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## Fluticasone or montelukast for preschool children with asthma-like symptoms: Randomized controlled trial

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### ABSTRACT

**Rationale:** Beneficial effects of anti-inflammatory therapy such as fluticasone propionate (FP) and montelukast (Mk) have been demonstrated in preschool children with asthma. However, comparative studies are lacking in this age group. Therefore, we conducted a study to evaluate and compare the effect of FP and Mk in preschool children with asthma-like symptoms.

**Methods:** In this multicenter, randomized, placebo-controlled, double-blind, double-dummy trial, children aged 2–6 years with asthma-like symptoms were included. In total, 63 children were randomly allocated to receive FP (25), Mk (18) or placebo (20) for 3 months. The primary outcome was the daily symptom score (wheeze, cough, shortness of breath) as recorded by caregivers in a symptom diary card. Secondary endpoints were rescue medication free days, blood eosinophils and lung function (interrupter technique and forced oscillation technique (FOT)).

**Results:** During the 3 months study period, symptoms improved in all 3 groups, with a statistically significant difference between FP and placebo in favor of the FP group ( $p = 0.021$ ). A significant reduction in circulating eosinophils after 3 months of treatment was found in the Mk group only ( $p = 0.008$ ), which was significantly different from the change found in the placebo group ( $p = 0.045$ ). With the exception of frequency dependence (measured by FOT), which showed a difference between FP and Mk after 3 months of treatment in favor of the FP group ( $p = 0.048$ ), no differences in lung function within or between groups were found.

**Conclusions:** In spite of a lack of power, our results suggest that FP has a beneficial effect on symptoms and Mk on blood eosinophil level as compared to placebo. Except for a difference in one lung function parameter after 3 months between FP and Mk in favor of the FP group, this study revealed no differences between FP and Mk.

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### 1. Introduction

Respiratory symptoms like cough, wheeze or shortness of breath are common in preschool children. By 6 years of age many children will have outgrown their symptoms, while a minority of children will go on to develop persistent symptoms and eventually be diagnosed with asthma [1]. The crucial issue is the difficulty in accurately diagnosing asthma in preschool children. For clinicians it is difficult to distinguish children with persistent asthma from those with transient respiratory symp-

toms. The consequence of this diagnostic dilemma is that an adequate therapeutic choice—maintenance therapy with inhaled corticosteroids (ICS), or leukotriene-receptor antagonists (LTRA), or just symptomatic treatment with a bronchodilator—is challenging. Treatment with anti-inflammatory agents in preschool children with assumed asthma might be prescribed in order to improve symptom control, lung function and to prevent airway remodeling. ICS and LTRA are anti-inflammatory agents that have become important therapeutic strategies in the management of asthma in adults and school-aged children [2]. In school-aged children the efficacy of ICS as well as LTRA has been demonstrated. Nevertheless, ICS appeared to be more effective than LTRA in asthma in adults and school-aged children [3–7]. In preschool children with asthma, beneficial effects of ICS on symptoms and

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lung function have been found [8,9]. Effects on the natural history of asthma or wheeze (e.g. a disease-modifying effect) of ICS, however, have not been demonstrated [10,11]. The effectiveness and safety of Montelukast (Mk), an LTRA, have been demonstrated in young children (aged 2–5 years) with persistent [12] or intermittent asthma [13]. So far, studies comparing the effectiveness of ICS and LTRA in preschool children have been performed only in retrospective or open label designs and showed no differences between the two treatment regimes with regard to asthma-related health-care resource utilization [14], or  $\beta_2$ -agonist or oral steroids use [15]. Until the results of clinical trials in preschool children with symptoms suggestive of asthma become available it will remain unclear as to whether monotherapy with ICS or monotherapy with LTRA should be recommended in this difficult-to-diagnose age group.

Clinical trials in young children predominantly rely on the use of subjective outcome measurements, such as symptom-assessment by the child's caregivers. So far, few studies have included objective outcome measurements such as inflammatory parameters or lung function to evaluate the effectiveness of medication [9,16–19]. The standard measurement for measuring lung function—spirometry—is not suitable for use in preschool children, but the development of non-invasive lung function techniques such as the interrupter [20] and forced oscillation technique (FOT) [21,22], which require only passive cooperation, enables us to measure characteristics of the airways in preschool children. Both resistance and reactance of the total respiratory system are measured by the FOT. In addition, the frequency dependence of the resistance can be calculated. Frequency dependence might be an appropriate measure in preschool children with recurrent wheeze as it is a sensitive parameter of small airways patency [22].

We therefore carried out a randomized controlled trial to evaluate and compare the effectiveness of fluticasone propionate (FP) and Mk monotherapy as compared to placebo using subjective as well as objective outcome parameters in preschool children with asthma-like symptoms.

## 2. Methods

### 2.1. Recruitment

Pediatricians from three outpatient clinics (secondary care) in The Netherlands approached potential participants. Children aged 2–5 years with asthma-like symptoms (wheeze, cough and/or shortness of breath) of sufficient severity to justify the use of prophylactic asthma treatment were eligible for inclusion. Children and parents who were willing to participate were invited for a screening visit at one of the three centers. ICS or LTRA use was not allowed for a period of 4 weeks preceding the trial. Other exclusion criteria were as follows: use of systemic corticosteroids in the last 2 months; hospitalization for asthma-related symptoms in the last 2 weeks; respiratory disorders other than asthma and poorly controlled systemic diseases. Subsequently, eligible children entered a run-in period of 2 weeks in which the caregivers of the child recorded their child's respiratory symptoms in a diary. Children with symptoms on less than 4 days of the 2-week run-in period or children who used anti-inflammatory medication in this period were excluded at the second visit.

### 2.2. Study design

This was a multi-center, double-blind, double-dummy, randomized placebo-controlled trial performed in a secondary care

setting, to investigate the effect of Mk and FP mono-therapy in preschool children with asthma-like symptoms. Children who fulfilled the eligibility criteria were randomly assigned to either Mk, FP or placebo. For a period of 3 months, children used chewable tablets containing 4 mg of either Mk or placebo once daily and 100 mcg (either FP or placebo) twice daily from a metered dose inhaler via a plastic spacer device (Aerochamber<sup>®</sup>). Investigators, caregivers and children participating in the study were blinded to the intervention. Throughout the study period, participants were permitted to use salbutamol 100 mcg by inhalation as required for symptom relief.

Follow-up visits took place 1, 2 and 3 months after randomization.

### 2.3. Symptom score

The primary outcome variable was the daily symptom score as assessed by diary record cards (DRC), which were filled out by the parents/caregivers twice daily during the run-in period and 1 month prior to each follow-up visit. Parents rated their child's night-time and day-time symptoms (cough, wheeze and shortness of breath) on a scale from 0 (no symptoms) to 3 (severe symptoms) each morning and evening. Thus, the total daily symptom score ranged from 0 to 18.

### 2.4. Rescue medication use, blood eosinophils and lung function

Secondary outcome variables were rescue medication free days, blood eosinophils and lung function.

*Data on rescue medication use* were derived from the DRC. The percentage of days on which no rescue medication (salbutamol) was used was calculated.

*Eosinophils* were measured in venous blood at baseline and after 3 months.

*Lung function* was measured using two non-invasive techniques: the interrupter technique and the FOT [20–22].

#### 2.4.1. The interrupter technique

By means of a commercial device (MicroRint<sup>®</sup>, Micro Medical Ltd, Rochester, UK) airway resistance (Rint) is estimated according to a previously described procedure in the literature [23,24].

#### 2.4.2. FOT

Using a pseudo-random signaling (4–48 Hz) i2m<sup>®</sup> device (Chess, Ghent, Belgium) FOT measurements were carried out according to the European Respiratory Society recommendations and previously described method [22,25]. Briefly, FOT measures respiratory resistance (Rrs, hPa.s.L-1) and reactance (Xrs, hPa.s.L-1) at various frequencies (4–48 Hz) during quiet spontaneous breathing. In addition, the frequency dependence of resistance, the mean slope of the resistance vs. frequency (4–24 Hz) curve, can be calculated, which proved to be a sensitive measure of peripheral airway patency [26]. Reactance is computed by two false resistant properties of the respiratory system: elasticity and inertia. The oscillation frequency at which Xrs is zero is called the resonance frequency (Fres, Hz). For both techniques the median of 5 technically acceptable were used for analyses. Measurements showing glottic closure, swallowing, use of vocal cords, or episodes of irregular breathing were discarded. Measurements were also excluded in case of incorrect pressure curves on the screen.

### 2.6. Adverse events and concomitant medication use

In addition, adverse events and concomitant medication use were derived from the DRC.

## 2.7. Sample size

The sample size calculation was based on data from a previous trial [27] with a design and inclusion criteria comparable to our study. In this previous study, treatment (with ICS) resulted in a reduction of daily symptom score of 0.9 compared with placebo. The residual SD of the daily symptom score was 1.4 with an upper 95% confidence limit equal to 1.5. It was calculated that a sample size of 198 (66 per group) provided 90% power (two-sided alpha 0.05) to detect a mean difference in daily symptom scores of 0.9 (= 0.60 SD-units) between FP or Mk and placebo.

## 2.8. Data analysis

Data were analyzed in an intention to treat manner. Treatment effects were tested using multiple regression analysis, correcting for baseline-values. Furthermore, analyses of lung function variables were adjusted for age, weight and height. A two-sided  $p$ -value  $<0.05$  was considered statistically significant. All statistical analyses were carried out with the Statistical Package for Social Sciences (SPSS, version 12.0.2, 2005).

## 2.9. Ethics

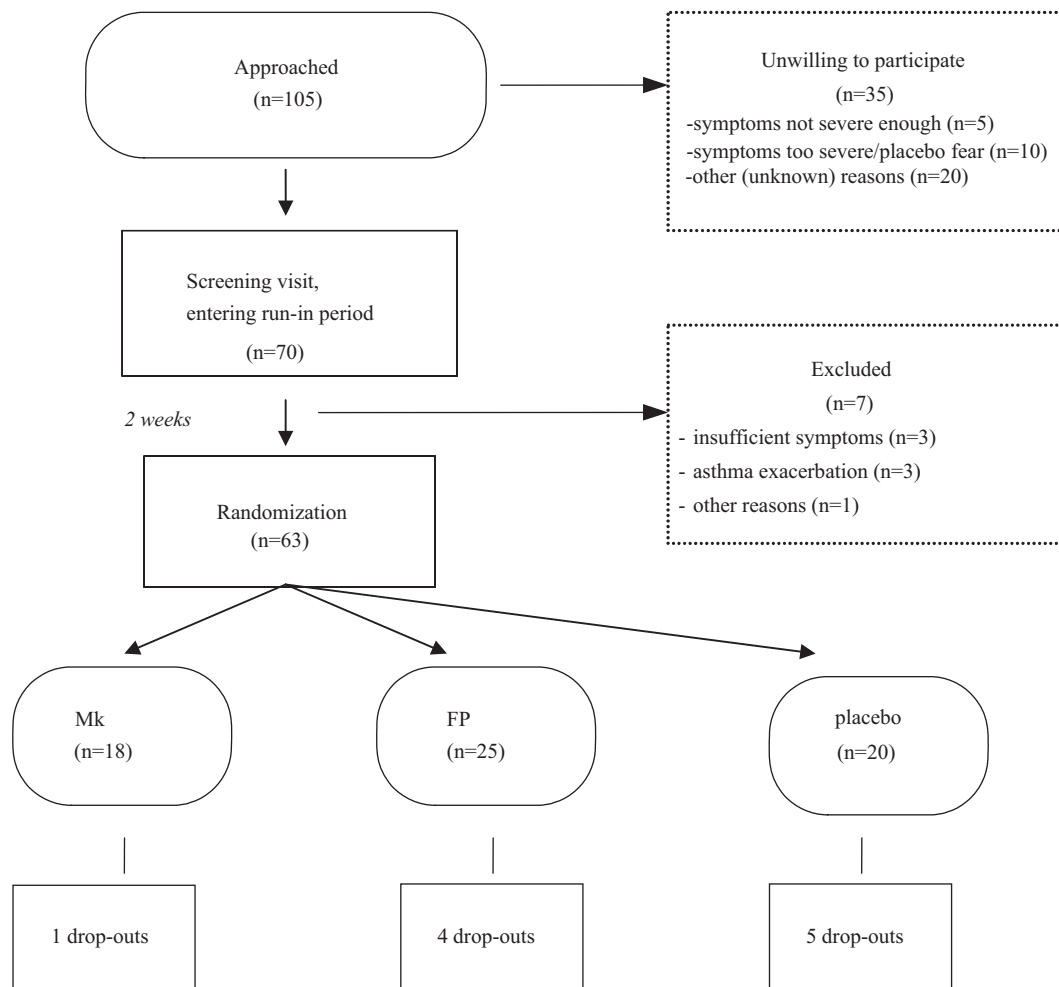
The study was approved by the local medical ethical committees of the three participating centers and registered at

Current Controlled Trials (ISRCTN 38475879). Prior to study participation parents or guardians of all children gave their written informed consent.

## 3. Results

### 3.1. Study population

In the period between September 2002 and September 2004, 105 subjects were approached. Of these 105 children, parents of 70 children agreed to participate and those children entered the run-in period after the screening visit. In 10 of the 35 children whose parents refused to participate refusal was due to the severity of the child's respiratory symptoms: specifically, these parents were afraid that their child might be allocated to the placebo group. Subsequently, seven children did not meet the inclusion criteria and were excluded—three due to an insufficient number of days with symptoms during the run-in period, three due to an asthma exacerbation and need for corticosteroid treatment during the run-in period. Finally, 63 children were randomly assigned to one of the three treatment groups: Mk ( $n = 18$ ), FP ( $n = 25$ ) or placebo ( $n = 20$ ) for 3 months. During the treatment period 10 children dropped out: four due to withdrawal (two in FP group and two in the placebo group), three due to asthma exacerbations (two in placebo group and one in Mk group), one due to hyperactivity symptoms (FP group), one due to



**Fig. 1.** Flow chart. Mk: one asthma exacerbation; FP: two withdrawals, one hyperactivity, one lost to follow-up; placebo: two asthma exacerbations, two withdrawals, one non-compliant.

non-compliance (placebo group) and one subject was lost to follow up (FP group). Details on enrollment are given in Fig. 1.

The mean age of the included children was 3.8 years, 62% were boys. Baseline characteristics are summarized in Table 1.

3.2. Symptom score

Fig. 2 shows an improvement in the daily symptom score in each group. A statistically significant difference in change in daily symptom score was found between FP and placebo in favor of the FP group. Comparisons between the other treatment groups (Mk vs. FP and Mk vs. placebo) revealed no differences.

3.3. Rescue medication free days

A significant decrease in rescue medication free days was found within each treatment group with no statistically significant differences between groups (Fig. 3). Moreover, Fig. 3 shows a wide range in rescue medication free days at baseline which was reduced at the end of the study period.

3.4. Eosinophils

A significant decrease in blood eosinophils after 3 months was found in the Mk group only. Except for a significant difference in change in eosinophil level between Mk and placebo (in favor of the Mk group,  $p = 0.045$ ) no differences between groups were found (Fig. 4).

3.5. Lung function

Of the 63 children included 51 and 38 children were able to perform Rint and FOT measurements, respectively. Except for a significant lower frequency dependence of resistance in the FP group as compared to the Mk group after 3 months of treatment (Fig. 5), no significant changes in lung function were found either within or between treatment groups.

3.6. Adverse events and concomitant medication use

In Table 2 the adverse events and concomitant medication use in the treatment groups are shown. In the Mk and FP group more children experienced upper respiratory tract infections as compared to the placebo group ( $p = 0.011$ ). The use of concomitant medication such as antibiotics was also higher in children in the Mk and FP groups as compared to the placebo group.

4. Discussion

To our best knowledge this is the first study designed, using subjective as well as objective measures, to evaluate and compare the effect of Mk or FP monotherapy vs. placebo in preschool children with asthma-like symptoms. Although we acknowledge

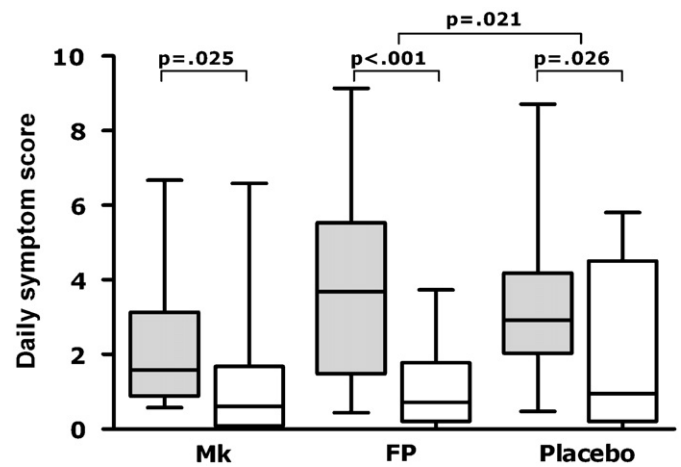


Fig. 2. Symptom scores. Daily symptom score measured by DRC (possible range 0–18) shown for baseline and after 3 months for all treatment groups. Grey boxes represent data measured at baseline, white boxes after 3 months. Each box shows the median and interquartile ranges.

Table 1 Patient baseline characteristics

	Mk	FP	Placebo	p-Value
n	18	25	20	
Gender (male/female)	12/6	13/12	14/6	ns
Age (years)	3.8 (±1.4)	3.9 (±1.1)	3.8 (±1.3)	ns
Height (cm)	104.5 (±10.8)	103.2 (±9.4)	101.8 (±9.7)	ns
Weight (kg)	18.7 (±3.9)	17.1 (±2.7)	17.0 (±2.8)	ns
Positive specific IgE (for pollen, dog, cat, mite, milk, egg, soy, wheat and peanut)	5/17 (29%)	9/19 (47%)	7/16 (35%)	ns
Atopy in family (history)	16/18 (89%)	21/25 (84%)	18/20 (90%)	ns
Smoke exposure during pregnancy	6/18 (33%)	3/25 (12%)	8/20 (40%)	ns
Current smoke exposure	7/18 (39%)	14/25 (56%)	11/20 (55%)	ns
ICS use in past	16/18 (89%)	22/25 (88%)	15/20 (75%)	ns
LTRA use in past	2/18 (11%)	1/25 (4%)	0/20 (0%)	ns
Daily symptom score	1.58 (0.57–6.67)	3.68 (0.44–9.14)	2.90 (0.47–8.71)	Mk-FP: .02 Mk-pla: .06
% Rescue free days	91.7 (0–100)	42.9 (0–100)	57.1(0–100)	ns
Serum eosinophils *10 <sup>9</sup> /l	0.44 (0–1.7)	0.25 (0–1.3)	0.40 (0.2–0.8)	ns
N: Rint, FOT	15,10	20,15	16,13	ns
Rint (kPa/L/s)	1.0 (±0.4)	1.1 (±0.5)	1.2 (±0.4)	ns
Rrs (hPa/L/s)	6.1 (±1.1)	7.1 (±1.5)	7.8 (±2.1)	Mk-pla: .03
Rrs6Hz (hPa/L/s)	7.8 (±2.1)	9.3 (±2.5)	9.3 (±2.7)	ns
Xrs (hPa/L/s)	0.43 (±0.9)	0.19 (±0.9)	0.07 (±1.0)	ns
Fres (Hz)	23.3 (±2.1)	23.8 (±3.4)	24.6 (±5.7)	ns
dRrs/df (4–24 Hz) (hPa/L/s/Hz)	-0.16 (±0.1)	-0.18 (±0.1)	-0.13 (±0.1)	ns

Data are represented as mean (±SD) or median (range) unless otherwise stated. Pla = placebo, Rrs = resistance of respiratory system, Rrs6HZ = Resistance at 6 Hz, Xrs = reactance of respiratory system, Fres = resonance frequency, dRrs/df is frequency dependence. Baseline values were compared using the Mann-Whitney, Chi-square or Student's-t-test as appropriate.

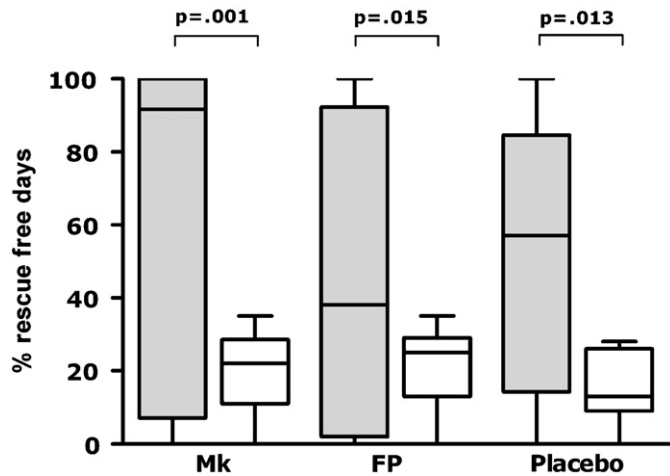


Fig. 3. Rescue free days. Rescue free days measured as a percentage of days on which rescue medication was not used. Baseline data in grey and data after 3 months in white. Each box shows the median and interquartile ranges.

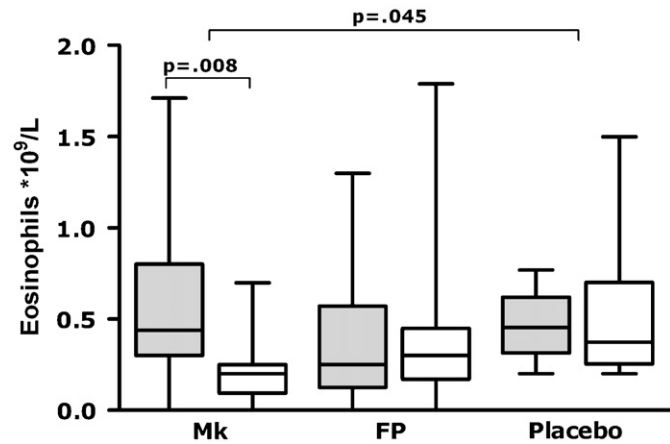


Fig. 4. Eosinophils. Circulating eosinophils measured at baseline and after 3 months. Grey boxes represent data measured at baseline, white boxes after 3 months. Each box shows the median and interquartile ranges.

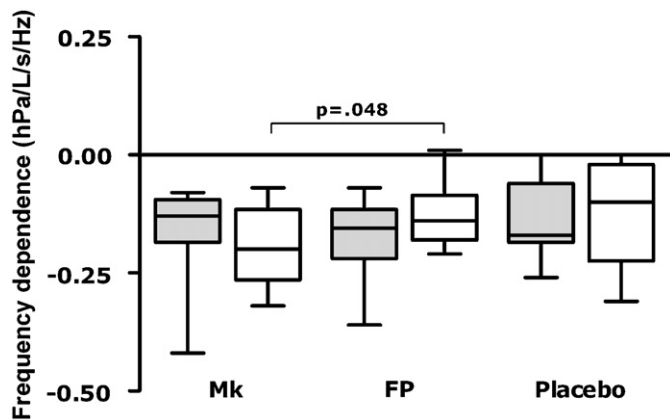


Fig. 5. Frequency dependence. Frequency dependence is defined as the mean slope of the resistance curve as a function of oscillation frequency ( $dR_r/df$  (4–24 Hz)). Zero frequency dependence means a horizontal curve; a steeper curve (more negative slope) is associated with airway obstruction. Grey boxes represent data measured at baseline, white boxes after 3 months. Each box shows the median and interquartile range.

Table 2  
Adverse events and concomitant medication use

	Mk	FP	Placebo
<i>Adverse events</i>			
URTI	6	6	1
(Other) respiratory symptoms	3 (1)	3	2 (2)
Gastroenteritis	3	1	1
Local skin infection	2	0	1
Chickenpox	2	0	0
Eczema	0	2	1
Hyperactivity	0	2 (1)	0
Rash	0	0	1
<i>Concomitant medication use</i>			
Antibiotics	5	3	1
Local corticosteroids	1	1	1
Systemic corticosteroids	1	1	1
Nasal corticosteroids/decongestives	1	4	1
Cough syrup	1	2	0
NSAID/pain medication	1	2	1

Number of patients experiencing described adverse event (number of drop-outs due to that event) or using concomitant medication. URTI = upper respiratory tract infection. Differences between a total of adverse events per group:  $p = 0.011$  (chi square).

that our study sample is too small to draw definite conclusions, in spite of a lack of power, we would like to emphasize the importance of our study findings below.

With respect to our main outcome parameter—the daily symptom score—an improvement in symptoms during the 3-month study period in both intervention and placebo groups was found. A spontaneous improvement in symptoms in the placebo group has also been found in other studies in this area and might reflect the natural course of respiratory symptoms in this population (e.g. self-limiting). It has been shown that symptoms in this age group are often virally induced and probably do not need maintenance asthma treatment at all [28]. In our study, however, a beneficial effect of FP vs. placebo on symptoms was found, although no difference was observed in symptom improvement between FP and Mk. In spite of randomization, children assigned to the Mk group appeared to have milder symptoms at baseline as compared to the other two groups, which might have resulted in a regression to the mean, possibly masking a treatment effect of Mk. ICS have been shown to be more effective than montelukast with respect to clinical outcomes in school-aged children [3,7,29,30]. In preschool children positive effects of both ICS [13,31] and Mk [12,13] on comparable subjective outcome parameters have been described. So far, in this age group no studies have been conducted in which a direct comparison between ICS and Mk has been made [30].

Our finding that Mk has a beneficial effect on circulating eosinophils as compared to placebo is consistent with previously conducted trials both in asthmatic preschool children [12] and in older children [32]. Effects of Mk on other inflammatory parameters such as exhaled nitric oxide have also been found in preschool children [17,33], supporting the anti-inflammatory effect of Mk. In our study no difference was found between Mk and FP with respect to eosinophil level. On the other hand, in school-aged children exhaled NO has been found to improve significantly more with FP than with Mk [7,30].

Results of most of the lung function measurements in the present study revealed no differences either within or between groups. Measurement of the frequency dependence of resistance by the FOT, however, proved to be significantly better in the FP group as compared to the Mk group after the 3-month study period. We would like to emphasize this outcome, as in our opinion it is a clinically relevant parameter, which may be

sensitive to small changes in airway narrowing and lung growth [34,35]. Several studies have found beneficial effects of FP on lung function as compared to Mk [3,6,7,30] in school-aged children with asthma.

Remarkably, a decrease in the percentage of rescue medication free days was found in all three study groups. A wide variation in rescue medication use was found at baseline. This might be explained by differences in the understanding and interpretation of the parents/caregivers of how and when to use rescue medication. Parents were informed about the benefits of rescue medication use and instructions were given during the study. For example, in children with exercise-induced respiratory symptoms, parents were instructed to use a bronchodilator before the child was going to be physically active. This might have resulted in a decrease in rescue medication use.

In the present study, upper respiratory tract infections were reported more often in both the FP and the Mk group than in the placebo group. Accordingly, more concomitant medication was used in these groups. However, upper respiratory tract infection seems unlikely to be an effect of medication. The drop-out rate in the Mk group was lower as compared to FP or placebo, respectively, 1, 4 and 5. However, numbers are too small to draw definite conclusions. The daily dosage of both Mk (4 mg) and FP (200 mcg) used during this study has proven to be appropriate and safe for preschool children [28,31,36,37].

Our study population consisted of children with symptoms suggestive of asthma. As in real life we probably included a broad range of respiratory disorders ranging from viral-induced wheeze to true asthma. Children with asthma-like symptoms referred to secondary care who would otherwise—when not participating in the study—be using maintenance treatment were included. According to the Dutch asthma guidelines [38] ICS should be prescribed to children with persistent respiratory symptoms. Although it remains difficult to establish a diagnosis of asthma in this age group, we assume that in the majority of children included in our study the respiratory symptoms were persistent. Baseline values of daily symptom scores in the three treatment groups were 1.6, 3.7 and 2.9, respectively, suggesting the presence of moderate persistent symptoms. Moreover, only children in which respiratory symptoms persisted during the run-in period were included. Furthermore, a positive family history for atopy—a risk factor for asthma persistence [39]—was present in almost 90% of the children.

We aimed to include 198 children in order to reach 90% power. In spite of all our efforts we were only able to include 63 children. Therefore we must acknowledge that our results are subject to a type-2 error, which hampers the interpretation of the negative findings.

By means of a post-hoc power analysis using the means and standard deviations as found in the current study, we estimated the actual power to detect differences between groups and the desired sample size. We actually had power of 34% (with  $\alpha = 0.05$ ) to detect a difference of 0.8 in the mean symptom score, after 3 months, between the Mk group (1.3 (SD = 1.8)) and the placebo group (2.1 (SD = 2.2)). Moreover, group sample sizes of 51 were needed to achieve 80% power (with  $\alpha = 0.05$ ) to detect a difference of 0.8 between both groups. Despite this, we would like to stress the significant differences regarding both primary and secondary outcome parameters as found in our study.

The recruitment rate for this study was low: we approached 105 children of whom 63 were randomized. Time pressure and forgetfulness may have resulted in this low recruitment rate as pediatricians were asked to identify children suitable for participation in the study during consultations. Actually most children with asthma-like symptoms already used asthma maintenance treatment when referred to secondary care and therefore, in our

opinion, fear to withdraw this medication (either by the physician or caregiver) was the major reason for low inclusion rates.

In conclusion, the effectiveness of both FP and Mk monotherapy in preschool children with asthma-like symptoms was assessed using both subjective and objective outcome parameters. Though a lack of power is likely to hamper the interpretation of our study results, the results do suggest a beneficial effect of ICS on symptoms, whereas Mk might have a more pronounced effect on circulating eosinophils as compared to placebo. Comparisons between FP and Mk revealed no differences between both treatment groups except for a difference in frequency dependence at 3-month study in favor of the FP group.

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### Conflicts of interest statement

All authors state that they do not have any special financial interest concerning this manuscript.

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