Synopsis

Clinical Report Synopsis for Protocol 197-02-218

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

Name of Product: Tetomilast (OPC-6535)

Study Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-arm Study of the Efficacy and Safety of OPC-6535 Tablets in the Treatment of Subjects with Active Ulcerative Colitis

Investigator(s) and Study Center(s): Multicenter (106 centers; Multinational [Australia, Canada, Czech Republic, Hungary, Romania, and the USA])

Publications: None to date.
Studied Period:

Date of first signed informed consent: 18 Jun 2003

Date of last study observation: 02 Aug 2006

Clinical Phase: 3

Objectives: The purpose of the study was to confirm the efficacy and safety of 25 mg and 50 mg once daily (QD) doses of tetomilast in the treatment of active ulcerative colitis.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-arm, dose comparison study of tetomilast in subjects with active ulcerative colitis. Baseline assessments (including Disease Activity Index [DAI] and Inflammatory Bowel Disease Questionnaire [IBDQ] scores and at least 3 days of electronic diary entries) were obtained for each subject before the subject was randomized to study drug. The randomization was stratified by concomitant treatment with or without oral (PO) 5-aminosalicylic acid (5-ASA). Subjects were randomized to one of 3 treatment groups (approximately 125 subjects per group): 25 mg tetomilast PO QD with or without 5-ASA for the duration of the treatment period (8 weeks); 25 mg PO QD with or without 5-ASA for 1 week followed by titration to 50 mg PO QD with or without 5-ASA for 7 weeks; or placebo PO QD with or without 5-ASA for the duration of the treatment period (8 weeks). Subjects were contacted by telephone 2 weeks after the last visit for assessment of adverse events (AEs) and concomitant medications. Efficacy was primarily measured by clinical improvement. Sparse sampling for tetomilast plasma concentrations was done. Safety was assessed based on the results of the vital signs, electrocardiograms (ECGs), clinical laboratory tests, AEs, and use of concomitant medications.

Number of Subjects: Approximately 375 male or female subjects (no restrictions on ethnicity) were planned for enrollment in this study. A total of 379 subjects were enrolled.

Diagnosis and Main Criteria for Inclusion: Male or female subjects, 18 to 80 years of age (inclusive), with active ulcerative colitis experiencing an acute flare of symptoms, on or off a stable dose of 5-ASA for at least 14 days, with baseline rectal bleeding (RB) and flexible sigmoidoscopy (FS) scores of ≥ 2 and a DAI total score of < 12.

Test Product, Dose, Mode of Administration, Batch or Lot No(s): The tetomilast 25 mg tablets (lot numbers 02K89A025D, 02K89A025B, and 04C93A025A) and matching placebo tablets (lot numbers 02J00P000B, 03B93P000B, and 04C93P000A) for oral administration were manufactured by Otsuka Pharmaceutical Company, Ltd. (Tokushima, Japan).

Reference Product, Dose, Mode of Administration, Batch or Lot No(s): None

Criteria for Evaluation: The primary efficacy endpoint was clinical improvement at Week 8 based on an Intent to treat (ITT) analysis (denoted Clinical Improvement [ITT]), with the restriction that subjects who discontinued before completing the visit at Week 8 (Day 52 or later) were considered as not exhibiting clinical improvement, regardless of their DAI scores. Clinical improvement was defined as a reduction from a baseline RB score of 2 or 3 to a score of 0 or 1, and an improvement of at least one point in at least one other DAI symptom score: FS, physician's global assessment (PGA), or stool frequency (SF).

The secondary efficacy endpoints were:

1) Clinical improvement based on the last observation carried forward (LOCF) and observed case (OC) datasets,
2) Remission of disease, defined as a postbaseline FS score of 0 and an RB score of 0,
3) Improvement by at least one point in a postbaseline DAI symptom score (separate analysis for each symptom: FS, RB, PGA, and SF),
4) Change from baseline in the DAI total score,
5) Change from baseline in individual DAI symptom scores (FS, RB, PGA, and SF),
6) Time to discontinuation due to all reasons,
7) Change from baseline in health-related quality of life (QOL) score based on the IBDQ,
8) Change from baseline in ulcerative colitis symptom scores from daily diary data recorded by the subject (stool score, bleeding score, bowel urgency score, abdominal pain score, and general well-being score), and

9) Subgroup analyses (for 5-ASA users and nonusers of 5-ASA) for the primary and the secondary efficacy variables.

Sparse sampling was done for population pharmacokinetic (PK) analysis. Safety variables were vital signs, ECGs, laboratory measurements, (including hematology, clinical chemistry and urinalysis), AEs, and concomitant medications.

Statistical Methods: The primary efficacy variable, Clinical Improvement (ITT), was analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by 5-ASA (ie, being on or off 5-ASA). Weighted estimates of the differences in proportions and the corresponding confidence intervals (CIs) were also obtained. Hochberg's procedure was used (based on the p-values) to adjust for the multiple comparisons and maintain the overall Type I error at 0.05 (2-tailed).

Secondary efficacy variables: Clinical improvement (OC and LOCF) and improvement in each DAI symptom score were analyzed using the CMH test stratified by 5-ASA. Remission was analyzed using Fisher's exact test. Change from baseline in the DAI total score was analyzed by an analysis of covariance (ANCOVA) with terms for treatment group and 5-ASA strata, and with the baseline DAI total score as a covariate. Change from baseline in the individual DAI symptom scores were analyzed using the CMH test stratified by 5-ASA. Time to discontinuation was analyzed using the log-rank test for the comparisons of the distributions of time to discontinuation for each tetomilast group with that of the placebo group. Change from baseline in the QOL score based on the IBDQ was analyzed by ANCOVA with terms for treatment group and 5-ASA strata and with the baseline score as a covariate. Change from baseline in daily diary data were presented graphically by treatment group. Subgroup analyses by 5-ASA strata and exploratory analyses were also performed.

Pharmacokinetic/pharmacodynamic Methods: Bioanalytical: Plasma concentrations of tetomilast and DM-601 were simultaneously measured by a validated liquid chromatography with tandem mass spectrometric detection method. Blood samples for pharmacokinetic analysis were collected at screening, Week 1 (trough), Week 4 (trough and 2-4 h post dose), Week 6 (post dose), and Week 8 (trough and 2-4 h post dose) to obtain pharmacokinetic data from with ulcerative colitis for future population analysis. The analysis will include results obtained from other studies and will be reported separately.

Efficacy Results: The efficacy results for tetomilast for the primary efficacy endpoint (Clinical Improvement at Week 8) were not statistically significant when compared with placebo. However, numerical superiority over placebo was demonstrated by both tetolimast groups for non 5-ASA users at Week 8 for the primary efficacy endpoint; statistically significant results; however, were not demonstrated.

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

Safety Results: A total of 240/377 subjects (63.7%) experienced at least one TEAE. The percentage of subjects with TEAEs was similar among all treatment groups: 79/125 (63.2%) in the tetomilast 25-mg group, 84/128 (65.6%) in the tetomilast 50 mg group, and 77/124 (62.1%) in the placebo group. The majority of TEAEs were mild or moderate. The most frequently reported TEAEs for tetomilast-treated subjects (both dose levels combined) compared with placebo were nausea (23.3% versus 9.7%) and, headache NOS (21.3% versus 15.3%). There was no consistent dose response and no relationship between the incidences of the most common TEAEs (dyspepsia, nausea, vomiting, fatigue, headache, and aggravated headache) and the use/nonuse of 5-ASA was apparent.

Five subjects in the 25-mg tetomilast group and 3 subjects in the 50-mg tetomilast group (4.0% and 2.3%, respectively) experienced SAEs compared with 8 subjects (6.5%) in the placebo group. Of the 5 subjects treated with tetomilast 25 mg who had SAEs, three female subjects and 1 male subject experienced aggravated ulcerative colitis and one male subject experienced an aggravation of Crohn's disease; 3 of the 4 subjects experiencing ulcerative colitis and the subject experiencing an aggravation of Crohn's disease were 5-ASA users. All of the 5 SAEs in the 25-mg tetomilast subjects were considered unrelated (4 events) or not likely related (1 event) to trial drug. All events were resolved but 1 female subject with aggravated ulcerative colitis was discontinued from the study. Of the subjects treated with tetomilast 50 mg who had SAEs, all were male (2 taking 5-ASA) and experienced aggravated ulcerative colitis. All of these events were considered not likely to be related to trial medication by the investigator and all events resolved; however, two subjects were withdrawn from the trial.

The proportion of subjects who discontinued trial medication because of TEAEs was similar for the tetomilast 25-mg, tetomilast 50-mg, and placebo groups (15.2%, 14.8%, and 13.7%, respectively). The most common TEAE resulting in discontinuation was ulcerative colitis aggravated, which resulted in the discontinuation of 11 subjects (8.8%) in the tetomilast 25-mg group, 7 subjects (5.5%) in the tetomilast 50-mg group, and 16 subjects (12.9%) in the placebo group. The other TEAEs resulting in the discontinuation of more than one subject in any treatment group were nausea and vomiting.

Although various potentially clinically significant abnormal laboratory values were identified for individual subjects, they were not clinically meaningful. No clinically important treatment-dependent trends were observed in the analyses of clinical laboratory data.

Although various potentially clinically significant abnormal vital sign or ECG values were identified for individual subjects, only one AE of palpitations led to withdrawal. No clinically important treatment-dependent trends were observed in the analyses of vital sign or ECG data.

Conclusions:

- The efficacy results for tetomilast for the primary efficacy endpoint of Clinical Improvement (ITT) at Week 8 were not statistically significant when compared with placebo.
- Numerical superiority over placebo was demonstrated by both tetomilast groups for a secondary analysis of the primary efficacy endpoint, Clinical Improvement (ITT) at Week 8, by 5-ASA strata for non 5-ASA users; however, statistically significant results; were not demonstrated.
- Tetomilast doses of 25 mg and 50 mg were generally well tolerated in subjects with active ulcerative colitis.
- Although isolated clinically significant individual abnormalities were observed in clinical laboratory values, vital signs, and ECGs, no clinically important treatment-dependent trends were observed

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