Synopsis

Clinical Report Synopsis for Protocol 197-02-220

Name of Company: Otsuka Pharmaceutical Development & Commercialization, Inc.

Name of Product: Tetomilast (OPC-6535)

Study Title: A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Arm, 52-Week Dose Comparison Study of the Efficacy and Safety of 25 mg QD and 50 mg QD of OPC-6535 Oral Tablets and 800 mg BID of Asacol® in the Maintenance of Remission in Subjects with Ulcerative Colitis

Investigator(s) and Study Center(s): Multicenter (208 centers; Multinational)
Larry W. Weprin, MD, US (Coordinating Investigator)

Publications: None to date.

Studied Period:

Date of first signed informed consent: 30 Apr 2004

Date of last study observation: 04 Mar 2007

Clinical Phase: 3

Objectives:
The purpose of the study was to compare the efficacy and safety of 25 mg once daily (QD) and 50 mg QD OPC-6535 doses to Asacol 800 mg twice daily (BID) in the maintenance of remission in ulcerative colitis.

Methodology:
This was a multicenter, randomized, double-blind, comparator-controlled, parallel-arm, dose comparison study of tetomilast in the maintenance of remission in ulcerative colitis. Approximately 1725 male or female subjects 18 to 80 years of age were planned for enrollment in this study at approximately 217 centers; the actual enrollment was 1186 subjects. The study consisted of a 3- to 21-day screening period, a baseline/randomization visit, a 52-week treatment period, and a 14-day follow-up (by telephone for assessment of adverse events [AEs] and concomitant medications). Subjects with ulcerative colitis in remission, defined as rectal bleeding (RB) and flexible sigmoidoscopy (FS) scores of 0, on or off a stable dose of sulfasalazine or oral 5-aminosalicylic acid (5-ASA) products for at least 6 weeks, were eligible for participation in the study.

Subjects must have had the diagnosis of ulcerative colitis established by prior colonoscopy. A colonoscopy was permitted to be substituted for FS in subjects who had to undergo colonoscopy during the screening period, in which case the FS score was determined from the appearance of the distal 45 cm of bowel. Subjects at increased risk for colorectal cancer (≥ 8 year history of ulcerative colitis) must have undergone colonoscopy with pan-colonic surveillance biopsies negative for dysplasia within 1 year of the screening period. Subjects must also have undergone treatment for a flare of ulcerative colitis, with symptomatic onset of remission occurring no more than 52 weeks from the screening period.

After meeting all entry criteria at baseline and discontinuing any sulfasalazine or 5-ASA containing products, subjects were randomized to one of 3 treatment groups: tetomilast 25 mg PO QD for the duration of the treatment period (52 weeks); tetomilast 50 mg PO QD (25 mg for 1 week followed by titration to 50 mg PO QD for 51 weeks); or Asacol 800 mg PO BID for the duration of the treatment period (52 weeks). Initial dosing in the 50 mg group was titrated from 25 mg in an attempt to reduce the possibility of nausea.

After randomization, if RB was reported on 5 out of the previous 7 patient diary entries, the subject was to undergo an FS to establish the occurrence of relapse. If the sigmoidoscopy demonstrated the presence of active inflammation (defined as FS ≥ 1), the subject was considered to have relapsed and was to be discontinued from the study. If the sigmoidoscopy failed to confirm recurrence of active inflammation, the subject was to continue in the study. Additional FS examinations were performed at the discretion of the investigator if the subject continued to bleed or subsequently showed new or worsening symptoms.

Number of Subjects:
A total of 1725 subjects were planned to be enrolled into the study and randomized in an approximate 1:1:1 ratio (tetomilast 25 mg: tetomilast 50 mg: Asacol 800 mg). A total of 1186 subjects were randomized at 190 centers: 396 subjects to the tetomilast 25 mg treatment group; 395 subjects to the tetomilast 50 mg treatment group; and 395 subjects to the Asacol treatment group.

Diagnosis and Main Criteria for Inclusion:
Male and female subjects, 18 to 80 years of age, with ulcerative colitis in remission, defined as RB and FS scores of 0, on or off a stable dose of sulfasalazine or oral 5-aminosalicylic acid (5-ASA) products for at least 6 weeks, were eligible for participation in the study. Subjects must have undergone treatment for a flare of ulcerative colitis, with symptomatic onset of remission occurring no more than 52 weeks from the screening period.

Test Product, Dose, Mode of Administration, Batch or Lot No(s):
Tetomilast 25 mg tablets or matching placebo tablets (25 mg group: one 25 mg tablet and one matching placebo tablet; 50 mg group: two 25 mg tablets; Asacol group: two

matching placebo tablets) were administered orally every morning. The following lot numbers were used in this study:

Tetomilast 25 mg tablets: lot numbers 04I86A025A, 04I86A025B, 04I86A025C, 04I86A025D, 04F90A025A, 04F90A025B, 04F90A025C, 04F90A025D, 03I74A025A, 03I74A025B, 03I74A025C, 03I74A025D, 03I74A025E, 03I74A025F, and 03I74A025G

Placebo tablets matching tetomilast 25 mg tablets: lot numbers 04I70P000A, 04I70P000B, 04F90P000A, 04F90P000B, 04F90P000C, 04F90P000D, 03H88P000A, 03H88P000B, 03H88P000C, 03H88P000D, 03H88P000E, 03H88P000F, and 03H88P000G

Reference Product, Dose, Mode of Administration, Batch or Lot No(s):
Asacol 400 mg capsules or matching placebo capsules (Asacol group: two Asacol capsules; 25 mg and 50 mg groups: two matching placebo capsules) were administered orally every morning and evening. The following lot numbers were used in this study:

Asacol (mesalamine, 5-ASA) delayed release tablet (Proctor & Gamble Pharmaceuticals, Cincinnati, Ohio) 400 mg capsules: manufacturer lot numbers 423590 and 418420; overencapsulated tablets 13866.4 and 10500.09

Placebo capsules matching Asacol 400 mg capsules: lot numbers 13866.9, 13866.10, 10500.05, and 10500.06

Criteria for Evaluation:
The primary efficacy measure was time to treatment failure, defined as relapse of ulcerative colitis or discontinuation from the study for any other reason at Week 26. Relapse was defined as RB $\geq$ 1 and FS $\geq$ 1 (as derived from the rectal bleeding and flexible sigmoidoscopy subscores of the Disease Activity Index [DAI]), or the need for other medication for treatment of an acute flare, as judged by the principal investigator.

Secondary efficacy measures included time to treatment failure at Week 52; treatment failure proportions at Weeks 26 and 52; time to relapse and relapse proportions at Weeks 26 and 52; endoscopic relapse proportions at Week 52; change from baseline in health related quality of life based on the Inflammatory Bowel Disease Questionnaire (IBDQ) at screening and Weeks 13, 26, 39, and 52; and change from baseline in stool frequency scores, bleeding scores, bowel urgency scores, abdominal pain scores, and general well being scores at Weeks 1, 13, 26, 39, and 52.

Sampling for tetomilast plasma concentrations was done at selected centers. Safety assessments were based on AEs, clinical laboratory tests, physical examinations, vital signs, electrocardiograms (ECGs), and use of concomitant medications.

Statistical Methods:

Primary Efficacy Analysis

The time to treatment failure was analyzed by the Cox proportional hazard model with treatment as a factor. The null hypothesis for testing non-inferiority was that the hazard for treatment failure in subjects treated with tetomilast (either 25 mg or 50 mg) was 1.346 times higher than the hazard for treatment failure in subjects receiving Asacol. The test for superiority was not performed for this study.

The primary treatment comparisons were (1) tetomilast 25 mg QD vs Asacol 800 mg BID, and (2) tetomilast 50 mg QD vs Asacol 800 mg BID. The Hochberg procedure was used to test these two comparisons. If the upper bound of the two-sided 95% confidence interval (CI) for the hazard ratio of the tetomilast doses were less than 1.346, then both of tetomilast doses were claimed to be non-inferior to Asacol in efficacy. If the upper bound of the 95% CI from only one tetomilast dose was less than 1.346, then a two-sided 97.5% CI for the hazard ratio of that tetomilast dose to Asacol was to have been constructed. If the upper bound of that CI had been less than 1.346, the corresponding dose of tetomilast was to have been claimed as non-inferior to Asacol.

Secondary Efficacy Analyses

The time to event variables were analyzed using Cox proportional hazards regression with treatment group in the model. For relapse of ulcerative colitis, subjects who completed the study or who discontinued early without relapse were treated as censored observations. For time to treatment failure endpoints, the same definition was used as for the primary analysis. The time to event for all variables started from the date of randomization. For each variable the two-sided 95% CI for the hazard ratio of tetomilast over Asacol was constructed. A hazard ratio of 1.346 was used for the tests of non-inferiority.

For the treatment failure and relapse proportions at Week 26 and at Week 52, and also for the endoscopic relapse proportions at Week 52, two-sided 95% CIs for the differences in the proportions between tetomilast and Asacol were constructed. The tetomilast doses were combined into one group for the tetomilast pooled endpoints. A difference in proportions of 9% was used for the test of non-inferiority. The normal approximation to the binomial was used to construct the CIs. The times to treatment failure and the times to relapse were shown by plotting Kaplan-Meier curves for each treatment group.

For 5-ASA categories (No 5-ASA taken prior to the time of randomization, 5-ASA taken prior to time of randomization at a daily dose ≤ 1.6 g/day, and 5-ASA taken prior to time of randomization at a daily dose >1.6 g/day), the proportion of subjects who were treatment failures and the proportion of subjects who relapsed were summarized by treatment group at Weeks 26 and 52. Endoscopic relapse proportions for tetomilast analyses by 5-ASA dose taken prior to the randomization were summarized at Week 52.

The IBDQ consisted of 32 questions, with a score of 1 to 7 associated with each question. The sum of the scores from all 32 questions was calculated for each subject. The change

from baseline in the sum was analyzed using analysis of covariance (ANCOVA), with a term for treatment group in the model, and with the baseline sum used as a covariate. Two-sided 95% CIs were constructed for the mean treatment differences. The change from baseline in each ulcerative colitis symptom score (stool scores, rectal bleeding score, bowel urgency scores, abdominal pain scores, and general well being scores) was also analyzed using ANCOVA, with a term for treatment group in the model, and with the baseline value used as a covariate. Two-sided 95% CIs were constructed for the mean treatment differences. Both IBDQ and ulcerative colitis symptom scores were also summarized for pooled tetomilast groups and by 5-ASA categories.

Safety
Safety assessments (AEs, physical examination and vital signs, ECGs, and clinical laboratory evaluations) were listed and, where appropriate, summarized by descriptive statistics. In particular, change from baseline at each visit for the continuous safety variables was summarized using descriptive statistics. However, no inferential statistical analyses of these safety variables were performed.

Pharmacokinetic/pharmacodynamic Methods:
Blood samples for future population analysis were collected at sites that had appropriate facilities for the handling/storage of the pharmacokinetic samples. A single blood sample was collected at screening and at predose at Weeks 13, 26, 39 and 52/Early Termination. Plasma concentrations of tetomilast and DM-601 were simultaneously measured by a validated high-performance liquid chromatography method with tandem mass spectrophotometric detection method. The pharmacokinetic population analysis will include results obtained from other studies and will be reported separately.

Efficacy Results:
The primary efficacy measure of time to treatment failure through 26 weeks did not demonstrate non-inferiority of tetomilast 25 mg or tetomilast 50 mg QD compared to Asacol 800 mg BID. Secondary analyses of time to treatment failure through 52 weeks, time to relapse through 26 and 52 weeks, and the proportion of treatment failures through 26 and 52 weeks also failed to demonstrate non-inferiority for tetomilast 25 mg or tetomilast 50 mg compared to Asacol. Non-inferiority was demonstrated for the proportion of relapses through 26 weeks and 52 weeks (tetomilast 25 mg and tetomilast 50 mg).

Pharmacokinetic/pharmacodynamic Results:
The concentration data and calculated time post last dose were reviewed for accuracy; errors and discrepancies were noted and, if possible, corrections were noted.

Safety Results:
A total of 846/1185 subjects (71.4%) experienced at least one treatment emergent adverse event (TEAE). The percentage of subjects with TEAEs was similar among all treatment groups: 284/396 (71.7%) in the tetomilast 25 mg group, 288/395 (72.9%) in the tetomilast 50 mg group, and 274/394 (69.5%) in the Asacol group. The majority of

TEAEs were mild or moderate in intensity. Ulcerative colitis was reported as a TEAE at similar rates across treatment groups (26.8% in the tetomilast 25 mg group, 25.1% in the tetomilast 50 mg group, and 24.9% in the Asacol group). The most frequently reported TEAEs for tetomilast-treated subjects (both dose levels combined) compared with Asacol were headache (13.8% versus 9.4%), diarrhoea (6.1% versus 4.8%), nausea (10.9% versus 3.6%), and vomiting (4.2% versus 2.0%). The incidence of gastrointestinal events appeared to increase with increasing dose of tetomilast.

Twenty-one subjects each in the tetomilast 25 mg and Asacol groups (5.3% each) and 15 subjects in the tetomilast 50 mg group (3.8%) experienced serious adverse events (SAEs), including one subject in the tetomilast 25 mg group who experienced a missed abortion and one death in the Asacol group due to myocardial infarction. The most common SAE across all groups was ulcerative colitis, reported for 6 subjects in the tetomilast 25 mg group (1.5%), 9 subjects in the tetomilast 50 mg group (2.3%), and 6 subjects in the Asacol group (1.5%).

The proportion of subjects who discontinued due to TEAEs was slightly higher in the tetomilast 25 mg (32.8%) and tetomilast 50 mg (35.7%) groups compared with the Asacol group (29.7%). The most common TEAE resulting in discontinuation was ulcerative colitis, reported for 97 subjects in the tetomilast 25 mg group (24.5%), 89 subjects in the tetomilast 50 mg group (22.5%), and 86 subjects in the Asacol group (21.8%). Other commonly reported TEAEs resulting in the discontinuation were nausea (5 subjects in the tetomilast 25 mg group, 7 subjects in the tetomilast 50 mg group and 2 subjects in the Asacol group), headache (3 subjects in the tetomilast 25 mg group, 7 subjects in the tetomilast 50 mg group and 1 subject in the Asacol group), rectal haemorrhage (1 subject in the tetomilast 25 mg group, 5 subjects in the tetomilast 50 mg group and 3 subjects in the Asacol group), and migraine (4 subjects in the tetomilast 50 mg group and 1 subject in the Asacol group). All other TEAEs resulting in discontinuation were reported by < 1% of subjects in any treatment group.

Although potentially clinically significant abnormal laboratory values were identified for individual subjects, no clinically important trends in clinical laboratory findings, vital signs, or ECGs were observed during the study.

Conclusions:
The efficacy results failed to demonstrate non-inferiority of tetomilast 25 mg or tetomilast 50 mg QD to Asacol 800 mg BID for the primary efficacy endpoint and most secondary endpoints, except for the proportion of relapses through 26 weeks and 52 weeks (tetomilast 25 mg and tetomilast 50 mg).

Tetomilast doses of 25 mg and 50 mg administered QD were safe and well tolerated in subjects during the study. The majority of TEAEs experienced were mild and moderate in intensity. No clinically important trends in clinical laboratory findings, vital signs, or ECGs were observed during the study.

Otsuka Pharmaceutical Development & Commercialization, Inc.

OPC-6535

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