective on PEF, it is possible this observation is due in part to the difficulty in obtaining good quality spirometry in children. This is supported by the post hoc analyses of FEV_1 by age and acceptable FEV_1 measurements.

Secondary endpoints generally supported the primary endpoint result. In particular, the assessed patient-reported outcomes suggested a favorable effect of FF treatment, with an additional 0.7 and 0.9 rescue-free days per week observed for FF 50 μg and FF 100 μg, respectively. Interestingly however, statistical significance was not reached for the change from baseline in percentage of symptom-free days over weeks 1-12. The relationship between asthma control and symptoms in children is complicated because better control often leads to an increase in physical activity.[23]

A greater proportion of children withdrew from the study because of a lack of efficacy in the placebo group (35%) than in the FF groups (14%-19%) and the FP group (16%). This finding suggests that, despite the modest effects on lung function, FF was a beneficial treatment in the current study. Withdrawal rates for children receiving active treatment were similar to those observed in previous studies of children with asthma receiving ICS treatment (10%-30%).[24]

In the PK analysis, a large number of FF plasma samples were below the lower limit of quantification; therefore, data from the current study were merged with historical data from FF 100 μg pediatric studies. Systemic exposure of FF over the dose range assessed was generally low and approximately dose-proportional. Peak FF plasma concentrations from the current study (22.4 pg/mL) were similar to those values estimated in children receiving FF 100 μg (24.68 pg/mL)[14] or FF/VI 100/25 μg (20.7 pg/mL).[15] The rate and extent of exposure of FF at steady state in children in the current study following FF 100 μg also was consistent with that observed in adults and adolescents ($AUC_{(0-24)}$ of 196 pg.h/mL compared with 181 pg.h/mL, respectively).[25]

Once-daily treatment with FF was well tolerated at all doses. The overall incidence of AEs was similar across the FF treatment groups and the FP 100 μg group and was slightly greater for the FF and FP groups compared with placebo. The most common on-treatment AEs in all treatment groups (cough, nasopharyngitis, and rhinorrhea) are commonly observed in an asthmatic population. No clinically significant UC suppression was observed at week 12.

Some important features of the study include the large number of children recruited, the opportunity to assess 3 doses of FF, and the inclusion of a positive (FP) and negative (placebo) control; however, the difficulty in recruiting children with poorly controlled asthma, and in coaching good-quality spirometry

techniques to children, combined with the large number of withdrawals, may have contributed to the smaller-than-expected improvement in PEF and FEV_1 observed. In addition, variability in PEF measurements has been reported[26-28] and may have resulted in under- or overestimations in the detected treatment benefit in this study. Finally, it is not possible to determine whether once-daily FF is equivalent to the standard twice-daily FP. To determine this, a noninferiority study should be conducted.

All 3 doses of FF investigated in this study (25 μg, 50 μg, and 100 μg) improved the change from baseline in daily predose morning PEF in children aged 5-11 years. Notable improvements over placebo were seen for all FF treatments in the percentage of rescue-free days. All treatments were well tolerated, and no new safety concerns were identified during the study, although the overall incidence of AEs was slightly greater in active treatment groups compared with placebo. The results of this study suggest that FF is an effective treatment for children with inadequately controlled asthma. ■

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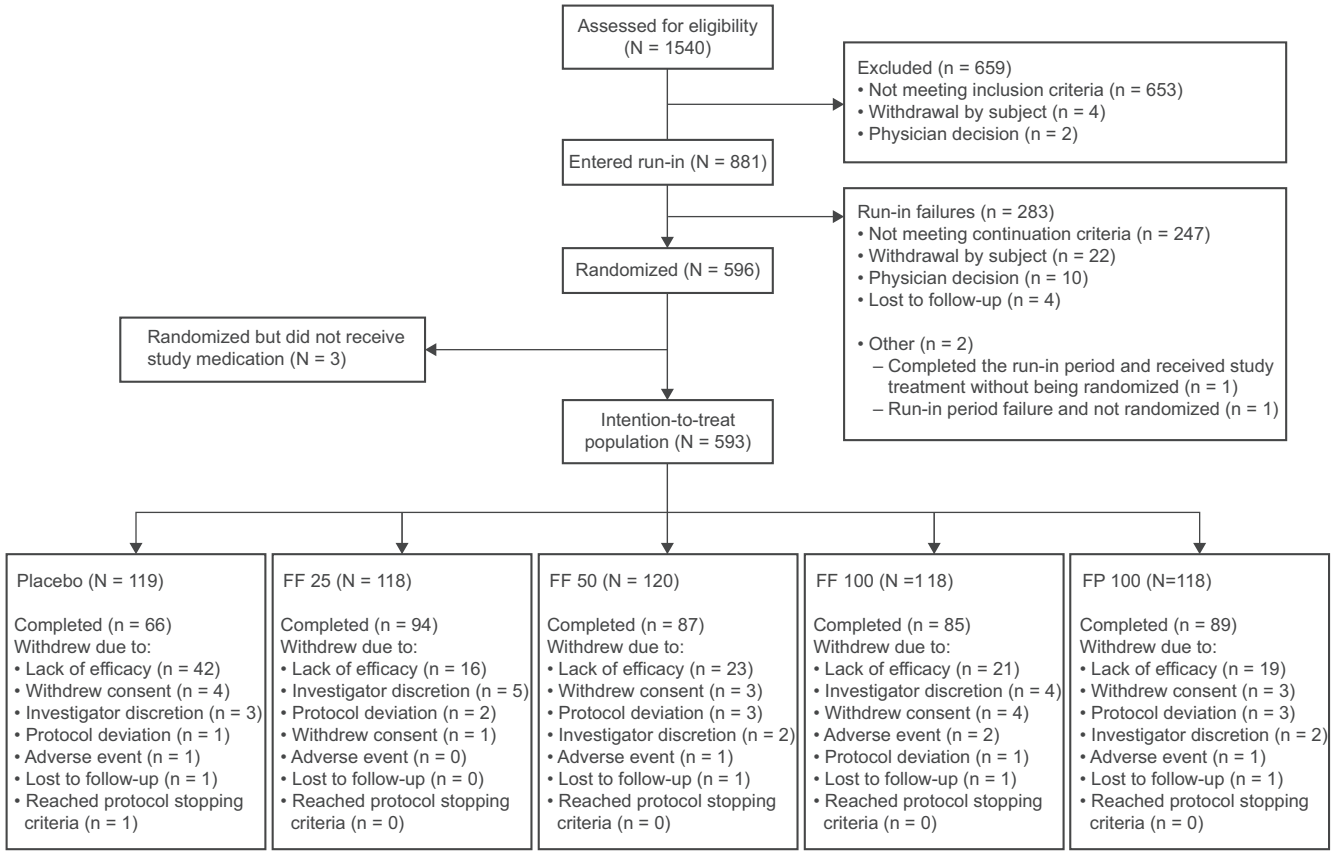

Figure 1. CONSORT flow diagram. Lack of efficacy was defined as experiencing an exacerbation, worsening asthma, or at the investigator's discretion.

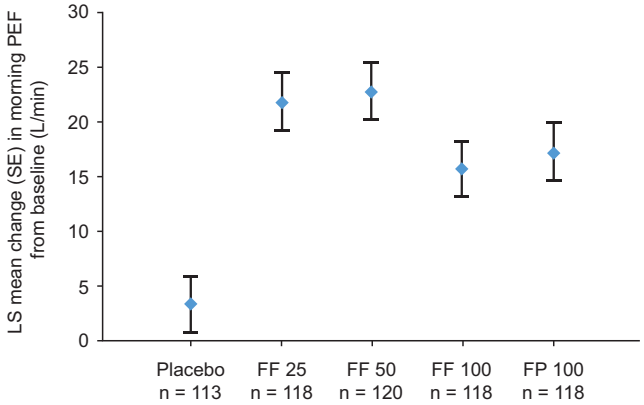

Figure 2. Mean changes from baseline in morning PEF averaged over weeks 1-12 (L/min). Error bars represent SE. *LS*, least squares.

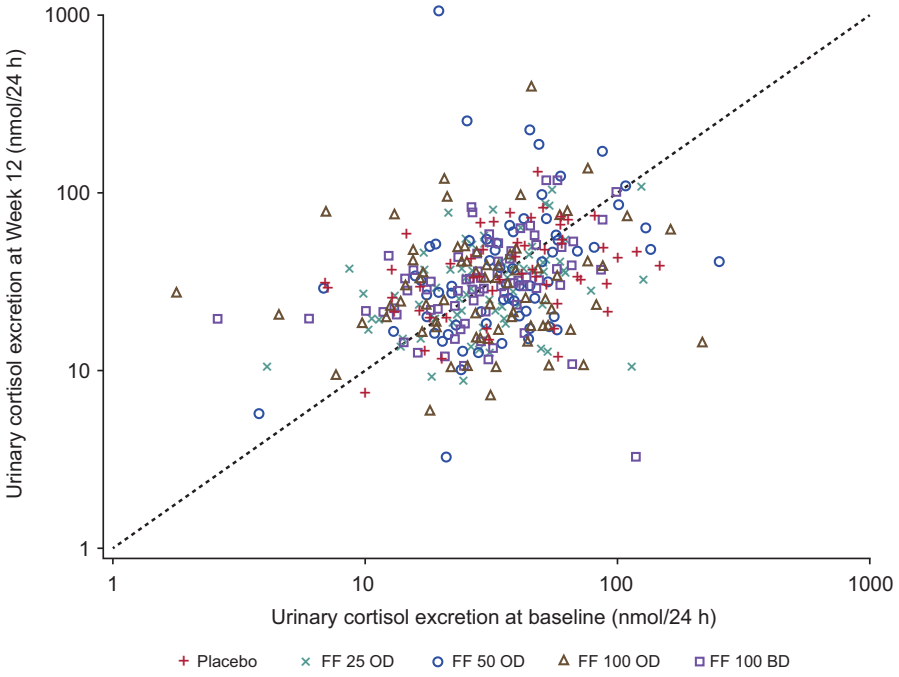

Figure 3. UC excretion (24-hour) at baseline and at week 12 (UC population). *BD*, twice daily; *OD*, once daily.

Table III. Post hoc analysis of change from baseline in evening trough FEV_1, week 12 (LOCF)

	Placebo, n = 119	FF 25 OD, n = 118	FF 50 OD, n = 120	FF 100 OD, n = 118	FP 100 BD, n = 118
Acceptable baseline and last on-treatment FEV_1					
n	65	63	70	56	71
LS mean, L	1.535	1.680	1.608	1.626	1.698
LS mean change, mL (SE)	79 (31)	224 (32)	152 (30)	170 (34)	242 (30)
Treatment vs placebo					
Difference, mL		145	73	91	163
95% CI		57, 223	−14, 159	1, 181	77, 249
By age subgroup					
5-7 y					
n	38	35	27	41	42
LS mean, L	1.249	1.218	1.188	1.191	1.206
LS mean change, mL (SE)	163 (37)	132 (39)	102 (44)	105 (37)	120 (34)
Treatment vs placebo					
Difference, mL		−31	−61	−58	−43
95% CI		−137, 75	−174, 53	−161, 46	−142, 56
8-11 y					
n	64	61	85	55	60
LS mean, L	1.671	1.883	1.755	1.763	1.811
LS mean change, mL (SE)	102 (36)	313 (37)	186 (31)	194 (39)	241 (37)
Treatment vs placebo					
Difference, mL		211	84	92	140
95% CI		110, 313	−10, 177	−12, 195	38, 241

LS, least squares; *BD*, twice daily; *OD*, once daily.

Table V. UC excretion at week 12 (UC population)*

	Placebo, n = 54	FF 25 OD, n = 75	FF 50 OD, n = 73	FF 100 OD, n = 73	FP 100 BD, n = 73
n	54	75	73	73	73
LS geometric mean	34.19	30.46	34.00	30.74	30.70
LS ratio to baseline	1.07	0.95	1.06	0.96	0.96
Treatment vs placebo					
Ratio		0.89	0.99	0.90	0.90
95% CI		0.70, 1.13	0.78, 1.26	0.71, 1.14	0.71, 1.14
P value		.340	.963	.377	.369

*Includes outlier.