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Add-on montelukast in inadequately controlled asthma patients in a 6-month open-label study: The MONtelukast In Chronic Asthma (MONICA) study

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Summary
Bronchial asthma often remains uncontrolled despite treatment with inhaled corticosteroids (ICS), long-acting β_2-agonists (LABA) or both, necessitating additional treatment. Patients $\geq$18 years ($n = 1681$) with mild-to-moderate asthma received oral montelukast 10 mg added to ICS or ICS + LABAs, and were followed for 6 months in a prospective, open-label observational study. The primary endpoint was change in Asthma Control Test (ACT) score. Secondary endpoints included mini-Asthma Quality-of-Life Questionnaire (mini-AQLQ) and FEV_1/PEF. Mean ACT scores improved from 14.6 ± 4.6 (baseline) to 19.4 ± 4.4 (month 6; $p < 0.0001$). Using ACT score categories, the percentage of patients with uncontrolled (57.5%) or poorly controlled (25.0%) asthma at baseline decreased at month 6 (17.6 and 21.7%, respectively); the percentage of patients with well controlled (13.9%) or completely controlled (1.2%) asthma at baseline increased at month 6 (47.5 and 11.4%, respectively). The mini-AQLQ score (mean $\pm$ SD) improved from 4.0 ± 1.1 to 5.3 ± 1.1 ($p < 0.0001$); FEV_1 increased from 2.46 ± 0.89 to 2.60 ± 0.92 L ($p < 0.0001$). Treatment with montelukast was generally well tolerated. In patients insufficiently controlled with ICS or ICS + LABAs, daily add-on montelukast improved both asthma control and asthma-related quality of life. Clinicaltrials.gov registry number NCT00802789.

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Introduction

Asthma affects 300 million people worldwide and is associated with considerable morbidity and, at times, mortality.[1,2] Current hypotheses suggest that inflammation is the underlying cause of symptoms, which include wheeze, breathlessness, chest tightness, and coughing.[3–5] The cellular bronchial infiltrations in asthma are associated with elevated levels of inflammatory mediators such as leukotrienes.

Current guidelines for asthma management concur that inhaled corticosteroids (ICS) are the mainstay of anti-inflammatory therapy in asthma.[1,6,7] Nevertheless, asthma is often inadequately controlled, even with high doses of ICS, warranting additional therapies. Accordingly, long-acting β_2 agonists (LABAs) are commonly used in combination with ICS.[1] While the addition of LABAs to ICS results in an improvement in symptom scores and reduces exacerbations, recent studies have shown that insufficiently controlled asthma remains a significant problem even when ICS and LABAs are titrated to the maximal dose.[8,9] Therefore, alternative therapies that can be added either to ICS or to ICS + LABA are needed.

Cysteinyl leukotrienes (CysLT) mediate tissue edema, infiltration and activation of inflammatory cells. Accordingly, leukotriene modifiers have been shown in randomized, placebo controlled clinical trials to improve airflow limitation and asthma symptoms.[10–14] Additionally, add-on therapy with leukotriene receptor antagonists (LTRAs) to ICS or ICS − β_2-agonist combinations have demonstrated improved asthma control and pulmonary function in similar, controlled trials.[15–18] However, translating randomized controlled clinical trial data to everyday clinical practice is often difficult when treating patients who might not fulfill the inclusion criteria of these studies. To complement the results of these randomized double-blind studies, increasing emphasis is put on the added value of open-label studies under ''real-world'' conditions that provide clinically relevant additional information about the actual benefits of these therapies in broader patient populations. Dupont et al.[19] reported that adding montelukast to a fixed combination of ICS and LABA improved asthma control and pulmonary function in a 2-month open-label pilot study in 313 insufficiently controlled asthma patients. Korn et al. found similar results in a comparably designed study in 5769 patients and provide further evidence of the efficacy of adding montelukast to the treatment regimens of inadequately controlled patients, although the study was also limited in that the duration was only 2 months and that the evaluation of treatment effects was limited to only one time point.[20] Because of the chronic nature of asthma and the possibility of a better safety profile with long-term LTRA therapy versus long-term LABA therapy,[16] studies examining treatment over longer durations are needed.

In this study, we report a substantially longer prospective open-label study in which montelukast was added to treatment regimens of patients whose asthma, as judged by their attending physician, was insufficiently controlled with ICS or ICS + LABA.

Methods

Patients included in this study were ≥18 years of age with a physicians' diagnosis of mild or moderate persistent asthma defined as Global Initiative for Asthma (GINA) stage II or stage III, respectively[1] who were insufficiently controlled with their current medication of ICS or ICS and LABAs. Uncontrolled asthma was defined according to GINA criteria.[1] No further restrictions were placed on qualifications for patient inclusion in order to emulate ''real world'' clinical practice. Patients were enrolled if they met the criteria of uncontrolled asthma according to their physicians' assessment.

This study was conducted at 290 sites in Germany by office-based pulmonary specialists. Each study site was to include a maximum of five patients in order to limit investigator bias. Patients were informed about the study and signed an informed consent prior to participation. The study was registered with the German federal authorities and the Ethics committee as per the German Medicines Act. The study was also registered with clinicaltrials.gov (NCT00802789) and within the registry of non-interventional studies of the Association of Research Based Pharmaceutical Companies.

This was a prospectively designed, open-label study conducted between April 2007 and September 2008; the duration was 6 months. At visit 1 (baseline visit), asthma control was assessed with the five-question Asthma Control Test (ACT) and asthma-related quality-of-life was assessed using the mini-Asthma Quality-of-Life Questionnaire (mini-AQLQ).[21] In addition, pulmonary function (spirometry) was measured in patients not well controlled. At the first visit, patients received montelukast 10 mg for daily self-administration, in addition to their current asthma treatment. These concomitant medications included short-acting β_2-agonists, ICS, LABA, fixed combinations of ICS + LABA, theophylline or, in some patients, oral corticosteroids.

At visit 2 (month 3) and visit 3 (month 6), ACT and mini-AQLQ evaluations were completed in the office, spirometry was conducted if deemed necessary by the physician, and satisfaction with therapy and adverse events (AEs) were documented. Between visits (1.5 and 4.5 months), patients filled out another ACT (at home) and gave self-assessments of compliance (by pill count); for compliance assessments, a four-stage scale was applied (zero to one tablet per week, two to three tablets per week, four to five tablets per week, six to seven tablets per week).

Efficacy analyses were performed for the intention to treat (ITT) population and for the per-protocol (PP) population; safety was evaluated using the total set. The PP population included patients fulfilling the following criteria: age of patient ≥18 years; uncontrolled asthma under previous therapy with either ICS or ICS + LABA; and at least one on-treatment efficacy value. The data presented in this report show results from the ITT.

The primary endpoint was the total score from the ACT, which consists of five questions rated on a scale from 1 to 5 (Table 1). The results of individual questions were added up to a total score, with a range between 5 (completely uncontrolled asthma) and 25 (completely controlled asthma). Patients were placed into the following four

Table 1 Individual questions of the ACT.

1	In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home as usual?
2	During the past 4 weeks, how often have you had shortness of breath?
3	During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?
4	During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as salbutamol)?
5	How would you rate your asthma control during the past 4 weeks?

*Score of 1 = worst asthma control for each question; score of 5 = best asthma control for each question. ACT = asthma control test.

different categories based on their results: (1) <16 (uncontrolled); (2) ≥16 to ≤19 (poorly controlled); (3) ≥20 to ≤24 (well controlled); and (4) 25 (completely controlled).

The German version of the validated mini-Asthma Quality-of-Life Questionnaire (mini-AQLQ) by Juniper et al. was used as a secondary endpoint.[21] This patient-completed questionnaire consists of 15 questions concerning four domains (symptoms, impairment in activities, emotional life, and environmental impulses). All questions are rated on a scale from 1 to 7. Low values represent poor quality of life; high values represent good quality of life.[21] Forced expiratory volume in 1 s (FEV_1; L) and peak expiratory flow (PEF; L/s) were documented by spirometry based on individual physician's decisions during the visits. Additionally, physicians' and patients' satisfaction with therapy were recorded.

All AEs were documented in detail in special case report forms, which were sent to the clinical research organization (CRO; Kendle, Munich). Serious AEs (SAEs) were AEs that resulted in death, hospitalization, birth defects, disability, malignancy, or were life threatening as well as incidences of overdose regardless of outcome; these were reported immediately to the CRO.

Sample mean and standard deviation were reported for continuous endpoints, and proportions were reported for the categorical endpoints at baseline, months 3 and 6. For changes in ACT, mini-AQLQ, and lung function parameters during the course of the study, 95% confidence intervals and significance tests at the 5% level were generated using the *t*-distribution. The tests are descriptive and have no confirmatory character.

No adjustment of significance level was made due to multiple testing. In order to validate the results in the absence of distributional assumptions for a *t*-test, a non-parametric test (i.e., sign test) was used for sensitivity. As a non-parametric test, a sign test does not require any specific distribution for the underlying values. The two tests had a very similar outcome, and the results of the sign test support those of the *t*-test. The number of patients with AEs and discontinuations from this study were also reported.

Results

A total of 1681 patients participated in this study. Patient demographics and symptoms are shown in Table 1. On average, the duration of asthma was 11.5 years. Patients on ICS alone constituted 23.1%, and those on ICS + LABA (free or fixed combination) were 69.5%. Despite these treatment approaches patients were determined by their physicians to be insufficiently controlled (Table 1).

For the majority of patients, montelukast treatment was continued after the study ended (86.8% were continued after month 3 and 87.3% after month 6). The most common reasons for specialists not to continue montelukast treatment were: continued prescription of montelukast by the family doctor, no improvement of the asthma status while treated with montelukast, patient's request to stop treatment, patient still had enough tablets at home, and discontinuation of treatment because asthma symptoms were seasonal. In 37 of 282 patients who discontinued treatment with montelukast, the asthma status improved so that further treatment was no longer necessary.

At baseline, the mean ACT score for all patients (intention-to-treat analysis) included in the study was 14.6 ± 4.6 and improved significantly at 3 (18.8 ± 4.4; $p < 0.0001$) and 6 months (19.4 ± 4.4; $p < 0.0001$) with add-on montelukast treatment. Results for the per-protocol (PP) analysis were consistent with that of the intention-to-treat (ITT) analysis: the mean ACT score at baseline for the PP-analysis was 14.4 ± 4.5 and improved significantly at 3 (18.7 ± 4.4; $p < 0.0001$) and 6 months (19.3 ± 4.4; $p < 0.0001$). In addition, patients' responses to the ACT were classified into four categories; the proportion of patients in each of the categories improved from baseline to month 6, reflecting an improvement in asthma control (Figure 1).

At baseline, when patients were grouped into different stages of control, more than half of all patients (57.5%) were uncontrolled (ACT total score <16) and 25.0% were poorly controlled (ACT total score 16 to ≤19); only 13.9% had well-controlled asthma (ACT total score 20 to ≤24) and 1.2% of patients had completely controlled asthma according to the ACT (ACT total score = 25). This distribution reflects that physicians still considered a need for additional therapy according to their clinical assessment even in some patients with a high ACT score. After 6 months of open-label treatment with montelukast, the percentage of patients with completely controlled asthma increased from 1.2 to 11.4% and those with well-controlled asthma increased from 13.9 to 47.5%. The percentage of patients with poorly controlled asthma decreased from 25.0 to 21.7%, and those with uncontrolled asthma decreased from 57.5 to 17.6%.

Figure 2 shows data for the individual questions of the ACT. There was a marked improvement from baseline by month 3 in mean scores for each question. These scores improved further, although less markedly, from months 3 (visit 2) to 6 (visit 3) of add-on LTRA treatment (Figure 2).

The overall score of the mini-AQLQ significantly improved at 3 and 6 months (Table 2). Improvements were observed in

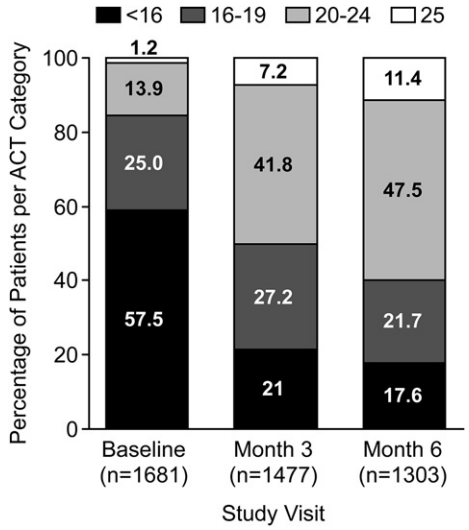

Figure 1 Percentage of patients with total ACT scores by category; <16 = uncontrolled asthma, 16–19 = poorly controlled asthma, 20–24 = well controlled asthma, 25 = completely controlled. ACT = asthma control test.

all four domains of the mini-AQLQ: mean ± SD improvements (visits 1–3) were 3.9 ± 1.2 to 5.2 ± 1.2 ($p < 0.0001$) for the ''symptoms'' domain; 4.3 ± 1.3 to 5.4 ± 1.3 ($p < 0.0001$) for the ''impairment in activities'' domain; 4.2 ± 1.4 to 5.5 ± 1.3 ($p < 0.0001$) for the ''emotional life'' domain, and 3.8 ± 1.3 to 4.8 ± 1.4 ($p < 0.0001$) for the ''environmental impulses'' domain (Table 3).

Total values for pulmonary function improved from an FEV_1 of 2.46 ± 0.89 L at baseline to 2.60 ± 0.92 L at 6 months ($p < 0.0001$), whereas the PEF increased from 5.76 ± 2.38 to 6.22 ± 2.47 L/s ($p < 0.0001$) (Table 2). Additionally, examination of the % of predicted normal value for FEV_1 and PEF show that, although spirometry was only conducted in patients who were deemed as not well controlled, the percent of patients experiencing suboptimal lung function dropped from the baseline visit to months 3 and 6 (Figure 3; Table 3).

After 6 months of treatment, 83.2% of physicians and 83.4% of patients rated the overall improvement in asthma as either ''better'' or ''very much better'' compared with baseline. Only 15.0% of patients and 15.3% of physicians reported ''no improvement.''

Non-serious AEs were reported by 76 patients (4.5% of all patients). The most frequently reported AEs as grouped by system-organ class were infections and infestations (26 patients, 1.6%), gastrointestinal disorders (17 patients, 1.0%) and skin and subcutaneous disorders (14 patients, 0.8%). The following were the most common individual AEs: infection (11 patients), headache (seven patients), nausea, and asthma (in each case six patients), nasopharyngitis and sleep disorder (in each case five patients). Psychiatric AEs were not commonly reported as a system-organ class. There were 11 patients reporting psychiatric AEs: three reported anxiety, one reported hallucination, one reported

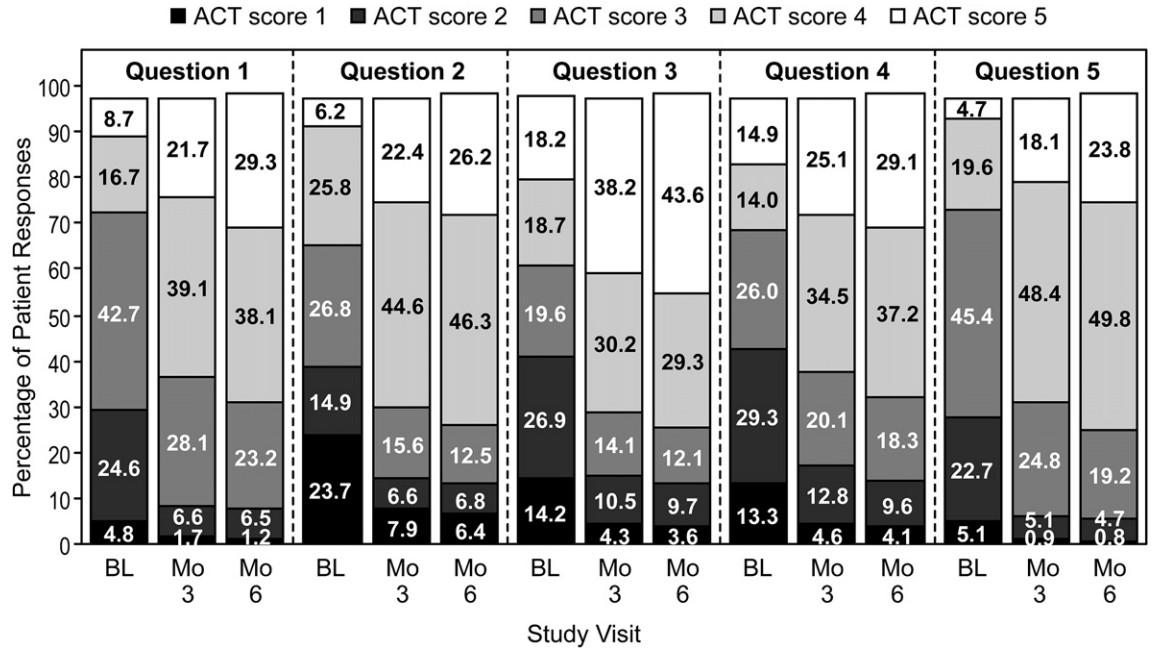

Figure 2 Responses to individual questions of the Asthma Control Test (ACT). Bars do not add up to 100% because of missing responses from some patients in the study. BL = baseline; Mo 3 = month 3; Mo 6 = month 6. Individual questions included the following with responses from 1 (worst) to 5 (best): Question 1: In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school, or at home? Question 2: During the past 4 weeks, how often have you had shortness of breath? Question 3: During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning? Question 4: During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication? Question 5: How would you rate your asthma control during the past 4 weeks?

Table 2 Patient demographics.

	n	Value
Total patients included in study	1681	N/A
Age, yr, mean ± SD	1665*	45.7 ± 15.9
Gender, %		
Male	567	33.7
Female	1097	65.3
Presence of allergic rhinitis	986	58.7
Proportion of patients, %		
Lung function (PEF or FEV_1) <80% of predicted value	610	36.3
Asthma severity: mild asthma	572	34.0
Asthma severity: moderate asthma	1036	61.6
Daytime symptoms >2×/week	1213	72.2
Any constraint of physical activities	614	36.5
Any nocturnal asthma symptoms/nocturnal awakening	621	36.9
Rescue medication use >2×/week	964	57.3
Exacerbations ≥1/year	752	44.7
Asthma not controlled despite ICS or ICS + LABA	1590**	94.6

*There were 16 patients whose age was not documented. **All patients included in this study were inadequately controlled according to GINA guidelines; however, data on GINA criteria determining uncontrolled asthma is missing from 91 patients; FEV_1 = forced expiratory volume in 1 s; ICS = inhaled corticosteroid; LABA = long acting β_2 agonist; PEF = peak expiratory flow; SD = standard deviation.

Table 3 Secondary endpoint assessments.

	Visit	*n**	Mean value ± SD**
FEV_1 (L)	1	1445	2.46 ± 0.89
	2	1057	2.61 ± 0.92
	3	914	2.60 ± 0.92
FEV_1 (% of predicted value)	1	1441	79.2 ± 21.2
	2	1050	84.0 ± 22.2
	3	908	84.3 ± 21.9
PEF (L/s)	1	967	5.76 ± 2.38
	2	669	6.20 ± 2.33
	3	563	6.22 ± 2.47
PEF (% of predicted value)	1	967	78.1 ± 29.5
	2	663	84.7 ± 29.1
	3	557	85.3 ± 31.6
Mini-AQLQ overall score	1	1605	4.0 ± 1.1
	2	1409	5.0 ± 1.1
	3	1261	5.3 ± 1.1

*Not all patients were included in secondary endpoints. The performance of these tests were made at the discretion of individual investigators; **$P < 0.0001$ for differences between visit 1 and visits 2 and 3 for all assessments; AQLQ = asthma quality-of-life questionnaire; PEF = peak expiratory flow; FEV_1 = forced expiratory volume in 1 s; SD = standard deviation.

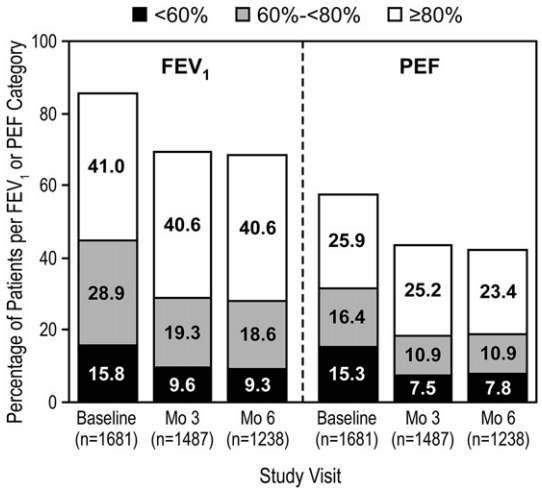

Figure 3 FEV_1 and PEF (% of predicted normal value). FEV_1 and PEF measurements were not performed for patients with well-controlled asthma; therefore, an increase in the percentage of patients with ≥80% FEV_1 or PEF would not be expected in this figure. Totals <100% due to missing values for those patients whose lung function was not measured due to well controlled asthma; *n* = total number of patients. FEV_1 = forced expiratory volume in 1 s; PEF = peak expiratory flow.

insomnia, two reported nightmares, one reported restlessness, and five reported sleep disorder.

SAEs were reported by six patients (0.4% of all patients), none of which were considered related to montelukast. SAEs included one gastric cancer, one septic shock (with lethal outcome), one urinary bladder cancer, one meniscus damage, one asthma exacerbation, one asthma exacerbation due to an infection, and one acute bronchitis.

Discussion

In this large, real-life, multi-center study conducted by pulmonary specialists in private practice the addition of a leukotriene receptor antagonist to patients who were considered to be insufficiently controlled on ICS or ICS and LABAs resulted in a significant and clinically relevant improvement in asthma control as assessed by the ACT and in asthma related quality of life as assessed by the mini-AQLQ. While the recommended strategy for uncontrolled asthma patients on ICS is to add a LABA,[1] randomized, controlled trials have suggested that asthma exacerbations can also be reduced in patients receiving ICS by adding a LTRA such as montelukast.[22] Notably, in a randomized controlled study, the number of asthma attacks and nocturnal awakenings were similar in treatment regimens using ICS + LABA or ICS + LTRA.[15] Similarly, pulmonary function improvement was not different when the addition of an LTRA to a standard dose of ICS was compared with doubling the dose of steroids.[17]

Additionally, it is well recognized that not all patients achieve well-controlled asthma despite an appropriately high dose of ICS or ICS + LABA combination therapy;[8] in such patients, there is a need for additional add-on therapy such as treatment with a LTRA. In a 6-week study in symptomatic patients on high-dose ICS (≥1200 μg of BDP)

and short-acting β_2-agonists, the addition of an LTRA (zafirlukast) significantly improved lung function and reduced exacerbations.[18] In addition, in a smaller, open-label study of 313 patients with insufficiently controlled patients on fixed combination therapy with ICS and LABAs, Dupont et al. observed an improvement in asthma symptoms and pulmonary function with add-on LTRA therapy after 2 months of therapy.[19]

In this open-label study, add-on montelukast therapy in a real-world setting over 3 and 6 months improved asthma control in patients with mild to moderate persistent asthma who were not sufficiently controlled by ICS or the combination of ICS and LABA. Asthma control was assessed by the ACT, a short and relatively simple, validated, patient-based, five-item questionnaire that is one of the assessment tools for asthma control recommended by GINA.[1,23,24] The total ACT scores and responses to individual questions of the ACT in this study demonstrated improved asthma control with the addition of montelukast. Interestingly, results for the per-protocol population were consistent with those seen for the total population (ITT-analysis) which strongly suggests that the improvements observed are not due to a selective drop out of patients who did not positively respond to therapy.

Previous studies in asthma have shown that the assessment of asthma symptoms and severity can differ considerably between physicians and patients.[25] Interestingly, when asked about their overall impression about the effects of add-on montelukast in this study, the assessment of the respective individual improvement was almost identical when physicians' and patients' assessments were compared. Thus, these results support the use of the ACT as a primary outcome parameter in which patients and physicians effectively communicate their observations on asthma control on a common platform.

Additionally, add-on montelukast treatment was evaluated by the validated German version of the mini-AQLQ, the short form of the Asthma Quality-of-Life Questionnaire.[21] The total mini-AQLQ score as well as its individual questions also demonstrated a clinically meaningful improvement when montelukast was added to current therapy. Improvements in all of the domains of the test were >0.5 points, which has been reported as the minimal important difference (MID) of clinical relevance.[21]

In this study, SAEs were rare and were deemed to be unrelated to montelukast. Psychiatric AEs were also rare; the most common among this category of AEs was sleep disorder, which was reported by five patients.

Thus, the results from this study confirm previous randomized, well-controlled studies in smaller patient populations with more rigid inclusion and exclusion criteria. There are, however, limitations to this study, due to the inherent biases introduced by an open-label design. In a controlled environment with a smaller number of patients, data such as the number of hospitalizations during the study, the rate of exacerbations, and actual doses of ICS and LABA medication taken by patients would be captured. Due to the non-interventional design of this open-label study, such data was not possible to capture. Another limitation to this open-label design was that a small number of patients were included in this study who were not uncontrolled according to a strict interpretation of the GINA guidelines. However, it should be noted that this study reflects results observed in a real-world setting; outside the setting of a randomized controlled trial, physicians continue to see patients who are unsatisfied with their asthma therapy despite being defined as well controlled by GINA criteria. Obviously, our study was not designed to test the sensitivity and specificity of the GINA criteria for ''controlled asthma''. The study reflects the clinical experience that some patients despite fulfilling the criteria of ''controlled'' asthma according to GINA will seek further treatment options. However, the number of such patients was very small and therefore does not affect or confound the interpretation of results of this trial where the vast majority of patients were uncontrolled as defined by GINA criteria. Another limitation that should be mentioned is that this study was conducted exclusively in patients who were treated in Germany; therefore similar studies in other countries are needed to confirm that these results could be replicated in other populations internationally.

Nevertheless, observational studies, particularly large ones such as the present study, provide useful and important additional and/or complementary information to randomized controlled trials and offer a view of treatment effects in a ''real-world'' setting. In fact, the Brussels Declaration on Asthma recently urged the funding of ''real-world'' studies such as the present one and supported that the results of such studies be used to inform treatment guidelines.[26]

In summary, the results from this large, open-label study under ''real-life'' conditions demonstrate clinically relevant improvements in patients with asthma when montelukast is added to current ICS or ICS + LABA therapy. These improvements included asthma control, quality of life, lung function, and asthma status with a good safety profile.

Conflict of interest

AM is an employee of Merck & Co., Inc. and owns stock/stock options in the Company. JCV and HM have received speaker fees from and have served as advisors for Merck & Co., Inc. and a number of other companies that produce drugs to treat asthma. LL has no conflicts of interest to disclose.

JCV, AM, LL, and HM are responsible for the work described in this paper. All authors were involved in at least one of the following: conception, design, acquisition, analysis, statistical analysis, interpretation of data and drafting the manuscript and/or revising the manuscript for important intellectual content. All authors provided final approval of the version to be published.

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