Efficacy and safety of ciclesonide in the treatment of 24,037 asthmatic patients in routine medical care

Claus F. Vogelmeier a, Thomas Hering b, Thomas Lewin c, Peter Sander c, Thomas D. Bethke c,*

a Dept. of Pneumology, University of Marburg, Baldingerstraße, 35043 Marburg, Germany
b Pneumology practice, Schloßstr. 5, 13507 Berlin (Tegel), Germany
c Nycomed Deutschland GmbH, Moltkestraße 4, 78467 Konstanz, Germany

Summary

Background: The efficacy and safety profile of ciclesonide (CIC) in the treatment of asthma was evaluated in a large patient population in a real-life setting in Germany.

Methods: 24,037 patients with persistent mild/moderate bronchial asthma were enrolled into three observational studies with identical design. Data were pooled and analyzed. Patients received ciclesonide (160 µg/day) and were observed for 3 months. FEV1, PEF, NO, asthma episodes, use of rescue medication and adverse drug reactions (ADR) were recorded.

Results: Mean (95% CI) FEV1 significantly increased from 80.7 [80.5; 80.9]% of predicted at baseline to 90.1 [89.9; 90.2]% after 3 months (n = 20,297), mean PEF significantly increased from 338 [335; 340] l/min to 392 [390; 395] l/min (n = 8100). NO was significantly reduced from 53.6 [51.8; 55.4] ppb to 26.2 [25.2; 27.1] ppb (n = 971). The percentage of patients with daily symptoms declined from 24.3% to 1.9%, night-time symptoms from 13.3% to 1.3%, and β2-agonists use from 26.9% to 8.8%. ADRs were reported by 51 patients (0.2%). Most frequent ADRs were: dysphonia (n = 11), cough (n = 10), dyspnoea, throat irritation, and oral candidiasis (n = 5 each). 46 patients terminated the study prematurely, 41 due to ADR and 5 due to unknown/missing reason. One patient died due to cardiac failure (no causal relation).

Conclusion: These observational studies under real-life conditions support findings from controlled clinical studies regarding efficacy and tolerability of ciclesonide in patients with mild to moderate bronchial asthma. No unexpected ADRs were detected.

© 2010 Elsevier Ltd. All rights reserved.
Introduction

Inhaled corticosteroids (ICS) are so far the most effective controller drugs for patients with asthma. Unfortunately, ICS are generally underused due to lack of compliance, steroid fear, and concerns about systemic side effects. ICS of the first and second generation have some limitations, such as a low systemic bioavailability and a potential for side effects such as oral candidiasis, hoarseness, and dysphonia. Ciclesonide shows an improved therapeutic index and pharmacologic profile and can, therefore, be regarded as the prototype of a third generation of ICS. In 2005 ciclesonide was approved in the European Union for the treatment of mild to severe persistent asthma in adults, and since 2006 for the treatment of asthma in adolescents (12 years and older).

Pharmacology of ciclesonide

Ciclesonide is administered using a metered-dose inhaler in a solution of hydrofluoroalkane propellant that allows for the production of small, highly respirable particles resulting in a significant deposition in the lungs. Numerous studies have investigated the pharmacological properties of the lung-activated ciclesonide demonstrating high local efficacy, reduced drug load, and a lower potential for local side effects. Furthermore, the active ciclesonide forms a lipid-conjugated depot, which is retained in the lungs, leading to an increased pulmonary residence time. In addition, 99% of ciclesonide is bound to plasma proteins and is metabolized and cleared rapidly by the liver (>99% in the liver), which reduces the potential for systemic side effects.

Ciclesonide in clinical trials

The efficacy and safety of ciclesonide has been demonstrated in a number of double-blind, randomized, placebo-controlled studies in doses of 80–1280 μg per day. The safety and tolerability data demonstrated ciclesonide to be safe in asthma. In comparison to other ICS, it provided a noticeably enhanced tolerability profile. Local side effects (candidiasis, pharyngitis, dysphonia) occurred with a low frequency (<2%), whereas other ICS show these side effects with a frequency of 5–30%. The potential for systemic side effects is reduced due to the high protein binding and rapid clearance of ciclesonide: this could be shown using laboratory parameters, such as serum cortisol.

Real-life medical care

Nowadays, drug research and surveillance after authorisation becomes more and more important. As efficacy is only checked once, at the time of authorisation, critical voices have been raised over the years, that there should be the possibility to monitor also drug efficacy and not only safety post-authorisation in real world populations and real-life conditions. Several international guidelines for Good Epidemiological Practice (GEP) were published by the U.S. Food and Drug Administration (FDA) and various societies for epidemiology laying down the basic principles of good epidemiological practice. In this context, the FDA encourages sponsors to consider all methods to evaluate a particular safety signal, including non-randomized observational studies of the product’s use in the “real-world”. The non-interventional studies [NIS], which include Anwendungsbeobachtungen (AWB) as the most common form in Germany, are considered as effective instruments for assessing safety of a medicinal product and for confirming the results obtained in randomized clinical trials. In early 2007 then, the German Association of Research-Based Pharmaceutical Companies (VFA) consolidated the essential elements of NIS, that ensure high quality standards. In 2008, the Brussels Declaration of Asthma urged the funding of “real-world” studies and supported that the results should be used to inform treatment guidelines. Many studies of this type have been performed with various compounds in asthma either retrospectively e.g. or prospectively e.g.

For the first time, the use of ciclesonide was investigated in three non-interventional cohort studies, all designed to assess the tolerability and efficacy of ciclesonide in routine medical practice. The focus of the present analysis is on the pooled tolerability and efficacy data of these three non-interventional trials that were performed after approval and market introduction of ciclesonide (Trade name: Alvesco®) in 2005 in a time period between February 2006 and December 2007. The acronyms of the studies were BASIS (Basistherapie bei Asthma mit Alvesco®), ATALL (Alvesco® für die Therapie des persistierenden Asthma mit/ohne allergischen Komponenten), and ART (Alvesco® für die Therapie des persistierenden und/oder allergischen Asthmas). These large-scale studies included more than 24,000 patients with mild to moderate persistent asthma treated with ciclesonide over 3 months in Germany.

Methods

Study design and study subjects

Three prospective, multicenter, open-label, observational studies were conducted in accordance with the recommendations of the German Federal Institute for Drugs and Medical Devices (BfArM) on observational studies (§67 section 6 German Drug Law) and national sickness fund associations in Germany (BKK) on behalf of Nycomed Deutschland Ltd (formally Altana Pharma Deutschland GmbH), who is the authorisation holder for marketing of Alvesco®. According to the EU Directive 2001/20/EG article 2c and § 4 German Drug Law, non-interventional studies (NIS) are studies where “findings from the treatment of persons with drugs according to the terms of the marketing authorisation are analyzed with epidemiological methods; thereby treatment, including diagnosis and control, does not follow any predefined study plan but only the medical practice. Hence, NIS are not subject of the conditions of §§10, 40, 41, and 42 German AMG, and no ethics committee approval was mandatory at that time.

Investigators were pneumologists, specialists in internal medicine or general practitioners that were selected on the basis of their experience in conducting non-interventional studies. As the studies were designed to reflect the current
practice of diagnostic assessment and treatment in a naturalistic setting, all treatment decisions were left to the discretion of the investigator. The diagnosis was confirmed by standard lung function evaluation procedures, i.e. assessment of forced expiratory volume in 1 second (FEV₁), peakflow measurement (PEF) and frequency of day- and night-time symptoms, according to the guideline of the German Respiratory Society and the German airway league (*Deutsche Atemwegsliga*, 2005).

Severity of asthma was graded accordingly, with patients having mild persistent asthma if FEV₁ was ≥80% of the predicted value, PEF-variability 20–30%, frequency of daytime symptoms >1 per week, but <1 per day, and night-time symptoms >1 per week. Asthma was diagnosed as being of moderate severity if FEV₁ was 60–80% of the predicted value, PEF-variability 20–30%, frequency of daytime symptoms daily, and night-time symptoms >1 per week. Study design and all details for implementation of the studies were defined in the respective study protocols. Only those data were documented that are routinely assessed in the diagnosis and treatment of asthma.

Patients were recruited independently from their cultural background, age, or socioeconomic status, and informed by the investigator about the study. Patients were followed up for a period of 3 months. The studies were conducted between February 2006 and December 2007 (duration per study 9, 10, and 20 months, respectively). The trials were identical in scope and design so that data could be pooled and analyzed.

**Inclusion criteria**

The studies included male and female patients (12 years and older) with a diagnosis of persistent asthma of mild to moderate severity who newly started or switched to treatment with ciclesonide. No further inclusion or exclusion criteria were specified. As with all inhaled corticosteroids, patients with the following contra-indications for treatment with ICS as stated in the Summary of Product Characteristics, were not included in the studies; patients with active or quiescent pulmonary tuberculosis, fungal, viral or bacterial infections (only if these patients were adequately treated), and patients with status asthmaticus or other acute episodes of asthma where intensive measures are required. Further, ciclesonide is contraindicated in patients with a hypersensitivity to any of its ingredients.

**Assessments**

Data were collected at an initial baseline visit and after 3 months. At the initial visit, the investigator documented demographic data, medical history, and disease-related information, including duration of asthma and current medication, further respiratory and other concomitant diseases (e.g. hypertension, diabetes mellitus, osteoporosis, allergies), concomitant medication and smoking status.

Visits included standard spirometry, i.e. FEV₁ (total and percentage of predicted value), mean PEF, and exhaled nitric oxide (NO) (only documented in BASIS and ATALL), as well as an assessment of the frequency of daytime (<1 per week, ≥1 per week but not daily, daily) and night-time asthma episodes (<2 per month, >2 per month, 1 per week, >1 per week), as reported by the patient. Further, adverse drug reactions (ADRs) were collected the following way: in cases that patients spontaneously reported an adverse drug reaction, investigators had to fill in an ADR documentation form to be submitted to the sponsor and/or the authorities. Further, the impact of an acute worsening of symptoms on the quality of sleep during the previous month was evaluated. In addition, the use of rescue medication (short- or long-acting β₂-sympathomimetics) was recorded (none, daily, ≤1 per week, ≥2 per week) by the physician. Uncontrolled asthma was defined according to GINA criteria. Patients were assessed as uncontrolled by the physician if they met these criteria. All ADRs were documented in detail in a special section of the case report form and transferred to a clinical research organisation (CRO; Medidata, Konstanz, Germany). Serious ADR as well as incidences of overdose regardless of outcome were reported immediately to the CRO. At the final visit, the investigators repeated the questioning of ADR, spirometry, NO, and symptom assessments.

**Sample size considerations and statistics**

It was planned to enrol 4000 (BASIS), 12,000 (ATALL), and 16,000 patients (ART) into the studies. This sample size was calculated assuming that a rare adverse drug reaction could be observed at least once with an incidence of 0.1% (resulting in a sample size of 4,000 patients), 0.03% (12,000 patients), and 0.02% (16,000 patients), with α = 0.05, assuming binomial distribution. This assumption is in accordance with current guidelines on the use of statistical signal detection methods in the eudragivigilance data analysis system.

The primary objective of the studies was the change in spirometry-derived FEV₁ from baseline to study end, as well as improvement of symptoms as rated by the investigator. Other endpoints included evaluation of tolerability as assessed by spontaneous reporting of adverse drug reactions, handling of ciclesonide and changes of need for rescue medication.

The statistical analysis of the study results was performed according to a statistical analysis plan. Data entry and analyses were carried out by MEDIDATA Inc., Konstanz, Germany, using the statistical software package SAS. Entry of medications and diseases was supported by thesaurus files. Medications were analyzed on the basis of International Nonproprietary Name (INN) listing. Before start of analysis, plausibility checks were performed and errors were corrected. The analyses were exploratory, no confirmatory statistical tests were performed, and no confirmatory statements derived. For the parameters, FEV₁, PEF and NO, the 95% confidence intervals of the means were calculated. Continuous variables were summarized using descriptive statistics (number of patients, mean, median, SD, range and binary or categorical variables using frequency distribution tables as appropriate). Adverse drug reactions (ADRs) were analyzed descriptively (number of events and corresponding 95% confidence intervals with coding according to Medical Dictionary for Regulatory Activities (MedDRA)). Furthermore, 95% confidence intervals of the means were calculated. A
significant difference between baseline and final visit mean values could then be concluded if the 95% two-sided confidence intervals were not overlapping, which corresponds to a conservative two-sided test at the 5% level.

**Administration of ciclesonide**

All treatment decisions were solely left to the discretion of the investigator, i.e. choice of dose as well as concomitant rescue medication (short- or long-acting β₂-sympathomimetics). As stated in the summary of the European product characteristics (Alvesco®), the recommended dose of ciclesonide is 160 μg once daily, which leads to asthma control in the majority of patients. Dose reduction to 80 μg once daily may be an effective maintenance dose for some patients. It is recommended to administer ciclesonide in the evening. The final decision on evening or morning dosing was left to the discretion of the physician. Once symptom control is achieved, the dose of Alvesco® could be individualised and titrated to the minimum dose needed.

**Results**

**Patient population and course of the studies**

A total number of 4401 (BASIS), 8280 (ATALL), and 11,356 patients (ART) were enrolled into the studies, hence, data from 24,037 patients were pooled for analysis. The originally planned sample size of a total of 32,000 patients could not be reached due to slow patient recruitment. A total of 6236 study centers participated in the studies. Of all patients included in the studies, 90.3% (n = 21,695) completed the studies according to the protocol, and 1.9% (n = 465) discontinued the treatment with ciclesonide prematurely (7.8% patients (n = 1877) with missing data). The most common reasons for premature discontinuation (>5% of entries) were recovery from their symptoms (n = 202), patient decision or non-compliance (n = 90), lack of need for maintenance treatment (n = 60), insufficient efficacy (n = 57), change to other medication (n = 46), and adverse drug reactions (n = 41).

The data quality was acceptable within the present capabilities of observational studies, which is, among others, reflected by the number of missing data: The frequency of missing data with respect to key parameters were in the range of 1.2% and 3.8%. Regarding demographic patient characteristics data was missing in 0.3%–16.5% (depending on the parameter) of cases.

**Patient population**

Of all patients included in the studies, 55% were female (n = 13,228), the mean (SD) age was 46.3 ± 16.8 years (range 6–102 years) (Table 1). Although ciclesonide is approved for patients of 12 years and older, also 20 children (0.08%) at the age of 6–11 years were treated with ciclesonide and documented.

Patients suffered from asthma for 7.7 years (±8.5 years; median 5 years). Based on the spirometric data and the symptom assessment at the start of the observation period, the severity of asthma was classified as mild in 51.3% (n = 12,333), moderate in 44.6% (n = 10,712), and severe in 1.5% (n = 356) of all patients (missing data: 2.6% (n = 626)). Of those 356 patients with severe asthma, 44.1% were smokers (n = 118) or ex-smokers (n = 39) and 53.1% were non-smokers (n = 189; n = 10 with missing data). A total of 4.7% (n = 1119) of the study population additionally suffered from other respiratory diseases, whereas 95.3% (n = 22,918) of the study population did not. Among these, cold (n = 282) and bronchitis (n = 198) occurred most frequently. A total of 23.8% of patients (n = 5710) were smokers and 9.8% (n = 2357) were ex-smokers.

The most frequent concomitant diseases were allergies (68.6%, n = 5383), hypertension (24.6%, n = 5911), and ophthalmological disorders (10.8%, n = 847).

At study entry, 69.5% of the patients took short-acting β₂-agonists and 24.0% long-acting β₂-agonists as concomitant medication; 22.3% did not take any concomitant medication or had missing data. Other medication for the treatment of asthma was taken by 10.5% of patients, with montelukast, theophylline and tiotropiumbromide being used most frequently (19.7%, 19.0%, and 6.3%, respectively).

Due to the observation that about 25% of the patients were smokers and some of the included individuals were ex-smokers and based on the fact that the use of tiotropiumbromide was observed in about 6% of patients it cannot be excluded that a proportion of the patients also suffered from chronic obstructive pulmonary disease (COPD).

55.5% (n = 13,335) of the study population was treatment-naive at study start, and 41.5% (n = 9977) have been treated previously with other ICS. Budesonide (58.5%, n = 5838) was prescribed most frequently, followed by beclometasone (17.0%, n = 1693) and fluticasone (14.6%, n = 1454). Most of the pre-treated patients took the ICS as monotherapy (budesonide: 89.7%, beclometasone 88.8%, fluticasone 78.8%), all others in combination with other drugs.

**Treatment with ciclesonide**

The mean (SD) duration of treatment observation from baseline to final visit was 13.0 ± 3.7 weeks. The vast majority of the patients (91.7% (n = 22,040)) were started on the recommended dose of 160 μg per day (i.e. 1 puff), and 5.9% (n = 1408) of the patients were started on 2 times 160 μg per day. At the final visit, 91.8% (n = 22,073) of patients were treated with 160 μg/day (at baseline: 91.7%), 3.1% (n = 757) with 2 × 160 μg/day (at baseline: 5.9%), and 1.0% (n = 242) with 80 μg/day (at baseline: 0.5%).

**Efficacy**

**Lung function**

With regard to the efficacy endpoint the mean [95% confidence interval (CI)] FEV₁-value significantly increased during the observational period from 2.66 [2.65; 2.67] l to 3.00 [2.99; 3.01] l, i.e. increased by 9.4% from 80.7 [80.5; 80.9]% to 90.1 [89.9; 90.2]% predicted (Fig. 1) as indicated by non-overlapping 95% confidence intervals. The mean PEF was assessed in 8100 patients at both initial and final visit. In these patients, a significant increase in PEF of 14%, i.e. from 338 [335; 340] l/min to 392 [390; 395] l/min could be observed (non-overlapping CIs).
Exhaled NO
The assessment of NO was performed in 971 patients: The concentration of NO significantly decreased from 53.6 [51.8; 55.4] ppb to 26.2 [25.2; 27.1] ppb, which represents a reduction of 51%.

Asthma episodes
The incidence of asthma-related symptoms were reduced during the course of the study (Fig. 2). The proportion of patients that suffered from daily symptoms at daytime was reduced from 24.3% to 1.9% after 3 months of treatment with ciclesonide, and the proportion of patients with symptoms that occurred >1 per week was reduced from 59.4% to 24.4% (Fig. 2a). Accordingly, the number of patients reporting less frequent symptoms (<1 per week) increased from 14.1% to 68.9%. A similar improvement could also be observed for night-time symptoms (Fig. 2b). Here, the proportion of patients with frequent (>1 per week) night-time symptoms decreased from 13.3% to 1.3%, whereas the proportion with only rare night-time episodes (≤2 per month) increased from 34.7% to 77.7%.

The number of nights of the preceding month with nocturnal symptoms decreased from 5.4 ± 5.1 at study start to 2.5 ± 2.8 after 3 months of treatment.

Quality of sleep
The negative impact of acute worsening of asthma symptoms on the quality of sleep was reduced. The proportion of patients whose quality of sleep was impaired, was 39.8% at study entry. This proportion was reduced to 8.2% after 3 months of treatment. Vice versa, the proportion of patients without impaired sleep quality due to worsening of symptoms increased from initially 25.4% to 55.7%.

Safety
During the 3 month treatment period, ADRs were reported in 51 (0.2%) patients, and 46 patients discontinued therapy, 41 due to ADRs and 5 due to unknown or missing reasons (Table 2). The 51 ADRs all were considered as definitely, probably, or possibly related to the treatment. Most ADRs were of mild or moderate intensity. Most commonly reported non-serious ADRs (n = 50) were dysphonia (n = 11) and cough (n = 10). In 1 patient, the ADR was classified as serious, with fatal outcome due to myocardial infarction (no relation to ciclesonide as assessed by the investigator). Two further patients experienced serious events, which both were not considered as drug related: one patient with a cataract and one patient with a severe anxiety with subsequent hospitalization.

As assessed by the investigator, three of the 50 non-serious ADRs (6.0%) were considered definitely related to therapy (strong urge to cough after inhalation, throat

Exhaled NO
The assessment of NO was performed in 971 patients: The concentration of NO significantly decreased from 53.6 [51.8; 55.4] ppb to 26.2 [25.2; 27.1] ppb, which represents a reduction of 51%.

Asthma episodes
The incidence of asthma-related symptoms were reduced during the course of the study (Fig. 2). The proportion of patients that suffered from daily symptoms at daytime was reduced from 24.3% to 1.9% after 3 months of treatment with ciclesonide, and the proportion of patients with symptoms that occurred >1 per week was reduced from 59.4% to 24.4% (Fig. 2a). Accordingly, the number of patients reporting less frequent symptoms (<1 per week) increased from 14.1% to 68.9%. A similar improvement could also be observed for night-time symptoms (Fig. 2b). Here, the proportion of patients with frequent (>1 per week) night-time symptoms decreased from 13.3% to 1.3%, whereas the proportion with only rare night-time episodes (≤2 per month) increased from 34.7% to 77.7%.

The number of nights of the preceding month with nocturnal symptoms decreased from 5.4 ± 5.1 at study start to 2.5 ± 2.8 after 3 months of treatment.

Quality of sleep
The negative impact of acute worsening of asthma symptoms on the quality of sleep was reduced. The proportion of patients whose quality of sleep was impaired, was 39.8% at study entry. This proportion was reduced to 8.2% after 3 months of treatment. Vice versa, the proportion of patients without impaired sleep quality due to worsening of symptoms increased from initially 25.4% to 55.7%.

Safety
During the 3 month treatment period, ADRs were reported in 51 (0.2%) patients, and 46 patients discontinued therapy, 41 due to ADRs and 5 due to unknown or missing reasons (Table 2). The 51 ADRs all were considered as definitely, probably, or possibly related to the treatment. Most ADRs were of mild or moderate intensity. Most commonly reported non-serious ADRs (n = 50) were dysphonia (n = 11) and cough (n = 10). In 1 patient, the ADR was classified as serious, with fatal outcome due to myocardial infarction (no relation to ciclesonide as assessed by the investigator). Two further patients experienced serious events, which both were not considered as drug related: one patient with a cataract and one patient with a severe anxiety with subsequent hospitalization.

As assessed by the investigator, three of the 50 non-serious ADRs (6.0%) were considered definitely related to therapy (strong urge to cough after inhalation, throat

Table 1 Demographic data and patient characteristics at baseline.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Population (N = 24,037)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10,702 (44.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>13,228 (55.0%)</td>
</tr>
<tr>
<td>Missing data</td>
<td>107 (0.4%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>46.3 (16.8)</td>
</tr>
<tr>
<td>Median</td>
<td>46.0</td>
</tr>
<tr>
<td>Minimum-Maximum</td>
<td>6.0–102.0</td>
</tr>
<tr>
<td>Weight, kg (SD)</td>
<td>76.0 kg (14.6)</td>
</tr>
<tr>
<td>Minimum-Maximum</td>
<td>25.0–188.0</td>
</tr>
<tr>
<td>Height, cm (SD)</td>
<td>170.8 (9.1)</td>
</tr>
<tr>
<td>Minimum-Maximum</td>
<td>114.0–206.0</td>
</tr>
<tr>
<td>Duration of asthma (years)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>7.7 (8.5)</td>
</tr>
<tr>
<td>Median</td>
<td>5.0</td>
</tr>
<tr>
<td>Minimum-Maximum</td>
<td>0.042–85.0</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>12,333 (51.3%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>10,712 (44.6%)</td>
</tr>
<tr>
<td>Severe</td>
<td>356 (1.5%)</td>
</tr>
<tr>
<td>Missing data</td>
<td>626 (2.6%)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>5710 (23.8%)</td>
</tr>
<tr>
<td>Ex-Smoker</td>
<td>2357 (9.8%)</td>
</tr>
<tr>
<td>Non-Smoker</td>
<td>15,729 (65.4%)</td>
</tr>
<tr>
<td>Missing data</td>
<td>241 (1.0%)</td>
</tr>
<tr>
<td>Allergies</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>7698 (32.0%)</td>
</tr>
<tr>
<td>Missing data</td>
<td>5058 (21.0%)</td>
</tr>
<tr>
<td>Allergies, yes</td>
<td>11,281 (46.9%)</td>
</tr>
<tr>
<td>Against:</td>
<td></td>
</tr>
<tr>
<td>Pollen</td>
<td>8969 (79.5%)</td>
</tr>
<tr>
<td>House dust mites</td>
<td>4573 (40.5%)</td>
</tr>
<tr>
<td>Animal protein</td>
<td>2203 (19.5%)</td>
</tr>
<tr>
<td>Fungal spores</td>
<td>911 (8.1%)</td>
</tr>
<tr>
<td>Chemical agents</td>
<td>419 (3.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>234 (2.1%)</td>
</tr>
<tr>
<td>Missing data</td>
<td>359 (3.2%)</td>
</tr>
</tbody>
</table>

SD = standard deviation.

a Other allergenes were: food, medications, metals, plants, insect poison, gum arabic/latex.

Figure 1 Improvement of the lung function with once daily 160 µg ciclesonide. Data presented are mean values (standard deviation) of FEV1 [l] (N = 19,953) and % of the predicted value (N = 20,297) from patients with complete data at both visits.
Clinical studies. In the present analysis, mean FEV1 was 9.4% higher after 3 months, which is in the same range as the reported median improvement of FEV1 of 11% after 3 months of treatment with 80 µg ciclesonide once daily in a randomized study.16 A placebo-controlled study by Langdon et al. also noted significant improvements in FEV1 (significant increases of +0.13 l with 80 µg and +0.19 l with 320 µg ciclesonide versus placebo after 3 months) and PEF in patients treated with 80 µg or 320 µg daily ciclesonide for 3 months compared to placebo.12 Other 3-month, randomized, double-blind, active controlled studies also demonstrated a significant increase in FEV1 from baseline to study end with non-inferiority to budesonide and fluticasone.37–39

Similarly, the mean PEF increased in the course of the treatment with 160 µg ciclesonide by 14% which is comparable to the previously reported clinical trials with 22.4 l/min with half the dose.12

In addition, in two of the three non-interventional trials (BASIS and ATALL) exhaled NO was reduced by 51% in a subgroup of patients after 3 months of treatment. This is in accordance with a comparative study investigating the impact of 3 months treatment with ciclesonide or fluticasone on exhaled NO reported by Zietkowski et al., who found that NO was reduced by 56.4% with 80 µg, and 70.0% with 160 µg, ciclesonide once daily (fluticasone 100 µg once daily: 38.2%).30

The improvement of lung function was accompanied by a reduction of daytime and night-time asthma episodes. The proportion of patients that suffered from daily asthma episodes during the daytime was reduced from 24.3% at study start to 1.9%. Similar results were observed for frequent asthma episodes during the night-time, with a reduction from 13.3% to 1.3%. These findings are supported by the results of numerous randomized, placebo-controlled studies that demonstrated a significant decline of day- and night-time asthma episodes after a 3-month application of 160 µg ciclesonide once daily in children and adults.39–42 The need for rescue medication is another important parameter for the assessment of asthma therapy in routine clinical care. In our analysis, the daily consumption of β2-agonists decreased from 26.9% at baseline to 8.8% after 3 months. Significant reductions in rescue medication use from day 1 after start of ciclesonide treatment has been reported previously in several randomized, controlled clinical studies e.g.30,36

Overall, concerning the most relevant parameters, ciclesonide supported efficacy data previously shown in randomized, controlled trials in smaller patient populations with more rigid inclusion and exclusion criteria.36,39,40

The incidence of ADRs was low in this large-scale patient population, with only 51 patients (0.2%) experiencing an adverse event, compared to an AE incidence rate of about 4% reported in pivotal trials studying ciclesonide at doses ranging from 80 µg to 1280 µg per day. This low incidence of ADR might be explained by the non-interventional design of the studies in which only spontaneously reported ADRs were documented and not as thoroughly reported as in clinical trials. Investigators had to fill in a ADR documentation form to be submitted to the sponsor and/or the authorities. It cannot be ruled out that investigators only used this form in case of ADRs that seemed to be unusual to the investigator. Further, it is well known that ADRs tend to be under-reported in routine medical care, especially for drugs recently marketed or for less severe and known side effects.43,44 Thus, it is likely that in the present observational studies the absolute number of documented ADRs

![Figure 2](image_url) Reduction of asthma episodes a) during daytime, and b) during night-time (N = 24,037).

Discussion

For the first time data on the use of ciclesonide in real-life setting are reported. The results of the present pooled analysis of three non-interventional, prospective, large-scale multicenter studies conducted in Germany with over 24,000 patients support the results from previous studies that therapy with ciclesonide (160 µg once daily) is safe in patients with persistent mild to moderate asthma also under conditions of routine clinical care. Considerable improvement of FEV1, PEF, NO, and asthma symptom control were observed after 3 months of treatment compared to baseline. A low incidence of ADRs was observed (51/24,037 patients, or 0.2%).

The results of the present studies are in accordance with findings from previously performed randomized, controlled clinical studies. In the present analysis, mean FEV1 was 9.4% higher after 3 months, which is in the same range as the reported median improvement of FEV1 of 11% after 3 months of treatment with 80 µg ciclesonide once daily in
was biased by under-reporting. However, as under-reporting seems to be positively selective, one can assume that serious, severe or rare reactions were still detected in the present studies.

In the observational studies, the incidence of cough, dysphonia, and irritations was \(<0.05\%\). Oral candidiasis was reported by 5 out of 24,037 patients. In the summary of product characteristics of Alvesco\(^{34}\) an overall ADR incidence rate of about 5\% is reported. Most of these AEs were of mild nature and did not lead to discontinuation of therapy. One death was documented, but was considered "definitely unrelated" to the prescribed medication.

Observational studies in asthma may provide important additional data in the "real-world setting" as suggested by Holgate et al.\(^{23}\) Recently, a study also showed clinically relevant improvements with montelukast in a large observational study\(^{28}\) with 1681 patients with mild to moderate asthma confirming earlier data from randomized, controlled studies.

**Limitations**

Observational studies can make an important contribution to medical knowledge, but naturalistic, non-interventional study designs generally have a number of limitations. Most importantly, the studies did not include a placebo arm or an active comparator arm, so that the degree to which the results reflect drug-specific effects remains uncertain. This study has limitations due to the inherent biases introduced by the open-label design. However, there are plenty of randomized controlled trials and meta-analyses in the literature, who have

<table>
<thead>
<tr>
<th>Adverse drug reactions (ADRs)</th>
<th>Patients, n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall ADRs</td>
<td>51</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Non-serious ADRs in ≥2 patients (MedRA preferred term)</td>
<td>50</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Dysphonia</td>
<td>11</td>
<td>0.05</td>
<td>0.02–0.07</td>
</tr>
<tr>
<td>Cough</td>
<td>10</td>
<td>0.04</td>
<td>0.02–0.07</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>7</td>
<td>0.03</td>
<td>0.01–0.05</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>5</td>
<td>0.02</td>
<td>0.00–0.04</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>5</td>
<td>0.02</td>
<td>0.00–0.04</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>5</td>
<td>0.02</td>
<td>0.00–0.04</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>&lt;0.01</td>
<td>–0.00–0.02</td>
</tr>
<tr>
<td>Oral discomfort</td>
<td>2</td>
<td>&lt;0.01</td>
<td>–0.00–0.02</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>2</td>
<td>&lt;0.01</td>
<td>–0.00–0.02</td>
</tr>
</tbody>
</table>

**Serious ADRs**

Myocardial infarction (no relation) 1 \(<0.01\) Exitus

**Discontinuing patients**

46

**ADRs leading to discontinuation with probable or definite causal relation to Ciclesonide**

MedRA preferred term\(^a\) 45 ADRs in 41 patients

Cough 9
Dyspnoea 6
Dysphonia 6
Throat irritation 4
Oral candidiasis 3
Nausea 2
Oral discomfort 2
Stomatitis 2
Chest discomfort, Dry mouth, Eczema, 1 each
Gingival disorder, Infection, Insomnia, Mucosal inflammation, Myalgia, Palpitations, Pharyngolaryngeal pain, Skin haemorrhage

**ADRs leading to discontinuation with improbable causal relation or missing information**

MedRA preferred term\(^a\) 17 AEs in 5 patients

Pregnancy 4
Cough 3
Anxiety, Cataract, Dyspepsia, Dyspnoea, Headache, Insomnia, Nausea, Pruritus, Urticaria, Throat irritation 1 each

Abbreviations: ADR = adverse drug reaction; MedRA = Medical Dictionary for Regulatory Activities.

\(^a\) More than one ADR in one patient possible.
answered such research questions sufficiently for ciclesonide. Further, the impact of possible confounding factors have not been investigated and data were not evaluated as carefully as in a randomized clinical trial.

Factors that may bias the results of observational studies can be broadly categorized as selection bias resulting from the way study subjects are recruited or from differing rates of study participation depending on the subject’s cultural background, age, or socioeconomic status, and information bias. The studies were not based on an epidemiological sample, but on a sample recruited by investigators who were willing to participate in this observational trial. Hence, unspecific factors such as rater bias, expectation effects, and time effects cannot be ruled out. Furthermore, the studies were carried out exclusively in Germany. Thus, the results may not be generalizable to countries with other health care systems. Furthermore, the number of ADRs reported was surprisingly low with only 51 of the 24,037 patients experiencing an ADR. Presumably, this is also a consequence of the non-interventional design in which data are not thoroughly reported as in monitored clinical trials. One further limitation is the result of incomplete recording of data regarding medication-naïve and pre-treated patients. Therefore, analyses were not possible in this respect. Also, only two visits (at start and at 3 months) were scheduled, hence, no information about compliance/adherence and about speed of onset of action could be derived from the data. It should also be mentioned that not everything was “real-life” in the studies. In particular, the decision to start ciclesonide instead of another inhalation corticosteroid may have been influenced by the fact that this study with a new molecule was running with priority on the department.

One of the strengths of this pooled analysis of three non-interventional trials, however, is the large sample size of over 24,000 patients drawn from over 6000 private practices. This, and the observation period of 3 months, makes it more likely that a rare ADR would be detected. In addition, the many participating centers and patients can be regarded as representative for the primary health care situation in Germany, although recruitment was not as strict as in epidemiological investigations. Therefore, these observational studies, particularly large ones, provide extensive and useful information about treatment outcomes in daily medical practice.

Conclusions
The pooled results from these three observational studies in a large patient population of more than 24,000 patients with mild to moderate bronchial asthma support the findings from clinical trials that ciclesonide is efficacious and well tolerated, also in a routine clinical care setting and that ciclesonide is suitable for use in the first-line therapy of asthma.

Acknowledgements
Research was funded by Nycomed Deutschland GmbH. The authors wish to thank all participating physicians for participating in these studies, and MEDIDATA, Constance, Germany, for statistical analysis. The authors also thank Birgit Eschweiler, PhD, Medical Writing Services, for support in writing and editing of the manuscript.

Conflict of interest
C. Vogelmeier and Th. Hering serve as advisors of Nycomed Deutschland GmbH and give lectures for the company. Th. Lewin, P. Sander and T.D. Bethke are full-time employees of Nycomed Deutschland GmbH. Ciclesonide is marketed as Alvesco® by Nycomed Deutschland GmbH. Investigators received an allowance according to the medical fee structure in Germany (GOÄ, Gebührenordnung Ärzte).

References
17. Derom E, Van De Velde V, Marissens S, Engelstätter R, Vincken W, Pauweis R. Effects of inhaled ciclesonide and


