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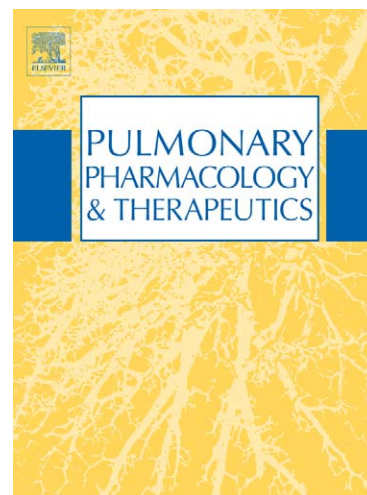
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**Ciclesonide is more effective than budesonide in the treatment of persistent asthma**

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**ABSTRACT**

**Background:** Ciclesonide is a lung-activated inhaled corticosteroid that provides effective control of persistent asthma. The objective of this study was to compare the efficacy and safety of once-daily ciclesonide versus once-daily budesonide in patients with asthma.

**Methods:** A total of 399 patients with asthma were randomised to receive once-daily ciclesonide 320 µg ex-actuator (equivalent to 400 µg ex-valve) or once-daily budesonide 400 µg for 12 weeks. The primary endpoint was forced expiratory volume in 1 second (FEV<sub>1</sub>). Additional efficacy variables included forced vital capacity (FVC), peak expiratory flow (PEF), asthma symptoms, use of rescue medication and time to onset of effect. Adverse events were monitored throughout the study.

**Results:** Both ciclesonide and budesonide significantly increased FEV<sub>1</sub> from baseline (416 and 321 ml, respectively;  $p < 0.0001$ ). The increase in FEV<sub>1</sub> was significantly greater in ciclesonide-treated patients (95% confidence interval: 0.016 to 0.174;  $p = 0.019$  versus budesonide). Similarly, ciclesonide and budesonide significantly improved FVC and PEF from baseline ( $p < 0.0001$ ), and significantly greater increases occurred with ciclesonide ( $p = 0.034$  and  $0.019$  versus budesonide, respectively). Analysis of morning PEF revealed an earlier onset of action for ciclesonide versus budesonide; a significant improvement was seen by Day 2 ( $p = 0.039$  versus baseline) with ciclesonide compared with Day 7 for budesonide ( $p = 0.047$  versus baseline). Adverse events occurred with a similar incidence in both treatment groups. Neither treatment caused significant changes in urinary cortisol levels.

**Conclusion:** Once-daily ciclesonide was more effective than once-daily budesonide in improving FEV<sub>1</sub>, FVC and PEF. Ciclesonide also had an earlier onset of action than budesonide in patients with persistent asthma. Both ciclesonide and budesonide had good safety and tolerability profiles.

**Key words:** Ciclesonide, budesonide, asthma, inhaled corticosteroids, cortisol, once-daily

## 1. INTRODUCTION

Inhaled corticosteroids (ICS) are the most effective anti-inflammatory therapy for the long-term control of persistent asthma.[1, 2] However, poor adherence with prescribed ICS medication may be a major factor contributing to the suboptimal control of persistent asthma. Therefore, ongoing efforts are aimed at improving the level of treatment adherence in patients with asthma, including the development of ICS that are effective, have a rapid onset of action and are suitable for once-daily dosing.[3, 4]

Ciclesonide is delivered as a solution to the lung via a hydrofluoroalkane-propelled metered-dose inhaler (HFA-MDI).[5] Pulmonary esterases convert ciclesonide into the active metabolite, desisobutyryl-ciclesonide (des-CIC).[6, 7] Subsequently, des-CIC undergoes reversible esterification to form fatty acid conjugates in the lung that serve as a depot for the slow release of the active drug.[8] Finally, des-CIC is converted into a series of inactive metabolites that are eliminated from the body.[9]

Several clinical studies have reported the efficacy and safety profiles of ciclesonide in patients with persistent asthma over a range of doses (80–640  $\mu\text{g}$ ).[10-12] For example, ciclesonide 160 and 640  $\mu\text{g}$  once daily has been shown to maintain pulmonary function with a side-effect profile comparable to that of placebo.[12] In addition, although the pathophysiology of asthma is responsive to circadian changes,[13] it has been demonstrated that ciclesonide 160  $\mu\text{g}$  can be administered once daily either in the morning or evening with comparable improvements in lung function and asthma symptom control.[10] Budesonide is approved for use either once or twice daily in patients with asthma, providing similar improvements in lung function in asthma patients when administered as a once-daily 400- $\mu\text{g}$  dose or a twice-daily 200- $\mu\text{g}$  dose.[14] In a comparative study, ciclesonide 160  $\mu\text{g}$  administered once daily, either in the morning or evening, was shown to be comparable to budesonide 200  $\mu\text{g}$  twice daily (400  $\mu\text{g}$  per day) in maintaining lung function, asthma symptoms and rescue-medication use.[15] A further study compared the effects of a similar dose of ciclesonide (320  $\mu\text{g}$ ) and budesonide (400  $\mu\text{g}$ ) once-daily. Due to the circadian fluctuations in asthma, it is important to determine the effects of ICS at different times of the day. When administered in the

morning, ciclesonide was at least as effective as budesonide in patients with persistent asthma.[16] However, the corresponding comparison of ciclesonide versus budesonide using a similar dose and once-daily dosing in the evening has not been performed.

Therefore, the aim of the current study is to determine the effects of once-daily ciclesonide 320 µg (ex-actuator dose), administered via HFA-MDI in the evening, and once-daily budesonide 400 µg, administered via dry powder inhaler (DPI; Turbohaler™; AstraZeneca GmbH, Wedel, Germany) in the evening, in patients with moderate, persistent asthma.

## 2. METHODS

### 2.1 Patients

Patients (aged 12–75 years), with at least 6 months' history of asthma as defined by American Thoracic Society criteria [17], were recruited at 43 study centres. Pre-treatment with ICS ( $\leq 500$  µg/day beclomethasone dipropionate or equivalent) and/or other asthma medications (cromones, leukotriene antagonists or theophylline) was permitted with no change in treatment during the 4 weeks immediately before enrollment. Patients who used only rescue medication were also allowed to participate in this study. Patients with an asthma exacerbation or lower respiratory tract infection in the 4 weeks immediately before enrollment were excluded. Additional exclusion criteria were use of systemic steroids during the 4 weeks before enrollment or more than three times in the previous 6 months, use of injectable steroids for 6 weeks before enrollment, or use of rescue medication other than short-acting  $\beta_2$ -agonists. Pregnancy, current smoking or previous smoking (history of  $\geq 10$  pack-years), chronic obstructive pulmonary disease or hypersensitivity to ICS also resulted in patient exclusion. Upon study entry, patients discontinued their current therapy except for the use of short-acting  $\beta_2$ -agonists, as needed. After a run-in period of up to 4 weeks, patients were eligible for randomisation if forced expiratory volume in 1 second ( $FEV_1$ ) was 50%–90% predicted (or if  $FEV_1$  was  $>90\%$  of predicted, the  $FEV_1$ :forced vital capacity (FVC) ratio was  $\leq 0.7$ ). Patients treated with ICS before the run-in period had to exhibit a decrease in  $FEV_1$  of  $\geq 10\%$  during the

run-in period to demonstrate their need for ICS. In addition, reversible bronchial obstruction ( $FEV_1$  increase of  $\geq 15\%$  of initial value after application of salbutamol or a  $\geq 15\%$  variation in the diurnal peak expiratory flow [PEF]) ( $\geq 3$  of the last 7 days of the run-in period) was required.

## 2.2 Study design and treatment

This was a double-blind, double-dummy, randomised, parallel-group study. After the run-in period, patients were randomised (at baseline) to receive either ciclesonide 320  $\mu\text{g}$  (HFA-MDI, 160  $\mu\text{g}/\text{puff}$ ) or budesonide 400  $\mu\text{g}$  (Turbohaler<sup>TM</sup>, DPI; 200  $\mu\text{g}/\text{puff}$ ), administered once daily in the evening for 12 weeks. All study related procedures were conducted in accordance with the International Conference on Harmonisation guidelines of Good Clinical Practice [18] and the Declaration of Helsinki.[19]

## 2.3 Patient assessments

Patients were evaluated during the run-in period and during treatment visits (Weeks 1, 2, 4, 8, and 12) and at follow-up (ongoing adverse events only). At each study visit,  $FEV_1$ , PEF and FVC were measured by spirometry. Diary data (morning and evening PEF, daytime and nighttime asthma symptom scores and number of puffs of rescue medication) were recorded electronically using an electronic asthma monitor (AM2, VIASYS; H"ochberg, Germany) that captured the time and date of data entry. Asthma scores were recorded on 5-point scales as follows: daytime asthma scores were recorded on a scale from 0 (very well, no symptoms) to 4 (asthma very bad, unable to carry out daily activities as usual); and nighttime asthma scores ranged from 0 (no symptoms, slept through the night) to 4 (bad night, awake most of the night because of asthma).

The onset of effect of ciclesonide and budesonide treatment was determined by comparing values for morning PEF, sum of asthma symptom scores and rescue-medication use on a daily basis during the first week and on a weekly basis thereafter compared with the week before randomization (baseline). Patients exhibiting an asthma exacerbation, i.e. deterioration in asthma (e.g. increase in asthma symptoms, distinct drop in lung function) requiring treatment with oral

steroids were withdrawn from the study. Safety was evaluated by monitoring 24-hour urinary free cortisol levels, adverse events, vital signs and laboratory parameters.

#### 2.4 Statistical analysis

Statistical analysis of each study endpoint was conducted in the full analysis set (intention to treat; patients who received at least 1 dose of study medication) and valid cases set (per-protocol; patients who completed the study without any major protocol violations). Results are reported for the full analysis set only unless there were differences in statistical conclusions between the full analysis set and valid cases set. For the primary variable, FEV<sub>1</sub>, treatment comparisons were based on differences between the end of treatment and the baseline value at the time of randomisation (last value analysis). An analysis of covariance was performed with the value at baseline and age as covariates, and sex and study centre as factors. Initially, a test of non-inferiority was performed based on the per-protocol population and a non-inferiority acceptance limit of -200 ml. If non-inferiority was demonstrated, a subsequent test of superiority of ciclesonide over budesonide was performed using the full analysis set. Two-sided p-values are presented, with least-squares means and two-sided 95% confidence intervals (CI) calculated for treatment differences. A sample size of 200 patients per treatment group was required to ensure a power of 90% to demonstrate superiority of ciclesonide versus budesonide ( $\alpha=0.025$ , one sided; expected difference in means=150 ml; common standard deviation=450 ml).

Secondary variables – FVC, PEF by spirometry, and morning and evening PEF from diaries – were analysed analogously to FEV<sub>1</sub> (non-inferiority limits were as follows: FVC -0.20 l; PEF -25 l/min). Differences in the sum of asthma symptom scores and the use of rescue medication were analysed by non-parametric tests using the modification of Wilcoxon's signed-rank test according to Pratt (within groups) and the Mann-Whitney U test (between groups). Between-treatment comparisons for asthma symptom-free days and rescue-medication-free days were analysed using Mann-Whitney U tests. The time to onset of treatment effect was determined by comparing pre-treatment and post-treatment values of each of the relevant efficacy variables (morning PEF, sum of asthma symptom scores and rescue-medication use) for



significant changes. These comparisons were conducted by means of a step-down procedure using sequentially earlier and shorter time periods until differences were no longer significant. Changes in urinary cortisol levels were analysed by paired  $t$  tests (within groups) and independent  $t$  tests (between groups).

### 3. RESULTS

#### 3.1 Study population

A total of 437 patients were enrolled in this study, and 399 patients were randomised to either ciclesonide 320  $\mu\text{g}$  once daily ( $n=198$ ) or budesonide 400  $\mu\text{g}$  once daily ( $n=201$ ; full analysis set). Patient demographics and baseline characteristics were similar in both treatment groups (Table 1). Based on % predicted FEV<sub>1</sub>, the majority of patients had moderate, persistent asthma. Forty-one percent of patients in the ciclesonide group and 35% in the budesonide group had received previous ICS treatment.

During the study, 10 patients withdrew from the ciclesonide group and 18 patients withdrew from the budesonide group. Reasons for study discontinuation were asthma exacerbations (ciclesonide, two patients; budesonide, one patient), other adverse events (ciclesonide, three patients; budesonide, two patients) and non-medical reasons (ciclesonide, five patients; budesonide, 15 patients). All cases of study discontinuation due to adverse events were assessed as unrelated to study medication. A total of 54 patients had protocol violations during the study; 30 patients in the ciclesonide group and 24 patients in the budesonide group. The majority of these violations related to randomisation criteria (8% of patients) and use of prohibited concomitant medications (3% of patients). Therefore, 168 ciclesonide patients and 177 budesonide patients were included in the valid cases set.

[Table 1 near here]

#### 3.2 Efficacy

##### 3.2.1 Lung function variables

During the first 7 days of treatment, FEV<sub>1</sub> rapidly increased from baseline in patients

treated with either ciclesonide or budesonide (Figure 1). In both treatment groups, FEV<sub>1</sub> reached a plateau after 2 weeks and remained at constant levels until the end of the study. After 12 weeks of treatment (last value analysis), FEV<sub>1</sub> increased by 416 ml in the ciclesonide group and by 321 ml in the budesonide group ( $p < 0.0001$  versus baseline for both; Figure 2, Table 2), resulting in a between-treatment difference of 95 ml. As the lower limit of the 95% CI (16 to 174 ml) for the difference in FEV<sub>1</sub> improvements between ciclesonide and budesonide exceeded not only the non-inferiority margin of -200 ml, but also 0, superiority of ciclesonide over budesonide was demonstrated ( $p = 0.019$ , full analysis set). The significantly greater improvement in FEV<sub>1</sub> for ciclesonide compared with budesonide was even more pronounced in the subgroup of patients with a history of smoking (171 ml;  $p = 0.033$ ). In the subgroup of non-smokers, ciclesonide was numerically better than budesonide (35 ml), but not statistically superior ( $p = 0.498$ ).

Ciclesonide- and budesonide-treated patients also experienced significant improvements in FVC and PEF by spirometry after 12 weeks of treatment ( $p < 0.0001$  versus baseline for both) (Table 2). In addition, patients treated with ciclesonide achieved a significantly greater increase in FVC (0.46 versus 0.35 l;  $p = 0.034$ ) and PEF by spirometry (80 versus 61 l/min;  $p = 0.019$ ) compared with budesonide.

[Figures 1 and 2, and Table 2 near here]

### 3.3 Asthma symptoms and rescue-medication use

Statistically significant increases in asthma symptom scores (sum of daytime and nighttime symptoms) and decreases in use of rescue medication were observed after 12 weeks of treatment (last value analysis) with either ciclesonide or budesonide (Figure 3; Table 3). Ciclesonide significantly improved asthma symptom scores from baseline (change -0.62 units;  $p < 0.0001$ ). A similar improvement from baseline was observed in patients receiving budesonide (change -0.74 units;  $p < 0.0001$ ). The difference in the sum of asthma symptom scores between ciclesonide and budesonide treatment was not significant ( $p = 0.863$ ). Furthermore, ciclesonide and budesonide improved rescue-medication use relative to baseline ( $p < 0.0001$ ) (Figure 3; Table 3). The reduction in rescue-medication use was

comparable in the ciclesonide and budesonide treatment groups (−0.42 versus −0.57 puffs/day, respectively;  $p=0.687$ ).

[Figure 3 and Table 3 near here]

### 3.4 Onset of treatment effect

The time required to detect a change from baseline in morning PEF, asthma symptom scores and rescue-medication use was assessed to determine the onset of effect of ciclesonide and budesonide treatment. Ciclesonide treatment achieved a significant improvement in morning PEF by Day 2 ( $p=0.039$  versus baseline) compared with Day 7 for budesonide ( $p=0.047$  versus baseline; full analysis set) (Figure 4). In patients who completed the study according to the protocol (valid cases set), ciclesonide achieved a significant improvement in morning PEF by Day 3 ( $p=0.004$  versus baseline) compared with Week 2 for budesonide ( $p<0.001$  versus baseline). Both treatments significantly improved asthma symptom scores ( $p<0.0001$  ciclesonide;  $p<0.001$  budesonide) and decreased rescue-medication use ( $p<0.0001$  ciclesonide;  $p=0.001$  budesonide) on the first treatment day.

[Figure 4 near here]

### 3.5 Safety

Adverse events occurred with a similar incidence in both treatment groups. Seventy-three adverse events occurred in 28% of patients treated with ciclesonide and 71 adverse events occurred in 27% of patients treated with budesonide. The most frequent adverse events were related to the respiratory system, in particular upper respiratory tract infection, rhinitis and bronchitis, which occurred in  $\geq 3\%$  of patients in both treatment groups. Most adverse events were of mild or moderate intensity and were assessed as unrelated to the study drug. There were four adverse events (dyspnoea, voice alteration, cough and headache) potentially related to ciclesonide and none in the budesonide group.

During the follow-up period, one patient in the budesonide group reported oral candidiasis, which was assessed as “likely related” to study medication. Three

serious adverse events were reported in the ciclesonide group (surgery, stroke, dyspnoea/heart failure), all of them being assessed as unrelated to the study medication. There were no statistically significant or clinically relevant differences from baseline or between the two treatment groups in 24-hour urinary free cortisol or standard laboratory variables.

#### 4. DISCUSSION

This study demonstrated that once-daily evening administration of ciclesonide (320 µg ex-actuator; HFA-MDI) achieved significantly greater improvements in spirometric lung function measurements (FEV<sub>1</sub>, FVC and PEF) compared with once-daily evening administration of budesonide (400 µg; Turbohaler™) in patients with persistent asthma. Comparable improvements in PEF by diary, asthma symptom scores and rescue-medication use were observed in ciclesonide- and budesonide-treated patients. Treatment adherence was not measured in this study because of technical reasons. However, due to the applied administration pattern (2 puffs of active treatment and placebo device each, given in the evening) it is unlikely that differences in lung function between ciclesonide- and budesonide-treated patients were related to differences in adherence rates.

In a previous study, ciclesonide 160 µg administered once daily was shown to be comparable to budesonide 200 µg twice daily (400 µg per day) in maintaining lung function, asthma symptoms and rescue medication.[15] In addition, a study comparing the effects of ciclesonide 320 µg and budesonide 400 µg once daily when administered in the morning showed that ciclesonide was at least as effective as budesonide in patients with persistent asthma.[16] Ciclesonide was non-inferior to budesonide for FEV<sub>1</sub>, and statistically superior to budesonide (p=0.010) for FVC. In addition, asthma symptom scores were comparable and median percentage of symptom-free days was significantly higher for ciclesonide versus budesonide (p=0.017).[16] Therefore, due to the circadian fluctuations in asthma, [13] the current study compared the same once-daily doses of ciclesonide and budesonide administered in the evening. Importantly, the current study provided similar findings to those of the previous study administering both treatments in the morning, [16]

providing further support for the similar efficacies of ciclesonide and budesonide, regardless of timing of administration.

The onset of effect of ciclesonide treatment appeared to be more rapid compared with budesonide in the current study; improvements in morning PEF were evident by Day 2 in the ciclesonide group, whereas budesonide did not significantly increase morning PEF until Day 7. In a recent study, budesonide 1,600 µg/day increased FEV<sub>1</sub> and morning PEF after the first week of treatment,[20] which is in line with the results seen in the current study. Asthma symptom scores and rescue-medication use improved in both groups after the first dose. It is important to note that electronic diaries were used in this study to record assessments suitable to determine the onset of treatment effect. Compared with traditional patient diaries, electronic diaries are a more reliable tool for data collection because they capture the date and time at which assessments were recorded and, thereby, confirm the validity of the study data. The rapid onset of effect of ciclesonide treatment compares favourably with that of budesonide.

Previous studies have reported that ciclesonide and budesonide undergo fatty acid esterification in the lung.[8, 21, 22] Ciclesonide fatty acid conjugates are five-fold more lipophilic than budesonide fatty acid conjugates.[7] Increased lipophilicity and the ability to form fatty acid conjugates may increase ciclesonide retention in the lung [7, 8] and, thereby, may contribute to the clinical efficacy of once-daily ciclesonide observed in this study. In addition, the high pulmonary deposition of ciclesonide and the high affinity of the active metabolite for the glucocorticoid receptor potentially contribute to the improvements in lung function and asthma symptoms.[23, 24] Approximately 52% of the ciclesonide dose, administered via HFA-MDI, is delivered to the lungs, with the highest deposition (55% of the deposited dose) in the peripheral regions of the lung.[23] In contrast, pulmonary deposition of budesonide via dry powder inhaler is lower (15%–28% of the administered dose) and deposition is localised primarily to the central region of the lung.[25, 26] Furthermore, the active metabolite of ciclesonide (des-CIC) has a high relative glucocorticoid receptor affinity (1200 versus 900 for budesonide; dexamethasone reference is 100) and possesses substantial anti-inflammatory activity.[24, 27]

The most common side effects in both treatment groups were related to the respiratory system. However, most were of mild or moderate intensity and did not result in treatment discontinuation. No serious adverse events were assessed as related to the study drug. Furthermore, neither ciclesonide nor budesonide demonstrated any significant or clinically relevant changes in urinary cortisol measurements. Previous studies have shown that ciclesonide does not induce cortisol suppression at daily doses as high as 1280 µg.[28, 29] Similarly, budesonide 400 µg once daily did not demonstrate significant cortisol suppression in healthy subjects or patients with asthma.[30, 31] In another study, twice-daily budesonide 200 µg (400 µg per day) was shown to significantly suppress urinary cortisol compared with once-daily ciclesonide 320 µg ( $p < 0.05$ ).[32]

In conclusion, this study demonstrated that once-daily ciclesonide achieved a significantly greater improvement in lung function (FEV<sub>1</sub>, FVC and spirometric PEF) compared with once-daily budesonide. Furthermore, ciclesonide was shown to have a faster onset of action compared with budesonide based on improvements in morning PEF. Ciclesonide maintained asthma symptom scores and use of rescue medication as effectively as budesonide. Both ICS displayed a similar safety and tolerability profile.

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## CONFLICT OF INTEREST STATEMENT

Dieter Ukena has participated in advisory board meetings at ALTANA Pharma AG and AstraZeneca, and received lecture fees from AstraZeneca, Boehringer, Pfizer, ALTANA Pharma AG, Merck Sharp & Dohme and GlaxoSmithKline. Christian

Biberger and Volker Steinijans are full time employees of ALTANA Pharma AG, Konstanz, Germany. Volker von Behren, Ronitta Malek, Hans H. Weber, Ekkehard Beck and Anneliese Linnhoff have no conflicts of interest to disclose.

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## TABLES

Table 1. Demographic and baseline characteristics

Characteristics	Ciclesonide	Budesonide
	320 µg once daily	400 µg once daily
Patients, n	198	201
Sex (male/female), %	43/57	49/51
Median age, years (range)	44 (12–74)	46 (13–75)
Patients without/with history of smoking, %	64/36	67/33
ICS not pre-treated/ICS pre-treated, %	59/41	65/35
Asthma severity, %		
Mild (FEV <sub>1</sub> ≥80% predicted)	18	24
Moderate (FEV <sub>1</sub> >60% but <80% predicted)	70	61
Severe (FEV <sub>1</sub> ≤60% predicted)	12	15
FEV <sub>1</sub> , ml ± SD	2323 ± 632	2337 ± 641
FEV <sub>1</sub> , % predicted ± SD	71 ± 11	72 ± 11
Reversibility: change in FEV <sub>1</sub> , % ± SD	24 ± 11	24 ± 11
Morning PEF (diary) l/min ± SD	365 ± 117	352 ± 113
Morning PEF (diary), % predicted ± SD	79 ± 20	76 ± 21
PEF variability, % ± SD	12 ± 7	12 ± 6

ICS = Inhaled corticosteroid; FEV<sub>1</sub> = Forced expiratory volume in 1 second; SD = Standard deviation; PEF = Peak expiratory flow.

Full analysis set.

Ciclesonide 320 µg is an ex-actuator dose, equivalent to 400 µg ex-valve.

Patients with a history of smoking were defined as individuals having a history of <10 pack years or ≥3 months of smoking abstinence.

Table 2. Change in pulmonary function after 12 weeks of treatment

Variable	Ciclesonide 320 µg once daily	Budesonide 400 µg once daily
<b>Spirometry</b>		
<b>FEV<sub>1</sub>, ml</b>		
Change from baseline (LS mean ± SEM)	+416 ± 32	+321 ± 32
p value vs baseline	<0.0001	<0.0001
Change vs BUD		
LS mean ± SEM (95% CI)	95 ± 40 (16, 174)	
p value	0.019	—
<b>FVC, l</b>		
Change from baseline (LS mean ± SEM)	+0.46 ± 0.04	+0.35 ± 0.04
p value vs baseline	<0.0001	<0.0001
Change vs BUD		
LS mean ± SEM (95% CI)	0.10 ± 0.05 (0.01, 0.20)	
p value	0.034	—
<b>PEF, l/min</b>		
Change from baseline (LS mean ± SEM)	+80 ± 6	+61 ± 6
p value vs baseline	<0.0001	<0.0001
Change vs BUD		
LS mean ± SEM (95% CI)	19 ± 8 (3, 34)	

p value	0.019	—
<b>Diary</b>		
<b>Morning PEF, L/min</b>		
Change from baseline (LS mean $\pm$ SEM)	+46 $\pm$ 5	+36 $\pm$ 5
p value vs baseline	<0.0001	<0.0001
Change vs BUD		
LS mean $\pm$ SEM (95% CI)	11 $\pm$ 6 (-2, 23)	
p value vs BUD	0.091	—
<b>Evening PEF, L/min</b>		
Change from baseline (LS mean $\pm$ SEM)	+34 $\pm$ 5	+24 $\pm$ 5
p value vs baseline	<0.0001	<0.0001
Change vs BUD		
LS mean $\pm$ SEM (95% CI)	10 $\pm$ 6 (-3, 22)	
p value vs BUD	0.126	—
<p>FEV<sub>1</sub> = Forced expiratory volume in 1 second; BUD = Budesonide; LS = Least squares; SEM = standard error of the least squares mean; CI = Confidence interval; FVC = Forced vital capacity; PEF = Peak expiratory flow.</p> <p>Data are presented for the full analysis set.</p> <p>P values are two sided at the 5% level for test of differences.</p> <p>Ciclesonide 320 <math>\mu</math>g is an ex-actuator dose, equivalent to ciclesonide 400 <math>\mu</math>g ex-valve.</p>		

**Table 3. Change in asthma symptom scores and rescue-medication use after 12 weeks of treatment**

<b>Variable</b>	<b>Ciclesonide 320 µg once daily</b>	<b>Budesonide 400 µg once daily</b>
<b>Asthma symptom score sum</b>		
Change from baseline	-0.62	-0.74
p value vs baseline	<0.0001	<0.0001
Change vs BUD		
PE (95% CI)	0.00 (-0.21, 0.29)	
p value vs BUD	0.863	—
<b>Daytime symptom score</b>		
Change from baseline	-0.39	-0.33
p value vs baseline	<0.0001	<0.0001
Change vs BUD		
PE (95% CI)	0.00 (-0.14, 0.17)	
p value vs BUD	0.586	—
<b>Nighttime symptom score</b>		
Change from baseline	-0.21	-0.20
p value vs baseline	<0.0001	<0.0001
Change vs BUD		
PE (95% CI)	0.00 (-0.13, 0.10)	
p value vs BUD	0.797	—
<b>Rescue-medication use</b>		



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**(diary, puffs/day)**

Change from baseline	-0.42	-0.57
p value vs baseline	<0.0001	<0.0001
Change vs BUD		
PE (95% CI)	0.00 (-0.14, 0.29)	
p value vs BUD	0.687	—

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BUD = Budesonide; PE = Point estimate; CI = Confidence interval.

P values are two sided at the 5% level for test of differences.

Full analysis set.

Data are presented as medians (change from baseline) and non-parametric point estimates (PE, changes vs BUD).

Ciclesonide 320 µg is an ex-actuator dose, equivalent to ciclesonide 400 µg ex-valve.

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**FIGURE LEGENDS**

**Figure 1.** Change in forced expiratory volume in 1 second (FEV<sub>1</sub>) during 12 weeks of treatment (time course).

Full analysis set. Values are presented as least squares means  $\pm$  standard error of the least squares mean. Ciclesonide 320  $\mu$ g is an ex-actuator dose, equivalent to 400  $\mu$ g ex-valve. FEV<sub>1</sub> = Forced expiratory volume in 1 second; CIC = Ciclesonide; BUD = Budesonide.

**Figure 2.** Change in forced expiratory volume in 1 second (FEV<sub>1</sub>) after 12 weeks of treatment (last value analysis).

Full analysis set. Values are presented as least squares means  $\pm$  standard errors of the least squares mean. Ciclesonide 320  $\mu$ g is an ex-actuator dose, equivalent to 400  $\mu$ g ex-valve. \*p<0.0001 vs baseline; †ciclesonide vs budesonide. FEV<sub>1</sub> = Forced expiratory volume in 1 second; CIC = Ciclesonide; BUD = Budesonide.

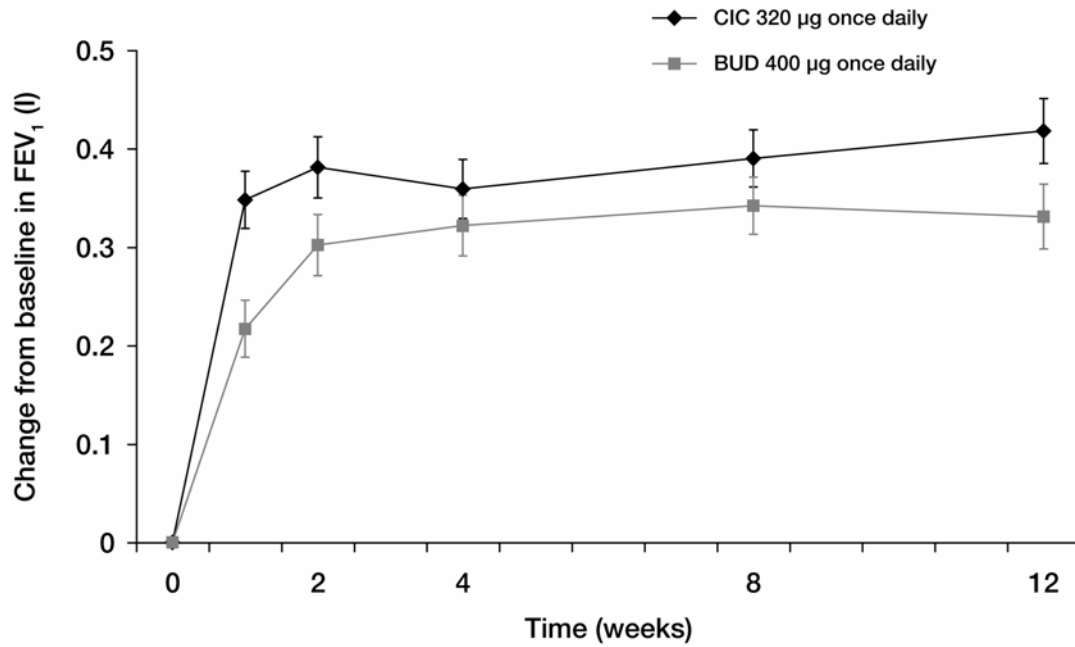
**Figure 3.** Asthma symptom scores and rescue-medication use after 12 weeks of treatment.

Full analysis set. Data are presented as non-parametric point estimates. Asthma symptom scores are sum of morning and evening scores. Ciclesonide 320  $\mu$ g is an ex-actuator dose, equivalent to 400  $\mu$ g ex-valve. \*p<0.0001 vs baseline; †ciclesonide vs budesonide (last value analysis). CIC = Ciclesonide; BUD = Budesonide.

**Figure 4.** Onset of action: change in morning peak expiratory flow (PEF) during first 4 weeks of treatment. Improvements with ciclesonide and budesonide therapy compared with baseline first reached statistical significance on day 2 (\*p=0.039) and day 7 (†p=0.047), respectively (dashed lines).

Full analysis set. Data reported as least squares mean  $\pm$  standard error of the least squares mean. †p<0.0001 vs baseline. Ciclesonide 320  $\mu$ g is an ex-actuator dose, equivalent to 400  $\mu$ g ex-valve. PEF = Peak expiratory flow; CIC = Ciclesonide; BUD = Budesonide.

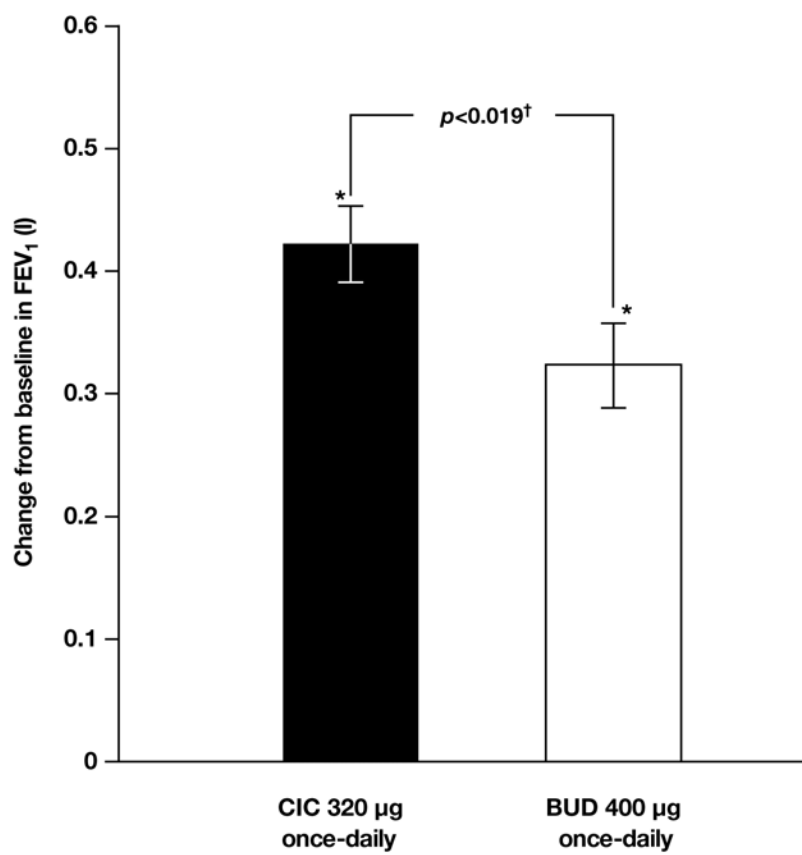
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Figure 2:

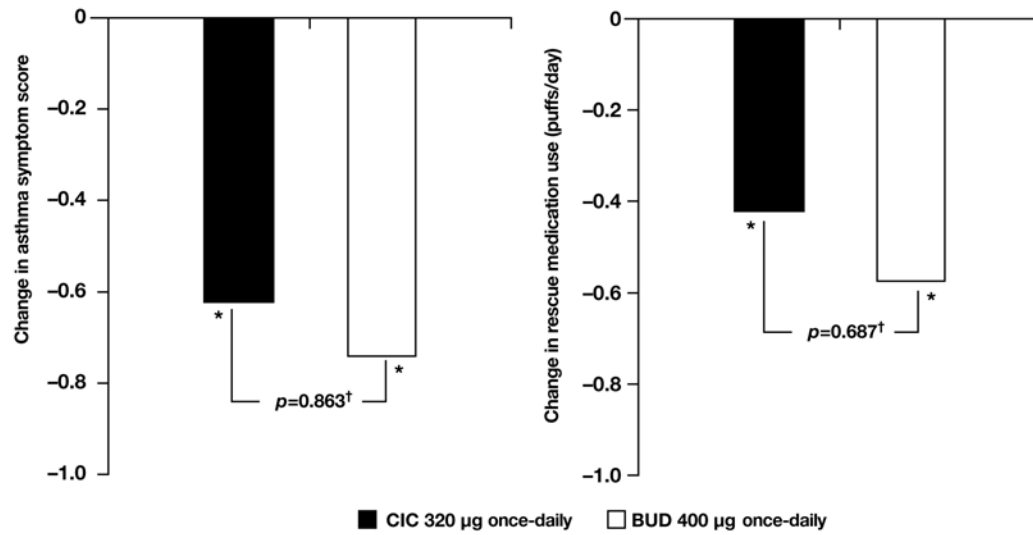
Figure 2



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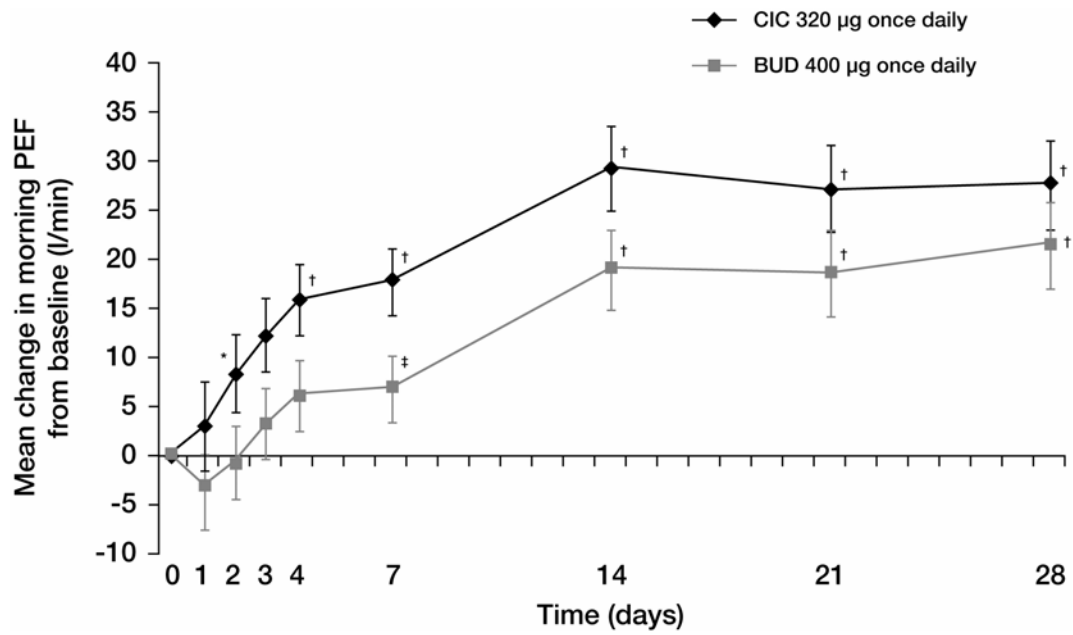
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