

Zafirlukast improves asthma symptoms and quality of life in patients with moderate reversible airflow obstruction

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Background: Previous trials demonstrated the effectiveness of the leukotriene receptor antagonist zafirlukast in patients with mild-to-moderate asthma.

Objectives: We sought to assess the efficacy and safety of zafirlukast and its effect on patients' quality of life (QOL) during a 13-week, double-blind, placebo-controlled, multicenter trial in adults and adolescents with moderate reversible airflow obstruction.

Methods: Patients (age range, 12 to 68 years) with total daytime asthma symptoms scores of 10 or greater over 7 consecutive days (maximum, 21/wk), FEV₁ 45% or greater but less than or equal to 80% of predicted value (≥ 6 hours after β_2 -agonist), and reversible airway disease were randomized to 20 mg zafirlukast twice daily ($n_Z = 231$) or placebo twice daily ($n_P = 223$). Efficacy was assessed from changes in daytime and nocturnal symptoms, β_2 -agonist use, nasal congestion score, and pulmonary function. QOL was evaluated with a disease-specific Asthma Quality of Life Questionnaire. Safety was determined from adverse event information and clinical laboratory test results.

Results: Zafirlukast was significantly ($P < .001$) more effective than placebo, with reductions from baseline in the daytime asthma symptoms score (-23%), nighttime awakenings with asthma (-19%), and β_2 -agonist use (-24%) and improvements from baseline in morning ($+25$ L/min) and evening ($+18$

L/min) peak expiratory flow rates. Compared with placebo, zafirlukast significantly ($P \leq .018$) improved scores for QOL domains (activity limitations, symptoms, emotional function, and exposure to environmental stimuli) and overall QOL, with a significantly greater proportion of zafirlukast-treated patients demonstrating clinically meaningful improvements (≥ 0.5 -unit change from baseline; $P \leq .037$). The safety profile of zafirlukast was clinically indistinguishable from that of placebo.

Conclusions: Zafirlukast is effective and well tolerated and improves QOL in the long-term treatment of patients with moderate reversible airflow obstruction. (J Allergy Clin Immunol 1998;102:935-42.)

Key words: Asthma, leukotriene receptor antagonist, nasal congestion, number needed to treat, peripheral blood eosinophils, pulmonary function, quality of life, reversible airflow obstruction, zafirlukast

Investigations into the role of leukotrienes in the pathophysiology of asthma gave rise to new therapeutic strategies directed at controlling asthma symptoms and the underlying disease by either modulating the generation of leukotrienes or antagonizing their action at specific receptors. The oral leukotriene receptor antagonist (LTRA) zafirlukast (ACCOLATE; Zeneca Pharmaceuticals, Wilmington, Del) competitively inhibits the binding of leukotriene D₄ at its receptor.¹

Zafirlukast is indicated for the prophylactic treatment of patients (12 years of age or older) with mild-to-moderate asthma, and evidence from 6- and 13-week clinical investigations demonstrated its safety and clinical benefits.^{2,3} Fish et al³ report that over 40% of patients enrolled in a 13-week trial with zafirlukast had an FEV₁ of 80% or greater of predicted value (approximate mean FEV₁ 78% of predicted value). In this 13-week trial, the effects of zafirlukast therapy were investigated in patients with more moderate airway obstruction (ie, mean FEV₁ 66.6% of predicted value). In addition, patient quality of life (QOL) was assessed by means of an asthma-specific questionnaire.

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Abbreviations used

ANCOVA:	Analysis of covariance
AQLQ:	Asthma Quality of Life Questionnaire
LTRA:	Leukotriene receptor antagonist
PEFR:	Peak expiratory flow rate
QOL:	Quality of life
WBC:	White blood cell

QOL measurements specifically focus on a patient's physical and emotional well being. Disease-specific questionnaires emphasize areas that are relevant to patients with a particular disease, such as their feelings about the disease, its impact on daily activities, and its treatment. QOL measurements are more responsive to clinically significant changes that are not evaluated by conventional clinical measures. The Asthma Quality of Life Questionnaire (AQLQ), which was developed by Juniper et al and previously validated in clinical asthma trials, was used in this trial.⁴⁻⁶ The AQLQ was chosen over generic health-status questionnaires (eg, SF-36 Questionnaire) and other asthma-specific questionnaires for its relative ease of administration and brevity.

The objectives for this trial were to assess the efficacy and safety of zafirlukast (20 mg twice daily) over 13 weeks in adult and adolescent patients with moderate reversible airflow obstruction and to determine zafirlukast's effect on patients' QOL.

METHODS**Study design**

This randomized, double-blind, placebo-controlled, parallel-group, multicenter trial comprised a 1-week screening period; a 2- to 3-week, single-blind, placebo run-in period; and a 13-week double-blind treatment period. The effect of zafirlukast on asthma symptoms, lung function, β_2 -agonist use, nasal congestion, QOL, and overall drug safety were assessed.

Forty-five clinical research centers in the United States enrolled patients in this trial. The trial was approved by appropriate institutional review boards, and all patients gave their written, informed consent.

Patient population

Nonsmoking (<10 pack-years) men and women (without child-bearing potential) 12 years of age or older with a documented history of asthma were enrolled if they met the following criteria: current treatment with inhaled β_2 -agonist only; FEV₁ between 45% and 80% of predicted value without medication (a minimum of 6 hours after β_2 -agonist use); and reversible airway disease demonstrated by a 15% or greater increase in FEV₁ after inhaled bronchodilator use.

Patients were excluded if they had an acute illness or disease, seasonal asthma (symptoms or therapy for ≤ 2 months per year), a history of alcohol or drug abuse, an upper or lower respiratory tract infection within 6 weeks of screening, or an influenza or hepatitis B vaccination within 6 weeks of screening. Patients were also excluded if they used the following medications because of their potential confounding effects on clinical assessments: salmeterol or oral β_2 -agonists within 48 hours of screening; barbiturates or other drugs affecting liver-drug metabolism within 4 weeks of screening; cromolyn sodium, nedocromil sodium, theophylline, oral or inhaled

corticosteroids within 4 weeks of screening; and astemizole within 3 months of screening. Nasal corticosteroids were permitted provided the dosage remained unchanged during the trial.

Screening and placebo run-in periods

During the screening period, each patient provided a complete medical history and underwent a comprehensive physical examination, 12-lead electrocardiographic examination, laboratory tests, urine drug screen, pulmonary function testing, and an interview for subjective symptoms. Airway reversibility was determined by comparing an initial FEV₁ to an FEV₁ collected 15 to 30 minutes after β_2 -agonist use. QOL was assessed with the AQLQ. All procedures, except the medical history, urine drug screen, and airway reversibility testing, were repeated at the end of the placebo run-in period. FEV₁ was measured 6 or more hours after β_2 -agonist use during both screening and run-in periods. Patients also received diary cards to record daily asthma symptoms, β_2 -agonist use, and morning (measured before bronchodilator use) and evening peak expiratory flow rates (PEFRs). Albuterol inhalers (VENTOLIN; Allen and Hanburys, Research Triangle Park, NC) were provided to patients as rescue medication throughout the trial.

Randomization

At each center, only patients with a cumulative daytime asthma symptoms score of 10 or greater over the last 7 consecutive days (score 0 to 3 per day; maximum of 21 per week) of the run-in period were randomized (1:1) sequentially to double-blind treatment with either 20 mg zafirlukast twice daily or matching placebo. The daytime asthma symptom score was determined from self-assessments of daily asthma symptoms (no symptoms, 0; mild symptoms that did not interfere with activities, 1; moderate symptoms that interfered with some activities, 2; and severe symptoms that interfered with many activities, 3). Patients were allowed one 7-day course of oral prednisone for an acute asthma exacerbation during the double-blind treatment period.

Efficacy assessments

Diary card assessments. Daily throughout the double-blind treatment period, patients recorded on diary cards their daytime asthma symptoms scores, nighttime awakenings with asthma, mornings with asthma symptoms (asthma symptoms on awakening for the day), β_2 -agonist use, and morning and evening PEFRs. Nasal congestion scores were also recorded daily by using a 4-point scale ranging from 0 (no congestion) to 3 (severe congestion).

Pulmonary function assessments. Patients used a Mini-Wright peak flow meter (Clement Clarke Inc, Columbus, Ohio) and recorded the best of 3 forced exhalations each morning and evening before β_2 -agonist use. FEV₁ was measured 6 or more hours after β_2 -agonist use at each clinic visit (weeks 4, 8, and 13) during the double-blind treatment period. The best result of 3 forced expiratory maneuvers, meeting American Thoracic Society criteria, was recorded.⁷

AQLQ

Patients were administered an AQLQ by a trained interviewer at screening, before receiving randomized treatment, and at the end of the 13-week double-blind treatment period (or at the time of withdrawal).⁴ The AQLQ contains 32 questions in 4 domains that assess the effect of drug treatment on activity limitations, symptoms, emotional function, and exposure to environmental stimuli. For the activity limitations domain, each patient was instructed to select 5 activities from a list of 26 that were expected to remain important to them throughout the trial. The other 3 domains have standard response items. All items are rated on a scale ranging from 1 (maximal impairment) to 7 (no impairment).

Peripheral blood eosinophils

Blood samples to determine peripheral blood eosinophil counts were collected at weeks 4, 8, and 13 and analyzed by SmithKline Beecham Clinical Laboratories (Van Nuys, Calif).

Safety assessments

The safety of the study medication was evaluated from the results of physical and electrocardiographic examinations, laboratory tests (including chemistry, hematology, and urinalysis), and interviews for subjective symptoms.

Statistical analyses

Statistical analyses were performed jointly at Thomas Jefferson University (Philadelphia, Pennsylvania) and Zeneca Pharmaceuticals (Wilmington, Delaware).

A sample size of 200 patients per treatment group was required to provide sufficient power (90%) to detect a daily 0.2-unit difference (with a standard deviation estimate of 0.6 units) in the daytime asthma symptoms score at α values of .05 between zafirlukast and placebo groups and sufficient power (85%) to detect a 15-L/min difference in morning PEFR (with a standard deviation estimate of 50 L/min).

Diary card data were summarized weekly during 13 weeks of randomized treatment. Nighttime awakenings and mornings with asthma symptoms were characterized as weekly totals, whereas the daytime asthma symptoms score, β_2 -agonist use, and morning and evening PEFRs were characterized as weekly means (average daily value for the week). The last 7 days of the placebo run-in period were used as baseline, and the last 7 days of randomized treatment were used as end point.

Linear modeling was used to analyze serial diary card assessments. For a given patient, the week-to-week values are presumed to be positively correlated; therefore a repeated-measures design was used to assess the treatment effects over the double-blind period, with serial correlation modeled as a first-order autoregressive process.⁸ Analysis of covariance (ANCOVA) was used to analyze spirometric assessment collected at scheduled office visits and at end point (week 13 or last observation carried forward for patients who did not complete the double-blind treatment period). For both analyses, baseline values were used as covariates in testing for treatment differences (calculated as least-squares means) in mean outcomes. To be included in these analyses, the patients needed to have both a baseline and double-blind assessment. Additionally, to evaluate treatment effects in patients with varying asthma severity, strata defined by baseline FEV₁ percent of predicted value (ie, <65% and $\geq$ 65%) were described in the protocol and an a posteriori ANCOVA was performed.

Individual responses to AQLQ items were weighted equally; therefore domain scores for each patient were calculated as the simple mean of items in that domain. The overall QOL assessment score was calculated as the mean of all 32 questions. QOL results collected at the first administration of the AQLQ (ie, screening) were used as the baseline measure. For each domain and the overall QOL score, mean changes from baseline were compared between treatments by using an ANCOVA at end point. Additionally, a Cochran-Mantel-Haenszel test was used to investigate the proportion of patients between treatments who demonstrated a minimal clinically meaningful change from baseline (ie, improvement or deterioration $\geq$ 0.5 units at end point) in the individual domains and overall QOL assessment score.⁹

Peripheral blood eosinophil data (expressed as a proportion of total white blood cells [WBCs]) were analyzed by using a repeated-measures, mixed-effect ANCOVA to assess treatment differences across the 13-week treatment period.

Adverse events were tabulated by treatment group and body system. Fisher's exact tests were used to detect pairwise treatment group differences in the proportion of patients with each type of adverse event. Clinical laboratory tests, vital signs, and electrocardiographic results were summarized by relative time on drug for each clinic visit and were carefully examined to detect treatment-related changes. Patients whose clinical laboratory test results deviated significantly from normal ranges over the course of treatment were also examined.

RESULTS

Of 454 patients randomized to double-blind treatment with zafirlukast ($n_Z = 231$) or placebo ($n_P = 223$), 374 completed 13 weeks of therapy ($n_Z = 189$; $n_P = 185$). Eighteen percent ($n_Z = 42$) of patients in the zafirlukast group and 17% ($n_P = 38$) in the placebo group were withdrawn from the trial for the following reasons: asthma became worse ($n_Z = 2$; $n_P = 6$); lost to follow-up ($n = 12$ both treatments); protocol noncompliance ($n_Z = 13$; $n_P = 8$); adverse event or intercurrent illness ($n_Z = 3$); and other reasons ($n = 12$ both treatments).

Demography and baseline characteristics

Demographic characteristics were similar between treatment groups (Table I). Overall, the mean duration of asthma was approximately 16 years (range, <1 to 65 years), 87% of patients had their asthma precipitated by a known allergen, and 80% of patients entered the trial with physician-diagnosed seasonal and/or perennial allergic rhinitis. At trial enrollment, 34% of patients had an FEV₁ less than 65% of predicted value.

Efficacy assessments

Efficacy analyses excluded data from patients after they received a burst of oral prednisone for an acute asthma exacerbation ($n_Z = 13$; $n_P = 22$) to avoid the confounding effects of oral corticosteroids.

Asthma symptoms, rescue β_2 -agonist use, and nasal congestion score. Patients receiving zafirlukast had statistically significant reductions in mean daytime asthma symptoms score, nighttime awakenings, β_2 -agonist use, and nasal congestion score compared with patients receiving placebo (Table II). Figs 1 to 3 illustrate the least-squares means for daytime asthma symptoms score, nighttime awakenings with asthma, and nasal congestion score, respectively, during 13 weeks of double-blind treatment. These effects were seen by the end of the first week of treatment with zafirlukast and were generally maintained throughout the 13-week treatment period. The improvements in asthma symptoms and β_2 -agonist use reflected the following percent changes from baseline to end point for the zafirlukast and placebo groups, respectively: daytime asthma symptoms score -22.8% versus -16.1% ; nighttime awakenings -18.7% versus 8.7% ; mornings with asthma symptoms -16.3% versus -9.8% ; and β_2 -agonist use -23.7% versus -0.6% .

Pulmonary function. Significant improvements in mean morning and evening PEFRs were noted in the zafirlukast group compared with the placebo group ($P <$

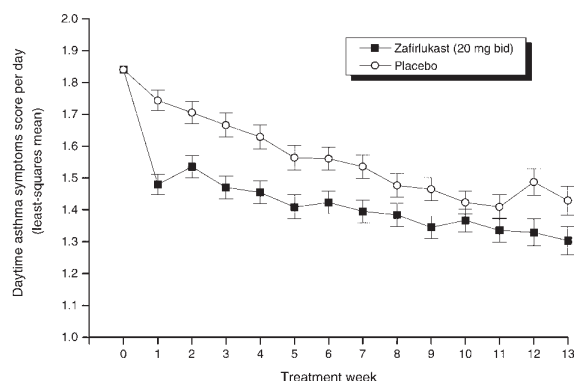


FIG 1. Least-squares means (repeated-measures analysis) for daytime asthma symptoms score during 13 weeks of double-blind treatment with zafirlukast or placebo. A significant treatment difference, favoring zafirlukast, was noted across the treatment period ($P < .001$).

TABLE I. Demographic characteristics of patients randomized to treatment with zafirlukast (20 mg twice daily) or placebo

Characteristic	Zafirlukast ($n_Z = 231$)	Placebo ($n_P = 223$)	Total ($n_{Z+P} = 454$)
Sex, n (%)			
F	127 (55)	132 (59)	259 (57)
M	104 (45)	91 (41)	195 (43)
Race, n (%)			
White	195 (84)	190 (85)	385 (85)
Black	19 (8)	17 (8)	36 (8)
Other	17 (7)	16 (7)	33 (7)
Mean age, y (range)	33.2 (12 to 68)	32.1 (12 to 68)	32.6 (12 to 68)
Age, n (%)			
12 to 17 y	28 (12)	29 (13)	57 (13)
18 to 55 y	188 (81)	185 (83)	373 (82)
≥ 56 y	15 (6)	9 (4)	24 (5)
Patients with AR, n (%)	177 (77)	185 (83)	362 (80)

AR, Allergic rhinitis (seasonal, perennial, or both).

TABLE II. Effect of zafirlukast (20 mg twice daily) and placebo on serial diary card (repeated-measures analysis) and end-point spirometry and QOL (ANCOVA) assessments

Efficacy assessment	Baseline (mean)	Zafirlukast (LS mean)	Placebo (LS mean)	Treatment difference (SEM)	P value
Daytime asthma score (per day)	1.84	1.40	1.55	-0.14 (0.03)	<.001
Nighttime awakenings (per week)	3.56	2.07	2.69	-0.63 (0.17)	<.001
Mornings with asthma (per week)	4.89	3.83	4.07	-0.23 (0.14)	.085
β_2 -Agonist use (puffs/day)	4.97	3.60	4.25	-0.64 (0.14)	<.001
Nasal congestion score (per day)	1.30	1.09	1.22	-0.13 (0.04)	<.001
Morning PEFr (L/min)	361.6	387.5	374.4	13.1 (2.9)	<.001
Evening PEFr (L/min)	398.0	416.1	404.6	11.5 (2.7)	<.001
FEV ₁ (L)	2.37	2.64	2.60	0.05 (0.05)	.331
FEV ₁ % predicted	66.6	66.8	66.4	1.3 (1.3)	.305
Overall QOL assessment score (units)	4.28*	5.08	4.82	0.26 (0.09)	.004

For diary card data, $n_Z = 227$ and $n_P = 215$; for spirometry data, $n_Z = 218$ and $n_P = 205$; and for QOL data, $n_Z = 196$ and $n_P = 175$.

LS mean, least-squares mean.

*QOL evaluation used the screening assessment as baseline.

.001; Table II). Increases from baseline to end point in morning and evening PEFr were 24.8 and 17.5 L/min, respectively, for the zafirlukast group and 13.1 and 2.8 L/min, respectively, for the placebo group.

No statistically significant differences were observed between zafirlukast and placebo for FEV₁ and FEV₁ percent of predicted value (treatment differences: 0.05 ± 0.05 L and $1.3\% \pm 1.3\%$, respectively; $P \geq .31$). However, in patients with more severe airway impairment characterized by an FEV₁ less than 65% of predicted value at baseline ($n_Z = 82$; $n_P = 73$), zafirlukast significantly increased FEV₁ compared with placebo at end point (2.41 vs 2.13 L; $P < .01$) and at each office visit ($P < .01$) during treatment (Fig 4). At end point, zafirlukast improved FEV₁ from baseline by 21% (0.38 L) compared with 9% (0.18 L) after placebo.

QOL assessments. Three hundred seventy-one patients ($n_Z = 196$; $n_P = 175$) who completed both a baseline and

double-blind AQLQ were included in the ANCOVA analysis. The baseline mean values for overall QOL assessment scores were equal (4.28 units) in patients that ultimately were randomized to zafirlukast or placebo. Least-squares mean changes from baseline to end point indicated significant treatment differences, favoring zafirlukast, in the overall QOL assessment score (ie, 0.26-unit change over placebo; $P = .004$) and all 4 QOL domains ($P \leq .018$). In addition to presenting the ANCOVA results, Fig 5, A illustrates the mean change from baseline to end point in AQLQ assessments for both treatments.

As shown in Fig 5, B, a significantly greater proportion of patients in the zafirlukast group demonstrated a 0.5-unit or greater improvement from baseline in their overall QOL assessment score (ie, zafirlukast 56% vs placebo 46%; $P = .021$) and all 4 QOL domains ($P \leq .037$) compared with the placebo group. The differences

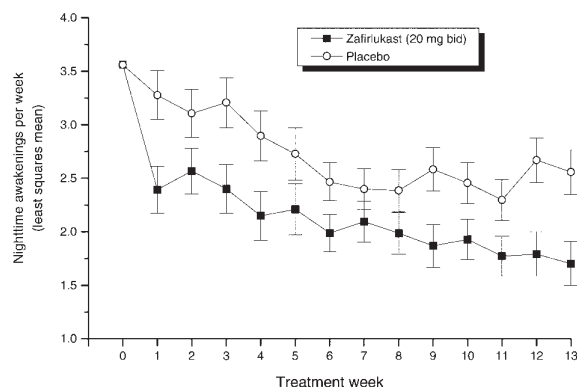


FIG 2. Least-squares means (repeated-measures analysis) for nighttime awakenings with asthma during 13 weeks of double-blind treatment with zafirlukast or placebo. A significant treatment difference, favoring zafirlukast, was noted across the treatment period ($P < .001$).

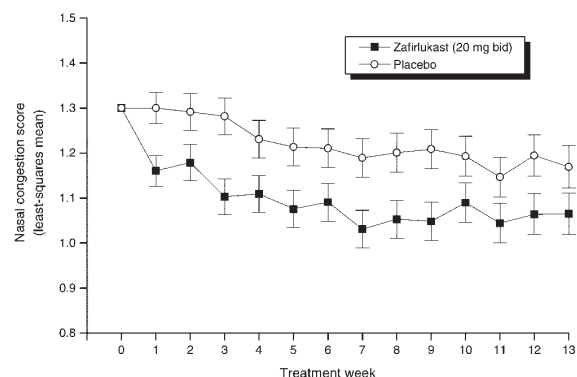


FIG 3. Least-squares means (repeated-measures analysis) for nasal congestion score during 13 weeks of double-blind treatment with zafirlukast or placebo. A significant treatment difference, favoring zafirlukast, was noted across the treatment period ($P < .001$).

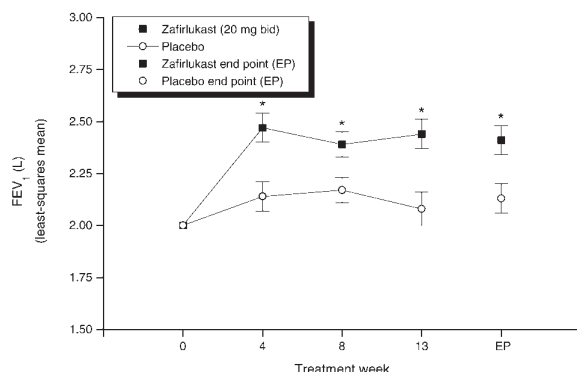


FIG 4. Least-squares means (ANCOVA) for FEV₁ (L) during double-blind treatment for patients in zafirlukast or placebo groups who had a baseline FEV₁ less than 65% of predicted. Asterisk (*) denotes significant treatment differences, favoring zafirlukast, at all time points, including end point ($P < .01$).

between treatments are primarily attributed to more moderate improvements (≥ 1.0 unit) in AQLQ results.⁹

Peripheral blood eosinophils. At baseline, the overall mean peripheral blood eosinophil value was 6.71% of

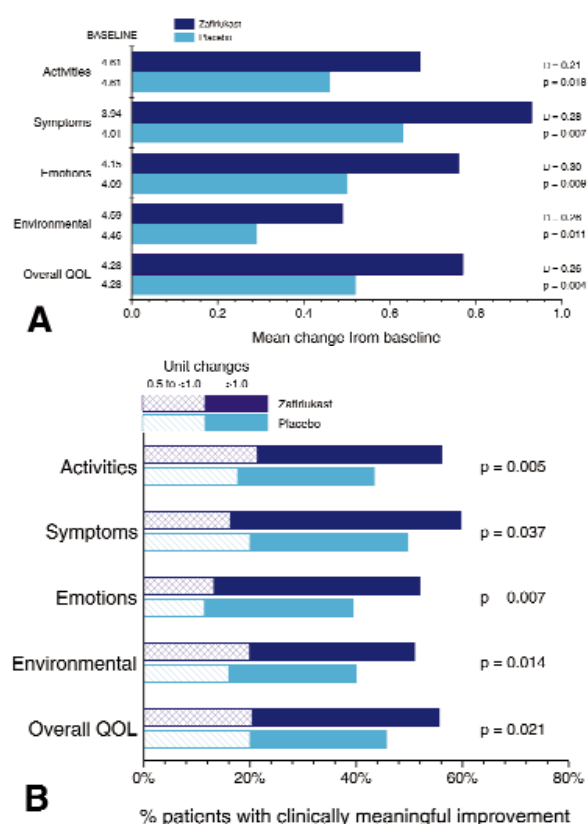


FIG 5. A, Mean change in AQLQ results from baseline to end point for the zafirlukast and placebo groups. At end point, ANCOVA showed that the zafirlukast group ($n_z = 196$) had significantly greater improvements from baseline in all 4 QOL domains and the overall QOL assessment score ($P \leq .018$) compared with the placebo group ($n_p = 175$). Δ indicates the least-squares mean treatment difference at end point (zafirlukast minus placebo). **B,** Percentage of patients in zafirlukast and placebo groups with a clinically meaningful improvement at end point (≥ 0.5 -unit change from baseline) in the 4 QOL domains and overall QOL assessment score (Cochran-Mantel-Haenszel Test). Compared with the placebo group, significantly more patients in the zafirlukast group had clinically meaningful improvements in all QOL domains and the overall QOL assessment score ($P \leq .037$). Treatment bars are stratified to show the proportion of patients with clinically meaningful improvements of 0.5 or greater through less than 1.0 units (minimal improvement) and 1.0 units or greater (moderate improvement or better).

total WBCs. Over the 13-week treatment period, a significant reduction in peripheral blood eosinophils was noted in the zafirlukast group compared with the placebo group (least-squares mean values across the double-blind treatment period were 6.03% vs 6.50% of total WBCs for zafirlukast and placebo, respectively; $P < .05$).

Safety assessments

Adverse events were reported for 54% ($n_z = 125$) of patients in the zafirlukast group and 59% ($n_p = 132$) of patients in the placebo group. No statistically significant treatment differences were reported in the incidence of any adverse events. Pharyngitis and headache were the most frequent adverse events reported in both treatment groups (18.6% and 10.0% for zafirlukast vs 18.8% and

11.27% for placebo, respectively). Of interest in this patient population, the incidence of sinusitis and rhinitis was lower in the zafirlukast group compared with the placebo group (3.5% vs 5.8% and 2.2% vs 3.6%, respectively). Adverse events led to 5 patient withdrawals in the zafirlukast group and 6 patient withdrawals in the placebo group. Two of 5 patients in the zafirlukast group and all 6 patients in the placebo group were withdrawn from treatment because of worsening asthma (1 patient receiving placebo also had bronchitis listed as a reason for withdrawal). The remaining patients receiving zafirlukast were withdrawn because of abdominal pain ($n_z = 1$), palpitation ($n_z = 1$), and hypertonia ($n_z = 1$). No clinically significant changes were observed in the results of physical or electrocardiographic examinations.

Elevations in the following liver function test results were reported for 7 patients in the zafirlukast group and 10 patients in the placebo group: alanine transaminase ($n_z = 1$; $n_p = 5$), aspartate transaminase ($n_z = 1$; $n_p = 3$), total bilirubin ($n_z = 4$), alkaline phosphatase ($n = 1$ for both treatments), and lactic dehydrogenase ($n_p = 1$). Only 2 patients, both in the placebo group, had changes judged treatment related. In all cases, elevated levels were either normal or returning to normal by the end of treatment.

DISCUSSION

Our results corroborate and extend earlier findings that showed a twice daily, 20-mg dose of zafirlukast alleviates daytime and nocturnal asthma symptoms and improves pulmonary function while reducing β_2 -agonist use by patients with mild-to-moderate asthma.^{1,2} In this 13-week trial, zafirlukast was significantly ($P < .001$) more effective than placebo in reducing from baseline the daytime asthma symptoms score (–23%), nighttime awakenings (–19%), and β_2 -agonist use (–24%) while increasing morning (+25 L/min) and evening PEFr (+18 L/min) in both adult and adolescent patients with moderate reversible airway obstruction. Although zafirlukast treatment did not result in a statistically significant improvement in FEV₁ for the overall patient population, a subset analysis in patients with a higher degree of lung function impairment (ie, baseline FEV₁ <65% of predicted value) revealed a significant and sustained improvement in FEV₁ after zafirlukast treatment compared with placebo. This finding supports the previously reported contention that zafirlukast has a greater effect on pulmonary function in patients who have a greater potential to improve.²

Few long-term trials (ie, 12 weeks or longer) with oral leukotriene-modifying agents have been reported to date; however, the results of this 13-week trial with zafirlukast appear comparable with those reported by Israel et al⁵ in a 3-month trial with the 5-lipoxygenase inhibitor zileuton (ZYFLO; Abbott Laboratories, Abbott Park, Ill). The zileuton trial enrolled patients with a baseline FEV₁ ranging between 40% and 80% of predicted value (approximate mean FEV₁ 60% of predicted value at baseline) and showed that, compared with placebo, 4 times daily treatment with a 600-mg dose of zileuton offered statistically significant

improvements from baseline in daytime symptoms (–28%), β_2 -agonist use (–26%), and morning (+18 L/min) and evening (+19 L/min) PEFr.⁵

Our results also suggest that zafirlukast has an effect in the upper respiratory tract, as shown by a statistically significant reduction from baseline in the mean nasal congestion score compared with placebo. Interestingly, this effect was associated with fewer adverse events related to the upper airways, such as sinusitis and rhinitis, in the zafirlukast group. Previous studies have demonstrated that zafirlukast and zileuton diminish nasal congestion compared with placebo in patients with allergic rhinitis.^{10,11} The ability of these drugs to reduce nasal congestion is most likely related to their leukotriene-modulating effects in the upper airways. Leukotrienes are potent inflammatory mediators that are speculated to have a significant inflammatory role in the upper airways.¹² Leukotrienes have been found to be at least 1000 times more potent on a molar basis than histamine in inducing nasal allergic responses.¹³ However, to further elucidate the mechanism by which zafirlukast affects inflammation in the upper airways of patients with allergic rhinitis and asthma, more studies are needed to evaluate the effects of zafirlukast on other markers of allergic inflammation.

For QOL results, 2 approaches for determining clinical meaningfulness are commonly used, namely the distribution-based and anchor-based interpretations.^{14,15} Distribution-based interpretations examine the magnitude of effect by means of the mean difference between treatments, whereas anchor-based interpretations compare (or anchor) patient perceptions of QOL changes with changes in other clinical measures to determine the threshold for clinically meaningful improvements or deteriorations. In clinical trials this threshold value is applied prospectively to determine the proportion of patients exhibiting such changes from baseline, and treatment comparisons are then made. In this trial we used both approaches in demonstrating that statistically significant AQLQ results, favoring zafirlukast, were observed in terms of mean changes between treatments and the proportion of patients with a clinically meaningful improvement at end point. Statistically significant mean treatment differences in AQLQ results have also been reported for 2 other leukotriene-modifying agents, namely zileuton and the LTRA montelukast (SINGULAIR; Merck & Co, West Point, Pa).^{5,16}

Guyatt et al¹⁷ suggest that small mean treatment differences in QOL results may not be indicative of the actual benefit an active therapy provides many patients over a control, and therefore these and other researchers advocate the use of the number needed to treat (NNT), along with the distribution- and anchor-based approaches, as a way of making QOL results more interpretable.^{17,18} The NNT is calculated from the proportion of patients with a clinically meaningful improvement or deterioration for each treatment over a specified treatment period and extends this anchor-based approach.^{15,17} For the current trial, an NNT value of 7.7 was calculated

for the overall QOL assessment score at end point by using the minimal clinically meaningful threshold of 0.5 units according to the method reported for randomized, parallel-group trials by Guyatt et al.¹⁷ This NNT value indicates that between 7 and 8 patients need to be treated with zafirlukast for 1 patient to have a clinically important improvement in QOL over and above that which the patient would have had on placebo. However, it is difficult to place the NNT value for zafirlukast into an appropriate clinical perspective because NNT values have not been reported for asthma treatments studied in trials with comparable designs, duration of treatment, asthmatic patient populations, and QOL instrument, all of which are necessary for valid comparisons of NNT values.¹⁸

Compelling evidence from preclinical and clinical investigations exists for the proinflammatory role of eosinophils in the pathophysiology of asthma, including observed bronchospasm and bronchial hyperresponsiveness. Studies with conscious guinea pigs and guinea pig tracheal explant preparations have shown that LTB₄ and the cysteinyl leukotrienes, particularly LTD₄, promote chemotaxis of eosinophils into the airway and that various leukotriene-modifying agents, including zafirlukast, inhibit eosinophil influx.^{19,20} Additionally, correlations between peripheral blood eosinophilia and markers of disease activity in patients with either intrinsic or extrinsic asthma have been reported, suggesting that peripheral eosinophil counts reflect disease activity and possibly the degree of airway inflammation present.²¹

Reiss et al¹⁶ reported that montelukast (10 mg once daily) significantly reduced peripheral blood eosinophil counts over placebo in patients with asthma (FEV₁ 50% and 85% of predicted value) during a 12-week trial ($P < .001$).¹⁶ In the present trial, compared with placebo, zafirlukast demonstrated a small but statistically significant reduction (reduction = 0.47% of total WBCs; $P < .05$) in peripheral blood eosinophils over 13 weeks. Although the clinical relevance of these results is uncertain, the results from these trials nonetheless suggest that LTRAs may have systemic inhibitory effects on specific components of the inflammatory cascade, resulting in improvements in asthma severity.

Clinical experience from this and other long-term trials with zafirlukast demonstrate that the drug has a safety profile clinically indistinguishable from placebo.^{2,3} Importantly, zafirlukast appears to have no adverse effect on liver function, with no evidence of hepatotoxicity. In this trial the only treatment-related changes in liver function tests were identified in the placebo group. These results corroborate findings from a previous 13-week trial.³

Current asthma guidelines recommend the use of leukotriene-modifying agents as an option for first-line controller therapy for asthma.²² Although the changes from placebo for certain individual assessments in this trial may be considered modest in terms of clinical significance, the consistency of effect across multiple assessments (including nasal congestion score, AQLQ results, and peripheral blood eosinophils) and early and sustained improvement during 13 weeks of treatment are

indicative of the overall clinically relevant effects with zafirlukast. Zafirlukast's efficacy and safety profiles, as demonstrated in this trial, together with clinical information reported for other leukotriene-modifying agents suggest that this emerging therapeutic class may also be beneficial to patients with more moderate airway obstruction.

In conclusion, treatment with the oral LTRA zafirlukast (20 mg twice daily) over 13 weeks was well tolerated and effective in alleviating signs and symptoms of asthma in patients with moderate reversible airflow obstruction. Moreover, QOL evaluations showed that zafirlukast has benefits beyond its physiologic effects, suggesting that zafirlukast may reduce the impact of asthma on patients' lives.

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