Once-daily ciclesonide via metered-dose inhaler: Similar efficacy and safety with or without a spacer

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Summary
Background: Inhaled corticosteroids (ICS) are recommended as first-line treatment for adults and children with persistent asthma. The Global Initiative for Asthma recommends that patients taking medium- or high-dose ICS delivered by metered-dose inhalers (MDIs) should use a spacer device.

Methods: This randomized, open-label, 12-week, non-inferiority study compared the efficacy and safety of ciclesonide 160 μg once daily delivered via hydrofluoroalkane-MDI alone (CIC160) or with a spacer (either an AeroChamber Plus [CIC160P] or an AeroChamber MAX [CIC160M]) in patients with persistent asthma. The primary efficacy variable was change in forced expiratory volume in 1 s (FEV1) from baseline to study end.

Results: Significant improvements in FEV1 were observed from baseline to study end in each treatment group; least squares mean change from baseline ranged between 0.32 and 0.34L in the per-protocol (PP) analysis and similar results were observed for the intention-to-treat (ITT) analysis (p < 0.0001 for all). Non-inferiority of CIC160P and CIC160M to CIC160 was observed for both PP and ITT populations (p < 0.0001 [one-sided]). In all groups, daily asthma symptom scores were reduced to 0 and significant reductions were observed in rescue medication use at study end (p < 0.0001 versus baseline for all). Ciclesonide was well tolerated in all groups and no cases of oral candidiasis were reported. Morning serum cortisol levels significantly increased in all groups from baseline to study end (p ≤ 0.0389), with no significant between-treatment differences.

Conclusion: In patients with persistent asthma, ciclesonide was shown to have similar efficacy and tolerability when administered via MDI alone or with a spacer.

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Introduction

Inhaled corticosteroids (ICS) are the recommended first-line therapy for adults and children of all ages with persistent asthma.1 ICS elicit a potent anti-inflammatory action, resulting in decreases in bronchial hyperresponsiveness, improvements in lung function, and reductions in asthma symptoms and rescue medication use.1-3 In addition, ICS are generally well tolerated at therapeutic doses and have an excellent risk–benefit ratio.1,3

Spacer devices developed for use with pressurized metered-dose inhalers (MDIs) can be used to increase the quantity of ICS deposited in the lung and, therefore, potentially improve efficacy in patients who have problems with inhalation coordination.4,5 Furthermore, as spacers retain the large drug particles that might ordinarily be deposited in the oropharynx, their use may result in lower oropharyngeal deposition and oral bioavailability, thereby reducing the occurrence of oropharyngeal AE.6,7 and the systemic bioavailability of some ICS.6-7 The Global Initiative for Asthma (GINA) recommends that patients of all ages taking medium- or high-dose ICS delivered by MDIs should use a spacer device.8

Ciclesonide is a novel lung-activated ICS that has a small particle size, low oral bioavailability and high pulmonary deposition.8-10 One pharmacokinetic study showed that the use of a spacer (AeroChamber Plus®; Trudell Medical International, Ontario, Canada) did not change lung deposition and systemic exposure;11 however, new regulatory guidelines from the European Medicines Agency require additional clinical data on the use of spacers.12,13 Therefore, the aim of the current 12-week study was to compare the efficacy and safety of ciclesonide MDI with or without the use of a spacer. As the AeroChamber Plus® is recommended in the product characteristics for ciclesonide in most countries, this spacer was used in the current study, as well as a newly available spacer, the AeroChamber MAX® (Trudell Medical International, Ontario, Canada). This spacer differs from the AeroChamber Plus® as it is manufactured from an anti-static polymer, which may help improve aerosol suspension time and drug availability for patients with lower tidal volumes, as well as for those who have difficulty coordinating the actuation of pressurized MDIs and inhaling correctly.

Methods

Patients

Male and female patients aged 12–75 years with a ≥6-month history of persistent asthma (as defined by GINA guidelines 2004)14 were eligible for inclusion in the study. Both patients previously receiving rescue medication only and patients treated with a controller drug during the past 4 weeks were enrolled. During run in, only rescue medication (salbutamol) was permitted. Patients were randomized into the treatment period if they had an FEV1, 61–90% of predicted and FEV1 reversibility of ≥15% after inhalation of salbutamol 200–400 µg. If the latter was not demonstrated, a ≥15% fluctuation in diurnal peak expiratory flow (PEF), airway responsiveness or historical data were also accepted.

Patients were excluded from the study if they had: other relevant lung diseases, including chronic obstructive pulmonary disease, a smoking history of ≥10 pack years (≥2 pipe years), a concomitant severe disease, or a disease that contraindicated ICS use. Female patients were excluded if they were pregnant, breast feeding or were not using appropriate contraception. Patients who had used systemic steroids 4 weeks prior to baseline, or >3 times during the last 6 months before baseline were also excluded.

Study design

This was a randomized, open-label, parallel-group, multinational, multicenter, non-inferiority study, with three treatment arms. The study consisted of a 1–3-week run-in period and a 12-week treatment period, and was conducted in 52 study centers worldwide (Canada, France, Germany, Hungary, India and Italy). Patients visited their study centers up to four times during the run-in period and at Weeks 0, 4, 8, and 12 during treatment. Patients who fulfilled the inclusion criteria were randomized into three groups to receive ciclesonide 160 µg once daily in the evening (PM) via hydrofluoroalkane (HFA) MDI only (CIC160), via HFA—MDI and an AeroChamber Plus® spacer (CIC160P) or via HFA—MDI and an AeroChamber MAX® spacer (CIC160M). With the exception of study medication and rescue medication, no other asthma drugs were permitted during the treatment period.

Randomization was carried out in a stratified manner using the following factors: current smoking (yes/no), inhaled corticosteroid pretreatment (yes/no), inhalation technique without spacer (good/bad) and FEV1 value (high/low). Treatment was balanced at a ratio of 1:1:1 within each stratum. The randomization list was generated by the sponsor using a validated multiplicative congruential pseudo-random number generator and transferred to the randomization service provider. Investigators interacted with the randomization service provider by means of an automated facsimile form and the automated system allocated the patient randomly to one of the three treatment groups via a return fax.

The protocol for this study was reviewed and approved by the appropriate regional Institutional Review Boards or Independent Ethics Committees, and the study was conducted in accordance with the Declaration of Helsinki in its revised versions of Tokyo (1975), Venice (1983) and Somerset West (1996). The study followed the rules of the International Conference on Harmonization and the Consolidated Good Clinical Practice Guideline E6. Written, informed consent was obtained from all patients before enrollment into the trial.

Efficacy measures

Pulmonary function

FEV1 and forced vital capacity (FVC) measurements were taken between 6 and 10 am (±1.5 h from the measurements

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taken at the first visit) at each visit, following a 15–30-min rest period and after rescue medication had been withheld for ≥4 h. The highest of three technically acceptable readings was noted in patient case-report forms, and all spirometers were checked for acceptability and reproducibility in accordance with American Thoracic Society guidelines.15

Home PEF readings were taken daily using a Mini-Wright PEF meter (Clement Clarke International Limited, Essex, UK). Measurements were taken in the morning immediately after getting up. The highest of three recorded values was used for evaluation.

Asthma control, rescue medication use and asthma symptom scores
Asthma control was evaluated daily, and was defined as a day with no asthma symptoms and no rescue medication use. Salbutamol use was recorded in patient diaries throughout the study period. Asthma symptom scores were also recorded in patient diaries and rated twice daily on a scale of 0–4 (0 = very well, no symptoms; 4 = asthma very bad, unable to carry out daily activities).

Asthma exacerbations
Patients with asthma exacerbations requiring treatment with oral corticosteroids were withdrawn from the study and were treated accordingly.

Safety evaluation
Safety was assessed by recording the occurrence of adverse events (AEs) during each study visit and in patient diaries. Cases of suspected oral candidiasis were to be confirmed by a swab test and positive culture. Vital sign measurements, physical examination and routine laboratory investigations, including hematology, biochemistry and urinalysis, were also assessed at baseline and the end of the study. Blood samples drawn at baseline and the end of the treatment period were used to measure AM cortisol levels.

Statistical analysis
The primary efficacy variable was change in FEV\(_1\) (L) from baseline to study end. Secondary efficacy variables included change from baseline to study end in morning PEF, FVC, asthma symptom score, rescue medication use, number of patients with an asthma exacerbation and asthma control. Variables evaluated for safety included AEs, number of patients with local oropharyngeal AEs, serum cortisol, vital signs (blood pressure and heart rate), physical examination and compliance to study medication.

All lung function variables (FEV\(_1\), FVC and PEF absolute values) were assessed using analysis of covariance models.16,17 Non-parametric comparisons of asthma symptom scores, rescue medication use and percentage of days with asthma control were assessed with Pratt’s modified Wilcoxon’s signed-rank test for within-group comparisons and the Mann–Whitney U-test for between-group comparisons. Pratt’s modified Wilcoxon’s signed-rank test was also used to evaluate serum cortisol. The between-treatment differences for this variable were adjusted for country utilizing the non-parametric van Elteren test.18

For all variables, the between-treatment differences from baseline until study end were determined in a pairwise manner. Two-sided 95% confidence intervals (CIs) were provided for both within- and between-treatment differences. For between-treatment differences, a one-sided p-value was given for non-inferiority tests. The non-inferiority acceptance limits were set to −200 mL for FEV\(_1\) and FVC and −25 L/min for morning PEF. For asthma symptom scores, the non-inferiority acceptance limit was ±0.30.

For efficacy variables, the intention-to-treat (ITT) patient population was analyzed, and included all randomized patients who had taken at least one dose of study medication. Non-inferiority of CIC160P and CIC160M to CIC160 was assessed using the per-protocol (PP) population. The PP population included all patients in the ITT population who had no major protocol violations, and who had participated in the study as intended. The safety analysis included all randomized patients who had received at least one dose of study medication.

To achieve a power of 90% for correctly concluding non-inferiority at a one-sided significance level of 0.0125 for CIC160P or CIC160M to CIC160, 127 patients per group (n = 381 total) were needed, assuming a mean difference of 0 mL in FEV\(_1\) for CIC160P or CIC160M to CIC160 in the presence of a standard deviation of 450 mL and a non-inferiority acceptance limit of −200 mL. Assuming that about 15% of patients would not be included in the PP analysis, 150 patients were planned to be randomized per group (450 randomized patients in total).

Results

Patients

Of the 498 patients enrolled, 469 were randomized to treatment (CIC160, n = 150; CIC160P, n = 162; CIC160M, n = 157). One randomized patient in the CIC160 group failed to take at least one dose of study medication and was, therefore, excluded from analysis; leaving a total of 468 randomized patients. A total of 21 patients (CIC160, n = 5; CIC160P, n = 7; CIC160M, n = 9) withdrew early from the study. The main reason for study discontinuation was the occurrence of AEs (CIC160, n = 2; CIC160P, n = 2; CIC160M, n = 4). The PP population consisted of 423 patients (CIC160, n = 135; CIC160P, n = 144; CIC160M, n = 144).

The demographic and baseline characteristic data were similar between treatment groups (Table 1). Median compliance to study medication during the treatment period, recorded by daily diary entries, was 100% in all three treatment groups in the PP analysis (range: CIC160, 86–103%; CIC160P, 92–104%; CIC160M, 90–100%).

Efficacy measures

Pulmonary improvements in FEV\(_1\) from baseline to study end were noted in each treatment group (least squares [LS] mean change from baseline ranged between 0.32 and 0.34 L for the PP analysis and between 0.33 and 0.34 L for the ITT analysis; p < 0.0001 for all; Table 2; Fig. 1). Non-inferiority of CIC160P and CIC160M to CIC160 was shown in both the PP and ITT populations (p < 0.0001 [one-sided]; Table 2). For the PP analysis, the LS mean for the treatment difference
was 0.020L (95% CI: −0.073, 0.112) for CIC160P versus CIC160, and 0.018 L (95% CI: −0.075, 0.111) for CIC160M versus CIC160.

For FVC, significant within-treatment increases in all three treatment groups were observed from baseline to study end (p < 0.0001 for all, PP and ITT analyses). Non-inferiority of CIC160P (95% CI: −0.100, 0.117) and CIC160M (95% CI: −0.0112, 0.106) to CIC160 was shown in the PP analysis (p < 0.0002 [one-sided]; Table 2). Similar findings were obtained for the ITT analysis.

In the PP analysis, median daily asthma symptom scores (Table 2). In the PP analysis for morning PEF, group improvements observed for CIC160 (p < 0.0001 for all versus baseline; Table 2), and PP analyses). Non-inferiority of CIC160P and CIC160M to treatment period (p < 0.0001 for all; Table 2); the median rescue medication use decreased to 0.00 puffs/day at the end of the treatment period in all groups. No between-treatment group differences were observed (Table 2).

Asthma exacerbations
No asthma exacerbations were reported in the CIC160 group. Two patients in the CIC160P group and three patients in the CIC160M group experienced asthma exacerbations.

Days with asthma control
Significant increases were observed during the study in all groups for the median percentage of days with asthma control (all p < 0.0001; Fig. 2). No statistically significant between-treatment differences were observed in asthma control.

Safety
Ciclesonide was well tolerated in all treatment groups. A total of 104 patients (CIC160, n = 29 [19.5%]; CIC160P, n = 34 [21.0%]; CIC160M, n = 41 [26.1%]) reported 145 AEs (CIC160, n = 41; CIC160P, n = 51; CIC160M, n = 53) throughout the study period. Frequently reported AEs were: nasopharyngitis (CIC160, n = 3 [2.0%]; CIC160P, n = 6 [3.7%]; CIC160M, n = 6 [3.8%]); asthma (CIC160, n = 4 [2.7%]; CIC160P, n = 6 [3.7%]; CIC160M, n = 4 [2.5%]); upper respiratory tract infection (CIC160, n = 3 [2.0%]; CIC160P, n = 1 [0.6%]; CIC160M, n = 4 [2.5%]); bronchitis (CIC160, n = 3 [2.0%]; CIC160P, n = 1 [0.6%]; CIC160M, n = 3 [1.9%]); acute bronchitis (CIC160, n = 4 [2.7%]; CIC160P, n = 1 [0.6%]; CIC160M, n = 1 [0.6%]); and rhinitis (CIC160, n = 0 [0.0%]; CIC160P, n = 0 [0.0%]; CIC160M, n = 4 [2.5%]). The majority of AEs were mild or moderate in intensity.

In those patients who experienced AEs, over 96% of patients had AEs that were judged by investigators and the study sponsor as being not related or unlikely related to
study medication. Seven serious AEs were reported overall: CIC160, n = 2 (hypertensive crisis, osteotomy); CIC160P, n = 4 (two occurrences of cholangitis, pancreatic carcinoma, pancreatitis chronic); and CIC160M, n = 1 (abortion spontaneous), although none were considered to be related to study medication. There were no cases of oral candidiasis throughout the study.

Morning serum cortisol levels significantly increased in all groups from baseline to study end (p < 0.0389; safety population; Table 3). No significant between-treatment differences in serum cortisol levels were observed. No clinically relevant changes in laboratory values, vital sign assessments or physical examinations were observed in any treatment group over the course of the study.

Discussion

In patients with persistent asthma, ciclesonide was demonstrated to have similar efficacy when administered via MDI alone or with a spacer. In addition, there was no difference in the safety of ciclesonide when administered with or without a spacer.

In all treatment groups, ciclesonide demonstrated significant improvements from baseline to study end in pulmonary function (FEV1, FVC and AM PEF), asthma symptom scores, rescue medication use and percentage of days with asthma control. Non-inferiority of ciclesonide when administered via a spacer compared with administration without a spacer was shown for the primary efficacy variable (change in FEV1 from baseline to study end), as well as for the secondary variables FVC, AM PEF and asthma symptom scores. No significant differences between treatments were noted for the changes in rescue medication use and percent days with asthma control.

Although guidelines recommend that patients of all ages taking medium- or high-dose ICS delivered by MDIs should use a spacer device, the use of spacers has been largely based on data with older chlorofluorocarbon (CFC)-MDIs.

### Table 2

Within- and between-treatment differences for primary and secondary variables (per-protocol and intention-to-treat analyses).

<table>
<thead>
<tr>
<th>Variable</th>
<th>ITT population</th>
<th>PP population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CIC160</td>
<td>CIC160P</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>149</td>
<td>160</td>
</tr>
<tr>
<td>LS mean at baseline</td>
<td>2.36</td>
<td>2.36</td>
</tr>
<tr>
<td>LS mean change from baseline</td>
<td>0.33 ± 0.07</td>
<td>0.34 ± 0.07</td>
</tr>
<tr>
<td>p-Value versus baseline</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>One-sided p-value for non-inferiority</td>
<td>N/A</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FVC (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>149</td>
<td>160</td>
</tr>
<tr>
<td>LS mean at baseline</td>
<td>3.14</td>
<td>3.14</td>
</tr>
<tr>
<td>LS mean change from baseline</td>
<td>0.37 ± 0.08</td>
<td>0.37 ± 0.08</td>
</tr>
<tr>
<td>p-Value versus baseline</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>One-sided p-value for non-inferiority</td>
<td>N/A</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Morning PEF (L/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>147</td>
<td>160</td>
</tr>
<tr>
<td>Median score at baseline</td>
<td>0.66</td>
<td>0.91</td>
</tr>
<tr>
<td>Median score at study end</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>p-Value versus baseline</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asthma symptom sum score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>140</td>
<td>150</td>
</tr>
<tr>
<td>Median score at baseline</td>
<td>0.71</td>
<td>1.00</td>
</tr>
<tr>
<td>Median score at study end</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>p-Value versus baseline</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>p-Value versus CIC160</td>
<td>N/A</td>
<td>0.0718</td>
</tr>
</tbody>
</table>

ITT = intention to treat; PP = per protocol; CIC160 = ciclesonide 160 μg; CIC160M = ciclesonide 160 μg administered by AeroChamber Max® spacer; CIC160P = ciclesonide 160 μg administered by AeroChamber Plus® spacer; FEV1 = forced expiratory volume in 1 s; LS = least squares; SE = standard error; FVC = forced vital capacity; and PEF = peak expiratory flow.
With CFC-MDIs, spacers improve drug delivery, increase lung deposition, and may reduce local and systemic side effects. However, for some ICS, the HFA formulations replacing the old phased-out CFC inhaler devices provide an aerosol of smaller particle size, resulting in less oral deposition and greater lung deposition.\textsuperscript{19} This may result in a reduction in oral side effects and greater local efficacy at equivalent ex-actuator doses, but also greater systemic exposure and risk of systemic side effects.\textsuperscript{19} Therefore, for HFA-MDIs, the focus of concern may switch and the use of a spacer may depend on the properties of the individual ICS.

The current findings suggest that the addition of a spacer to the ciclesonide HFA-MDI device did not further increase the efficacy of ciclesonide in an average patient with persistent asthma. This is also supported by other studies where ciclesonide administered without a spacer significantly improved asthma control in large patient populations.\textsuperscript{20–24} However, patients having problems with inhalation coordination may still benefit from spacer use.\textsuperscript{5}

It should be noted that to avoid bias in the current study, none of the participants were selected based on their inhalation technique. In addition, because of the use of the spacers in the current study, blinding was not possible and the study had an open design. However, in order to improve the quality of the study, an automated randomization procedure was used so that the investigators were guided in the randomization of the patients, preventing any subjective choices.

Over the 12-week study, safety data revealed no safety issues when ciclesonide was administered either with or without a spacer. Ciclesonide use did not result in any cases of oral candidiasis during the current study in any treatment group. These findings support those of previous studies that have demonstrated that ciclesonide is associated with minimal local AEs.\textsuperscript{23–25} No clinically relevant effects on laboratory, physical or vital sign measurements were observed in any of the treatment groups. Furthermore, ciclesonide had no suppressive effects on morning serum cortisol levels in the current study. Although morning cortisol levels provide only very limited information on any HPA-axis suppressive effects, the relatively low dose of ciclesonide administered in this study, as well as previously reported data that found no suppressive effect at higher doses of ciclesonide, make it extremely unlikely that 24-h serum profiles or other markers of HPA-axis function would have revealed a different outcome.

In conclusion, ciclesonide is effective and well tolerated in patients with asthma when administered with or without the addition of a spacer. In addition, the AeroChamber MAX\textsuperscript{d} had no apparent benefits over the AeroChamber Plus.\textsuperscript{d}
to declare.

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manuscript and in the decision to submit the manuscript for

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References

Dr Egelsta¨tter and Dr Gerber are employees of Nyomed

Conflict of interest statement

Dr Egelstätter and Dr Gerber have no conflicts of interest to declare.

Clinical and Safety of Ciclesonide with or Without a Spacer

Table 3 Change in median morning serum cortisol.

<table>
<thead>
<tr>
<th>Serum cortisol (µmol/L)</th>
<th>Safety population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CIC160 (N = 114)</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.30</td>
</tr>
<tr>
<td>Study end</td>
<td>0.36</td>
</tr>
<tr>
<td>HL point estimate</td>
<td>0.04</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.02, 0.06</td>
</tr>
<tr>
<td>p-Value versus baseline</td>
<td>0.0001</td>
</tr>
<tr>
<td>p-Value versus CIC160</td>
<td>N/A</td>
</tr>
</tbody>
</table>

CIC160 = ciclesonide 160 µg; CIC160 M = ciclesonide 160 µg administered by AeroChamber Max® spacer; CIC160P = ciclesonide 160 µg administered by AeroChamber Plus® spacer; and HL = Hodges-Lehmann.

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Conflict of interest statement

Dr Egelstätter and Dr Gerber are employees of Nycomed GmbH. Dr Szlávik and Dr Beck have no conflicts of interest to declare.

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