Knemometry Assessment of Short-term Growth in Children With Asthma Receiving Fluticasone Furoate for 2 Weeks: A Randomized, Placebo-controlled, Crossover Trial

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ABSTRACT

Purpose: A dry powder inhaler formulation of the inhaled corticosteroid fluticasone furoate (FF) is being evaluated for use in children. An important potential risk associated with the use of inhaled corticosteroids in children is growth suppression. Therefore, the aim of this study was to assess the short-term lower leg growth in children with asthma treated for 2 weeks with inhaled FF versus placebo from the ELLIPTA inhaler.

Methods: Prepubertal children with persistent asthma (n = 60; aged 5 to <12 years) were recruited into a randomized, double-blind, placebo-controlled, 2-way crossover, noninferiority study. The study consisted of four 2-week periods: run-in, 2 treatment periods, 1 washout period, and a 1-week follow-up period. Interventions were FF 50 μg and placebo once daily in the evening. Lower leg length was measured by using knemometry.

Findings: The randomized ITT population comprised 36 boys and 24 girls with a mean age of 8.7 (standard deviation, 1.5; range, 5–11) years; 58% had a duration of asthma ≥5 years. Fifty-eight subjects completed both treatment periods. The least squares mean growth rate was 0.31 mm/week during treatment with FF and 0.36 mm/week during the placebo period. The difference in adjusted least squares mean growth rates between FF and placebo was –0.052 mm/week with a 95% CI of –0.122 to 0.018. This finding was greater than the prespecified noninferiority margin of –0.20 mm/week. The overall incidence of adverse events was 35% with placebo and 22% with FF.

Implications: Inhaled FF 50 μg provided once daily for 2 weeks was noninferior to placebo in terms of effects on short-term lower leg growth in children with asthma. To further quantify the risk of growth suppression in children, intermediate-term growth studies should be conducted. Inhaled FF 50 μg was well tolerated in this study population. ClinicalTrials.gov identifier: NCT02502734. (*Clin Ther.* 2017;39:1191–1199) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

Key words: asthma, children, fluticasone furoate, inhaled corticosteroids, knemometry, lower leg growth.

INTRODUCTION

Asthma is a chronic disease of the lungs that is characterized by airway inflammation, bronchoconstriction, and increased airway responsiveness. Inhaled corticosteroids (ICSs) are considered the most effective anti-inflammatory treatment for all severities of persistent asthma.[1] The benefits of ICSs include control of asthma symptoms, improvement in lung function, and a decrease in airway hyperresponsiveness. Fluticasone furoate (FF) is a glucocorticoid delivered via the ELLIPTA dry powder inhaler (GlaxoSmithKline Ware, UK), approved in the United States and 7 other countries for use as a once-daily (OD) ICS for the maintenance treatment of asthma in patients aged ≥12 years. However, because growth suppression is an important potential risk associated with the use of ICSs

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in children, safety studies to evaluate the effect of a new ICS on growth is a requirement for pediatric use.[2–5]

Before undertaking long-term growth studies, knemometry may be used as a validated, sensitive, highly reproducible, and noninvasive method of measuring short-term lower leg growth.[6] Although the results of knemometry studies cannot accurately predict the effect of a compound on long-term growth, the absence of an effect on short-term lower leg growth rate would be reassuring because it suggests that an adverse effect on growth rate is unlikely to occur with long-term use.[6] The objective of the present study therefore was to evaluate the effect of 2 weeks' treatment with inhaled FF versus placebo OD on short-term lower leg growth.

SUBJECTS AND METHODS

The study was a single-center, randomized, double-blind, placebo-controlled, 2-way crossover study consisting of four 2-week periods (run-in [2 weeks], treatment period 1 [2 weeks], washout [2 weeks], and treatment period 2 [2 weeks]) and a 1-week follow-up period (Figure 1). The primary safety end point was the mean growth rate (in mm/week) in lower leg growth, as determined by using knemometry. The mean lower leg growth rate for the placebo recipients was expected to range from 0.40 to 0.50 mm/week based on previous knemometry studies.[6] FF 50 μg OD would be considered to be noninferior to placebo with respect to lower leg growth rate if the lower limit of the 2-sided 95% or one-sided 97.5% CI for the treatment difference (FF minus placebo) was greater than –0.20 mm/week (~40%–50% of growth rate seen with placebo in previous studies). With 50 completed subjects (25 subjects per treatment sequence), the study would provide 90% power, assuming an SD of 0.30 mm/week based on previous studies and a true treatment difference in lower leg growth rate of 0.00 mm/week.[6] At least 60 subjects were required to be randomized to treatment to achieve at least 50 eligible subjects for the lower leg growth rate analysis.

Inclusion criteria were prepubertal children 5 to 11 years of age at visit 1 within the normal height and weight ranges (3rd–97th centiles) for their age according to Danish growth charts and with a documented diagnosis of persistent asthma for at least 3 months before screening. Pubertal development using the Tanner staging system was recorded by a pediatrician (O.D.W.).[7] Subjects were also required to demonstrate a pre-bronchodilator forced expiratory volume in 1 second (FEV_1) of ≥80% predicted at screening, without the previous use of a short-acting β-agonist (SABA) within 4 hours of the measurement. Before entry into the study, subjects were required to be using either a SABA inhaler alone on an as-required basis, or regular non-ICS controller medications for asthma, or been previously treated with an ICS but not to have used an ICS within 2 weeks of screening. Informed consent was obtained from at least 1 parent or legal guardian and accompanying informed assent from the subjects, where the subject was able to provide assent, before admission into the study.

Exclusion criteria were a history of life-threatening asthma or asthma exacerbation requiring the use of systemic corticosteroids, or emergency department attendance within 3 months, or hospitalization within 6 months before screening. Subjects were also not eligible for the study if they had an active pulmonary

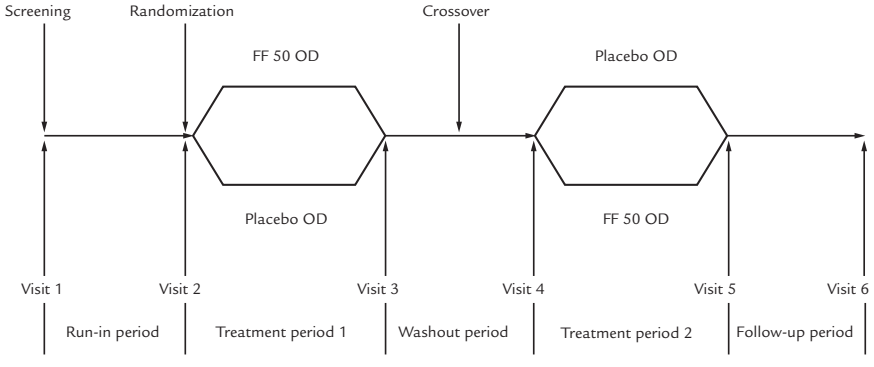

Figure 1. Study design. FF 50 = fluticasone furoate 50 μg; OD = once daily.