Effect of fluticasone propionate/formoterol and fluticasone furoate/vilanterol on adolescents with chronic bronchial obstruction

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Background: The combination of an inhaled corticosteroid (ICS) and long-acting β-agonist (LABA) (ICS/LABA) has shown superiority in improving lung function (FEV_1) compared with an ICS alone. The clinical effect of a ICS/LABA combination depends on the fine-particle fraction and the pulmonary deposition.

Objective: We sought to compare the efficacy of 2 combinations of an ICS and LABA, namely, fluticasone propionate (FP) and formoterol (FORM) (FP/FORM) and fluticasone furoate (FF) and vilanterol (VI) (FF/VI), in asthmatic adolescents with chronic bronchial obstruction.

Methods: FP/FORM (125 μg/5 μg, 2 doses twice daily via the k-haler [Mundipharma, Cambridge, UK]) and FF/VI (92 μg/22 μg, once daily via the Ellipta inhaler [GlaxoSmithKline]) were administered to adolescents aged 12 to 17 years who required regular antiasthmatic medication and had a ratio of FEV_1 to forced vital capacity (FEV_1/FVC) less than –1.65 SD in a 2-sequence, 16-week crossover trial. The primary efficacy end point was change in FEV_1 compared with baseline. Secondary end points were FEV_1/FVC ratio, maximal expiratory flow at 50% of the FVC, impulse oscillometry indices respiratory resistance at 5 Hz (R5), difference between R5 and respiratory resistance at 20 Hz (R20), area of reactance, and Asthma Control Test score.

Results: Both ICS/LABA combinations resulted in a significant improvement in FEV_1 and maximal expiratory flow at 50% of the FVC *z* scores without any significant difference between FP/FORM and FF/VI, with 40% of patients with either treatment achieving a normal prebronchodilator FEV_1/FVC *z* score. Neither area of reactance nor difference between R5 and R20 improved significantly with either treatment.

Conclusion: Both ICS/LABA combinations demonstrated significant improvements in FEV_1 *z* score. More than one-third of the asthmatic adolescents with prolonged bronchial obstruction achieved a normal prebronchodilator FEV_1/FVC ratio. (J Allergy Clin Immunol Global 2024;3:100268.)

Key words: *Adolescent, asthma, fluticasone furoate, fluticasone propionate, formoterol, inhaled corticosteroid, ICS, long-acting β-agonist, LABA, lung function, vilanterol*

Asthma is a chronic heterogenous disease characterized by reversible airway obstruction, airway inflammation, and bronchial hyperresponsiveness.[1] Coughing, wheezing, and difficulty in breathing are commonly associated with asthma.[1] Controlling symptoms, maintaining normal activity level, and reducing the risk of future exacerbations and persistent airflow limitation are the long-term goals of asthma management.[1] In cases in which asthma control with an inhaled corticosteroid (ICS) alone is insufficient, a long-acting β-agonist (LABA) is commonly added to the therapy.[1]

When evaluating asthma control, both symptom control and risk of future adverse outcomes (including exacerbations and progressive loss of lung function) should be considered.[1] FEV_1 and the ratio of FEV_1 to forced vital capacity (FVC) (FEV_1/FVC) are primary measurements used to evaluate lung function.[1] Impaired FEV_1 and lower FEV_1/FVC values are associated with asthma exacerbations in the future,[2] which in turn predict decreased lung function later.[3] FEV_1 achieves its highest level in late adolescence or early adulthood.[4] FEV_1 growth and possible decline in childhood are crucial for lung function later in life; reduced growth of lung function with limited highest level of FEV_1 or abnormally early decline of FEV_1 predisposes individuals to development of chronic airflow obstruction.[5] In the Childhood Asthma Management Program (CAMP) study, the proportion of asthmatic patients with a prebronchodilator FEV_1/FVC value less than the lower limit of normal increased significantly from preschool age to early adulthood.[6] In the Children, Allergy, Milieu, Stockholm, Epidemiology (BAMSE) birth cohort study, all asthma phenotypes were associated with a lower postbronchodilator FEV_1/FVC value at age 24 years.[7] In the CAMP study, 11% of the participants with mild-to-moderate persistent asthma met the diagnostic criteria[8] for chronic obstructive pulmonary disease (COPD) (which is defined by postbronchodilator FEV_1/FVC value less than 0.7) before age 30 years.[4]

Repeated asthma exacerbations accelerate lung function decline, particularly in patients younger than 40 years.[3] ICSs have been demonstrated to control asthma symptoms, improve lung function, and reduce asthma exacerbations, especially in patients with eosinophilic asthma.[9] Uncontrolled asthma may affect everyday life owing to symptoms and exacerbations.

In a recent systematic review and network meta-analysis, a low-dose ICS/LABA combination showed superiority in improving lung function (as measured by FEV_1 value) compared with other asthma treatments.[10] An ICS/LABA combination with

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Abbreviations used

ACT: Asthma Control Test
AX: Area of reactance
BAMSE: Children, Allergy, Milieu, Stockholm, Epidemiology
CAMP: Childhood Asthma Management Program
COPD: Chronic obstructive pulmonary disease
FEV_1/FVC: Ratio of FEV_1 to forced vital capacity
FF: Fluticasone furoate
FF/VI: Fluticasone furoate and vilanterol
FORM: Formoterol
FP: Fluticasone propionate
FP/FORM: Fluticasone propionate and formoterol
FPF: Fine-particle fraction (ie, proportion of dose containing particles <5 μm in aerodynamic diameter)
FVC: Forced vital capacity
ICS: Inhaled corticosteroid
LABA: Long-acting β-agonist
MEF_{50}: Maximal expiratory flow at 50% of the forced vital capacity
MMAD: Mass median aerodynamic diameter
R5: Respiratory resistance at 5 Hz
R20: Respiratory resistance at 20 Hz
VI: Vilanterol

a high pulmonary deposition has the potential to improve treatment response in asthma. Fluticasone propionate (FP) plus formoterol (FORM) (FP/FORM) and fluticasone furoate (FF) plus vilanterol (VI) (FF/VI) are combinations of an ICS and a LABA (ICS/LABA).[11,12] The combination FF/VI delivered through the Ellipta inhaler (GlaxoSmithKline, Brentford, UK) has a smaller fine-particle fraction (FPF), [13] which means a lower proportion of the dose containing particles smaller than 5 μm in aerodynamic diameter and lower pulmonary deposition[14] than with FP/FORM administered through the k-haler (Mundipharma, Cambridge, UK).[15] However, the impact of these differences on treatment response between these 2 ICS/LABA combinations has not been determined. The FPF has a considerable effect on total lung deposition. Despite the nearly similar particle aerodynamic size in FP/FORM and FF/VI, FP/FORM, with its higher FPF and pulmonary deposition, was expected to improve lung function more effectively than FF/VI was. We aimed to investigate whether chronic bronchial obstruction in adolescents with asthma could be reversed by using a potentially highly efficacious combination of ICS/LABA. This study compared the efficacy of FP/FORM (125 μg/5 μg, 2 doses twice daily delivered through the k-haler) with that of FF/VI (92 μg/22 μg, once daily delivered through the Ellipta inhaler) in asthmatic adolescents with chronic bronchial obstruction.

METHODS

Patients

Altogether, 47 adolescents aged 12 to 17 years with chronic bronchial obstruction fulfilling the following characteristics entered the randomized trial: (1) age 12 to 17 years, (2) doctor-diagnosed asthma with regular antiasthmatic medication required for at least 3 months (except for Relvar Ellipta and Flutiform k-haler), (4) insufficient asthma control, (5) FEV_1/FVC z score is below the lower limit of normal (< –1.65 SD),[16] and (6) sufficient skills to communicate in Finnish. Exclusion criteria were pregnancy, lactation, pulmonary disease other than asthma, active and uncontrolled cardiovascular or other systemic disease, and malignancy. A total of 44 patients were included in the final analyses. The study was approved by the center's institutional review board. Written informed consent was signed by the patient and the parent (for patients aged <15 years), according to the Finnish legislation.[17]

Study protocol

This 16-week randomized 2-sequence crossover study was conducted between March 2020 and May 2022 at the Skin and Allergy Hospital, Helsinki University Hospital, Finland. The study was designed to compare the effects of FP/FORM in the k-haler[11] versus FF/VI in the Ellipta inhaler[12] on lung function of adolescents with asthma and prolonged obstructive lung function. The FP/FORM used was Flutiform delivered through the k-haler (Mundipharma; 125 μg/5 μg per dose) administered as 2 doses twice daily. The FF/VI used was Relvar delivered through the Ellipta inhaler (GlaxoSmithKline; 92 μg/22 μg per dose) administered once daily. Before the first treatment period, patients used their prior asthma control therapy (Table I). Patients were randomized by the biostatistician before the intervention to treatment arm 1 (starting with FP/FORM) or treatment arm 2 (starting with FF/VI). The study consisted of a screening visit (visit 0), an enrollment/randomization visit (visit 1), and 2 follow-up visits (visits 2 and 3). The treatment visits were separated by approximately 8 weeks (+1 week) (Fig 1). The patients received the study medications for free. Nonasthma medications were permitted as used before the study. The patients were asked to call the investigator immediately for possible adverse effects.

Procedures

Background data, including sex, height, parental history of asthma and smoking, and asthma control therapy used before the study, were collected. Laboratory tests, including measurement of complete blood count; levels of specific IgE to birch, ragweed, timothy, horse, cat, dog, *Dermatophagoides pteronyssinus,* and *Cladosporium herbarum*; and total IgE level, were performed once during the study. Serum IgE antibody concentrations were measured with ImmunoCAP technology (Thermo FisherScientific, Uppsala, Sweden). A serum IgE value greater than 0.35 kU/L was considered a positive reaction.

Outcome measures

The following outcomes were determined at baseline and each follow-up visit. Spirometry maneuvers and oscillometry were measured by the study nurse with a Masterscreen Pneumo spirometer (Jaeger GmbH, Würzburg, Germany) in accordance to American Thoracic Society/European Respiratory Society guidelines.[18,19] For spirometry, we documented prebronchodilator and postbronchodilator FEV_1, FVC, and maximal expiratory flow at 50% of the FVC (MEF_{50}) in absolute values and z scores,[16,20] as well as FEV_1/FVC value. Obstruction was defined as a z score less than –1.65 in FEV_1/FVC ratio. If the patient had symptoms of an acute respiratory infection, lung function tests were rescheduled 1 week later. The study medications were taken normally before the follow-up visits. Short-acting β-agonists were not administered for 12 hours before the lung function tests.

TABLE I. Baseline characteristics

Characteristic (n = 44)	Total	Treatment arm 1	Treatment arm 2	*P* value indicating difference between treatment arms
Age (y), median (IQR)	14 (13-16)	14 (13-15)	15 (13-16)	.395*
Height (cm), median (IQR)	165 (159-169)	166 (159-169)	164 (158-169)	.906*
Male, no. (%)	26 (59)	15 (68)	11 (50)	.220†
≥1 aeroallergen-specific IgE-positive result, no. (%)	35 (80)	17 (77)	18 (82)	1.000†
Total eosinophils				
Total eosinophils, %, (IQR)	2.5 (2-6)	2.0 (2-6)	3.0 (2-6)	.783*
Total eosinophils E9/L, count (IQR)	0.16 (0.09-0.32)	0.14 (0.09-0.33)	0.17 (0.10-0.31)	.672*
IgE concentration (kU/L), median (IQR)	336 (116-700)	202 (67-673)	447 (207-741)	.159*
Parental asthma, no. (%)	23 (52)	9 (41)	14 (64)	.131†
Parental smoking, no. (%)				
Mother at the moment, no. (%)	8 (18)	4 (18)	4 (18)	1.000†
Father at the moment (n = 41), no. (%)	5 (12)	2 (10)	3 (15)	.663†
Antiasthmatic treatment, no. (%)				
ICS	9 (20)	4 (18)	5 (23)	1.000†
ICS/LABA	14 (32)	7 (32)	7 (32)	1.000†
ICS + montelukast	3 (7)	2 (9)	1 (5)	1.000†
ICS/LABA + montelukast	16 (36)	8 (36)	8 (36)	1.000†
ICS/LABA + montelukast + tiotropium	2 (5)	1 (5)	1 (5)	1.000†
Asthma Control Test score, median (IQR)	22 (21-25)	22 (21-24)	23.5 (21-25)	.396*
Baseline lung function				
FEV_1 *z* score (SD), mean (95% CI)	–1.41 (–1.68 to –1.13)	–1.68 (–2.10 to –1.27)	–1.13 (–1.49 to –0.78)	**.043**‡
FEV_1 abs (L), median (IQR)	2.89 (2.57-3.39)	2.83 (2.40-3.31)	2.95 (2.68-3.52)	.291*
FEV_1/FVC *z* score (SD), median (IQR)	–2.37 (–2.97 to –1.93)	–2.31 (–2.87 to –1.89)	–2.43 (–3.34 to –1.95)	.511*
MEF_{50} *z* score (SD), mean (95% CI)	–2.31 (–2.52 to –2.10)	–2.41 (–2.72 to –2.09)	–2.21 (–2.52 to –1.91)	.358*
R5 abs kPa/(L/s), median (IQR)	0.40 (0.32-0.49)	0.43 (0.38-0.50)	0.37 (0.30-0.46)	.188*
R5 – R20 abs kPa/(L/s), median (IQR)	0.06 (0.02-0.13)	0.12 (0.03-0.13)	0.04 (0.00-0.09)	**.036***
AX abs (kPa/L), median (IQR)	0.40 (0.20-1.02)	0.77 (0.28-1.12)	0.33 (0.18-0.65)	.100*
Postbronchodilator FEV_1 *z* score, (SD), mean (95% CI)	–0.91 (–1.20 to –0.62)	–1.15 (–1.58 to –0.71)	–0.67 (–1.07 to –0.28)	.101‡
Postbronchodilator FEV_1/FVC *z* score (SD), median (IQR)	–1.73 (–2.34 to –1.26)	–1.71 (–2.00 to –1.21)	–1.89 (–2.72 to –1.35)	.260*

Boldface indicates statistical significance.
abs, Absolute; *IQR*, interquartile range.
*Independent samples Mann-Whitney *U* test.
†Chi-square test.
‡Independent samples *t* test.

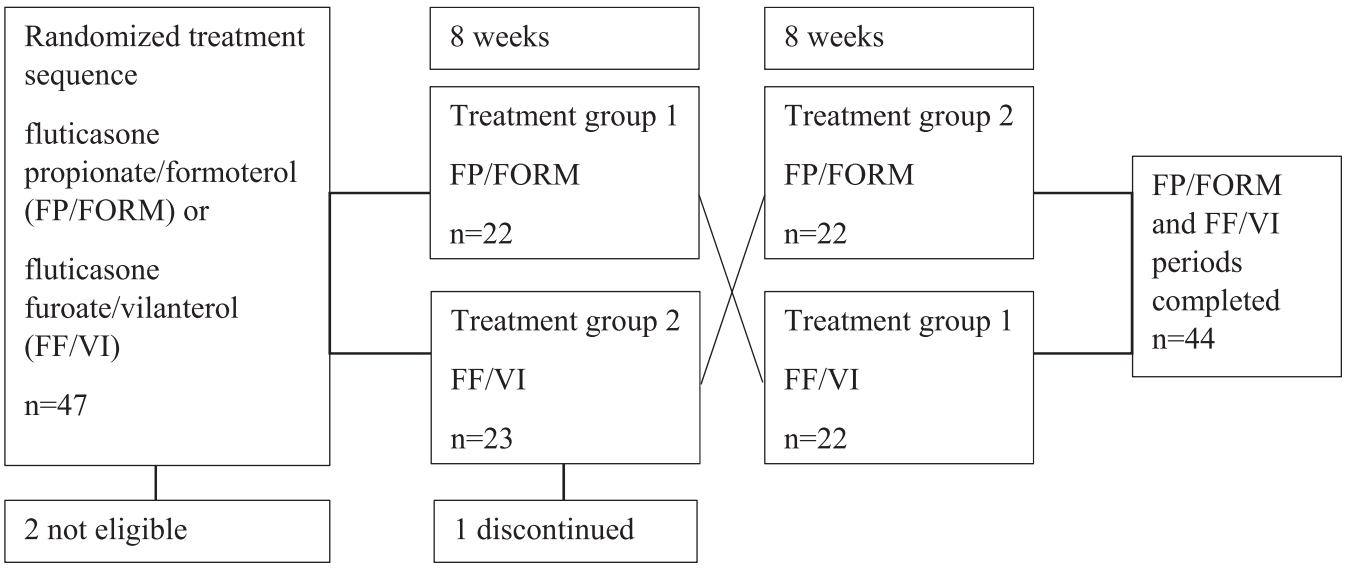

FIG 1. Study flowchart.

In impulse oscillometry, we measured respiratory resistance at 5 Hz (R5), the frequency dependence of resistance in terms of the difference between R5 and respiratory resistance at 20 Hz (R20), and area of reactance (AX) in absolute values. Because both lung deposition and particle fraction are potentially important for treating small airway obstruction, we measured impulse oscillometry indices R5, difference between R5 and R20, and AX to assess the putative degree of obstruction in the small airways.[18] Impulse oscillometry was performed before spirometry by using at least 3 separate measurements. Postbronchodilator impulse oscillometry and spirometry were performed 10 minutes after inhalation of a total of 0.4 mg of salbutamol through a Vortex (PARI, Starnberg, Germany). The patient completed the Asthma Control Test[21] (ACT), with higher ACT scores indicating better asthma control (with well-controlled asthma defined as an ACT score > 19). The investigator interviewed the patient and performed the clinical examination. Thereafter, the study nurse provided education on the inhalation technique of the intervention treatment in order. Patients meeting all of the inclusion criteria and none of the exclusion criteria began their first intervention 2 days after visit 1 and used either FP/FORM delivered through the k-haler (125 μg/5 μg, 2 doses twice daily) or FF/VI delivered through the Ellipta inhaler (92 μg/22 μg, once daily) according to the randomization. The patients took each study medication for 8 weeks (+1 week) until the follow-up visit, with the other intervention beginning 2 days after visit 2 in a crossover arrangement.

Efficacy evaluations

The primary study objective was to investigate the change in FEV_1 between the 2 study formulations with FP/FORM delivered through the k-haler and FF/VI delivered through the Ellipta inhaler compared with baseline. The main secondary study objectives were to compare the efficacy of the study medications in terms of change in the spirometry measurements FEV_1/FVC, MEF_{50}, impulse oscillometry indices R5, difference between R5 and R20, and AX, and results of the ACT.[21] The safety end points included adverse effects and discontinuations.

Data analysis

The target sample size was 70 randomized adolescent asthmatics in this 2 × 2 crossover design. According to the calculations, a sample size of 44 provided 90% statistical power with a 2-sided, .05-significance level test. Previous studies with a similar design have shown that the first 4 weeks of the latter treatment period is sufficient time for study medication washout; therefore, comparison of the change from baseline to the measured indices after 8 weeks of treatment was considered justified regardless of the randomized sequence.[22]

Data normality was evaluated by using the Shapiro-Wilkins test. For continuous data, *t* tests or Mann-Whitney *U*-tests were used for comparing the groups. For categoric data, the chi-square tests, Fisher exact tests, or Mann-Whitney *U*-tests were used. For comparisons between different time points, the related-samples Friedman 2-way ANOVA by ranks and pairwise comparisons with 2-sided tests, adjusted by Bonferroni correction for multiple tests, was used for continuous data. For comparisons in the crossover setup, paired *t*-tests or related-samples Wilcoxon signed-rank tests were used. *P* values less than .05 were considered significant. Analyses were performed using IBM SPSS software, version 25 (IBM Corp, Armonk, NY).

TABLE II. Proportion of prebronchodilator and postbronchodilator bronchial obstruction (n = 44)

Bronchial obstruction level before and after trial	Patients, no. (%)
Baseline prebronchodilator FEV_1/FVC ratio less than –1.65 SD	44 (100)
After-trial prebronchodilator FEV_1/FVC ratio less than –1.65 SD	27 (61)
After-trial prebronchodilator FEV_1/FVC ratio greater than or equal to –1.65 SD	17 (39)
Baseline postbronchodilator FEV_1/FVC ratio less than –1.65 SD	25 (57)
After-trial postbronchodilator FEV_1/FVC ratio less than –1.65 SD	26 (59)
After-trial postbronchodilator FEV_1/FVC ratio greater than or equal to –1.65 SD	18 (41)

Ethics

The Helsinki University Hospital ethics committee approved the study (approval no. HUS/3461/2019; January 22, 2020). Each participant provided signed informed consent before participating in the study. For participants younger than 15 years, 1 of the participant's parents also provided signed informed consent, according to the Finnish legislation.[17] The study was registered at The Helsinki University Hospital (registration no. HUS/3371/2019, March 3, 2020, and EudraCT identifier 2019-003864-27) and conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

RESULTS

Study cohort

A total of 47 adolescent patients with asthma participated in the study. Three patients were excluded from the analysis owing to dropout (n = 1) or after screening at visit 1 because of a spontaneously improved spirometry result (FEV_1/FVC *z* score greater than –1.65; n = 2).

Altogether, 44 patients completed this randomized crossover study. Baseline characteristics of the patients are presented in Table I. Most of the patients were male (59%); their median age was 14 years (range 12-17 years). In all, 80% of patients were sensitized to at least 1 aeroallergen, defined as an aeroallergen-specific IgE level greater than 0.35 kU/L. Half of the patients had at least 1 parent with a history of asthma. At baseline, 9 patients (20%) were taking an ICS; 14 (32%) were taking an ICS/LABA combination; 3 (7%) were taking an ICS plus montelukast; 16 (36%) were taking an ICS/LABA combination plus montelukast; and 2 (5%) were taking a combination of ICS/LABA, montelukast, and tiotropium. The median ACT score was 22 (range 11-25) at baseline. At baseline, 3 patients (7%) reported that they had smoked at some point in the past; no significant difference between arms was observed. At baseline, no significant differences between the treatment arms in terms of age, sex, height, IgE or eosinophil level, family history of asthma or smoking, ACT score, or asthma control treatment before the study were observed. Participant enrollment across seasons was also similar

TABLE III. Outcome variable responses to FP/FORM and FF/VI and differences between treatments

	Effects			Difference	
Outcome variable	**Baseline**	**After FP/FORM**	**After FF/VI**	**Difference between FP/FORM and FF/VI**	***P* value**
FEV_1 *z* score (SD), mean (95% CI) [min; max]	–1.41 (–1.68 to –1.13) [–3.85; 0.74]	–0.97 (–1.27 to –0.67) [–2.85; 1.49]	–0.94 (–1.21 to –0.68) [–2.48; 0.92]	0.03 (–0.31 to 0.22) [–1.06; 1.76]	.717*
FEV_1 abs (L), median (IQR) [min; max]	2.89 (2.57-3.39) [1.81; 5.08]	3.11 (2.69-3.74) [1.99; 5.38]	3.10 (2.74-3.72) [2.18; 5.28]	–0.01 (–0.06 to 0.04) [–0.35; 0.54]	.655†
FEV_1/FVC *z* score (SD), median (IQR) [min; max]	–2.37 (–2.97 to –1.93) [–4.15; –1.68]	–2.17 (–2.72 to –1.64) [–4.35; –0.88]	–2.10 (–2.62 to –1.56) [–4.07; –0.84]	–0.13 (–0.31 to 0.05)[–1.18; 1.77]	.165*
MEF_{50} *z* score (SD), mean (95% CI) [min; max]	–2.31 (–2.52 to –2.10) [–3.82; –0.53]	–1.81 (–2.07 to –1.56) [–3.40; –0.26]	–1.81 (–2.02 to –1.60) [–3.38; –0.17]	–0.02 (–0.19 to 0.15) [–1.02; 1.72]	.794*
R5 abs kPa/(L/s), median (IQR) [min; max]	0.40 (0.32-0.49) [0.24; 0.61]	0.37 (0.32-0.42) [0.17; 0.60]	0.37 (0.31-0.43) [0.22; 0.66]	0.00 (–0.03 to 0.02) [–0.25; 0.11]	.934†
R5 – R20 abs kPa/(L/s), median (IQR) [min; max]	0.06 (0.02-0.13) [0.00; 0.23]	0.05 (0.01-0.10) [0.00; 0.23]	0.06 (0.01-0.10) [0.00; 0.21]	0.00 (–0.01 to 0.02) [–0.14; 0.08]	.714†
AX abs (kPa/L), median (IQR) [min; max]	0.40 (0.20-1.02) [0.08; 2.01]	0.39 (0.19-0.73) [0.06; 1.56]	0.36 (0.21-0.70) [0.05; 1.68]	0.02 (–0.12 to 0.11) [–0.93; 0.52]	.905†
ACT score, median (IQR) [min; max]	22 (21-25) [11; 25]	23 (21-24) [11; 25]	23 (22-25) [15; 25]	–0.50 (–2.0 to 1.0) [–9; 5]	.069†
Postbronchodilator FEV_1 *z* score (SD), mean (95% CI) [min; max]	–0.91 (–1.20 to –0.62) [–3.70; 0.77]	–0.75 (–1.07 to –0.44) [–2.99; 1.75]	–0.85 (–1.12 to –0.58) [–2.49; 1.51]	0.09 (–0.05 to 0.24) [–1.18; 1.02]	.207*
Postbronchodilator FEV_1/FVC *z* score (SD), median (IQR) [min; max]	–1.73 (–2.36 to –1.26) [–3.74; –0.87]	–1.81 (–2.22 to –1.29) [–3.83; –0.55]	–1.99 (–2.36 to –1.52) [–3.96; 0.24]	0.05 (–0.09 to 0.19) [–0.93; 1.12]	.452*

abs, Absolute; *IQR*, interquartile range.
*Paired samples *t* test.
†Related samples Wilcoxon signed rank test.

for both treatment groups; no seasonal differences between the 2 groups were observed.

Baseline lung function

The mean FEV_1 *z* score was –1.41 (95% CI = –1.68 to –1.13) at baseline (Table I). All patients were obstructed initially, with a median prebronchodilator FEV_1/FVC *z* score of –2.37 (interquartile range –2.97 to –1.93). In all, 25 patients (57%) had a postbronchodilator FEV_1/FVC *z* score less than the lower limit of normality[16] (Table II). Other baseline lung function measurements are shown in Table I.

Primary variable

A significant improvement in FEV_1 *z* score was observed during both interventions; no significant difference was observed between the 2 interventions (Tables III and IV and Fig 2). Absolute FEV_1 increased significantly during both interventions (Tables III and IV and Fig 2). The mean improvement in absolute FEV_1 compared with baseline was 0.19 liters for FP/FORM (95% CI = 0.11-0.26 liters) and 0.20 liters for FF/VI (95% CI = 0.13-0.27). There was no significant difference between FP/FORM and FF/VI ($P = .655$).

Secondary variables

A normal prebronchodilator FEV_1/FVC *z* score was achieved by 17 of 43 (40%) of the initially obstructed patients after at least 1 treatment with either combination; 1 patient was unable to perform spirometry at the second visit owing to facial trauma. FEV_1/FVC *z* score improved statistically with FF/VI ($P = .001$) but not with FP/FORM (Table IV). A total of 47% of patients achieved a normal postbronchodilator FEV_1/FVC *z* score at least after either treatment. MEF_{50} *z* score improved statistically significantly with both treatments, without any significant difference between them (Tables III and IV and Fig 3).

R5 improved during the study, without any significant difference between treatments (Tables III and IV and Fig 3). However, neither the impulse oscillometry parameters (difference between R5 and R20 or AX) nor the ACT showed significant improvement with either treatment (Table IV).

Safety

One patient did not complete the study owing to noncompliance. No severe adverse effects were observed during the study.

TABLE IV. Improvements during the treatments with FP/FORM and FF/VI

Outcome variable	Value	*P* value
FEV_1 *z* score (SD), median (IQR)		**<.001**
FP/FORM vs baseline	0.37 (0.07-0.78)	**<.001**
FF/VI vs baseline	0.36 (0.01-0.82)	**.002**
FP/FORM vs FF/VI	0.03 (–0.31 to 0.22)	1.000
FEV_1 abs (L), mean (95% CI)		**<.001**
FP/FORM vs baseline	0.19 (0.11-0.26)	**<.001**
FF/VI vs baseline	0.20 (0.13-0.27)	**<.001**
FP/FORM vs FF/VI	–0.01 (–0.06 to 0.04)	1.000
FEV_1/FVC *z* score (SD), mean (95% CI)		**.002**
FP/FORM vs baseline	0.33 (0.11-0.54)	.157
FF/VI vs baseline	0.44 (0.22-0.67)	**.001**
FP/FORM vs FF/VI	–0.13 (–0.31 to 0.05)	.317
MEF_{50} *z* score (SD), median (IQR)		**<.001**
FP/FORM vs baseline	0.43 (0.06-0.71)	**.002**
FF/VI vs baseline	0.30 (0.01-1.00)	**<.001**
FP/FORM vs FF/VI	–0.07 (–0.42 to 0.26)	1.000
R5 abs kPa/(L/s), median (IQR)		**.001**
FP/FORM vs baseline	–0.03 (–0.08 to 0.01)	**.014**
FF/VI vs baseline	–0.02 (–0.07 to 0.00)	**.002**
FP/FORM vs FF/VI	0.00 (–0.03 to 0.02)	1.000
R5 – R20 abs kPa/(L/s), median (IQR)		.071
FP/FORM vs baseline	–0.01 (–0.04 to 0.01)	
FF/VI vs baseline	–0.01 (–0.04 to 0.00)	
FP/FORM vs FF/VI	0.00 (–0.01 to 0.02)	
AX abs (kPa/L), median (IQR)		.082
FP/FORM vs baseline	–0.05 (–0.39 to 0.03)	
FF/VI vs baseline	–0.05 (–0.37 to 0.05)	
FP/FORM vs FF/VI	0.02 (–0.12 to 0.11)	
ACT score, median (IQR)		.096
FP/FORM vs baseline	0.00 (–1.00 to 0.75)	
FF/VI vs baseline	1.00 (–1.00 to 2.00)	
FP/FORM vs FF/VI	–0.50 (–2.00 to 1.00)	
Postbronchodilator FEV_1 *z* score (SD), median (IQR)		.266
FP/FORM vs baseline	0.07 (–0.24 to 0.40)	
FF/VI vs baseline	–0.10 (–0.34 to 0.26)	
FP/FORM vs FF/VI	0.19 (–0.10 to 0.41)	
Postbronchodilator FEV_1/FVC *z* score (SD), median (IQR)		.404
FP/FORM vs baseline	–0.10 (–0.35 to 0.24)	
FF/VI vs baseline	–0.18 (–0.54 to 0.29)	
FP/FORM vs FF/VI	0.08 (–0.21 to 0.32)	

Related samples Friedman 2-way ANOVA results by ranks and pairwise comparisons, which have been adjusted by Bonferroni correction for multiple tests. Significant differences are in boldface.
abs, Absolute; *ACT*, Asthma Control Test; *IQR*, interquartile range.

DISCUSSION

We observed an improvement of FEV_1 *z* score with both ICS/LABA combinations during this study. Surprisingly, more than one-third of the initially obstructed asthmatic adolescents (up to 40%) achieved a normal prebronchodilator FEV_1/FVC *z* score. Although there was no statistically significant difference in improvement in absolute FEV_1 between the combinations, FEV_1/FVC *z* score improved significantly versus baseline with FF/VI. Additionally, up to 47% of the patients achieved a normal postbronchodilator FEV_1/FVC *z* score, suggesting improvement in airway function. There seemed to be no significant impact on small airway function, as indicated by the nonsignificant changes in oscillometric indices AX and difference between R5 and R20 in the 2 interventions.

FEV_1 and FEV_1/FVC values are considered the criterion standards for assessing lung function and airflow limitation.[1] Impaired FEV_1 and FEV_1/FVC values are indicators of reduced lung function and predict declining lung function over time.[2,23] There is no criterion standard to assess small airway function specifically.[24] However, impulse oscillometry has been suggested as an additional instrument for monitoring lung function, especially that in the small airways.[24] Small airway dysfunction may precede reduction in FEV_1.[24] Resistance at 5 Hz, reflecting the function of the small airways, is better at predicting future

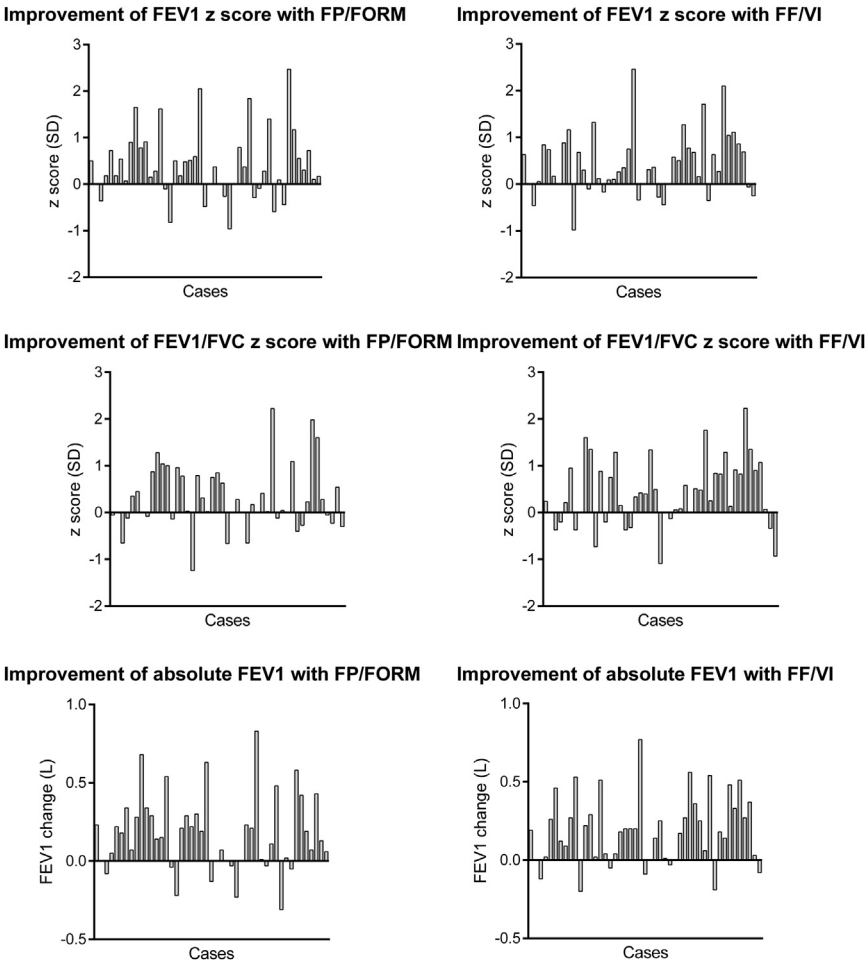

FIG 2. Improvement in lung function from baseline with FP/FORM or FF/VI. **A,** Improvement in lung function from baseline with FP/FORM in terms of FEV_1 *z* score. **B,** Improvement in lung function from baseline with FF/VI in terms of FEV_1 *z* score. **C,** Improvement in lung function from baseline with FP/FORM in terms of FEV_1/FVC *z* score. **D,** Improvement in lung function from baseline with FF/VI in terms of FEV_1/FVC *z* score. **E,** Improvement in lung function from baseline with FP/FORM in terms of absolute FEV_1. **F,** Improvement in lung function from baseline with FF/VI in terms of absolute FEV_1.

loss of asthma control than is spirometric measurements alone.[25] Small airways are known to contribute remarkably to the clinical manifestations and severity of asthma and the challenge in achieving asthma control.[26,27] In most cases in the current study cohort, asthma control was good according to the ACT results, with a median ACT score of 22 (Table I), which may indicate that small airway dysfunction was not particularly prevalent.

The Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) cohort study revealed that children who developed asthma by age 7 years had impaired lung function at infancy.[28] The BAMSE cohort study found an association between asthma onset before age 4 years and impaired spirometry results at age 8 years.[29] The CAMP study revealed that of the children with mild-to-moderate persistent asthma, three-fourths had abnormal lung function growth and decline in early adulthood,[4] and the proportion of asthmatic patients with a prebronchodilator FEV_1/FVC value lower than the lower limit of normal increased significantly from preschool age to age 18 years.[6] According to the BAMSE cohort study, 2% of participants with at least normal lung function experienced growth failure in lung function, which usually happens between ages 8 and 16 years.[30] Similar patterns of growth failure in lung function were replicated in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) cohort.[30] According to the BAMSE birth cohort, all asthma phenotypes were associated with a lower postbronchodilator FEV_1/FVC value at age 24 years, reflecting a persistent impact of childhood asthma on lung function in adulthood.[7] As stated in the BAMSE cohort study, the prevalence of reversible airflow limitation was 5.3%, and for irreversible airflow limitation, the prevalence was 2.0% in young adults.[31] Decreased reversibility in a subset of young adults was also revealed in the New Zealand birth cohort study.[32]

The patients had an improvement in their asthma treatment in this study. Usually, FEV_1 value improves with regular ICS use, reaching a plateau after approximately 2 months.[33] Intervention with both FP/FORM and FF/VI had a favorable effect on FEV_1 *z* score, without a significant difference between them. Absolute FEV_1 value improved significantly; the mean improvement compared with baseline was 0.19 liters for FP/FORM and 0.20 liters for FF/VI, which is comparable to the changes seen in asthma

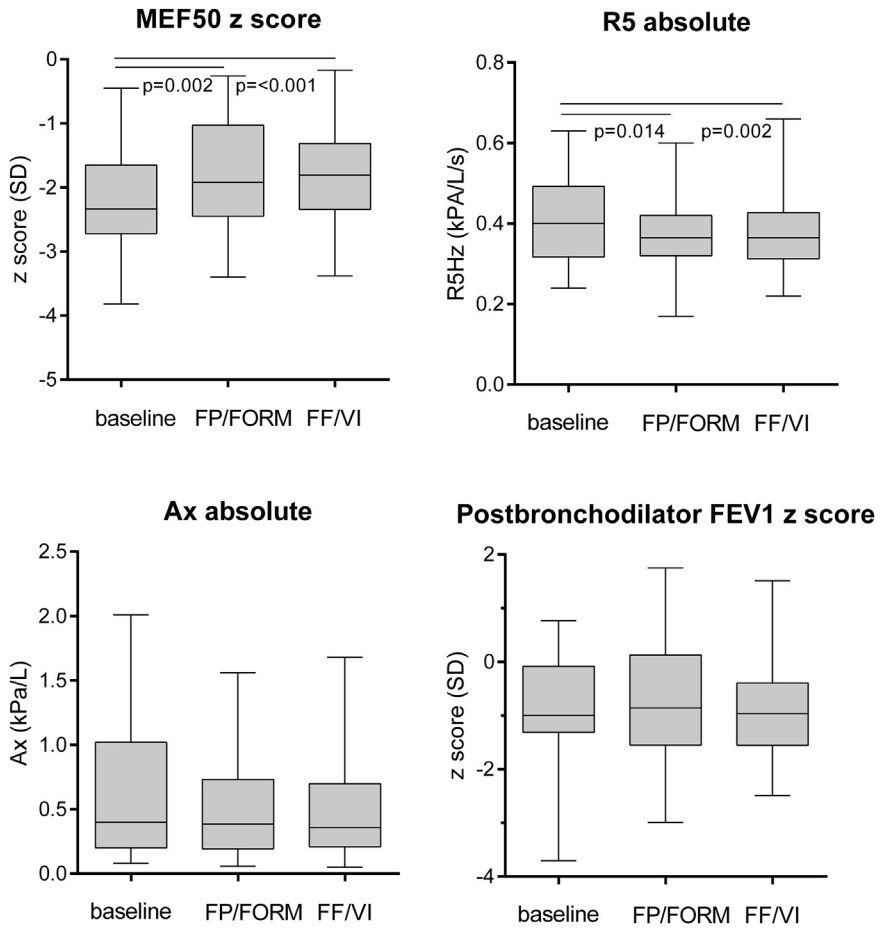

FIG 3. Change in secondary lung function measurements with FP/FORM or FF/VI. **A,** Change in MEF_{50} *z* score. **B,** Change in AX absolute. **C,** Change in R5 absolute. **D,** Change in postbronchodilator FEV_1 *z* score.

trials with biologic treatments.[34] MEF_{50} *z* score and absolute R5 improved statistically significantly with both FP/FORM and FF/VI, without any significant difference between treatments. Neither AX nor difference between R5 and R20 showed statistically significant improvement with either treatment, which may indicate that small airway function was not affected by the treatment. Estimating the prevalence of small airway dysfunction in this study population before the intervention is challenging on account of the lack of appropriate reference values in this age group in the oscillometry indices of interest. Whether a larger population could replicate the improving trend observed in oscillometry indices reflecting the small airways would be interesting to study further.

Children with severe asthma in particular are at risk of developing COPD later in life, even in the absence of smoking.[35] In the CAMP study, 11% of participants met the diagnostic criteria[8] for COPD based on spirometry when younger than 30 years, as defined by a postbronchodilator FEV_1/FVC value less than 0.7.[4] In The Melbourne Asthma Cohort, 44% of patients with severe asthma during childhood were classified as having COPD at age 50 years.[35] The current inhaled asthma treatments are not sufficiently effective to prevent or reverse excessive lung function decline in asthmatic patients with fixed airway obstruction.[36] In our study, neither treatment significantly improved postbronchodilator FEV_1 *z* score or FEV_1/FVC *z* score.

In this study, 40% of the initially obstructed patients achieved a normal prebronchodilator FEV_1/FVC ratio at least after either treatment. One of the main targets in asthma care is achievement of a normal level of lung function.[1] FEV_1/FVC *z* score improved significantly with FF/VI but not with FP/FORM, which may be due to the high clinical efficacy and long activity of FF/VI.[37] In all, 47% of patients achieved a postbronchodilator FEV_1/FVC ratio over the lower limit of normal at least after either treatment with the study combinations.

It is worth noting that all of the study patients had been receiving long-term asthma medication and reported minimal symptoms in their everyday life. This was reflected in the baseline ACT scores, which were not impaired and understandably did not show significant improvement with either treatment. Patients may have adapted to their symptoms and thus lost their perception of them.[1] Airway inflammation and obstruction may often be objectively present even if the patient does not report symptoms.[1] This highlights the need for regular monitoring of lung function and objective response to treatment.

Compliance, correct inhalation technique, appropriate inhaler, and inhalation formulation characteristics, as well as pulmonary obstruction, affect pulmonary deposition.[38] Aerosols containing extra-fine particles (mass median aerodynamic diameter [MMAD] ≤ 2 μm), provide greater lung deposition than do aerosols with larger particles.[39] According to previous studies, FPF has a considerable effect on total lung dose, but MMAD may

also influence regional lung deposition.[40] Previous studies have shown a correlation of total lung deposition with the FPF.[40] Despite of their nearly similar aerodynamic size (MMAD) (ie, 3.2 to 3.5 μm for both the ICS and LABA components in FP/FORM[41] versus 4.0 μm for the ICS and 2.3 μm for the LABA in FF/VI[42]), there was a difference in FPF between the study medications (~40% for both ICS and LABA in FP/FORM[15] vs 21%-25% for the ICS and 25%-43% for the LABA in FF/VI[13]). Pulmonary deposition for FP/FORM delivered via the k-haler was 45% of the delivered dose in asthmatic patients,[15] and for FF/VI delivered via the Ellipta inhaler, it was 13% for the ICS and 20% for the LABA.[14] Because of its higher pulmonary deposition, FP/FORM delivered through the k-haler was expected to improve lung function, especially the small airways indices, more effectively than FF/VI delivered through the Ellipta inhaler.

Previous research has recommended comparative studies on 2 potentially highly effective combination formulas among teenagers. The strengths of this study include its crossover study design and the first comparison between these ICS/LABA combinations in asthmatic adolescents with comprehensive lung function measurements, including impulse oscillometry. Our study also showed that many young patients with prolonged bronchial obstruction can receive a benefit from either or both FP/FORM or FF/VI while aiming at their own maximal lung capacity: the bronchial obstruction can be reversed, and normal lung function (FEV_1/FVC ratio) can be reached in many asthmatic adolescents with these ICS/LABA combinations. The weaknesses of this study include the participants' mild symptoms and relatively well-preserved lung function to begin with, which may have influenced the ability to detect more significant differences between treatments. If the lung function indices were more compromised at baseline or the study sample were larger, it is possible that the differences in treatment response between the 2 combinations may have been more pronounced. Conversely, the level of symptoms in the participants may reflect their history of regular asthma follow-up. Medication used before the study was reported by the patients. We did not collect or weigh the inhalers after the study. The high motivation of the participants in the study may introduce selection bias, especially in adolescent populations, in which adherence and motivation may be challenging.[43]

In conclusion, FP/FORM (125 μg/5 μg, 2 doses twice daily delivered through the k-haler) and FF/VI (92 μg/22 μg, once daily delivered through the Ellipta inhaler) resulted in significant improvements in FEV_1 z score and MEF_{50} z score among adolescents aged 12 to 17 years with mild asthma symptoms despite prolonged bronchial obstruction. In this study, the prolonged bronchial obstruction improved in more than one-third of the adolescents with asthma. These results suggest that a change of medication to FP/FORM and FF/VI may help adolescent asthmatics to achieve better lung function.

DISCLOSURE STATEMENT

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