A QT Study Confirms Early PK/PD Modeling That a Supratherapeutic Dose of Omarigliptin, a Once-Weekly DPP-4 Inhibitor, Does Not Prolong the QT Interval

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Abstract

Background: Omarigliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor being developed as a once-weekly treatment for type 2 diabetes. Pharmacodynamic (PD) analysis was performed using the classical PK/PD model of the QT interval. The QT interval and each heart rate (HR) component (RR, PR, QRS) served as PD outcomes. Omarigliptin was selected as a supratherapeutic dose study based on preliminary half-life estimates of 50-100 hours for marigliptin.

Methods: Pharmacokinetics (PK) and Cardiodynamic Results

• Continuous 12-lead digital ECG data were obtained over 24 hours on Days 1 and 2 within each treatment period using Mortara H12+ Digital Holter Specialists. A standard lunch and dinner were provided at approximately 4 and 10 hours postdose, respectively, on each study drug administration day.

• Pharmacokinetics (PK)

A single dose of study drug was administered orally the morning of Days 1 (omarigliptin 25 mg or placebo) and 2 (omarigliptin 175 mg or placebo). Blood samples for plasma concentration measurements were collected using 1 mL tubes containing EDTA for PK analysis. A supratherapeutic dose of omarigliptin does not prolong the QTcP interval to a clinically meaningful extent.

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Results Based on QTcF were also calculated.

Conclusions: Omarigliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor being developed as a once-weekly treatment for type 2 diabetes. Pharmacodynamic (PD) analysis was performed using the classical PK/PD model of the QT interval. The QT interval and each heart rate (RR, PR, QRS) served as PD outcomes. Omarigliptin was selected as a supratherapeutic dose study based on preliminary half-life estimates of 50-100 hours for marigliptin.

A single dose of study drug was administered orally the morning of Days 1 (omarigliptin 25 mg or placebo) and 2 (omarigliptin 175 mg or placebo). Blood samples for plasma concentration measurements were collected using 1 mL tubes containing EDTA for PK analysis. A supratherapeutic dose of omarigliptin does not prolong the QTcP interval to a clinically meaningful extent.

The most common individual adverse experiences were contact dermatitis (at the ECG electrode sites), abdominal pain, and gastrointestinal upset.

Safety and Tolerability Results

• Cardiac outcomes, including creatine phosphokinase (CPK) and gamma-glutamyltransferase (GGT), were monitored during the study.

• Adverse events were classified using MedDRA version 17.3.

• The QTcP interval was calculated by dividing the QT interval by the square root of the RR interval for each ECG cycle.

• The area under the curve (AUC) for each treatment group was calculated using the trapezoidal rule.

• The safety and tolerability analysis population included all subjects who received at least one dose of study drug and had at least one postbaseline measure.

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