

Pharmacokinetic and Pharmacodynamic Effects of Multiple-Dose Administration of Omarigliptin, a Once-Weekly Dipeptidyl Peptidase-4 Inhibitor, in Obese Participants With and Without Type 2 Diabetes Mellitus*

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ABSTRACT

Purpose: Omarigliptin (MK-3102) is a potent, oral, long-acting dipeptidyl peptidase (DPP)-4 inhibitor approved in Japan and in global development as a once-weekly treatment for type 2 diabetes mellitus (T2DM). The aim of this study was to investigate the pharmacokinetic (PK) and pharmacodynamic (PD) effects of omarigliptin in obese participants with and without T2DM.

Methods: This was a Phase I, randomized, double-blind, placebo-controlled, multiple-dose study of 50-mg omarigliptin administered once weekly for 4 weeks. Participants included 24 obese but otherwise healthy subjects (panel A; omarigliptin, n = 18; placebo, n = 6) and 8 obese patients with T2DM (treatment naive, hemoglobin A_{1c} ≥ 6.5% and ≤ 10.0% [panel B]; omarigliptin, n = 6; placebo, n = 2). Participants were 45 to 65 years of age with a body mass index of ≥ 30 and ≤ 40 kg/m². Blood sampling occurred at select time points, depending on the study panel, to evaluate the PK properties of omarigliptin, DPP-4 activity, active glucagon-like peptide 1 levels, and plasma glucose concentrations. Body weight was an exploratory end point. Due to sparse sampling in panel A, a thorough PK analysis was performed in obese patients with T2DM (panel B) only. PD analyses were performed in the overall study population (pooled panels A and B).

Findings: PK profiles in obese participants with and without T2DM were similar to those observed in nonobese reference subjects (historical data). Steady state was achieved after 1 or 2 weekly doses in obese participants with and without T2DM. In obese patients with T2DM, omarigliptin was rapidly absorbed, with a median T_{max} of 1 to 2.5 hours (days 1 and 22). Compared with those in reference subjects, the geometric mean ratios (95% CI) (Obese T2DM/reference) for steady-state plasma AUC_{0–168h}, C_{max}, and C_{168h} were 0.80 (0.65–0.98), 0.86 (0.53–1.41), and 1.08 (0.88–1.33), respectively. Trough DPP-4 activity was inhibited by ~90%; postprandial (PP) 4-hour weighted mean active GLP-1 concentrations were increased ~2-fold; and PP glucose was significantly reduced with omarigliptin versus placebo in the pooled population. Omarigliptin was generally well-tolerated in the pooled population, and there were no hypoglycemic events. Consistent with other DPP-4 inhibitors, omarigliptin had no effect on body weight in this short-duration study.

Implications: The administration of omarigliptin was generally well-tolerated in obese participants with and without T2DM, and the favorable PK and PD profiles support once-weekly dosing. Omarigliptin may provide an important once-weekly treatment

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INTRODUCTION

Incretin hormones, specifically glucagon-like peptide (GLP)-1 and glucose-dependent insulintropic polypeptide, are released by the intestine into the bloodstream in response to a meal stimulus and increased blood glucose levels.^{1,2} These peptide hormones act to decrease blood glucose concentrations by stimulating insulin secretion from pancreatic β cells in a glucose-dependent manner, as well as by decreasing glucagon concentrations.³⁻⁶ In addition, GLP-1 reduces food intake, induces satiety, and delays gastric emptying and may exert beneficial effects on β -cell function and mass.^{1,2,7,8} These normal biological effects of incretin hormones are generally short-lived (1–2 minutes) due to rapid inactivation by the enzyme dipeptidyl peptidase (DPP)-4 in vivo.⁹⁻¹¹ One therapeutic approach to mitigate this limitation is prolongation of the effects of incretin hormones through pharmacologic inhibition of DPP-4.¹²

DPP-4 inhibitors are oral antihyperglycemic agents used for the treatment of type 2 diabetes mellitus (T2DM) that act by prolonging, and thereby augmenting, the action of incretin hormones.^{9,12,13} This action results in a lowering of blood glucose concentrations in a glucose-dependent manner, resulting in clinically significant reductions in hemoglobin A_{1c}.¹⁴⁻¹⁷ DPP-4 inhibitors have been shown to be well-tolerated in patients with T2DM and to improve glycemic control without weight gain, and they have been associated with a minimal risk for hypoglycemia.¹⁸⁻²⁰ Several orally administered DPP-4 inhibitors have been approved for the treatment of T2DM as either twice-daily or once-daily regimens.^{21,22}

Omarigliptin (MK-3102) is a novel, potent (half maximal inhibitor concentration, 1.6 nmol/L) oral DPP-4 inhibitor in development as a once-weekly treatment with the potential to increase drug adherence by simplifying the dosing regimen.²³ Omarigliptin has been shown to possess pharmacokinetic (PK) and pharmacodynamic (PD) profiles suitable for once-weekly dosing.^{23,24} Previous studies of omarigliptin in

healthy subjects showed that the PK profile is characterized by rapid absorption, with a T_{max} of 1 to 2 hours after single and multiple doses; biphasic elimination with a long $t_{1/2}$ exceeding 100 hours; and minimal accumulation after multiple doses, with steady-state plasma levels attained after only 2 to 3 weeks of dosing. Omarigliptin undergoes minimal metabolism and is eliminated primarily by the kidneys. Based on the urinary recovery of ~58% to 74% of the administered dose (10–100 mg) as intact omarigliptin in healthy subjects after multiple weekly doses, omarigliptin is expected to have a bioavailability of at least 58% to 74%.²⁵ The weekly AUC and C_{max} of omarigliptin displayed dose proportionality across the dose range of 10 to 100 mg at steady state. Omarigliptin-mediated plasma DPP-4 inhibition levels have been shown to be dose dependent, as well.²³ In preclinical experiments conducted in lean mice using a 0.3-mg/kg dose, plasma DPP-4 activity was inhibited by 85% (uncorrected for assay dilution), which exceeds the target inhibition (80%) associated with maximal glucose-lowering efficacy. After the administration of multiple weekly doses of omarigliptin in healthy men, the levels of inhibition of DPP-4 activity (ranging between 78% and 88% over the 10 to 100-mg dose levels) were generally consistent with those observed in preclinical studies.²⁵ In a double-blind, placebo-controlled clinical trial, once-weekly administration of omarigliptin 25 mg reduced trough plasma DPP-4 activity by 80.7% at week 12.²⁴

This article reports the results of a Phase I, randomized, double-blind, placebo-controlled, multiple-dose study designed to evaluate the tolerability and plasma PK and PD profiles (ie, plasma DPP-4 inhibition and active GLP-1 augmentation) of multiple, once-weekly, 50-mg doses of omarigliptin in obese participants with and without T2DM. The 50-mg dose was selected in order to evaluate a 2-fold margin above the anticipated clinical dose of 25 mg being studied in long-term clinical trials.²⁴ Obese subjects were also selected for evaluation in this study as these individuals closely mirror the general target population of patients with T2DM, many of whom are either overweight or obese.

STUDY PARTICIPANTS AND METHODS

Study Design

This was a Phase I, double-blind, randomized, placebo-controlled, multiple-dose study (sponsor

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