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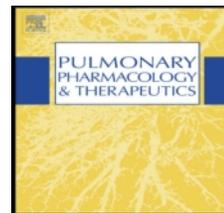
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Efficacy and safety of ciclesonide once daily and fluticasone propionate twice daily in children with asthma

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1.0 Abstract [255/400]

Background: Ciclesonide is a new inhaled corticosteroid (ICS). Information about its clinical efficacy and safety in relation to other ICS in children is needed for clinical positioning.

Objective: This 12-week, randomized, double-blind, double-dummy, three-arm, parallel-group study compared the efficacy and safety of ciclesonide with fluticasone propionate in children with mainly moderate and severe persistent asthma.

Methods: 744 patients (aged 6–11 years) were randomized to ciclesonide (80 or 160 µg once daily) or fluticasone propionate (88 µg twice daily), following a 2–4-week run-in. Efficacy measurements included forced expiratory flow in 1 second (FEV₁), morning peak expiratory flow (PEF), asthma symptom scores, rescue medication use and quality of life. Systemic effect was assessed by 24-hour urine free cortisol adjusted for creatinine.

Results: FEV₁ and morning PEF increased from baseline in all groups ($p < 0.0001$).

Ciclesonide 160 µg was non-inferior to fluticasone propionate 176 µg for FEV₁ ($p = 0.0030$, one-sided). In all groups, asthma symptom score sums and rescue medication use significantly improved ($p < 0.0001$). The percentage of asthma symptom-, rescue medication- and nocturnal awakening-free days were high, with no significant differences between treatments. Quality of life scores improved with all treatments ($p < 0.0001$). A significant dose-response occurred between low and higher doses of ciclesonide for exacerbations and asthma control definitions. The incidences of adverse events were comparable across treatments. Urine free cortisol levels decreased significantly with fluticasone propionate ($p = 0.0103$), but not with ciclesonide.

Conclusion: Once-daily ciclesonide has a clinical effect similar to that of fluticasone propionate, but does not suppress cortisol excretion, in children with moderate and severe asthma.

1.1 Keywords [Maximum 10]

Asthma; children; ciclesonide; efficacy; fluticasone propionate; hypothalamic–pituitary–adrenal axis; inhaled corticosteroids; safety

2.0 Introduction

Current asthma management guidelines recommend inhaled corticosteroids (ICS) as the preferred treatment option in pediatric patients with asthma.^{1,2} In spite of this, guideline recommendations are often not followed,^{3,4} even in patients with moderate or severe asthma. One of the reasons for this may be patient or physician concern about ICS-related adverse events (AEs).^{5,6} This is unfortunate as under-use of ICS has been linked to increased disease-related morbidity, including increased symptoms and rates of hospitalizations.⁷

Ciclesonide is a novel ICS for the treatment of persistent asthma that is administered via a metered-dose inhaler (MDI) using hydrofluoroalkane134a (HFA-134a) as the propellant. Previous studies, including comparative studies with other ICS, have shown that ciclesonide is effective in both adults and children with asthma.⁸⁻¹³ Furthermore, ciclesonide was well tolerated in these populations.^{8, 9, 14-19}

An earlier comparison of ciclesonide versus fluticasone propionate in children, using only one dose of each drug indicated similar efficacy of the two drugs.⁹ To further investigate the efficacy and safety of ciclesonide, the present study included bronchial hyperresponsiveness and definitions of asthma control using combinations of outcome measures, in addition to more traditional measures. A combination of variables is considered to be a sensitive measure for the detection of differences between various treatments.

The objective of this study was to evaluate and compare the efficacy and safety of ciclesonide MDI (80 µg [CIC80] or 160 µg [CIC160] once daily) with that of fluticasone propionate MDI (88 µg twice daily [FP176]) in children aged 6–11 years with persistent asthma.

3.0 Materials and methods

3.1 Study design

This was a double-blind, double-dummy, randomized, three-arm, parallel-group study performed in 50 centers in Brazil, Germany, Hungary, Poland, Portugal and South Africa. The study consisted of a run-in period (of at least 2 weeks and up to 4 weeks) and a 12-week treatment period. At the start of the run-in period, eligible patients discontinued previous ICS and other controller medications. During the treatment period, patients received either CIC80 or CIC160 (ex-actuator; equivalent to 100 and 200 µg ex-valve) in the evening, or FP176 (ex-

actuator; equivalent to 100 µg twice daily ex-valve) in the morning and evening without a spacer. Both treatments were administered via HFA134-a MDIs. The lower dose of ciclesonide was included for comparison, and to evaluate the dose–response relationship on the various outcomes that were tested.

Patients were randomized into one of the three treatment groups in a 1:1:1 randomization scheme by means of a computer-generated randomization list. During the treatment period patients were seen at the clinic every 4 weeks. Patients were allowed salbutamol (100 µg/puff) as rescue medication throughout the study. Patients were also allowed to continue regular nasal corticosteroids at a constant dose.

3.2 Patients

Male and female out patients aged 6–11 years with a history of persistent bronchial asthma, as defined by the American Thoracic Society, for ≥ 6 months were eligible for participation. Prior to the study, patients could either be treated with: rescue medication only; a constant dose of ICS of no more than fluticasone propionate 200 µg/day or equivalent for the last 30 days prior to study entry; or other controller medications. At the start of the run-in period, patients had to have forced expiratory volume in 1 second (FEV₁) values of: 50–90% of predicted (patients taking rescue medication only); 80–100% of predicted (patients using ICS); or 50–100% of predicted (patients using non-ICS controller medications).²⁰

To be entered into the treatment period, patients were required to have an FEV₁ 50–90% of predicted and a FEV₁ reversibility of $\geq 12\%$ predicted after inhalation of salbutamol 200–400 µg at the end of the run-in period. In addition, patients had to present asthma symptoms on at least 6 of the last 10 consecutive days of the baseline period, or to use at least 8 puffs of rescue medication within the last 10 consecutive days of the baseline period.

Furthermore, patients had to demonstrate a good inhalation technique when using a MDI without a spacer. The inhalation technique was reviewed at regular intervals during the study, and additional training was provided if necessary.

Exclusion criteria included: a history of near fatal asthma that required intubation; a respiratory tract infection or asthma exacerbation within the last 30 days prior to study entry;

more than two in-patient hospitalizations for asthma in the previous year; use of systemic steroids during the study, within the last 30 days prior to study entry or for more than 60 days in the previous 2 years.

The study was conducted in accordance with the rules of Good Clinical Practice and the ethical principles of the Declaration of Helsinki in its revised form. Written consent was obtained from the patients' parent(s) or legal guardian(s) before the start of the study, and the protocol was reviewed and approved by the appropriate Independent Ethics Committee or Institutional Review Boards for each participating center.

3.3 Outcomes

Spirometry (FEV₁ and peak expiratory flow [PEF]) measurements were performed at each clinic visit (at approximately the same time of the day at all visits) after a resting period of 15 minutes and withholding of rescue medication for ≥ 4 hours. The spirometry equipment was calibrated on a daily basis.

Patients' daily morning PEF measurements were performed at home on an electronic peak flow meter and the highest of three readings was recorded in a daily diary. Patients also recorded their asthma symptoms, using a nine-point scale (sum of daytime symptoms [on a scale of 0–4] and nighttime symptoms [on a scale of 0–4]), as per previous studies,^{9, 10, 13, 19} in the daily diary. Use of salbutamol was also recorded in the diary.

3.4 Quality of life assessments

The impact of asthma on the quality of life of both patients and caregivers was assessed using the standardized Pediatric Asthma Quality of Life Questionnaire (PAQLQ) and the Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ).^{21, 22}

3.5 Methacholine challenge

A methacholine (MCh) challenge was performed at a subgroup of sites. Challenges were not to be performed in children aged < 8 years, or patients with a basal FEV₁ $< 70\%$ predicted. The MCh challenge was performed at baseline (randomization) and study end (Week 12) using a five-step reservoir method.²³ The challenge was continued until a drop in FEV₁ of $\geq 20\%$ (provocative dose of MCh, causing a 20% drop in FEV₁ [PD₂₀FEV₁]) versus the basal

value was observed, or until the top dose of MCh was administered (243 µg, equating to a cumulative dose of 471 µg).

3.6 Safety assessments

Safety was assessed by AE reporting, physical examination, vital signs and laboratory investigations, including hematology, urinalysis and biochemistry. In all patients reporting oropharyngeal events, an oropharyngeal examination was performed and cultures were obtained via a swab for laboratory confirmation. The effects of study medication on the hypothalamic–pituitary–adrenal axis were evaluated by measuring cortisol in 24-hour urine samples during the run-in period and at the end of the study. Patients were withdrawn from the study in the case of an asthma exacerbation, which was defined as a worsening of asthma symptoms that required additional asthma medication other than increased use of rescue medication.

3.7 Statistical analysis

The primary efficacy variable was change in FEV₁ (L) from baseline to end of treatment. Key secondary variables included changes in home morning PEF and PD₂₀FEV₁ to MCh, and secondary variables included changes in PEF from spirometry (L/min), PAQLQ and PACQLQ, asthma symptom scores and use of rescue medication.

As a combination of outcomes was assumed to be clinically more relevant and also more likely to show differences between treatments than single outcomes, three different definitions (combined endpoints from patient diaries) of asthma control were included as secondary outcomes. These combinations were: 1) percentage of days without asthma symptoms or use of rescue medication; 2) percentage of days without asthma symptoms or use of rescue medication, plus a morning PEF >80% predicted; and 3) percentage of days without asthma symptoms or use of rescue medication, plus a morning PEF >80% predicted, plus a peak expiratory flow fluctuation of <15%. These combinations were analysed for the whole population, as well as for the three different asthma severity groups (mild, moderate and severe) of the patients at baseline.

A per-protocol (PP) analysis based on the PP population (i.e. the set of patients without any major protocol violation) was performed for each efficacy endpoint in this non-inferiority

study. Additionally, to confirm results, an intention-to-treat (ITT) analysis was also performed. The statistical analysis focused on non-inferiority of ciclesonide compared with fluticasone propionate. Predefined non-inferiority acceptance limits were: -100 mL for the primary endpoint change in FEV_1 ; -12.5 L/min for PEF measurements; -0.5 for PAQLQ and PACQLQ scores; $+0.15$ scores for nighttime asthma symptom score; and $+0.30$ scores for asthma symptom score sum.

The results from statistical testing of the primary variable and the key-secondary variables were confirmatory. Results from statistical testing of the secondary variables were interpreted in an exploratory manner. The *a priori* ordered hypothesis started with the test for non-inferiority of CIC160 versus FP176 with regard to the difference in FEV_1 and subsequently for the difference in morning PEF. The next test was for non-inferiority of CIC80 versus FP176 with regard to the difference in FEV_1 and subsequently for the difference in morning PEF.

A total of 250 patients per group were to be randomized to achieve 198 patients per group in the PP analysis, thereby providing a 90% power to demonstrate non-inferiority of ciclesonide to fluticasone propionate under the assumption of a between-treatment difference of 15 mL at most, a non-inferiority acceptance limit of -100 mL and a standard deviation of 260 mL for changes in FEV_1 at the 2.5% level, one-sided.

The primary variable of FEV_1 (L) was analysed by means of an analysis of covariance (ANCOVA) with treatment, gender and center pool as fixed factors and baseline value and age as covariates. The post/pre-ratios of the $PD_{20}FEV_1$ (MCh) were analysed by means of an ANCOVA after logarithmic transformation, with the $PD_{20}FEV_1$ value at randomization and age as covariates and with treatment, gender and center as fixed factors. For the analysis of PEF from spirometry, morning PEF (L/min), PAQLQ and PACQLQ, an analogous model was applied as for the analysis of FEV_1 . Change in asthma symptom scores, use of rescue medication, urine cortisol variables and percentage of days with asthma control were analysed within treatments using Pratt's modification of the Wilcoxon signed-rank test and the Mann-Whitney *U*-tests for differences between treatment groups. Non-parametric between-group comparisons of 24-hour urinary free cortisol were performed using the van Elteren test stratifying by center pool. Asthma exacerbations were analysed using the Cox

proportional hazard regression.

Due to the *a priori* ordered hypotheses and the principle of closed testing procedures, no adjustment of the α -level for multiplicity was performed. Least squares mean and 95% confidence intervals (CI) were used to determine differences within and between treatment groups.

4.0 Results

Overall, 904 patients were enrolled and a total of 744 patients (82%) were randomized and entered the treatment period; 711 patients completed the study (CIC80=234; CIC160=232; FP176=245). A total of 33 patients (CIC80=18; CIC160=10; FP176=5) terminated the study prematurely. Of the 744 randomized patients, 50 (CIC80=16; CIC160=18; FP176=16) were protocol violators, leaving 694 patients in the PP population (Table 1). The majority of protocol violations were due to unapproved asthma pre-treatment, inclusion or exclusion criteria. The treatment groups were comparable in terms of their demographic and baseline characteristics (Table 1). Approximately half of the patients were pretreated with ICS.

[Insert Table 1 near here]

4.1 Lung function

FEV₁ increased significantly from baseline in all treatment groups ($p < 0.0001$) (Table 2 and Figure 1). Non-inferiority was demonstrated for CIC160 versus FP176 (95% CI: $-0.079, 0.027$; $p = 0.0030$, one-sided), whereas CIC80 was not shown to be non-inferior to FP176. The findings and conclusions were similar for the ITT population and for clinically measured PEF.

[Insert Figure 1 near here]

Morning PEF also increased significantly (all $p < 0.0001$) from baseline in all treatment groups (Table 2); both ciclesonide doses were non-inferior to fluticasone propionate (PP analysis; $p \leq 0.0063$, one-sided, for both doses).

[Insert Table 2 near here]

4.2 Methacholine challenge

Methacholine challenges were performed in 91 children at the start of and at the end of the treatment period. Baseline PD₂₀FEV₁ values were similar in the three treatment arms (Table 1). Significant and similar improvements from baseline were seen in PD₂₀FEV₁ in all treatment groups ($p \leq 0.0031$ for all). Changes in PD₂₀FEV₁, expressed in doubling doses, were 1.83, 1.22 and 1.62 for CIC80, CIC160 and FP176, respectively. The corresponding improvements in the ITT analysis were 1.80, 1.25 and 1.64 doubling doses, respectively (no significant differences between treatment groups).

4.3 Asthma exacerbations, asthma symptoms and rescue medication use

Asthma exacerbations occurred in 7.1% (n=18) of patients receiving CIC80, 2.9% (n=7) of patients receiving CIC160 and 2.0% (n=5) of patients receiving FP176 (ITT analysis). The difference between the higher-dose treatments was not statistically significant, but both these treatments were significantly superior to CIC80 with respect to time to onset of first exacerbation ($p \leq 0.021$, one-sided).

All three treatments significantly decreased asthma symptom score sums and need for rescue medication from baseline (ITT and PP analyses; all $p < 0.0001$) (Table 3). Between-treatment analyses confirmed non-inferiority of both ciclesonide groups to FP176 for asthma symptom score sums (95% CI: -0.14, 0.29; $p \geq 0.5713$, two-sided, for both doses). No statistically significant differences were found between treatment groups for asthma symptom score sums and rescue medication use.

[Insert Table 3 near here]

The percentage of asthma symptom-free days, rescue medication-free days and nocturnal awakening-free days were high and did not differ significantly between the treatment groups (Figure 2).

[Insert Figure 2 near here]

The proportion of patients achieving asthma control depended on asthma severity, as well as

the outcomes included in the definition of asthma control (Figure 3). The more variables included in the definition of control, the lower the proportion of patients that achieved control. This trend was more marked in patients with moderate and severe asthma. The results for CIC160 were similar to the results for FP176 for all definitions of asthma control, whereas CIC80 was inferior to CIC160 (but not to FP176) in the two definitions that included criteria on PEF.

[Insert Figure 3 near here]

4.4 Quality of life

Quality of life significantly improved from baseline for overall scores and all sub-categories of the questionnaires in all treatment groups (ITT and PP analyses; $p < 0.0001$ for all). Between-treatment analyses for the overall PACQLQ and PAQLQ scores confirmed non-inferiority of CIC80 and CIC160 to FP176 (ITT and PP analyses; $p < 0.0001$, one-sided, for all).

4.5 Safety

In total, 337 patients (45.3%) experienced 557 AEs during the treatment period. The percentage of patients experiencing AEs was comparable across all treatment groups (CIC80, 46.4%; CIC160, 41.7%; FP176, 47.6%).

In all treatment groups, the most frequently reported AEs were classified as infections and infestations (32–39%, depending on the treatment group). Two cases of oral candidiasis were reported, one in the higher-dose ciclesonide group and one in the fluticasone propionate group. ~~Asthma exacerbations, as reported in the efficacy section above, were also recorded as AEs.~~ The majority of AEs were mild-to-moderate in intensity and most were assessed as unrelated to study medication.

Asthma exacerbations, as reported in the efficacy section above, were also recorded as AEs. In total, 13 patients (5.2%) treated with CIC80, five (2.1%) treated with CIC160 and two (0.8%) treated with FP176 discontinued the study prematurely due to the AE asthma exacerbation. ~~Of these, asthma was the most frequently reported AE in all treatment groups.~~

Twenty-four-hour urine free cortisol adjusted for creatinine decreased significantly from baseline in the fluticasone propionate group (-1.21 nmol/mmol; $p=0.0103$) as assessed by the safety analysis, which excluded patients with concurrent nasal, ophthalmological or dermatological steroid treatment. No statistically significant decreases from baseline were observed in either ciclesonide treatment group (CIC80, -0.06 nmol/mmol; $p=0.8375$; CIC160, -0.67 nmol/mmol; $p=0.1509$). There were no statistically significant differences between the CIC80, CIC160 and FP176 treatment groups ($p \geq 0.0465$, one-sided for superiority).

There were no clinically relevant changes in laboratory values, physical examination findings and vital signs over time in any of the treatment groups.

5.0 Discussion

The findings from this study confirmed that, microgram-for-microgram, ciclesonide was clinically equi-effective with fluticasone propionate in children with mainly moderate and severe persistent asthma. These results are in good agreement with the findings of studies in adults^{10, 11, 24} and an earlier study in children.⁹ However, in contrast to the earlier studies, the present study included outcomes such as bronchial hyperresponsiveness and different definitions of asthma control, which are normally thought to be sensitive outcome measures for the detection of differences between various treatments. As most of the patients suffered from moderate and severe asthma, it was thought that these patients would require higher-dose ICS therapy to achieve optimal asthma control, even if dose-response studies with ICS in patients with mild and moderate asthma have found that low doses cause marked clinical improvements in lung function and outcomes such as day and nighttime symptoms.

The effectiveness of the lowest dose of ciclesonide in the study was in agreement with an earlier dose-response study with ciclesonide⁸ and confirmed that low doses of ICS even in patients with mainly moderate and severe asthma are efficacious. The patients with mild and moderate asthma in the current study reported more than 90% symptom-free days on treatment with CIC80. Such an effect would be difficult to improve significantly with any additional treatment or increased doses. Only for more comprehensive definitions of asthma control or exacerbations was the lower dose less effective than higher-dose therapy. This

lends indirect support to the recommendations in the Global Initiative for Asthma guidelines to include several clinical outcomes in the definition of asthma control in children.¹

The lack of a significant dose–response on the MCh PD₂₀FEV₁ was surprising as other studies have found various bronchial challenges to be useful in detecting dose–response relationships.²⁵ However, as the MCh challenge was only performed at a subgroup of sites, the study may not have been sufficiently powered for this variable. A placebo arm might have facilitated the interpretation of this result; however, this was not included because low doses of both ciclesonide and fluticasone propionate have previously been demonstrated to be clinically more effective than placebo in controlling asthma and improving lung function in patients with persistent asthma.^{8, 26, 27} Furthermore, 12 weeks of treatment with placebo in patients with moderate and severe asthma would have been deemed unacceptable by many ethics committees and could have caused excessive dropouts. This would have markedly reduced the value of a placebo arm.

Ideally, comparisons of two ICS should use two doses of each drug to establish accurate clinical effect ratios. In retrospect it would have strengthened the conclusion if a low dose of fluticasone propionate had also been included in the current study. However, the dose–response relationships of some of the outcomes, and the finding that for some of the composite measures of asthma control there was still room for additional improvements even at the higher doses used, suggests that the comparison of the two drugs did not take place at the plateau of the dose–response curve. All patients were selected for good inhalation technique to ensure good ICS deposition in the lung for both treatments.

The most useful outcome to investigate when comparing various ICS is the therapeutic ratio, i.e. the ratio between the desired therapeutic effect and AEs at a given dose. In the present study, 24-hour urine cortisol levels were used as a surrogate marker for adverse systemic effects because the duration of the study did not allow assessment of effects on growth or bone mineral density. This needs further assessment in long-term studies including other safety parameters. The lack of effect of ciclesonide on cortisol excretion in this study corroborates the findings in other studies in children,^{8, 28} as well as adults,¹⁴⁻¹⁷ in which minimal effects on the hypothalamic–pituitary–adrenal-axis were seen. Both drugs were well tolerated in the study and the AE rates were low, with similar profiles for the two drugs.

5.1 Conclusion

The data from this study suggest that ciclesonide and fluticasone propionate are clinically equi-effective on a microgram-for-microgram basis in children with mainly moderate and severe asthma. Low doses of ICS are clinically effective in children with persistent asthma, and differences between different doses of ICS are more likely to be detected if measures of asthma control including combinations of several outcomes are studied.

ACCEPTED MANUSCRIPT

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7.0 Conflict of interest statement

Professor S Pedersen has received consultancy fees and lecture honoraria from Nycomed and GlaxoSmithKline, and has worked on research projects supported by Nycomed, GlaxoSmithKline and AstraZeneca. Dr R Engelstätter and Dr S Hirsch are employees of Nycomed. Dr H-J Weber was an employee of Nycomed at the time of writing of the manuscript. Professor A Emeryk has received consultancy fees from Nycomed and lecture honoraria from Nycomed, GlaxoSmithKline and AstraZeneca, and has worked on research projects supported by Nycomed, Thorax-Chisei and Pierre Fabre Medicament. Dr J Vermeulen has worked on research projects supported by Nycomed. Professor L Barkai and Dr H Weber have nothing to disclose.

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Table 1. Demographics and baseline disease characteristics of the intention-to-treat and per-protocol populations

Variable	ITT			PP		
	CIC80 n=252	CIC160 n=242	FP176 n=250	CIC80 n=236	CIC160 n=224	FP176 n=234
Median age (years)	9	9	9	9	9	9
Range	6–11	6–11	6–11	6–11	6–11	6–11
Mean weight ± SD (kg)	33 ± 9	34 ± 11	33 ± 10	32 ± 9	34 ± 11	34 ± 10
Mean height ± SD (cm)	135 ± 11	137 ± 11	135 ± 10	135 ± 11	137 ± 11	136 ± 10
Sex, n (%)*						
Male	164 (65.1)	158 (65.3)	164 (65.6)	153 (64.8)	146 (65.2)	155 (66.2)
Female	88 (34.9)	84 (34.7)	86 (34.4)	83 (35.2)	78 (34.8)	79 (33.8)
ICS pre-treatment, n (%)*						
Not ICS pre-treated	128 (50.8)	116 (47.9)	134 (53.6)	121 (51.3)	107 (47.8)	123 (52.6)
ICS pre-treated	124 (49.2)	126 (52.1)	116 (46.4)	115 (48.7)	117 (52.2)	111 (47.4)
Mean FEV₁ ± SD (L) at randomization	1.510 ± 0.374	1.583 ± 0.412	1.523 ± 0.346	1.511 ± 0.376	1.581 ± 0.412	1.524 ± 0.350
Mean FEV₁ % predicted ± SD at randomization	77.1 ± 9.3	77.6 ± 10.3	77.1 ± 9.9	77.1 ± 9.1	77.7 ± 10.2	76.8 ± 9.5
Mean FEV₁ % predicted reversibility ± SD	17.3 ± 6.8	17.7 ± 7.3	17.9 ± 7.5	17.3 ± 6.5	17.9 ± 7.1	18.0 ± 7.4
Geometric mean PD₂₀FEV₁ §	33.7 (N=31)	28.8 (N=27)	30.18 (N=33)	33.8 (N=28)	27.5 (N=26)	30.18 (N=33)

Asthma severity, n (%)						
Intermittent	5 (2.0)	9 (3.7)	3 (1.2)	5 (2.1)	8 (3.6)	3 (1.3)
Mild persistent	19 (7.5)	21 (8.7)	13 (5.2)	17 (7.2)	21 (9.4)	12 (5.1)
Moderate persistent	80 (31.7)	73 (30.2)	87 (34.8)	74 (31.4)	67 (29.9)	82 (35.0)
Severe persistent	141 (56.0)	133 (55.0)	134 (53.6)	135 (57.2)	123 (54.9)	124 (53.0)
Not classified	7 (2.8)	6 (2.5)	13 (5.2)	5 (2.1)	5 (2.2)	13 (5.6)

*Percentages are based on the number of patients in a treatment group; §=μg; ITT=intention-to-treat; PP=per-protocol; CIC80=ciclesonide 80 μg once daily; CIC160=ciclesonide 160 μg once daily; FP176=fluticasone propionate 88 μg twice daily; SD=standard deviation; ICS=inhaled corticosteroid; FEV₁=forced expiratory volume in 1 second; PD₂₀FEV₁=provocative dose of MCh, causing a 20% drop in FEV₁.

Table 2. Lung function after 12 weeks of treatment with ciclesonide 80 µg once daily, ciclesonide 160 µg once daily and fluticasone propionate 100 µg twice daily

Variable	ITT			PP		
	CIC80	CIC160	FP176	CIC80	CIC160	FP176
Spirometry						
FEV₁ (L)						
N	249	239	250	214	212	224
Baseline	1.537	1.537	1.537	1.542	1.542	1.542
Study end	1.760	1.797	1.813	1.762	1.791	1.817
Change from baseline*	0.224 ± 0.021	0.260 ± 0.021	0.276 ± 0.021	0.220 ± 0.022	0.250 ± 0.022	0.276 ± 0.021
Difference versus FP176	-0.053 ± 0.027	-0.016 ± 0.028	N/A	-0.055 ± 0.027	-0.026 ± 0.027	N/A
95% CI	-0.071, 0.001	-0.071, 0.038	N/A	-0.108, -0.003	0.079, 0.027	N/A
p-value for non-inferiority versus FP176 (one-sided)	0.0426	0.0013	N/A	0.0485	0.0030	N/A
Diary						
AM PEF (L/min)						
N	248	237	249	224	217	228
Baseline	234.6	234.6	234.6	235.1	235.1	235.1
Study end	257.4	262.8	263.1	258.5	264.3	259.9
Change from baseline*	22.8 ± 3.6	28.2 ± 3.6	28.5 ± 3.5	23.4 ± 3.6	29.1 ± 3.5	24.8 ± 3.5
Difference versus FP176	-5.8 ± 4.7	-0.4 ± 4.7	N/A	-1.4 ± 4.4	4.3 ± 4.5	N/A

95% CI	-14.9, 3.4	-9.6, 8.9	N/A	-10.1, 7.2	-4.4, 13.1	N/A
p-value for non-inferiority versus FP176 (one-sided)	0.0746	0.0051	N/A	0.0063	0.0001	N/A

*All $p < 0.0001$ from baseline. P-values for non-inferiority are one-sided at a significance level of 2.5%. Predefined non-inferiority acceptance limits were: -100 mL for the primary endpoint change in FEV₁ and -12.5 L/min for PEF measurements. All data are least squares mean or least squares mean \pm standard error of the mean; ITT=intention-to-treat; PP=per-protocol; CIC80=ciclesonide 80 μ g once daily; CIC160=ciclesonide 160 μ g once daily; FP176=fluticasone propionate 88 μ g twice daily; FEV₁=forced expiratory volume in 1 second; CI=confidence interval; AM=morning; PEF=peak expiratory flow

Table 3. Median change in asthma symptoms score sums and rescue medication use after 12 weeks of treatment with ciclesonide 80 µg once daily, ciclesonide 160 µg once daily and fluticasone propionate 100 µg twice daily

Variable	ITT			PP		
	CIC80	CIC160	FP176	CIC80	CIC160	FP176
Asthma symptom score sum						
N	240	231	242	213	211	219
Baseline	1.43	1.29	1.33	1.43	1.29	1.29
Study end	0.14	0.14	0.00	0.14	0.14	0.00
Change from baseline*	-0.86	-0.86	-0.93	-0.93	-0.89	-0.93
Rescue medication use						
N	247	237	249	223	216	229
Baseline	1.57	1.57	1.71	1.57	1.43	1.71
Study end	0.00	0.00	0.00	0.00	0.00	0.00
Change from baseline*	-1.20	-1.13	-1.29	-1.21	-1.14	-1.29

*All $p < 0.0001$ from baseline. Predefined non-inferiority acceptance limits were: +0.30 scores for asthma symptom score sum. Data presented as Hodges-Lehman point estimate; ITT=intention-to-treat; PP=per-protocol; CIC80=ciclesonide 80 µg once daily; CIC160=ciclesonide 160 µg once daily; FP176=fluticasone propionate 88 µg twice daily

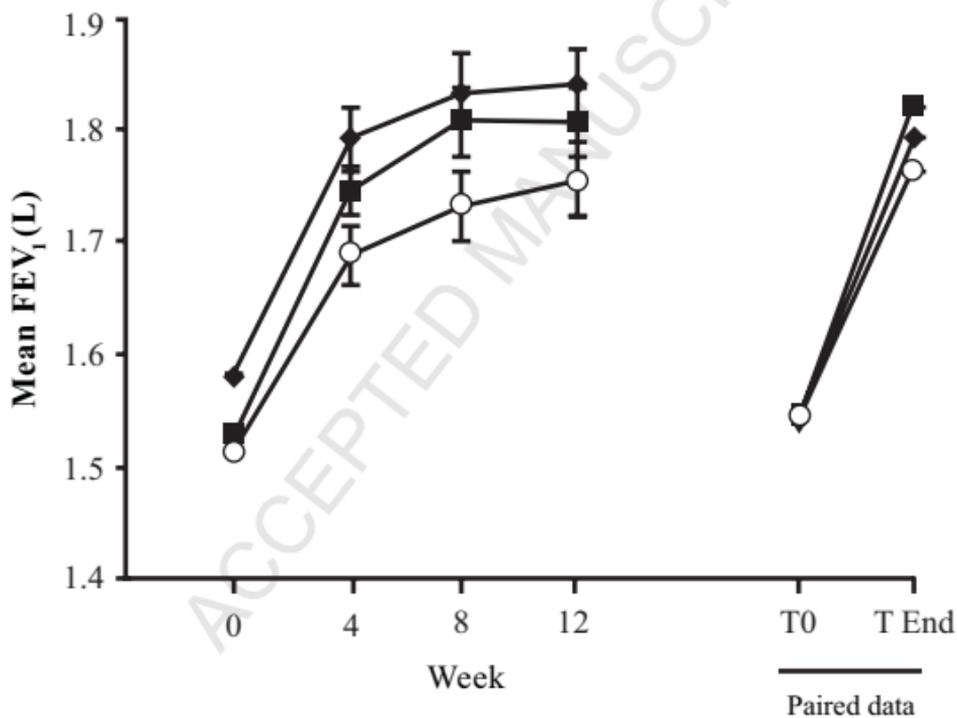
Figure legends**Figure 1. Mean forced expiratory volume in 1 second (L) over time (per-protocol population)**

The mean and standard error of the mean are presented for the time-course data. The least squares mean and standard error of the mean are presented for the paired data of the endpoint analysis.

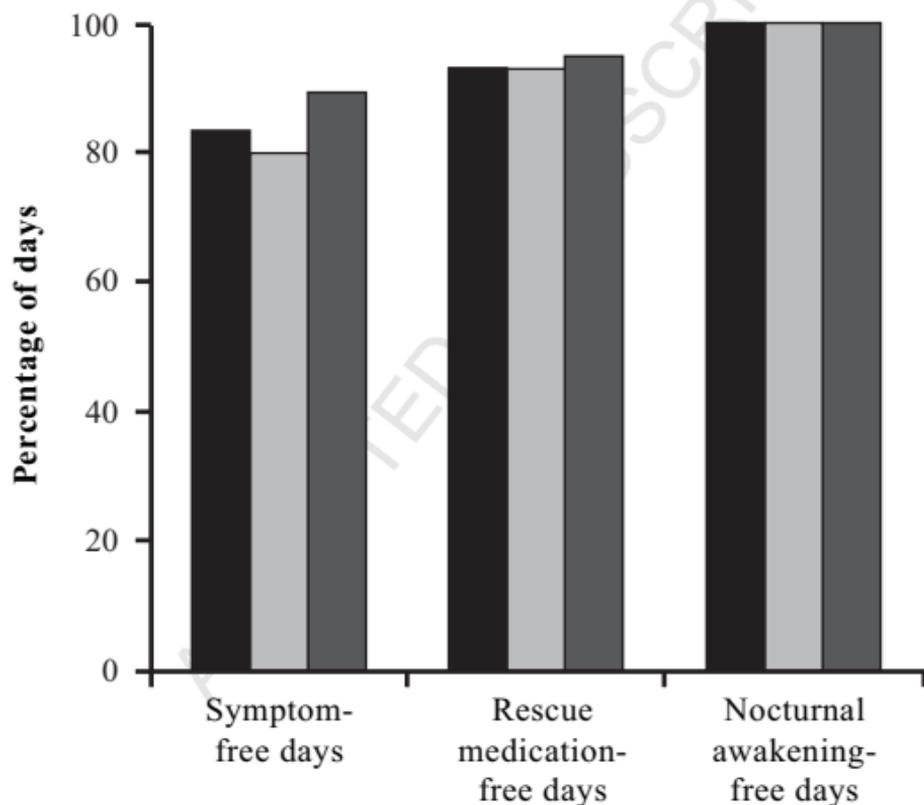
Figure 2. Median percentage of symptom-, rescue medication- and nocturnal awakening-free days over course of study (per-protocol population)**Figure 3. Median percentage of patients with asthma control by baseline asthma severity (per-protocol population)**

Patients with (a) no asthma symptoms or rescue medication use; (b) no asthma symptoms or rescue medication use, and morning peak expiratory flow >80%; (c) no asthma symptoms or rescue medication use, and morning peak expiratory flow >80% and peak expiratory flow fluctuation <15%. CIC80=ciclesonide 80 µg once daily; CIC160=ciclesonide 160 µg once daily; FP176=fluticasone propionate 88 µg twice daily.

- Ciclesonide 80 μg once daily
- ◆ Ciclesonide 160 μg once daily
- Fluticasone propionate 88 μg twice daily

**Figure 1**

- Ciclesonide 80 μg once daily
- Ciclesonide 160 μg once daily
- Fluticasone propionate 88 μg twice daily

**Figure 2**

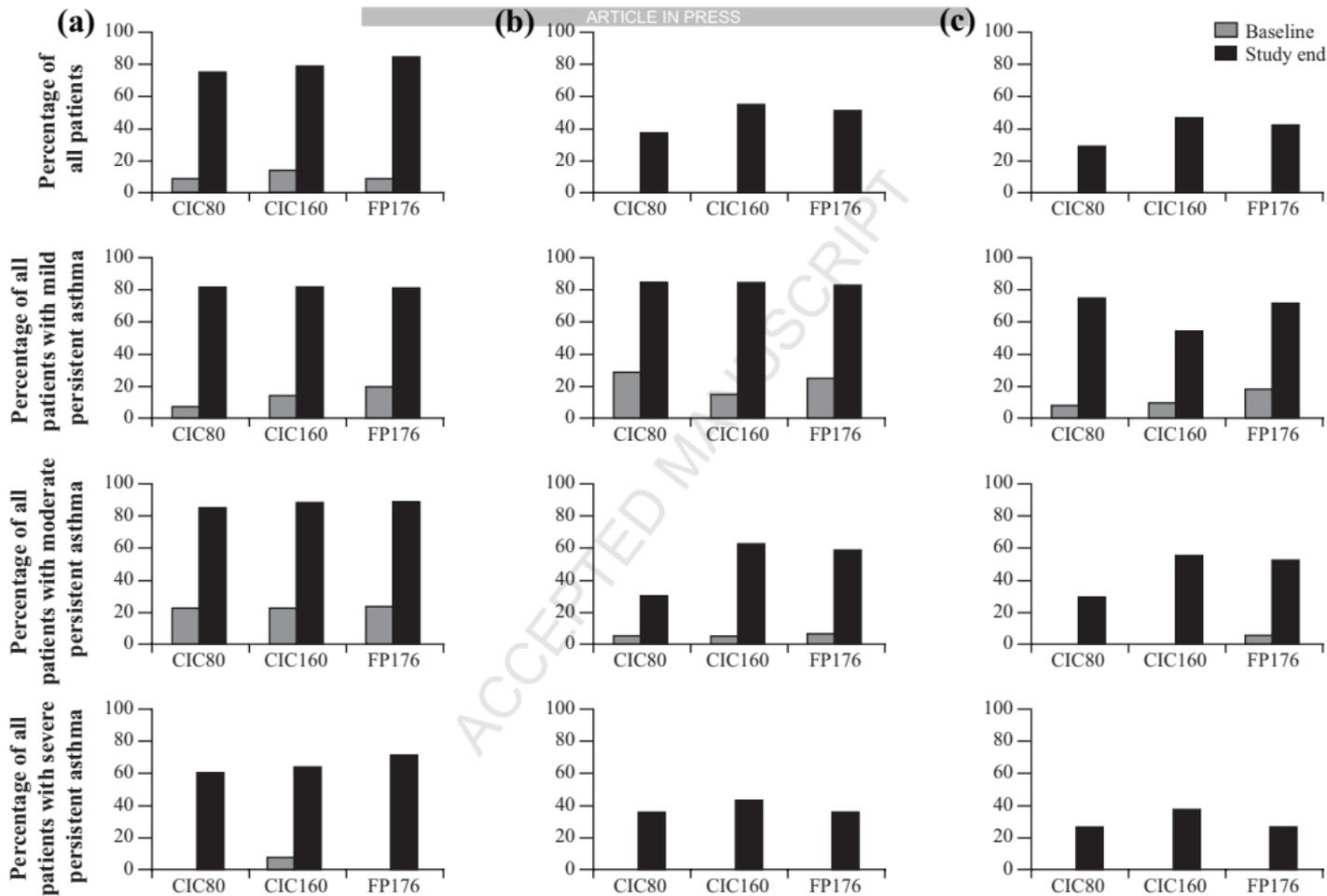


Figure 3