# A Randomized, Placebo-Controlled, Phase II Study of Tetomilast in Active Ulcerative Colitis

STEFAN SCHREIBER,* ALI KESHAVARZIAN,‡ KIM L. ISAACS,§ JOHN SCHOLLENBERGER,‖ JUAN P. GUZMAN,‖ CESARE ORLANDI,‖ and STEPHEN B. HANAUER¶

*Department of General Internal Medicine, Christian-Albrechts University, Kiel, Germany; ‡Rush Presbyterian St. Luke's Medical Center, Chicago, Illinois; §Division of Digestive Diseases and Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; ‖Otsuka Maryland Research Institute, Rockville, Maryland; and ¶University of Chicago Medical Center, Chicago, Illinois

See Turner D et al on page 103 for companion article in Clin Gastroenterol Hepatol.

***Background & Aims:*** **Tetomilast (OPC-6535), a novel thiazole compound, inhibits phosphodiesterase-4 and proinflammatory functions of leukocytes including superoxide production and cytokine release.** ***Methods:*** **One hundred eighty-six patients with mildly to moderately active ulcerative colitis (Disease Activity Index [DAI] 4–11 points) from 35 centers were randomized to receive an oral, once-daily dose of placebo or tetomilast 25 mg or 50 mg for 8 weeks.** ***Results:*** **Percentages of patients reaching the primary end point (improvement as defined by reduction in DAI ≥3 at week 8) were not significantly different between placebo (35%) and either the 25 mg tetomilast (52%) or the 50 mg tetomilast (39%) groups (intent-to-treat population). Remission rates (DAI 0-1) were 7%, 16%, and 21%, respectively (not significant). Mean reduction in DAI at week 8 was greater in the 25-mg group than under placebo (2.8 ± 0.4 vs 1.7 ± 0.36, respectively, $P = .041$) and approached statistical significance in the 50-mg group (2.8 ± 0.46, $P = .056$). A post hoc analysis focusing on patients with high activity scores (baseline DAI 7–11) suggested differences between tetomilast and placebo that will require further investigation. No significant safety concerns were raised. Main adverse effects included gastrointestinal problems (nausea, vomiting) and were preferentially seen in the 50-mg tetomilast group.** ***Conclusions:*** **This phase II trial of tetomilast in ulcerative colitis did not achieve statistical significance for the primary end point. Secondary end points indicate a potential clinical activity of tetomilast. The post hoc analysis suggests that further clinical development should focus on patients with objective parameters of inflammation.**

Ulcerative colitis (UC) is a chronic, relapsing inflammatory disease of the colon and rectum characterized by alternating episodes of remission and spontaneous relapse.[1–3] Clinical characteristics include rectal bleeding (RB), diarrhea, and abdominal pain as well as extraintestinal manifestations involving the skin, liver, and other sites.[4] Although the etiology of UC remains unknown, a dysregulation or overstimulation of the mucosal immune system appears to play a critical role in the pathophysiology of intestinal inflammation and contributes to mucosal ulceration.[5–7] Pharmacotherapy of ulcerative colitis is based on aminosalicylates, glucocorticoids, and various immunosuppressants and recently includes antibodies that target tumor necrosis factor (TNF) (eg, infliximab).[3,8,9] Although these drugs can provide clinical benefit, reduce signs and symptoms of disease, and improve quality of life, most do not significantly alter the long-term course of the disease or the underlying immunopathology. An additional burden is caused by comorbidities induced by adverse effects of some of these drugs. Thus, an unmet medical need exists for effective, safe, and well-tolerated orally active agents for inducing and maintaining remissions for patients with UC.

Leukocytes are among the main drivers of inflammatory pathophysiology in UC. An increased release of specific chemokines and proinflammatory cytokines has been associated with the mucosal inflammation of UC; in addition, accentuated production of destructive effector molecules including reactive oxygen species and proteolytic enzymes has also been demonstrated.[10–15] Consequently, pharmacologic interventions that interfere with the activation of neutrophils and the release of destructive mediators are anticipated to have a significant role in the management of this disease.

*Abbreviations used in this paper:* DAI, Disease Activity Index; FS, flexible sigmoidoscopy; IBDQ, Inflammatory Bowel Disease Questionnaire; LOCF, last observation carried forward; PDE, phosphodiesterase; RB, rectal bleeding.


0016-5085/07/$32.00
doi:10.1053/j.gastro.2006.11.029

Tetomilast was identified through an in vitro screening of thiazole-based compounds for anti-inflammatory properties in neutrophils.[16] Preclinical studies have demonstrated that tetomilast inhibits several specific proinflammatory functions of activated leukocytes including the release of superoxide anions and proteases. Tetomilast is active in a wide range of animal models for inflammatory bowel disease (IBD).[17–21] In vivo, tetomilast protected epithelial cells and barrier integrity against oxidative stress in animal models.[22] Although its mechanism of action has not been fully elucidated, tetomilast is known to inhibit phosphodiesterase-4 (PDE4) as one of the target molecules.[22–25] The inhibition of PDE4 has become a promising therapeutic mechanism for the development of anti-inflammatory drugs in various indications.[26] Its inhibition leads to a significant decrease in activation of proinflammatory cytokines and inflammatory signal transduction.[27]

The results of this study indicate a potential clinical efficacy of tetomilast in the management of active UC and gave rise to a presently ongoing large phase III program.

## Materials and Methods

### *Patient Populations*

Outpatients (male or female) 18–80 years of age with a clinical diagnosis of mild to moderately active UC involving the colon proximal to 15 cm above the anal verge and with a baseline Disease Activity Index (DAI)[28] score of 4 to 11 were eligible. The DAI is a composite index of 4 subscores (ie, stool frequency, RB, flexible proctosigmoidoscopy (FS), and Physician's Global Assessment), each with a 4-point scoring scale (covering values from 0–3).[28] Total scores can range from 0 to 12. As an additional eligibility requirement, the component scores for RB and FS before the start of treatment each had to be ≥1. Patients on a stable dose of mesalamine (regardless of dose) for at least 14 days prior to the start of treatment or patients not being treated with mesalamine were eligible for inclusion in the study. No other concomitant medication with activity in UC was allowed. Patients were of non-childbearing potential or practised acceptable forms of birth control.

This study was conducted in 35 outpatient clinics in the United States under the Food and Drug Administration's Investigational New Drug (IND) exemption. It was performed in compliance with the ethical principles for the protection of human research subjects, which have their origins in the Declaration of Helsinki and with "good clinical practice" and was approved prior to its conduct by the local institutional review boards or ethics committees.

### *Study Design*

This multicenter, randomized, double-blind, placebo-controlled study was designed to assess the efficacy and safety of tetomilast in patients with mild to moderately active UC. Patients were randomized to 1 of the 3 treatment groups in a parallel group design. Patients were randomized in a 1:1:1 ratio (25 mg tetomilast/50 mg tetomilast/placebo) across study centers, and randomization was stratified based on the use of concomitant mesalamine therapy. With the exception of the programmer and project statistician performing the interim analyses, all persons involved in the conduct and management of the study were blinded to the individual patient treatment assignments until after the database was locked. The blind was not broken for any patient during this study.

Patients returned to the study facility for study visits after 2, 4, and 8 weeks of treatment for scheduled evaluations. The DAI was scored at week 4 and week 8, and the clinical part of the DAI (all 3 subscores excluding the FS procedure) was scored at week 2. A patient diary of UC symptoms (number of stools, RB, abdominal pain, general well-being, bowel urgency) from the 3-day period preceding the study visit and the investigator's assessment during the visit were used as the basis for the DAI scoring by the investigator. The end point for the intent-to-treat (ITT) analysis was either the last visit in the 8-week treatment period or the termination visit if patients left the study (last data carried forward approach).

### *Interventions*

Tetomilast tablets (25 mg) and matching placebo tablets for oral administration were manufactured by Otsuka Pharmaceutical Company, Ltd. (Tokushima, Japan). Study medication was packaged in blister cards in a double-dummy fashion by Clinical Trial Services (Audubon, PA). Each patient was instructed to take 2 tablets per day in the morning after breakfast. Patients were randomized to receive tetomilast 25 mg, tetomilast 50 mg, or placebo once daily for up to 8 weeks. Patients randomized to the tetomilast 25-mg treatment group received 1, 25-mg tablet of tetomilast and 1 placebo tablet. Patients randomized to the tetomilast 50-mg treatment group received 2, 25-mg tablets of tetomilast. The control group received 2 placebo tablets. Prohibited medications included any drug used for anti-inflammatory treatment of IBD other than mesalamine in stable dose (eg, glucocorticoids, immunosuppressives, biologic agents, antibiotics, rectal topical therapies, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, probiotics including *Lactobacillus acidophilus*, nicotine resin, warfarin, bismuth subsalicylate, and loperamide hydrochloride).

### *Efficacy*

The primary efficacy parameter was improvement at week 8 for the tetomilast 50-mg group compared with the placebo group. Improvement was defined as a reduction of ≥3 points in the total DAI score in comparison with the baseline DAI score. The protocol specified pa-

tients from the ITT cohort with available DAI scores (last observation carried forward; LOCF) as the analysis population (the "efficacy population" see below). The primary efficacy parameter "improvement" was also analyzed in the ITT population in which all patients with incomplete clinical data sets were counted as failures. Secondary end points included proportion of patients in remission (DAI score, 0–1), clinical improvement at week 4, change from baseline in total DAI score and DAI component scores, change from baseline in quality of life based on the 32-item Inflammatory Bowel Disease Questionnaire (IBDQ),[29,30] proportion of patients with improvement in the FS score, time to clinical improvement (number of days from randomization to the first visit with clinical improvement), and time to remission (number of days from randomization to the first visit with remission).

### *Safety*

Safety parameters included physical examination findings, clinical laboratory results, vital signs, electrocardiograms, and adverse events. All patients who had taken at least 1 dose of study medication after randomization were included in the safety analysis.

### *Populations and Statistics*

The ITT population comprised 186 subjects (62 in each group). Both a baseline and a postbaseline efficacy evaluation were available for 178 of the 186 randomized subjects: 60, 57, and 61 subjects at 25 mg, 50 mg, and placebo, respectively. The missing 8 subjects had none of the DAI subscores completed. For 15 subjects, the DAI total score at week 8 or at the study end visit, respectively, was missing. The primary analysis was based—as specified in the protocol—on a comparison of the available DAI at study end to baseline and therefore included 163 remaining subjects (58, 50, and 55, respectively) who had both a baseline and a postbaseline total DAI score. This population was predefined in the protocol and the statistical analysis plan. Additionally, the ITT population was analyzed for the primary efficacy parameter "improvement."

The sample size estimation (62 subjects in each arm of the study) was based on 80% power (at a 2-tailed .05 significance level) to detect a treatment difference of 25% in the proportion of patients with clinical improvement in the tetomilast group compared with the placebo group. For the primary efficacy analysis only, the level of significance was adjusted to $\alpha = 0.0488$ (2-sided) because of the performance of a planned interim analysis. The comparison between the tetomilast group and the placebo group was made using the Cochran-Mantel-Haenszel test, with mesalamine use as a stratification factor. In the LOCF approach, missing data at a postbaseline visit were imputed by the data obtained at the nearest preceding visit. All other statistical tests for the efficacy analyses were 2-sided and performed at the $\alpha = 0.05$ level of significance using both the LOCF approach and observed cases (OC; ie, without imputation). The Cochran-Mantel-Haenszel test stratified by use of mesalamine at the .05 level (2-sided) was used for the secondary parameters of clinical improvement. An analysis of covariance was used to compare mean change from baseline in total DAI and IBDQ global scores, whereas the Cochran-Mantel-Haenzel test was used to analyze changes in DAI subscores. All data are provided as means ± standard error of mean (SEM) unless indicated otherwise.

To facilitate the design of further clinical studies with tetomilast, post hoc analyses were conducted after the final analysis was completed for identifying the patient population in which tetomilast showed the greatest efficacy. The end point for the post hoc analysis was a redefined clinical improvement documented by an RB subscore of 0 or 1 plus improvement in at least one other DAI subscore. This analysis was conducted at week 8 (LOCF) for all 178 subjects (60, 57, and 61) who were included in the efficacy population. In addition, this analysis was then conducted on patients stratified by their baseline DAI scores ($<7$ and $\geq 7$). In a second round, "remission" was also analyzed in the post hoc population. Results of the post hoc analyses are identified in the Results section as "post hoc analyses" to distinguish them from the analyses planned in the protocol.

All patients who received at least 1 dose of study medication after randomization were included in the safety analysis. Descriptive statistics were used to summarize safety variables (inferential statistics were not used). All adverse events were coded for consistency using the Medical Dictionary for Regulatory Activities. Shift tables were used to assess changes from baseline in laboratory values with respect to the normal ranges. Data entry utilized Clintrial software (Phase Forward Inc. Waltham, MA), version 3.3, and data analysis was performed by Otsuka Maryland Research Institute, primarily with Statistical Analysis System software, version 6.12 (SAS Institute, Cary, NC).

## Results

### *Patient Populations*

The first patient was randomized to the study on July 12, 2000, and the last patient completed the study on December 11, 2001. A total of 212 patients were screened, 186 patients were randomized to treatment (62 to each treatment group), and 122 of 186 patients (65.6%) completed the full treatment phase of the study. Sixty-four patients (34.4%) did not complete the study: 14 patients from the tetomilast 25-mg group (1 lost to follow-up, 6 because of adverse events, 1 because of noncompliance, and 6 withdrew consent), 27 from the tetomilast 50-mg group (13 because of adverse events, 5 because of noncompliance, 2 for protocol violations, and 7 withdrew

**Table 1.** Demographic and Baseline Disease Characteristics of the Patients Randomized

| Parameter | Tetomilast 25 mg n = 62 | Tetomilast 50 mg n = 62 | Placebo n = 62 | Total n = 186 |
|---|---|---|---|---|
| DAI score, mean (SD) | 7.4 (1.8) | 7.5 (1.7) | 7.5 (1.6) | 7.5 (1.7) |
| Stool frequency subscore | 1.9 (0.9) | 2.1 (0.8) | 1.8 (1.1) | 1.9 (0.9) |
| Rectal bleeding subscore | 1.6 (0.6) | 1.6 (0.7) | 1.7 (0.6) | 1.6 (0.6) |
| Proctosigmoidoscopy subscore | 2.0 (0.7) | 2.0 (0.6) | 2.1 (0.5) | 2.0 (0.6) |
| Physician's Global Assessment (subscore) | 1.9 (0.6) | 1.9 (0.6) | 1.9 (0.5) | 1.9 (0.5) |
| Extent of disease, n (%) | | | | |
| Not known | 6 (9.7) | 7 (11.3) | 7 (11.3) | 20 (10.8) |
| Rectum only | 1 (1.6) | 2 (3.2) | 1 (1.6) | 4 (2.2) |
| Rectosigmoid | 13 (21.0) | 15 (24.2) | 18 (29.0) | 46 (24.7) |
| Left colon | 17 (27.4) | 19 (30.6) | 23 (37.1) | 59 (31.7) |
| Left and transverse colon | 7 (11.3) | 4 (6.5) | 3 (4.8) | 14 (7.5) |
| Pancolitis | 18 (29.0) | 15 (24.2) | 10 (16.1) | 43 (23.1) |
| Age (*y*), mean (SD) | 43.5 (13.3) | 42.6 (14.5) | 45.5 (13.7) | 43.9 (13.8) |
| Weight (*kg*), mean (SD) | 76.7 (17.5) | 76.4 (20.0) | 79.0 (19.8) | 77.4 (19.0) |
| Height (*cm*), mean (SD) | 171.5 (9.2) | 170.0 (9.5) | 170.5 (8.6) | 170.7 (9.1) |
| Female sex, n (%) | 29 (46.8) | 30 (48.4) | 32 (51.6) | 91 (48.9) |

NOTE. Twenty-two subjects had a disease duration of 1 year or less with 10 patients having been diagnosed less than 1 month before screening. DAI, disease activity index.

consent), and 23 patients from the placebo group (13 because of adverse events, 2 because of protocol violations, and 8 withdrew consent). An increased activity of UC was the stated reason for withdrawal for 17 patients. More patients were withdrawn for this reason from the placebo group (10 patients) than from the tetomilast 25-mg (3 patients) and 50-mg (4 patients) arms. All patients with incomplete assessment of DAI scores at weeks 4 or 8 (n = 23) were part of the 64 patients who did not complete the study.

The total and component DAI scores at baseline were similar across the 3 treatment groups (Table 1). The proportion of patients with more extensive disease was greater in the tetomilast groups than in the placebo group (disease extending the left colon: 40.3% in the tetomilast 25-mg group, 30.7% in the 50-mg group, and 20.9% in the placebo population, Table 1). The use of mesalamine (oral or rectal) and/or oral sulfasalazine was reported at baseline by 75.3% of patients. There were no apparent imbalances across treatment groups for any of the demographic characteristics recorded (Table 1). Baseline parameters for patients who prematurely discontinued the study mediation were not different from the overall population (data not shown).

### *Efficacy*

**Primary efficacy analysis: improvement at study end.** The primary end point "improvement" was defined as a comparison of DAI scores between baseline and study end resulting in a reduction ≥3 points. The protocol had specified the primary end point in an efficacy population of patients in whom both baseline and study end DAI were available using LOCF. The analysis was per definition restricted to 163 patients in whom these data were available. In this primary analysis (clinical improvement at week 8, Table 2), neither 25 mg tetomilast (32/58 patients, 55%, $P = .108$) nor 50 mg tetomilast (24/50 patients, 48%, $P = .409$) was significantly superior to placebo (22/55 patients, 40%). Percentages of improvement in the 186 patients of the ITT population were 32 of 62 patients (52%), 24 of 62 patients (39%), and 22 of 62 patients (35%) for the tetomilast 25-mg, the tetomilast

**Table 2.** Primary Efficacy Parameter "Improvement"

| Time point and analysis | Tetomilast 25 mg | Tetomilast 50 mg | Placebo |
|---|---|---|---|
| ITT population | n = 62 | n = 62 | n = 62 |
| Patients with improvement (%) | 32 (52) | 24 (39) | 22 (35) |
| *P* value[a] | .07 | .71 | |
| LOCF population | n = 58 | n = 50 | n = 55 |
| Patients with improvement (%) | 32 (55) | 24 (48) | 22 (40) |
| *P* value[a] | .11 | .41 | |

NOTE. The Table demonstrates "improvement" at week 8 in the ITT population and the LOCF population (primary analysis population).
[a]*P* values for comparison with placebo were derived from the Cochran–Mantel–Haenszel test with mesalamine use as a stratification factor. Week 4 improvement rates (LOCF population) as a secondary analysis were 18 (38%, $P = .47$) patients in the tetomilast 25-mg group, 20 (45%, $P = .16$) patients in the tetomilast 50-mg group, and 16 (31%) patients in the placebo group. The week 4 and week 8 analysis in the LOCF population were based on patients in whom full DAI datasets were available.

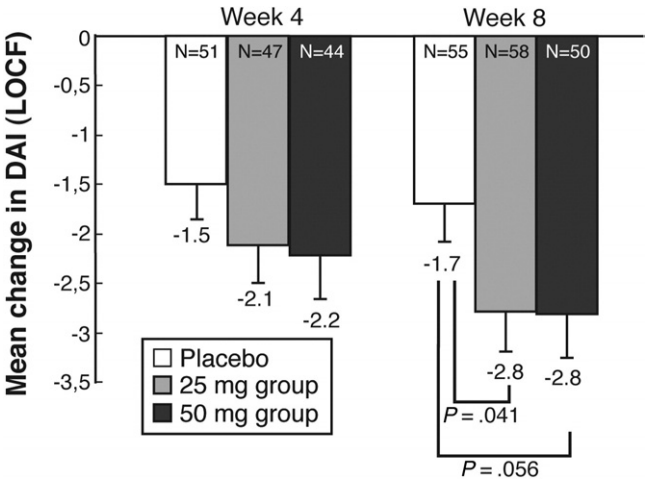



**Figure 1.** Mean changes in DAI score (LOCF). Values indicate mean change from baseline in total DAI scores with standard errors of means. An analysis of covariance (including baseline DAI score, treatment group, and concomitant mesalamine use in the model) was used for calculating statistical significance of tetomilast 25 mg and 50 mg vs placebo at weeks 4 and 8 of treatment. Lower total DAI scores indicate less disease activity. Total DAI scores ranged from 0 (no disease) to 12 (severe disease).

50-mg, and the placebo group, respectively (no significant differences). Similar results were obtained for clinical improvement at week 4, which was a secondary end point (Table 2).

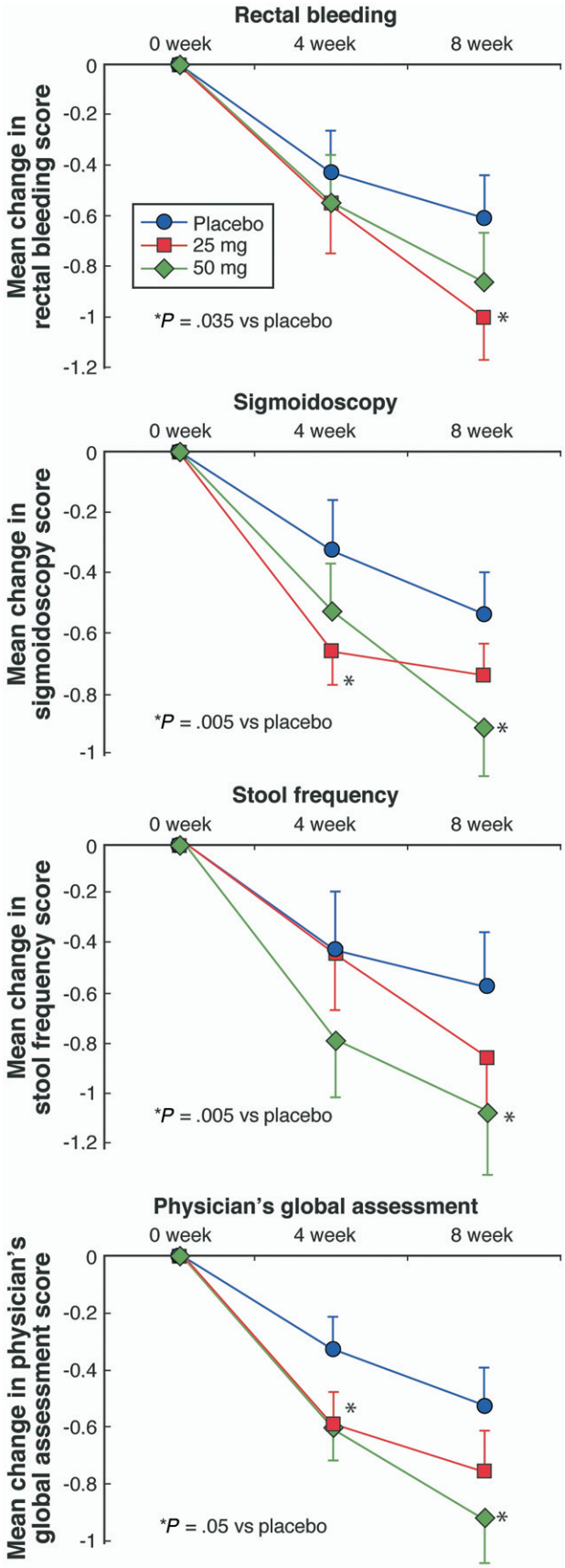
**Secondary end point: remission.** The proportion of patients in remission as defined in the protocol by a DAI of 0 or 1 at the week 8 visit (ie, DAI score, 0-1) was low (7%) in the placebo group. Remission rates for the 25-mg and 50-mg groups were 16% ($P = .24$ vs placebo) and 21% ($P = .08$ vs placebo), in the ITT population, respectively. The time to remission was not statistically different for either tetomilast-dose group compared with the placebo group.

**Secondary end point: analyses of DAI subscores.** Further secondary efficacy analyses using the DAI subscores were supportive of a clinical effect of tetomilast in UC. The mean reduction in total DAI scores at week 8 was statistically significant for tetomilast 25 mg (reduction by 2.8 ± 0.40) compared with placebo (reduction by 1.7 ± 0.36, $P = .041$), and the comparison of tetomilast 50 mg with placebo approached statistical significance (reduction by 2.8 ± 0.46, $P = .056$) (Figure 1). Both tetomilast groups showed numerical reductions in all 4 of the DAI subscores (ie, RB, FS, stool frequency, and Physician's Global Assessment) at week 8 compared with baseline and placebo in an exploratory analysis (Figure 2). Reduction in RB was significantly greater in the tetomilast 25-mg group compared with the placebo group at week 8 (reduction by 1.0 ± 0.12 vs 0.82 ± 0.13, respectively, $P = .035$). The reduction in stool frequency in the tetomilast 50-mg (1.08 ± 0.19) group was significantly different from placebo (0.58 ± 0.18) at week 8 ($P = .05$). Reductions in sigmoidoscopy scores differentiated from placebo at week 4 in the tetomilast 25-mg group (0.66 ± 0.11 vs 0.33 ± 0.15, respectively, $P = .03$) and at week 8 in the 50-mg group (0.91 ± 0.16 vs 0.54 ± 0.13, respectively, $P = .05$). Reduction in the Physician's Global Assessment score was significantly greater in patients treated with tetomilast 25 mg compared with placebo at week 4 (0.59 ± 0.09 vs 0.33 ± 0.09, respectively, $P = .05$) and at week 8 (0.92 ± 0.14 vs 0.53 ± 0.12, respectively, $P = .04$). The $P$ values that were detailed above were not corrected for multiple testing (16 parallel tests were carried out).

**Secondary end point: IBDQ.** The mean IBDQ scores increased by 36.3, 24.5, and 15.8 points in the 25-mg, the 50-mg, and the placebo groups at week 8 from baseline, respectively. The comparison of IBDQ scores obtained at each patient's last visit demonstrated that patients treated with tetomilast 25 mg had significantly higher quality-of-life scores than did patients treated with placebo (166 in the 25-mg group vs 151 under placebo, $P = .006$). Differences between the 50-mg group (IBDQ score 161) and placebo did not achieve statistical significance.

### *Post Hoc Analyses of Study Outcome*

The high percentage of placebo improvement rates could potentially be attributed to 2 factors: (1) that the criteria used for clinical improvement (ie, the primary end point) were not sufficiently stringent or (2) that less active patients could have over proportionally contributed to the placebo signal. Based on this hypothesis, a post hoc analysis was conducted with the additional intention to define the patient population and end points for the further clinical development program of tetomilast. In this analysis, the improvement end point (as evidenced by a decrease of the DAI by ≥3 points) was changed to a more stringent definition by requiring a postbaseline RB score of 0 or 1 and an improvement of at least 1 point in at least 1 other component of the DAI. The post hoc analysis also investigated whether the clinical effects of tetomilast were greater in patients with more significant symptoms at baseline as defined by a higher baseline DAI score (ie, 7–11) or by objective components of the DAI that are clearly linked to inflammatory activity (ie, high RB and FS scores). Using this much stricter end point of clinical improvement, the difference between the tetomilast 25-mg group and the placebo group at week 8 was statistically significant (75% vs 43%, respectively, $P = .0004$) (Table 3). A marked difference in placebo responses was seen between mildly to moderately active (65% in patients with a DAI score of 4–6) and moderately to severely active patients (34% for a DAI score of 7–11; $P = .03$, Table 3). This led to clearer separation between tetomilast groups in comparison with placebo in the more severe patients (25 mg tetomilast: 76%, $P = .0002$; 50 mg tetomilast: 57%, $P = .0506$ as




compared with 34% placebo. Further tightening of baseline activity criteria for patients (RB ≥ 2 plus FS ≥ 2) strengthened this difference (Table 3, $P = .0024$ for patients on active drug vs placebo). Figures for remission show a similar tendency, although patient numbers in the groups become small (Table 4).

An additional round of post hoc analysis used the improvement and remission definitions that were recently used in a large trial of infliximab in UC.[31] Improvement (defined as a reduction of the DAI score by at least 3 points and more than 30%) was seen in 40% of placebo patients in contrast to 54% in the tetomilast 50-mg group and 45% in the 25-mg group, respectively (not significant). Remission as defined by a total DAI score of 1 with scores of zero in both the endoscopy and the RB subscales was achieved by 7%, 18%, and 10%, of patients, respectively (placebo, tetomilast 50 mg, and tetomilast 25 mg).

### *Safety*

The most common adverse events (≥5% incidence) occurring after the start of treatment with tetomilast were nausea, vomiting, fatigue, dizziness, and headache. These events have been commonly observed in other studies of tetomilast and are probably class specific.[32] The incidences in the tetomilast 25-mg, tetomilast 50-mg, and placebo groups, respectively, were as follows: 8%, 29%, 13% for nausea; 5%, 7%, 2% for vomiting; 7%, 3%, 3% for fatigue; 0%, 7%, 2% for dizziness; and 26%, 23%, 10% for headache. Nausea and vomiting were self-limiting complications that were mainly seen in the 50-mg tetomilast group and occurred mostly within the first 7 days of treatment. Nausea led to 4 early terminations. The start day (counted from randomization) for the initial adverse event reports on nausea ranged from day 1 to day 42 for the tetomilast 50-mg group, from day 1 to day 33 for the 25-mg group, and from day 1 to day 41 for the placebo patients. The median start dates were day 1 in the tetomilast 50-mg group, day 7 in the 25-mg group, and day 10 in the placebo population. Median durations of this adverse effect were 12 days in the tetomilast 50-mg group, 13 days in the 25-mg group, and 3 days in the placebo group.

Serious adverse events (7 total) were reported in 3 patients (5%) in each of the tetomilast 25-mg and 50-mg dose

**Figure 2.** Mean changes in DAI subscores for all subjects (observed cases). Values indicate mean change from baseline in DAI subscores with standard errors of means. Significances were calculated using the Cochran–Mantel–Haenzel test. The stool frequency subscore ranged from 0 (normal number of stools) to 3 (5 or more stools than usual); the rectal bleeding subscore ranged from 0 (no blood seen) to 3 (blood alone passed); the flexible sigmoidoscopy subscore ranged from 0 (normal or inactive disease) to 3 (severe disease, spontaneously bleeding, ulceration); Physician's Global Index score ranged from 0 (normal) to 3 (severe disease).

**Table 3.** Post Hoc Analyses of Using a Redefined Clinical Improvement at Week 8

| Population | Tetomilast 25 mg n = 60 | Tetomilast 50 mg n = 57 | Placebo n = 61 |
|---|---|---|---|
| All patients (DAI score ≥4 to ≤11 at baseline) | n = 60 | n = 57 | n = 61 |
| With improvement, n (%) | 45 (75) | 34 (60) | 26 (43) |
| *P* value against placebo[a] | .0004 | .069 | |
| Patients with DAI score ≥4 to <7 at baseline | n = 22 | n = 15 | n = 17 |
| With improvement, n (%) | 16 (73) | 10 (67) | 11 (65) |
| *P* value against placebo[a] | .7302 | 1.0000 | |
| Patients with DAI ≥7 to ≤11 at baseline | n = 38 | n = 42 | n = 44 |
| With improvement, n (%) | 29 (76) | 24 (57) | 15 (34) |
| *P* value against placebo[a] | .0002 | .0506 | |
| Patients with RB ≥2 and FS ≥2 at baseline | n = 25 | n = 24 | n = 35 |
| With improvement, n (%) | 18 (72) | 11 (46) | 9 (26) |
| *P* value against placebo[a] | .0006 | 16 | |

NOTE. Clinical improvement was defined as a postbaseline RB score of 0 or 1 and at least a 1-point reduction in at least 1 other DAI subscale.
DAI, disease activity index; FS, flexible proctosigmoidoscopy; LOCF, last observation carried forward; RB, rectal bleeding.
[a]*P* values derived from Fisher exact test.

groups and in 1 patient (2%) in the placebo group. In the tetomilast 25-mg group, iron deficiency anemia, pulmonary embolism, and aggravated UC were serious events considered by the investigator as unrelated to the study drug. In the tetomilast 50-mg group, aggravated vomiting and aggravated UC were considered possibly related, whereas an event of reactivated UC was considered unrelated. In the placebo group, a transient ischemic attack was reported as a serious event. There were no deaths in the study.

Thirty-two patients (17%) discontinued the study medication because of adverse events. Seventeen of the 32 patients were withdrawn for aggravated UC, and, of these, the majority (10/17) were from the placebo group, compared with 3 patients from the tetomilast 25-mg group and 4 from the 50-mg group. Six of the 32 patients were withdrawn because of nausea: 1 in the tetomilast 25-mg group and 5 in the 50-mg group. Other adverse events causing withdrawal (1 patient per adverse event) were abdominal pain, hypersensitivity, headache, palpitations, defecation urgency, dyspepsia, rectal hemorrhage, and erythema nodosum.

Patients receiving tetomilast experienced slight weight loss during the study compared with patients receiving placebo (0.1–0.5 kg mean weight loss compared with 0.3–0.7 kg mean weight gain, respectively), which cannot be explained by the reported occurrences of nausea and vomiting because adverse event reports indicate a very small overlay between the weight loss population and those individuals reporting nausea and/or vomiting. Treatment with tetomilast did not appear to affect adversely the clinical laboratory (ie, liver and renal function tests, blood differential), vital signs, or electrocardiogram results. No safety concerns were raised during the study.

## Discussion

UC and Crohn's disease are chronic, relapsing or remitting idiopathic disorders of the intestinal tract that represent the major forms of IBD. IBD can result in long-term disability and have serious consequences on quality of life, and surgery is commonly required for both disorders.[33] The ideal therapeutic goal is to cure the

**Table 4.** Post Hoc Analyses of Remission at Week 8

| Population | Tetomilast 25 mg | Tetomilast 50 mg | Placebo |
|---|---|---|---|
| All patients (DAI score ≥4 to ≤11 at baseline) | n = 58 | n = 50 | n = 55 |
| With remission, n (%) | 9 (16) | 10 (20) | 4 (7) |
| *P* value[a] | .2400 | .0833 | |
| Patients with DAI score ≥7 to ≤11 at baseline | n = 37 | n = 37 | n = 39 |
| With remission, n (%) | 5 (14) | 7 (19) | 1 (3) |
| *P* value[a] | .1033 | .0266 | |
| Patients with RB ≥2 and FS ≥2 at baseline | n = 25 | n = 20 | n = 30 |
| With remission, n (%) | 2 (8) | 4 (20) | 0 (0) |
| *P* value[a] | .2020 | .0210 | |

NOTE. Remission is defined as DAI score = 0 or 1. Week 4 data were carried forward to week 8 if the week 8 data were missing because of early termination of treatment.
DAI, disease activity index; FS, flexible sigmoidoscopy; RB, rectal bleeding.
[a]*P* values from Fisher exact test.

disease or at least to modify its natural course. However, this goal is not achieved with currently available therapy. Presently, primary objectives include improvement of patients' quality of life by reduction of disease activity and maintenance of remissions. The widely accepted approach in treatment of UC is an escalation that starts with nontoxic and well-tolerated therapeutic agents. Accordingly, 5-aminosalicylate-based compounds are widely used, which are effective and tolerated in 50%–60% of patients with mild-to-moderate UC. However, there is a significant patient population that either does not respond to 5-aminosalicylate-based products or cannot tolerate them and then requires other therapy such as glucocorticoids. Although glucocorticoids are effective in remission induction in most 5-aminosalicylate refractory patients, they have significant early and long-term adverse effects. Glucocorticoids have no maintenance capability. Furthermore, at least 30% of patients do not respond to glucococorticoid therapy, which is an indication for the use of broadly acting immunosuppressives (eg, azathioprine, 6-mercaptopurine, and methotrexate) and subsequently targeted biologics (ie, anti-TNF therapy with infliximab).[3]

The currently available drugs have been of value in extending inflammation-free phases of remission, reducing early death rates, and providing symptomatic relief but, in general, do not provide long-term control of disease progression or influence the underlying immunopathology.[33] Several biologic therapies including monoclonal antibodies, peptides, and antisense oligonucleotides are being investigated for use in the management of IBD and, in some cases, have shown impressive clinical activity.[3,9,31,34–37] Many of the biologics are associated with various shortcomings, including serious adverse effects, need for parenteral administration, risk of eliciting an immune response against the therapeutic agent (immunogenicity), and high cost. This apparent unmet therapeutic need for an effective and well-tolerated oral medication for UC has prompted research for novel small molecules that are specifically targeting molecular events in the underlying immunopathology.

This phase II clinical trial represents the first study of the novel thiazole compound tetomilast in the treatment of patients with active UC. The primary end point, a treatment difference between the 50-mg group and placebo for clinical improvement as defined by a reduction of $\geq$3 points in the total DAI score, was not statistically significant. The 50-mg group showed a high drop-off rate mostly because of nausea and vomiting, which were drug-induced adverse effects that, although often of self-limiting nature, diminished the number of patients available for analysis. Per the sample size estimation, a 25% treatment difference between treatment group and placebo would have been statistically detectable, whereas the observed difference was 12%. Notably, a high rate of clinical improvement was seen in the placebo group. High placebo response and remission rates appear to be a feature of recent clinical trials in IBD.[38,39] A high placebo response could be associated with a low disease activity at inclusion and to the use of subjective outcome parameters in the definition of "response" as an end point. Placebo remission rates observed in the trial (7%) were in the range that is expected.[28,31] This would argue against a problem in the selection of the patient population for the trial.

Secondary analyses were conducted to provide better insights into the putative clinical activity of tetomilast. Mean changes from baseline in total DAI scores demonstrated significant treatment differences between 25 mg tetomilast and placebo as well as in subscores for RB and Physician's Global Assessment. A high proportion of patients with mild activity and increased DAI scores mainly based on subjective parameters may have obscured the signal of response to the drug. Post hoc analyses in the moderately to severely active patients (DAI between 7 and 11, inclusive; and RB $\geq$2 plus FS $\geq$2) confirmed this hypothesis with a significant difference between placebo and tetomilast, especially in the 25-mg dose group (Tables 3 and 4). A redefinition of end points that specified an improvement in RB by $\geq$2 points from baseline provided the largest difference in efficacy between tetomilast and placebo. Thus, assessment of RB, which like sigmoidoscopy is immediately linked to mucosal inflammation, could represent a stable component of the DAI score that better suited as an end point than subjective components of the score for evaluation of efficacy in randomized trials. An additional indirect support to this post hoc-derived conclusion that tetomilast may be clinically active is given by the observation that fewer patients were withdrawn because of aggravated UC in the active treatment groups than in the placebo group. This potential therapeutic effect of tetomilast should be directly confirmed in the future phase III trial.

The second part of the post hoc analysis applied the definition for improvement and remission used previously in other large trials.[31] From this analysis, it appears that the patient population that has been recruited for the trial presented here would be not far different from other trials conducted in moderate to severe UC. The proportion of patients achieving remission in the definition of a total DAI score of 0-1 was low regardless of treatment group (16% and 21% for the tetomilast 25-mg and 50-mg groups, respectively, vs 7% for the placebo group). Low overall remission rates using a hard definition have been seen in older trials evaluating 5-aminosalicylate compounds vs placebo, in which a clear differentiation from placebo was achieved.[28,40] The hard definition of remission used in this trial included a fully normal sigmoidoscopic appearance of the mucosa that was required to achieve a rating of 0. However, sigmoidoscopy findings in chronically active UC patients may not revert to a fully normal appearance in response to ther-

apy but may rather reach an inflammation-free state that is characterized by an intact mucosal surface but without transparence to the vasculature. Therefore, some other studies in UC have previously employed less restrictive definitions of remission by defining "symptomatic remission" (using only the clinical activity index) or have defined endoscopic improvement as an inflammation-free state (modifying the Baron score) or developed other indices of remission.[28,41–47] For the phase III development of tetomilast, the question arises whether a definition of remission based on the total DAI score reflects the anti-inflammatory activity of a drug or whether an inflammation-free state with an RB score of zero combined with an absence of inflammation by sigmoidoscopy would not be more meaningful as an instrument to prove clinical efficacy.

The clinical efficacy of tetomilast in active UC that is suggested by this trial would be consistent with the anti-inflammatory properties observed in vitro and in animal models.[15–27] Once-daily oral administration of tetomilast significantly reduces the area of colonic erosions/ulcerations and the incidence of diarrhea in animal models of colitis[17–22]; efficacy was associated with significant suppression of tissue levels of TNF-$\alpha$, myeloperoxidase, and thiobarbituric acid-reactive substances.[17–21] Inhibition of neutrophil infiltration into colonic tissue and suppression of proinflammatory cytokine production and superoxide anion release appear to be important aspects of the mechanism of action of tetomilast in suppressing colonic ulceration.

The major adverse effects of tetomilast were upper gastrointestinal symptoms, which appear to be drug class effects of PDE4 inhibitors, which is a major characteristic of tetomilast. The clinical utility of PDE4 inhibitors, which have been preferentially developed for indications in pulmonary medicine, has been compromised by potent gastrointestinal adverse effects, including nausea and vomiting. In the current study, the incidence of nausea was highest in the tetomilast 50-mg group and was the cause of the most patient withdrawals in this group. Based on this observation, doses higher than 50 mg cannot be tested for patients with UC. In studies of cilomilast, a typical PDE4 inhibitor developed for pulmonary indications, gastrointestinal tolerance was improved by dosing with food and by progressive upward titration of the dose.[48]

In conclusion, in this phase II study, once-daily dosing of tetomilast has suggested potential efficacy in the treatment of UC, especially in patients with higher disease severity. Once-daily dosing as used for tetomilast will have an advantage over multiple daily dosing in securing patient compliance with treatment and may reduce noncompliance.[49,50] The efficacy of tetomilast may be enhanced if patients are able to tolerate higher doses, which may be improved by dose-titration regimens introduced into the phase III development program. Most importantly, the phase III studies will put the hypothesis to the test that a clear demonstration of disease activity at inclusion and the use of end points that are directly related to inflammatory activity in UC such as RB and sigmoidoscopy scores may result in low placebo response rates and hence a clearer demonstration of drug efficacy. Rigid end points will also provide the ability to judge the true therapeutic potential of the substance. The results of this trial suggest an anti-inflammatory biologic activity of tetomilast. Clinical usefulness will depend on a proof of efficacy and documentation of clinically meaningful remission rates. A large and adequately powered phase III program for an assessment of the efficacy and safety profile of tetomilast for the treatment of active UC is currently under way.

## Appendix

The following principal investigators and centers participated in the study: Charles F. Barish (Raleigh, NC), Philip C. Bird (Norman, OK), Jeffrey R. Breiter (Manchester, CT), Judith F. Collins (Portland, OR), Ben J. Dolin (Peoria, IL), Charles O. Elson (Birmingham, AL), Gulchin A. Ergun (Houston, TX), Seymour Katz (Great Neck, NY), John S. Goff (Arvada, CO), Stephen B. Hanauer (Chicago, IL), David S. James (Tulsa, OK), Lori Kam (Los Angeles, CA), Steven Krumholz (West Palm Beach, FL), Daniel E. Gremillion (Nashville, TN), Kim L. Issacs (Chapel Hill, NC), David A Johnson (Norfolk, VA), Joshua Korzenik (St. Louis, MO), Mark Lamet (Hollywood, FL), Bret A. Lashner (Cleveland, OH), Philip B. Miner (Oklahoma City, OK), Herbert Rubin (Beverly Hills, CA), Jerrold L. Schwartz (Arlington Heights, IL), Timothy C. Simmons (Los Angeles, CA), Gary R. Lichtenstein (Philadelphia, PA), Daniel J. Pambianco (Charlottesville, VA), Howard Schwartz (Miami, FL), Bavikatte N. Shivakumar (Davenport, IA), Willem De Villiers (Lexington, KY), Douglas Wolf (Atlanta, GA), Isaac Bassan (Miami Beach, FL), Michael M. Gaspari (Charlotte, NC), William M. Pandak (Richmond, VA), Lawrence D. Wruble (Memphis, TN), David Dozer (Greenfield, WI), Ali Keshavarzian (Chicago, IL).

### References

1. Truelove SC. Ulcerative colitis beginning in childhood. N Engl J Med 1971;285:50–2.
2. Langholz E, Munkholm P, Davidsen M, Binder V. Course of ulcerative colitis: analysis of changes in disease activity over years. Gastroenterology 1994;107:3–11.
3. Podolsky DK. Inflammatory bowel disease. N Engl J Med 2002; 347:417–429.
4. Kirsner JB. Inflammatory bowel disease. Part II: Clinical and therapeutic aspects. Dis Mon 1991;37:669–746.
5. Fiocchi C. Inflammatory bowel disease: etiology and pathogenesis. Gastroenterology 1998;115:182–205.
6. MacDermott RP. Alterations in the mucosal immune system in ulcerative colitis and Crohn's disease. Med Clin North Am 1994; 78:1207–1231.

7. Schreiber S, Rosenstiel J, Albrecht M, Hampe J, Krawczak M. Genetics of Crohn's disease, an archetypal inflammatory barrier disease. Nat Rev Genet 2005;6:376–388.
8. Friedman S. General principles of medical therapy of inflammatory bowel disease. Gastroenterol Clin North Am 2004;33:191–208.
9. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462–2476.
10. Nikolaus S, Bauditz J, Gionchetti P, Witt C, Lochs H, Schreiber S. Increased secretion of pro-inflammatory cytokines by circulating polymorphonuclear neutrophils and regulation by interleukin 10 during intestinal inflammation. Gut 1998;42:470–476.
11. Pavlick KP, Laroux FS, Fuseler J, Wolf RE, Gray L, Hoffman J, Grisham MB. Role of reactive metabolites of oxygen and nitrogen in inflammatory bowel disease. Free Radic Biol Med 2002;33: 311–322.
12. Shiratora Y, Aoki S, Takada H, Kiriyama H, Ohto K, Hai K, Teraoka H, Matano S, Matsumoto K, Kamii K. Oxygen-derived free radical generating capacity of polymorphonuclear cells in patients with ulcerative colitis. Digestion 1989;44:163–171.
13. Langhorst J, Elsenbruch S, Mueller T, Rueffer A, Spahn G, Michalsen A, Dobos GJ. Comparison of 4 neutrophil-derived proteins in feces as indicators of disease activity in ulcerative colitis. Inflamm Bowel Dis 2005;11:1085–1091.
14. Keshavarzian A, Sedghi S, Kanofsky J, List T, Robinson C, Ibrahim C, Winship D. Excessive production of reactive oxygen metabolites by inflamed colon: analysis by chemiluminescence probe. Gastroenterology 1992;103:177–185.
15. Sedghi S, Fields JZ, Klamut M, Urban G, Durkin M, Winship D, Fretland D, Olyaee M, Keshavarzian A. Increased production of luminol enhanced chemiluminescence by the inflamed colonic mucosa in patients with ulcerative colitis. Gut 1993;34:1191–1197.
16. Chihiro M, Nagamoto H, Takamura I, Kitano K, Komatsu H, Sekiguchi K, Tabusa F, Mori T, Tominaga M, Yabuuchi Y. Novel thiazole inhibitors as inhibitors of superoxide production by human neutrophils: synthesis and structure-activity relationships. J Med Chem 1995;38:353–358.
17. Nagamoto H, Maeda T, Haruta J-P, Miyakoda G, Sekiguchi K, Osaka T, Nakashima T, Kikuchi M. OPC-6535, a novel oral thiazole compound, suppresses colonic damage in a rat model of TNBS-induced colitis (abstr). Gastroenterology 2004;26(Suppl 2):M1044.
18. Nagamoto H, Maeda T, Haruta J-P, Miyakoda G, Mori T, Tominaga M. OPC-6535 suppresses symptoms and colonic damage in a rat model of DSS-induced chronic colitis (abstr). Gastroenterology 2004;26(Suppl 2):M1045.
19. Maeda T, Sueyoshi S, Aoyama M, Nagamoto H, Miyakoda G, Mori T, Tominaga M. Effects of intravenous or oral administration of OPC-6535 in a rat model of 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis (abstr). Gut 1997;4(Suppl 3):A112.
20. Maeda T, Sato N, Haruta J, Nagamoto H, Miyakoda G, Kikuchi M, Sekiguchi K. Effects of OPC-6535 on a rat model of TNBS-induced colitis: its relation to produced thiobarbituric-reactive substances, IL-1β and TNF-α in the colonic tissue. Ulcer Res 2000; 27:198–201.
21. Miyakado G, Maeda T, Nagamoto T, Mori M, Tominaga M. Effects of intravenous or oral administration of OPC-6535 in a rat model of dextran sodium sulfate (DSS)-induced colitis. Gut 1997;41: A227.
22. OPC-compounds prevent oxidant-induced carbonylation and depolymerization of the F-actin cytoskeleton and intestinal barrier hyperpermeability. Free Radic Biol Med 2001;30:287–298.
23. Nagamoto H, Maeda T, Sueyoshi S, Aoyama M, Onogawa T, Miyakoda G, Mori T. OPC-6535 inhibits human and porcine monocyte tumor necrosis factor-α production in vitro and in vivo (abstr). Gastroenterology 2004;26(Suppl 2):W1090.
24. Nagamoto H, Maeda T, Aoyama M, Miyakoda G, Chihiro M, Mori T, Kikuchi M. OPC-6535, a novel thiazole compound inhibits superoxide production in leukocytes in vitro (abstr). Am J Resp Crit Care Med 2004;169:B65.
25. Nagamoto H, Kawasome H, Sueyoshi M, Aoyama M, Miyakoda G, Sekiguchi K, Mori T. OPC-6535, a novel thiazole compound, inhibits neutrophil adhesion to endothelial cells in vitro (abstr). Am J Resp Crit Care Med 2004;169:B66.
26. Houslay MD, Schafer P, Zhang KY. Keynote review: phosphodiesterase-4 as a therapeutic target. Drug Discov Today 2005;10: 1503–1519.
27. Kambayashi T, Jacob CO, Zhou D, Mazurek N, Fong M, Strassmann G. Cyclic nucleotide phosphodiesterase type IV participates in the regulation of IL-10 and in the subsequent inhibition of TNF-α and IL-6 release by endotoxin-stimulated macrophages. J Immunol 1995;155:4909–4916.
28. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately, active ulcerative colitis. N Engl J Med 1987;317:1625–1629.
29. Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, Tompkins C. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology 1989;96:804–810.
30. Irvine EJ, Feagan BG, Wong CJ. Does self-administration of a quality of life index for inflammatory bowel disease change the results? J Clin Epidemiol 1996;49:1177–1185.
31. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462–2476.
32. Smith VB, Spina D. Selective phosphodiesterase 4 inhibitors in the treatment of allergy and inflammation. Curr Opin Investig Drugs 2005;6:1136–1141.
33. Boonen A, Dagnelie PC, Feleus A, Hesselink MA, Muris JW, Stockbrugger RW, Russel MG. The impact of inflammatory bowel disease on labor force participation: results of a population sampled case-control study. Inflamm Bowel Dis 2002;8:382–389.
34. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, DeWoody KL, Schaible TF, Rutgeerts PJ. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor α for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997;337:1029–1035.
35. Schreiber S, Nikolaus S, Malchow H, Kruis W, Lochs H, Raedler A, Hahn E, Krummenerl T, Steinmann G. Absence of efficacy of subcutaneous anti-sense ICAM-1 treatment of chronic active Crohn's disease. Gastroenterology 2001;120:1339–1346.
36. Ghosh S, Goldin E, Gordon FH, Malchow HA, Rask-Madsen J, Rutgeerts P, Vyhnalek P, Zadorova Z, Palmer T, Donoghue S, Natalizumab Pan-European Study Group. Natalizumab for active Crohn's disease. N Engl J Med 2003;348:24–32.
37. Schreiber S, Rutgeerts P, Fedorak RN, Khaliq-Kareemi M, Kamm MA, Boivin M, Bernstein CN, Staun M, Thomsen OO, Innes A. Certolizumab pegol (CDP870) appears effective and is well tolerated in Crohn's disease: a randomized, placebo-controlled trial. Gastroenterology 2005;129:807–818.
38. Su C, Lichtenstein GR, Krok K, Brensinger CM, Lewis JD. A meta-analysis of the placebo rates of remission and response in clinical trials of active Crohn's disease. Gastroenterology 2004; 126:1257–1269.
39. Will M, Nikolaus S, Freitag S, Arpe N, Krawczak M, Schreiber S. Placebo response in the therapy of Crohn's disease: a compre-

hensive analysis of primary data from 733 patients from 13 randomized, controlled trials. 2005. Abstract No. 338 presented at Digestive Disease Week 2005, Chicago, IL.
40. Sninsky CA, Cort DH, Shanahan F, Powers BJ, Sessions JT, Pruitt RE, Jacobs WH, Lo SK, Targan SR, Cerda JJ, et al. Oral mesalamine (Asacol) for mildly to moderately active ulcerative colitis. A multicenter study. Ann Intern Med 1991;115:350–355.
41. Pruitt R, Hanson J, Safdi M, Wruble L, Hardi R, Johanson J, Koval G, Riff D, Winston B, Cross A, Doty P, Johnson LK. Balsalazide is superior to mesalamine in the time to improvement of signs and symptoms of acute mild-to-moderate ulcerative colitis. Am J Gastroenterol 2002;97:3078–3086.
42. Kruis W, Schreiber S, Theuer D, Brandes JW, Schutz E, Howaldt S, Krakamp B, Hamling J, Monnikes H, Koop I, Stolte M, Pallant D, Ewald U. Low-dose balsalazide (1.5 g twice daily) and mesalazine (0.5 g three times daily) maintained remission of ulcerative colitis but high-dose balsalazide (3.0 g twice daily) was superior in preventing relapses. Gut 2001;49:783–789.
43. Vecchi M, Meucci G, Gionchetti P, Beltrami M, Di Maurizio P, Beretta L, Ganio E, Usai P, Campieri M, Fornaciari G, de Franchis R. Oral versus combination mesalazine therapy in active ulcerative colitis: a double-blind, double-dummy, randomized multicentre study. Aliment Pharmacol Ther 2001;15:251–256.
44. Green JRB, Lobo AJ, Holdsworth CD, Leicester RJ, Gibson JA, Kerr GD, Hodgson HJ, Parkins KJ, Taylor MD. Balsalazide is more effective and better tolerated than mesalamine in the treatment of acute ulcerative colitis. Gastroenterology 1998;114:15–22.
45. Hanauer S, Schwartz J, Robinson M, Roufail W, Arora S, Cello J, Safdi M. Mesalamine capsules for treatment of active ulcerative colitis: results of a controlled trial. Pentasa Study Group. Am J Gastroenterol 1993;88:1188–1197.
46. Farup PG, Hinterleitner TA, Lukas M, Hebuterne X, Rachmilewitz D, Campieri M, Meier R, Keller R, Rathbone B, Oddsson E. Mesalazine 4 g daily given as prolonged-release granules twice daily and four times daily is at least as effective as prolonged-release tablets four times daily in patients with ulcerative colitis. Inflamm Bowel Dis 2001;7:237–242.
47. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. Br Med J 1989;298:82–86.
48. Zussman BD, Benincosa LJ, Webber DM, Clark DJ, Cowley H, Kelly J, Murdoch RD, Upward J, Wyld P, Port A, Fuder H. An overview of the pharmacokinetics of cilomilast (Ariflo), a new, orally active phosphodiesterase 4 inhibitor, in healthy young and elderly volunteers. J Clin Pharmacol 2001;41:950–958.
49. Greenberg RN. Overview of patient compliance with medication dosing: a literature review. Clin Ther 1984;6:592–599.
50. Kane SV, Cohen RD, Aikens JE, Hanauer SB. Prevalence of nonadherence with maintenance mesalamine in quiescent ulcerative colitis. Am J Gastroenterol 2001;96:2929–2933.

**Received July 27, 2006. Accepted October 12, 2006.**

**Address requests for reprints to: Stefan Schreiber, MD, Christian-Albrechts-University Kiel, Institute for Clinical Molecular Biology, Schittenhelmstrasse 12, Kiel Schleswig-Holstein 24105, Germany. e-mail: secretary@mucosa.de; fax: (49) 431597 1842.**

**Supported by Otsuka Maryland Research Institute, Rockville, MD, and the Competence Network Inflammatory Bowel Disease, financed by the German Ministery of Education and Science (www.kompetenznetz-ced.de).**

**The authors thank Jinhua Zhong (Otsuka Maryland Research Institute), who, along with J.S., performed the statistical analyses, and M. Scott Harris from OTUSKA Maryland Research Institute, who organized and started the trial from the operational side.**

**Author contributions were as follows: S.S. and J.G. wrote the paper and interpreted the results. A.K. and K.I.L. planned and organized large parts of the study. J.S. was the principal statistician for the study. S.H. and A.K. contributed to writing and discussion of results.**

**Parts of the results of this study have been presented at the Digestive Disease Week of the American Gastroenterological Association (New Orleans, May 15-20, 2004) and the United European Gastroenterology Week (Prague, September 25–29, 2004).**

**Please see Appendix for principal investigators and centers participating in the study.**