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Comparison of the efficacy and safety of ciclesonide 160 μg once daily vs. budesonide 400 μg once daily in children with asthma

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Ciclesonide is an onsite-activated inhaled corticosteroid (ICS) for the treatment of asthma. This study compared the efficacy, safety and effect on quality of life (QOL) of ciclesonide 160 μg (ex-actuator; nominal dose 200 μg) vs. budesonide 400 μg (nominal dose) in children with asthma. Six hundred and twenty-one children (aged 6–11 yr) with asthma were randomized to receive ciclesonide 160 μg (ex-actuator) once daily (via hydrofluoroalkane metered-dose inhaler and AeroChamber Plus™ spacer) or budesonide 400 μg once daily (via Turbohaler®) both given in the evening for 12 wk. The primary efficacy endpoint was change in forced expiratory volume in 1 s (FEV_1). Additional measurements included change in daily peak expiratory flow (PEF), change in asthma symptom score sum, change in use of rescue medication, paediatric and caregiver asthma QOL questionnaire [PAQLQ(S) and PACQLQ, respectively] scores, change in body height assessed by stadiometry, change in 24-h urinary cortisol adjusted for creatinine and adverse events. Both ciclesonide and budesonide increased FEV_1, morning PEF and PAQLQ(S) and PACQLQ scores, and improved asthma symptom score sums and the need for rescue medication after 12 wk vs. baseline. The non-inferiority of ciclesonide vs. budesonide was demonstrated for the change in FEV_1 (95% confidence interval: −75, 10 ml, $p = 0.0009$, one-sided non-inferiority, per-protocol). In addition, ciclesonide and budesonide showed similar efficacy in improving asthma symptoms, morning PEF, use of rescue medication and QOL. Ciclesonide was superior to budesonide with regard to increases in body height ($p = 0.003$, two-sided). The effect on the hypothalamic–pituitary–adrenal axis was significantly different in favor of ciclesonide treatment ($p < 0.001$, one-sided). Both ciclesonide and budesonide were well tolerated. Ciclesonide 160 μg once daily and budesonide 400 μg once daily were effective in children with asthma. In addition, in children treated with ciclesonide there was significantly less reduction in body height and suppression of 24-h urinary cortisol excretion compared with children treated with budesonide after 12 wk.

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Asthma is the most common chronic disease in children worldwide (1). Recent studies report that 9–16% of children in developed countries have asthma (2, 3). Paediatric asthma impairs the quality of life (QOL) of children and their families, and imposes a substantial economic burden on society. Approximately one-third of children with asthma have sleep disturbances and 60% of asthmatic children miss school days or experience activity limitations because of their disease (3). Asthma-related healthcare expen-

ditures account for 1–2% of total healthcare costs in developed countries (4).

Inhaled corticosteroids (ICS) provide the most effective treatment of chronic inflammation associated with asthma (1). Consistent ICS use improves lung function, decreases asthma symptoms and reduces the frequency of asthma exacerbations (5). Consequently, asthma management guidelines recommend the use of ICS in both adult and paediatric patients (1, 6, 7). However, high-dose ICS use can also be associated with a range of systemic side effects such as reduced growth, decreased bone mineral density and hypothalamic–pituitary–adrenal (HPA) axis suppression (8). Concerns about ICS-related side effects may contribute to the low rates of adherence to ICS therapy and poor long-term outcomes in patients with asthma (9, 10).

Ciclesonide is administered to the lungs as an inactive parent compound, where it undergoes on-site activation by airway esterases to form the active metabolite, desisobutyryl-ciclesonide (11). The characteristics of ciclesonide include low oropharyngeal deposition, high pulmonary deposition, high protein binding, low oral bioavailability, a short half-life and a high clearance rate (12–17). Gelfand et al. showed that ciclesonide 40, 80 or 160 μg once daily for 12 wk achieved improvements in lung function, control of asthma symptoms, use of rescue medication and QOL compared with placebo in children (18). Treatment discontinuation because of lack of efficacy was also significantly greater in the placebo group than in all of the ciclesonide groups ($p = 0.0146$; log-rank test for time to withdrawal), and ciclesonide 40, 80 or 160 μg once daily achieved significantly greater improvements in Pediatric Asthma Quality-of-Life Questionnaire [PAQLQ(S)] overall score from baseline vs. placebo ($p < 0.05$) after 12 wk of treatment (18). Another study compared ciclesonide 160 μg/day vs. fluticasone propionate 176 μg/day (ex-actuator; equivalent to 200 μg ex-valve) in children and adolescents (aged 6–15 yr) with mild-to-severe persistent asthma for 12 wk (19). Ciclesonide 160 μg/day was statistically non-inferior, microgram for microgram, to fluticasone propionate, as demonstrated by similar improvements in lung function, morning and evening peak expiratory flow (PEF), and equally effective in reducing asthma symptoms and use of rescue medication (19). In addition to the trials demonstrating the efficacy of ciclesonide, other placebo-controlled studies have shown that ciclesonide does not result in increases in oropharyngeal side effects, or significant cortisol suppression or growth retardation (20, 21).

The objective of this study was to compare the efficacy, safety and effect on patient QOL of ciclesonide 160 μg (ex-actuator) and budesonide 400 μg, administered once daily in the evening to children with moderate-to-severe asthma. To examine systemic exposure to ciclesonide and budesonide, the effect of both treatments on the HPA axis, as judged by 24-h urinary cortisol excretion adjusted for creatinine, and body growth after 12 wk were evaluated.

Methods

Patients

Male and female outpatients aged 6–11 yr with a documented diagnosis of persistent asthma for at least 6 months were eligible to participate in this study. Patients were required to have a forced expiratory volume in 1 s (FEV_1) > 50% to 90% of predicted in patients receiving rescue medication only, > 50% to 100% of predicted in patients pretreated with a constant dose of controller medication other than steroids for at least 30 days before inclusion or 80% to 105% of predicted in patients pretreated with ≤ 400 μg/day beclomethasone dipropionate (via a chlorofluorocarbon metered-dose inhaler (MDI)] or equivalent for at least 30 days before inclusion. Criteria for randomization included FEV_1 50–90% of predicted after withholding salbutamol for at least 4 h, reversibility of FEV_1 ≥12% of initial after inhalation of salbutamol 200–400 μg, and asthma symptom scores ≥1 on at least six of the previous 10 consecutive days or use of ≥8 puffs of rescue medication during the previous 10 consecutive days. The inclusion/randomization criteria, pre-specified in the protocol, were designed to include patients with moderate-to-severe asthma. Criteria that rendered patients ineligible to participate in this study included a history of life-threatening asthma, concomitant severe diseases or diseases contraindicated for ICS use, two or more hospitalizations for asthma within the previous 12 months, occurrence of an asthma exacerbation during the 4 wk before baseline, use of systemic corticosteroids during the 30 days before baseline, use of systemic steroids for more than 60 days within the previous 2 yr or participation in another study within the 30 days before baseline. No other asthma medication was allowed during the study.

Study design

This was a randomized, double-blind, double-dummy, two-arm, parallel-group study, conduc-

ted at 59 investigational centres in eight countries (Australia, Germany, Hungary, Poland, Portugal, Serbia and Montenegro, South Africa and Spain). All study-related procedures were conducted in accordance with the principles of International Conference on Harmonization Good Clinical Practice (CPMP 135/95), the revised Declaration of Helsinki (Somerset West, October 1996) and applicable local law. The study protocol was approved by the independent ethics committee at each study centre, and written informed consent was obtained from parents or legal guardians before their children's participation in the study.

Patients underwent a 2- to 4-wk run-in period during which they discontinued their previous asthma medication and received only salbutamol as rescue medication. Eligible patients were randomized at a ratio of 2:1 to receive ciclesonide 160 μg (ex-actuator; equivalent to 200 μg ex-valve) once daily (416 patients; 2×80 μg puffs) or budesonide 400 μg once daily (205 patients; 2×200 μg puffs) for 12 wk. Ciclesonide and budesonide were administered in the evening via a hydrofluoroalkane MDI with an AeroChamber Plus™ spacer and Pulmicort Turbohaler®, respectively. Patients who experienced an asthma exacerbation during the treatment period were withdrawn from the study because of lack of efficacy (defined as deterioration in asthma that required change in asthma treatment other than increased use of rescue medication).

Assessments

At the start and end of the study period, standard laboratory evaluations, physical examination and vital signs, body height (measured by stadiometry in selected centres only, or standard device), and Pediatric Asthma Caregivers' Quality-of-Life Questionnaire (PACQLQ) and PAQLQ(S) scores were assessed. Patients collected their urine during the 24-h period directly preceding the respective visit. Analysis of urinary cortisol only included samples with corresponding urinary creatinine values within the laboratory reference range (i.e. suggesting a complete collection of urine over the entire 24-h period).

At every visit, spirometry [FEV_1 and forced vital capacity (FVC)] and assessment of adverse events (AEs) were performed. Patients recorded their daily morning and evening PEF, intake of rescue medication and asthma symptoms in a diary. Treatment compliance was not formally determined; however, patients had to report deviations from the intended treatment schedule in their diaries.

The asthma symptom score sum included daytime and night-time symptom scores, each of which was based on a 5-point scale in which a score of 0 represented no asthma-related symptoms and a score of 4 represented the highest discomfort resulting from asthma-related symptoms (i.e. unable to carry out daytime activities because of asthma or awake most of the night because of asthma). Asthma exacerbations were defined as increasing asthma symptoms requiring change or addition of patient's medication other than increasing rescue medication. Number of asthma exacerbations and time-to-onset of first exacerbation were evaluated.

The effect of asthma on the QOL of children and their caregivers was assessed using the PAQLQ(S) and PACQLQ, respectively. The PAQLQ(S) is validated for children aged from 7 to 17 yr with asthma (22). The PACQLQ is validated for caregivers who care for a child suffering from asthma and measures the effect of childhood asthma on caregivers' QOL (22). The investigator and/or research nurse administered the interview-based version of the PAQLQ(S), whereas the PACQLQ was self-administered. Patients and their caregivers answered questions using a 7-point scale (1 indicated 'maximum impairment' and 7 indicated 'no impairment'). The net benefit in QOL (percentage of patients with an increase in overall score ≥ 0.5 minus percentage of patients with a decrease in overall score ≥ 0.5) provided by ciclesonide and budesonide was evaluated using the PAQLQ(S) and PACQLQ. AEs were assessed by open questioning, were classified by the investigator as mild, moderate or severe and were evaluated for causal relationship to the study medication.

Statistical methods

All patients who received at least one dose of study medication were included in the intention-to-treat (ITT) population, and patients who had no major protocol violations were included in the per-protocol (PP) population. Results obtained from the PP analysis (the primary analysis in this non-inferiority study) were confirmed by ITT analysis. The primary end-point – change in FEV_1 after 12 wk or after the last visit with valid measurements (referred to hereinafter as 12 wk) – was analysed for non-inferiority of ciclesonide 160 μg once daily vs. budesonide 400 μg once daily. The primary hypothesis for non-inferiority was assessed using the lower limit of the 95% confidence interval (CI) for differences between treatment groups (non-inferiority acceptance limit of FEV_1 was -100 ml). Subsequent testing

was applied to the co-primary variable of asthma symptom score sum (non-inferiority acceptance limit of asthma symptom score sum was 0.3), and the secondary variables of 24-h urinary cortisol adjusted for creatinine (superiority of ciclesonide 160 μg once daily vs. budesonide 400 μg once daily), and morning PEF (non-inferiority acceptance limit of morning PEF was −12.5 l/min). Because of *a priori* ordered hypotheses and the principle of closed testing procedures, no adjustment of the α-level for multiplicity was performed. All other variables were analysed in an exploratory manner.

In the PP population, a sample size of 298 patients in the ciclesonide group and 149 patients in the budesonide group was required to provide a power of 90% to correctly assess non-inferiority of ciclesonide vs. budesonide with regard to the primary variable, change in FEV_1 (assumptions: $\alpha = 0.025$; one-sided non-inferiority acceptance limit = −100 ml; differences between treatment groups = 15 ml; common s.d. = 26 ml). Assuming that 80% of all randomized patients are included in the PP population, 400 patients in the ciclesonide group and 200 patients in the budesonide group had to be randomized to ensure that there were at least 447 PP patients in the two treatment arms. A 2:1 randomization was chosen to collect more safety information on patients treated with ciclesonide.

The primary and secondary efficacy end-points were evaluated by an analysis of covariance that included baseline value at randomization visit and age as co-variates. For lung function variables, as well as morning and evening PEF, gender and centre pool were included as fixed factors. Least squares mean and 95% CI were used to determine differences within and between treatment groups. Non-parametric within- and between-group comparisons were performed using Pratt's modification of Wilcoxon's signed rank test and the Mann–Whitney *U*-test, respectively. Non-parametric between-group comparisons of 24-h urinary cortisol adjusted for creatinine were performed using the van Elteren test. Asthma exacerbations were analysed using the log-rank test. Differences between treatments with respect to local AEs were analysed by means of Fisher's exact test.

Results

Study population

A total of 774 patients were enrolled in this study. Six hundred and twenty-one patients were randomized to treatment [ciclesonide 160 μg once daily (n = 416) or budesonide 400 μg once daily (n = 205); ITT population]. Participation in the study was terminated prematurely by 27 (4.3%) patients [ciclesonide = 22 (5.3%) patients; budesonide = 5 (2.4%) patients]; the main reasons for premature study termination included worsening of asthma (ciclesonide = 2.9% of patients; budesonide = 1.0% of patients), other medical reasons (ciclesonide = 0.5% patients) and non-medical reasons (ciclesonide = 2.2% patients; budesonide = 1.5% patients). Therefore, 594 patients were treated for the full 12-wk study period and of these, 513 patients completed the study according to the protocol [PP population; ciclesonide = 340 patients (81.7% of the ITT population) and budesonide = 173 patients (84.4% of the ITT population)].

Baseline patient demographics were similar in both treatment groups (Table 1). More male patients (n = 394) than female patients (n = 227) were randomized to treatment, reflecting the known distribution of asthma in children. Based on Global Initiative for Asthma/National Institutes of Health severity classification, the majority of patients in the ciclesonide and budesonide treatment groups had moderate or severe persistent asthma. Patients also had a median

Table 1. Baseline patient and disease characteristics (full analysis set)

Characteristic	CIC 160 μg once daily*	BUD 400 μg once daily†
Patients (n)	416	205
Age (yr)		
Median (range)	9 (6–11)	9 (6–11)
Height (cm)		
Median (range)	135 (112–169)	137 (112–164)
Mean ± s.d.	135.5 ± 10.9	136.8 ± 10.9
Sex (male/female, %)	63/37	65/35
Mean FEV_1, l ± s.d.‡	1.53 ± 0.38	1.58 ± 0.38
Mean FEV_1, % predicted ± s.d.‡	77 ± 10	78 ± 10
Mean reversibility: change in FEV_1, % ± s.d.	20 ± 8.8	21 ± 8.9
Mean PEF fluctuation, % ± s.d.	14 ± 9	12 ± 8
Severity of asthma based on GINA/NIH guidelines, n (%)		
Intermittent	11 (3)	5 (2)
Mild persistent	29 (7)	12 (6)
Moderate persistent	158 (38)	73 (36)
Severe persistent	218 (52)	115 (56)
ICS pretreated/non-ICS pretreated, n (%)	219 (53)/197 (47)	100 (49)/105 (51)
Asthma symptom score sum (mean)	1.62	1.66

*CIC 160 μg is an ex-actuator dose, equivalent to 200 μg ex-valve/nominal dose.
†BUD 400 μg is a nominal dose.
‡Value at randomization.
CIC, ciclesonide; BUD, budesonide; s.d., standard deviation; FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow; GINA/NIH, Global Initiative for Asthma/National Institutes of Health; ICS, inhaled corticosteroid.

asthma symptom score sum of 1.6/day and median rescue medication use of 2 puffs/day before randomization. Approximately one-half of the patients in each treatment group were not ICS-pretreated before the start of the study. Compliance with treatment was 94% in both treatment groups in the ITT population, and 94% and 95% in the ciclesonide and budesonide groups, respectively, in the PP population.

Efficacy

Pulmonary function. Both ciclesonide 160 μg once daily and budesonide 400 μg once daily achieved statistically significant increases in FEV_1 after 12 wk of treatment (232 and 250 ml, respectively, ITT; 220 and 253 ml, respectively, PP; all $p < 0.0001$ vs. baseline; Fig. 1, Table 2). Non-inferiority of ciclesonide vs. budesonide was demonstrated for FEV_1 (95% CI: −75, 10 ml, $p = 0.0009$, one-sided non-inferiority, PP; 95% CI: −59, 22 ml, $p = 0.8158$, one-sided superiority, ITT). Furthermore, ciclesonide and budesonide achieved statistically significant increases in morning PEF, evening PEF and FVC after 12 wk of treatment ($p < 0.0001$ vs. baseline, two-sided, ITT and PP analyses; Table 2) and these increases were similar in both treatment groups (Table 2). Results obtained in the PP analysis were confirmed in the ITT analysis. No statistically significant treatment-by-centre interactions were observed for any of the lung function variables.

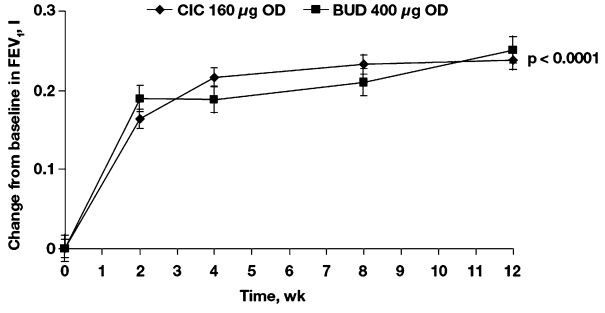

Fig. 1. Change in forced expiratory volume in 1 s during 12 wk of treatment with ciclesonide or budesonide (intention-to-treat population). Ciclesonide 160 μg is a delivered dose, equivalent to a nominal dose of 200 μg. Data are presented as least squares mean ± standard error of the mean $p < 0.0001$ vs. baseline for both groups at all time points. *Non-inferiority based on 95% CI for the difference between groups after 12 wk of treatment = −0.075, 0.010; $p < 0.0001$, one-sided non-inferiority. For the 2-, 4-, 8- and 12-wk time points, the 'n' values in the ciclesonide group were: 410, 407, 401 and 399, respectively. The corresponding 'n' values for the budesonide group were: 203, 202, 201 and 200. FEV_1, forced expiratory volume in 1 s; CIC, ciclesonide; OD, once daily; BUD, budesonide.

Asthma symptoms and use of rescue medication. Ciclesonide 160 μg once daily and budesonide 400 μg once daily achieved statistically significant improvements in asthma symptom score sum after 12 wk of treatment (−1.18 and −1.19, respectively, ITT; −1.21 and −1.21, respectively, PP; all $p < 0.0001$ vs. baseline, two-sided). The improvement in asthma symptom score sum was not significantly different between treatment groups (ITT: 95% CI: −0.14 to 0.21, $p = 0.8379$, two-sided; PP: 95% CI: −0.20 to 0.25, $p = 0.8868$, two-sided). Ciclesonide and budesonide treatment also achieved a statistically significant reduction in the need for rescue medication after 12 wk of treatment (ITT: −1.58 and −1.64 puffs/day, respectively; $p < 0.0001$ vs. baseline). The improvement in use of rescue medication was not significantly different between treatment groups (ITT: 95% CI: −0.26 to 0.29 puffs/day, $p = 0.8593$, two-sided).

The percentage of days without asthma symptoms and without need for rescue medication was 73% and 70% for patients in the ciclesonide 160 μg once daily and budesonide 400 μg once daily treatment groups, respectively, and there were no differences between treatment groups (ITT). The percentage of nocturnal awakening-free days was 98.5% in both treatment groups (ITT).

The percentage of patients with asthma exacerbations was small in both treatment groups (2.6% and 1% in the ciclesonide 160 μg once daily and budesonide 400 μg once daily treatment groups, respectively), and no significant between treatment difference in the time-to-onset of the first asthma exacerbation was observed.

Quality of life

Ciclesonide 160 μg once daily and budesonide 400 μg once daily achieved statistically significant improvements in overall scores vs. baseline on the PAQLQ(S) (ITT: 0.69 and 0.70, respectively; both $p < 0.0001$) and PACQLQ (ITT: 0.88 and 0.96, respectively; both $p < 0.0001$). Non-inferiority of ciclesonide vs. budesonide was demonstrated in the PAQLQ(S) and PACQLQ (ITT: 95% CI: −0.12 to 0.10, $p = 0.5738$, one-sided superiority and 95% CI: −0.27 to 0.13, $p = 0.7657$, one-sided superiority, respectively). A meaningful improvement in QOL (defined as ≥0.5) (22) was observed in more than 50% of patients in each treatment group as assessed with the PAQLQ(S) (ciclesonide 56.6%; budesonide 53.4%; ITT) and PACQLQ (ciclesonide 60.5%; budesonide 60.8%; ITT). A net benefit in QOL

Table 2. Change in lung function after treatment with ciclesonide or budesonide

	ITT		PP	
Parameter	CIC 160 μg once daily*	BUD 400 μg once daily†	CIC 160 μg once daily*	BUD 400 μg once daily†
FEV_1 (ml)				
Baseline (mean)	1529	1566	1526	1556
Change from baseline				
LS (mean ± s.e.m.)	232 ± 12	250 ± 17	220 ± 13	253 ± 18
p-Value	<0.0001	<0.0001	<0.0001	<0.0001
Change vs. BUD				
LS (mean)	−19		−33	
95% CI‡	−59 to 22		−75 to 10	
p-Value§	0.8158		0.9347	
FVC (l)				
Baseline (mean)	1.838	1.891	1.838	1.879
Change from baseline				
LS (mean ± s.e.m.)	0.207 ± 0.014	0.230 ± 0.019	0.204 ± 0.015	0.236 ± 0.020
p-Value	<0.0001	<0.0001	<0.0001	<0.0001
Change vs. BUD				
LS (mean)	−0.024		−0.032	
95% CI‡	−0.068 to 0.021		−0.079 to 0.015	
p-Value§	0.8531		0.9106	
Morning PEF (from diary; l/min)				
Baseline (mean)	202.1	204.6	199.3	201.2
Change from baseline				
LS (mean ± s.e.m.)	22.7 ± 2.0	25.0 ± 2.8	22.5 ± 2.2	26.3 ± 3.0
p-Value	<0.0001	<0.0001	<0.0001	<0.0001
Change vs. BUD				
LS (mean)	−2.3		−3.7	
95% CI‡	−8.9 to 4.3		−10.9 to 3.4	
p-Value§	0.7551		0.8491	
Evening PEF (from dairy; l/min)				
Baseline (mean)	215.1	221.0	211.2	216.7
Change from baseline				
LS (mean ± s.e.m.)	14.6 ± 1.9	11.3 ± 2.7	14.5 ± 2.1	14.9 ± 2.8
p-Value	<0.0001	<0.0001	<0.0001	<0.0001
Change vs. BUD				
LS (mean)	3.3		−0.4	
95% CI‡	−3.0 to 9.6		−7.0 to 6.3	
p-Value§	0.1537		0.5411	

*CIC 160 μg is an ex-actuator dose, equivalent to CIC 200 μg ex-valve/nominal dose.
†BUD 400 μg is a nominal dose.
‡95% CI for the difference between treatment groups.
§One-sided, superiority.
ITT, intention-to-treat; PP, per-protocol; CIC, ciclesonide; BUD, budesonide; FEV_1, forced expiratory volume in 1 s; LS, least squares; s.e.m., standard error of the mean; CI, confidence interval; FVC, forced vital capacity; PEF, peak expiratory flow.

of 50.4%, as assessed with the PAQLQ(S), and 51.2%, assessed with the PACQLQ, was demonstrated for ciclesonide, compared with 49.7% and 52.3%, respectively, for budesonide (ITT).

Safety

Changes in body height. Baseline height measurements in the total population are provided in Table 1. For the stadiometry subgroup, there were 58 children in the ciclesonide group and 26 in the budesonide group, with similar numbers of children aged 6–9 and 10–11 yr across the two treatment groups. Baseline mean ± s.d. height in the stadiometry subgroup was 134.4 ± 9.7 cm in the ciclesonide group and 135.4 ± 10.8 cm in the budesonide group. Body height increased by 1.18 and 0.70 cm in the ciclesonide and budesonide groups, respectively, as assessed by stadiometry, after 12 wk of treatment (both $p < 0.0001$ vs. baseline; Fig. 2). The increase in body height was significantly greater in ciclesonide-treated patients than in budesonide-treated patients (difference between ciclesonide and budesonide treatment groups = 0.481 cm, $p = 0.0025$, two-sided). The measurement of height by standard devices supported the stadiometry results.

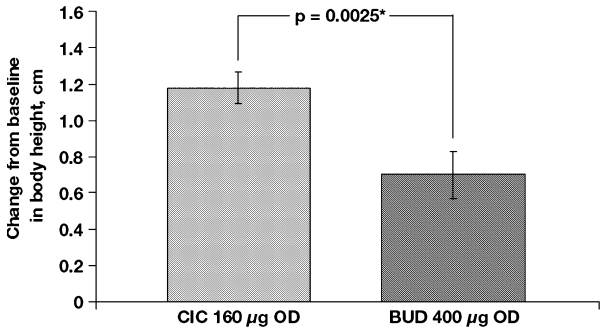

Fig. 2. Change in body height measured by stadiometry after 12 wk of treatment with ciclesonide (n = 58) or budesonide (n = 26) (intention-to-treat population). Ciclesonide 160 μg is a delivered dose, equivalent to a nominal dose of 200 μg. Data are presented as least squares mean ± standard error of the mean p < 0.0001 vs. baseline for both groups. *p-Value vs. budesonide is two-sided. CIC, ciclesonide; OD, once daily; BUD, budesonide.

24-H urinary cortisol adjusted for creatinine. Treatment with ciclesonide 160 μg once daily and budesonide 400 μg once daily resulted in statistically significant decreases (−2.17 and −5.16 nmol/mmol creatinine, respectively, in 24-h urinary cortisol adjusted for creatinine after 12 wk of treatment, amounting to median percentage decreases of −6.9% and −22.9%, respectively; both p < 0.0001 vs. baseline; Fig. 3). The decrease in 24-h urinary cortisol was significantly greater in the budesonide group compared with the ciclesonide group (difference between ciclesonide and budesonide treatment groups = 2.989 nmol/mmol creatinine; p < 0.0001, one-sided).

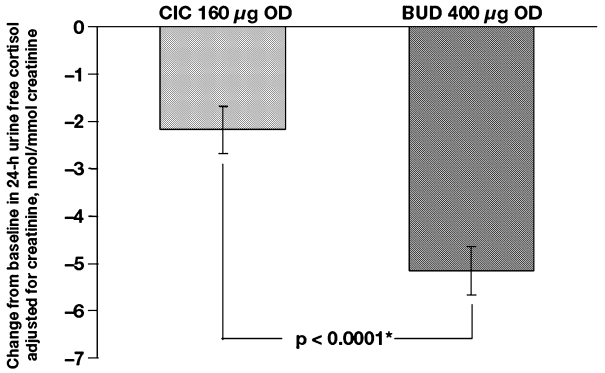

Fig. 3. Change in 24-h urinary cortisol adjusted for creatinine after 12 wk of treatment with ciclesonide (n = 353) or budesonide (n = 179) (intention-to-treat population). Urine samples with creatinine values in the normal range were included. Ciclesonide 160 μg is a delivered dose, equivalent to a nominal dose of 200 μg. Data are presented as least squares mean ± standard error of the mean p < 0.0001 vs. baseline for both groups. *p-Value vs. budesonide is one-sided. CIC, ciclesonide; OD, once daily; BUD, budesonide.

Adverse events. Adverse events occurred in approximately 38% of patients in both treatment groups. The majority of patients (96%) experienced AEs of mild-to-moderate intensity that were assessed as unrelated to the study medication. Pharyngitis (ciclesonide: 6.0%; budesonide: 6.8%), nasopharyngitis (ciclesonide: 4.1%; budesonide: 5.4%) and upper respiratory tract infection (ciclesonide: 3.6%; budesonide: 6.3%) were the most frequently reported respiratory-related AEs in both treatment groups. The incidence of local AEs (oral candidiasis and dysphonia) was low in ciclesonide- and budesonide-treated patients (0.2% and 1.5%, respectively). Four patients in each treatment group experienced a total of eight serious AEs, all of which were assessed as unrelated to the study medication. A total of 2.9% of patients in the ciclesonide group and 1.0% of patients in the budesonide group discontinued treatment prematurely, primarily because of worsening of asthma. This included all patients with asthma exacerbations as reported above, plus one additional case of worsening of asthma, not fulfilling the predefined criteria for asthma exacerbation. All AEs leading to study discontinuation were considered to be unrelated or unlikely to be related to the study medication. One patient in each treatment group discontinued treatment prematurely because of a serious AE.

Discussion

This study demonstrated that ciclesonide 160 μg once daily showed similar efficacy to budesonide 400 μg once daily in improving FEV_1, morning and evening PEF, asthma symptom score sum, use of rescue medication, percentage of days without asthma symptoms and without need for rescue medication and QOL of paediatric patients and their caregivers after 12 wk of treatment.

Effective treatment of asthma in childhood is important because patients who receive early ICS therapy experience greater improvements in pulmonary function compared with those who have a longer duration of untreated symptoms (23). ICS use is of particular concern in children because ICS are likely to be used for the long-term treatment of asthma and duration of therapy, as well as dose, frequency of administration, study population and prior systemic steroid therapy, is one of the factors that correlate with the extent of adrenal suppression (24).

The results of the current study are consistent with those of previous studies that examined the effect of ciclesonide treatment in children with asthma (19, 25). In this study, similar efficacy in

the treatment of asthma was achieved when ciclesonide was administered at half the daily dose of budesonide. This may be important because asthma management guidelines recommend early intervention with ICS at the lowest effective dose (1, 7). A previous comparative study with fluticasone propionate indicated that the efficacy of ciclesonide appeared to be similar to that of fluticasone propionate on a microgram for microgram basis in paediatric asthma patients; ciclesonide 160 μg/day had comparable efficacy with that of fluticasone propionate 176 μg/day (ex-actuator) for improving asthma symptoms and lung function in children and adolescents aged 6–15 yr with mild-to-severe persistent asthma (19).

In the present study, to avoid unnecessary complexity in drug application, budesonide was administered once daily at 400 μg (26). Several published studies have shown similar efficacy (with regard to FEV_1, morning PEF and withdrawal due to deterioration of asthma) of budesonide 400 μg once daily vs. budesonide 200 μg twice daily in children and adults with asthma (27). According to the prescribing information for budesonide, the recommended dose range of budesonide in paediatric patients is 200–800 μg/day (26). For these reasons, administration of budesonide at a dose of 400 μg was considered appropriate for the treatment of moderate-to-severe persistent asthma in children. Both ciclesonide and budesonide were administered in the evening in this study as evening dosing is in line with the preferred recommendation in the approved label of ciclesonide (28) and in the EU label of budesonide (26). Previous studies have indicated that the efficacy of both ICS do not depend on the timing of dosing (27, 29–31). In addition, as evening dosing of ICS may reduce nocturnal growth hormone activity (32), it was also considered important to determine the safety of both ICS when administered at this time. Therefore, the safety analysis included sensitive measures to investigate any potential systemic effects of ICS on HPA axis, as assessed by 24-h urinary cortisol, and on body height. Possible limitations of this study include the lack of a placebo control arm and the lack of adjustments made depending on the pubertal stage of the patients for the growth assessments; these issues are discussed further below.

The finding that budesonide treatment resulted in significantly smaller increases in body height compared with ciclesonide in this 12-wk study is consistent with published information regarding the safety profile of both of these agents. Previous studies investigating the effect of treatment with budesonide on children have shown significant reductions in body height compared with placebo, with the greatest reduction occurring during the first year of treatment (33, 34). However, most children and adolescents treated with inhaled budesonide ultimately seem to achieve their adult target height (35). In a previous placebo-controlled study, ciclesonide 40, 80 or 160 μg once daily was shown not to affect short-term lower leg growth rate in children, as assessed by knemometry (20, 36), as well as 1-yr growth velocity (20). The results of these studies conducted on childhood growth cannot be used to predict growth during long-term treatment. They are, however, suitable for comparing the growth-inhibiting effects of individual inhaled steroids (37). Hence, the impact and clinical relevance of the observed differences in growth-related parameters in several studies is yet unclear, but differences between ICS are reproducible. The current study included children aged 6–11 yr and, therefore, some may have already reached pubescence, which may have affected growth rate measurements. However, both treatment groups included children across the whole age range, so any variations caused by different stages of puberty would be expected to be seen in both treatment groups.

In this study, both ciclesonide and budesonide led to decreases in urinary cortisol (6.9% and 22.9%, respectively). Driven by the large sample size, these decreases were statistically significant. However, as no placebo control was included in the current study, the clinical relevance of the observed decrease from baseline to the end of the study cannot be evaluated conclusively. Previous studies with ciclesonide have shown a lack of significant effect on urinary cortisol levels compared with placebo (36, 38, 39). For example, a study by Lipworth et al. comparing the influence of placebo, ciclesonide 320 μg once daily and twice daily and fluticasone 440 μg twice daily on 24-h urinary cortisol demonstrated that even with placebo a decrease of 8.6% was observed after 12 wk of treatment (39). This indicates that a decrease in this order might be a normal variability of this parameter. The differences in body height and urinary cortisol excretion between treatments may indicate a favorable systemic safety profile of ciclesonide compared with budesonide.

A recent study reported that treatment with once daily ICS improves adherence rates and decreases healthcare costs relative to twice daily regimens (40). Therefore, treatment of paediat-

ric asthma with a once daily ICS may result in increased adherence to therapy, thereby improving long-term patient outcomes. While compliance was not formally measured in the current study, compliance as assessed in patient diaries was high in both treatment groups; however, as this study was performed under controlled conditions it does not reflect real life situations.

In conclusion, this study demonstrates that ciclesonide 160 μg once daily at half the dose of budesonide 400 μg once daily achieved similar improvements in lung function, asthma symptoms, use of rescue medication and QOL in paediatric patients with asthma. Moreover, the differences in body height and urinary cortisol excretion may indicate a favorable systemic safety profile of ciclesonide. This may reduce patient, caregiver and prescriber concerns about systemic side effects and improve long-term adherence to ICS therapy.

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