Pharmacokinetics of Omarigliptin (MK-3102), A Once-Weekly Dipeptidyl Peptidase-IV (DPP-4) Inhibitor, in Patients With Renal Impairment

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Abstract

Background: Omarigliptin is a long-acting DPP-4 inhibitory currently in Phase 3 development as a once-weekly treatment for type 2 diabetes. This study evaluated the pharmacokinetics (PK) and urinary excretion of omarigliptin in patients with varying degrees of renal impairment (RI).

Methods: In this open-label study, men and women, age 18-75 yrs, with varying degrees of RI based on estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m²: moderate (30-60 mL/min/1.73 m²), severe (< 30 mL/min/1.73 m²) or end-stage renal disease (ESRD; requiring hemodialysis) were enrolled. Patients and urine samples were collected in Panels A and H (healthy control subjects), B, C, D, E, F, and G (patients with varying degrees of RI) at baseline and at selected time points during the 12-week treatment.

Results: The geometric mean ratios for plasma AUCs (0-∞) were 0.94, 1.34, and 1.97 in patients with mild, moderate, and severe RI, respectively, when compared with healthy control subjects. In patients with ESRD, plasma exposures were comparable regardless of dialysis status. No change in omarigliptin CLD was observed in patients with mild or moderate RI when compared with healthy control subjects. Omarigliptin CLD decreased with worsening renal function in a linear manner. Omarigliptin 2 mg was generally well tolerated.

Conclusions: Omarigliptin is primarily eliminated as unchanged parent drug in urine. Omarigliptin may be administered without dosage adjustment in mild and moderate RI patients and without regard to timing of hemodialysis in ESRD patients.

Objectives

• To compare the single-dose pharmacokinetics (PK) and pharmacodynamics (PD) of omarigliptin in patients with varying degrees of RI to healthy control subjects.
• To investigate the safety and tolerability of a single dose of 2 mg omarigliptin in patients with varying degrees of RI as well as ESRD requiring hemodialysis.

Study Design

This was an open-label, 2-part, 2-panel study in which a single, 2-mg dose of omarigliptin was administered to healthy subjects and patients with varying degrees of RI requiring hemodialysis.

In Part I, 3 panels of 8 patients were enrolled for each level of RI as defined by the MDRD study equation. Each panel consisted of 4 men and 4 women, and each group consisted of patients with mild, moderate, severe, or ESRD requiring hemodialysis. Ovarian cycle was independent across groups.

In Part II, a parallel (Panel G) of 8 patients with ESRD who required hemodialysis was enrolled. An equal number of healthy matched to moderate RI patients was recruited for each group. Blood samples were collected 0-48 h following omarigliptin administration. Ovarian cycle was independent across groups and conditions.

Methods

Pharmacokinetics: For healthy control subjects to match Panel A

Pharmacodynamics and Pharmacometric analysis:

• Ovarian cycle, urine, and placebo comparisons
• Use of plasma samples for protein binding
• DPP-4 enzyme activity assay (uncorrected for dilution)

Safety and Tolerability Assessments:

• Safety and tolerability were assessed by clinical evaluation of adverse events, physical examinations, vital signs, SAEs, electrocardiograms (ECGs), and laboratory safety measurements.
• Adverse events that are generally unlikely in elderly, moderate, or severe, duration, severity, frequency, and relationship to study drug.

Pharmacometric analysis:

• Linear mixed-effects models (LMMs) were used to model the inter-individual and residual variability in omarigliptin area under the curve (AUC) following a single oral 2-mg dose of omarigliptin.

Table 1. Statistical comparison of plasma AUC0-∞ and Cmax of omarigliptin following the administration of a single oral 3-mg dose in patients with varying degrees of RI as well as ESRD requiring hemodialysis

Table 2. Baseline demographics of study population

Table 3. Comparison of plasma AUC0-∞ and Cmax of omarigliptin following the administration of a single oral 3-mg dose in patients with varying degrees of RI as well as ESRD requiring hemodialysis

Table 4. Omarigliptin plasma and diaphoresis pharmacokinetic parameters for healthy volunteers and patients with varying degrees of RI and ESRD during a single oral 3-mg dose

Results

• Omarigliptin plasma exposure (AUC0-∞) increased with increasing degrees of RI.
• Omarigliptin plasma exposures were approximately 2-fold higher in patients with ESRD versus healthy matched control subjects.
• Cmax values were similar in patients with mild, moderate, and severe RI whereas Cmax in ESRD patients was approximately 25% lower in patients with ESRD vs. healthy matched control subjects.
• In ESRD patients, both AUC0-∞ and Cmax were similar in Period 1 and 2 demonstrating equivalent pharmacokinetic exposure irrespective of dialysis schedule.
• There was also correlation-dependent protein binding of omarigliptin similar between patients with varying degrees of RI and healthy control subjects (data not shown).

Conclusions

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Figure 2. Individual PK values plotted by GMR values following the administration of a single oral 3-mg dose in patients with varying degrees of RI as well as healthy matched control subjects.

Figure 3. Mean DPP-4 inhibition profiles (left) and DPP-4 inhibition vs. drug concentration (right) for omarigliptin in healthy subjects following single oral 300 mg dose.