ONLINE SUPPLEMENT

Reduction of Diabetic Macular Edema by Oral Administration of the Kinase Inhibitor PKC412

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Study Design

This was a randomized, multicenter, double-masked, parallel-group, dose-finding study that compared the efficacy and safety of PKC412 (50, 100, and 150 mg/day) versus matching placebo in subjects with diabetic macular edema. Each subject attended 10 clinic visits over approximately 16.5 months, as follows: screening (visit 1), baseline/randomization (visit 2, within 2 to 6 weeks of screening), 3-month double-masked treatment period (visits 3-5), and 12-month follow-up (visits 6-10). Safety was evaluated throughout the study, with only selected assessments performed (collection of adverse events [AEs], vital signs, and laboratory tests) at months 2 (visit 4) and 5 (visit 7). Efficacy assessments were performed at baseline, months 1 and 3 (active therapy period) and months 4, 6, 9, and 15 (follow-up). Although safety was the primary focus of the follow-up period, efficacy data were also collected to monitor for any rebound effect of increased macular edema following the treatment period.

Exclusion Criteria

Subjects were excluded from the study if they 1) were female and pregnant or breast-feeding; 2) had panretinal photocoagulation within 4 months of screening; 3) had ocular disease other than diabetic macular edema (including moderate or severe proliferative diabetic retinopathy); 4) had intraocular surgery in the study eye within 3 months of screening; 5) had ischemic heart disease, cerebrovascular disease, uncontrolled congestive heart failure, intermittent claudication, vasculitis, active peptic ulcer disease or active asthma; 6) had clinically significant electrocardiogram (ECG) or laboratory abnormalities at screening; or 7) required concomitant topical ocular therapy with any non-steroidal anti-inflammatory drug.

Subjects and investigators had to agree to refrain from using focal, and/or grid, or panretinal laser photocoagulation during the first 6 months of the study. However, if macular edema worsened such that a previously uninvolved center of the macula developed retinal thickening or hard exudates and the subject experienced a decrease in visual acuity of ≥ 5 letters between baseline and any post-baseline visit, photocoagulation was allowed (but not required). Efficacy data from such subjects were excluded after laser photocoagulation.

Safety Assessments and Analysis

Subjects were closely monitored for safety and tolerability using the following assessments and procedures: slit lamp biomicroscopy, dilated indirect ophthalmoscopy, tonometry, manifest refraction, AE reporting, clinical chemistry and hematology under fasted conditions, 12-lead ECGs, vital signs, and physical examinations. In addition, subjects recorded daily glucose levels (morning and evening) on a diary card.

Treatment-emergent AEs were defined as those events that occurred after the first dose of masked study medication was administered through the date of last dose plus 2 weeks (month 3 + 2 weeks). Post-treatment events were those that initiated from 2 weeks after the last dose through month 15. Adverse events were assigned preferred terms using the MedDRA coding dictionary.

Laboratory samples were analyzed by a central laboratory and rated as normal, high (above normal range), or low (below normal). Subjects were given diaries to record blood glucose twice daily (morning and evening). Glucose levels were entered into the clinical database and evaluated to determine if there were any major changes in day-to-day glycemic control. Clinically notable vital signs abnormalities were defined as an increase from baseline in systolic blood pressure ≥ 30 mm Hg or an absolute value < 75 mm Hg; an increase from baseline in diastolic blood pressure ≥ 20 mm Hg; an absolute value > 115 mm Hg; or a decrease from baseline ≥ 30 mm Hg; and increases or decreases from baseline in pulse rate ≥ 20 bpm.

For continuous safety variables, summary statistics were calculated for observed values, changes from baseline, and percent changes from baseline. For categorical variables, changes from baseline were analyzed using shift-tables. Laboratory and ECG data were analyzed as both continuous and categorical (high, normal, low or normal/abnormal) variables. Adverse event incidence summaries were prepared by treatment group, body system, and preferred term.
Figure 1. Frequency Distribution of Change from Baseline in Retinal Thickening at Month 3: ITT Population (Study Eye, All Locations Combined)

Figure 2A. Frequency Distribution of Change from Baseline in Foveal Avascular Zone Size at Month 3: ITT Population (Study Eye)

Figure 2B. Frequency Distribution of Change from Baseline in Foveal Avascular Zone Outline at Month 3: ITT Population (Study Eye)
Figure 3. Frequency Distribution of Change from Screening in Diabetic Retinopathy Classification at Month 3: ITT Population (Study Eye)

Figure 4A. Changes in serum alanine aminotransferase (ALT) during the study

Figure 4B. Changes in serum aspartate aminotransferase (AST) during the study
Figure 5A. Changes in total serum cholesterol during the study.

Figure 5B. Changes in serum low-density lipoprotein cholesterol (LDL-C) during the study.

Figure 5C. Changes in serum high-density lipoprotein cholesterol (HDL-C) during the study.