

Pharmacokinetics and Pharmacodynamics of Inhaled GLP-1 (MKC253): Proof-of-Concept Studies in Healthy Normal Volunteers and in Patients With Type 2 Diabetes

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MKC253 is glucagon-like peptide 1 (GLP-1, 7–36 amide) adsorbed onto Technosphere microparticles for oral inhalation. The pharmacokinetics of inhaled GLP-1 and the pharmacokinetic–pharmacodynamic (PK–PD) relationship between inhaled GLP-1 and insulin were analyzed in two trials, one in healthy normal volunteers and the other in patients with type 2 diabetes. Inhaled GLP-1 was absorbed quickly, with peak concentrations occurring within 5 min, and levels returned to baseline within 30 min. Inhaled GLP-1 appeared to produce plasma levels of GLP-1 comparable to those of parenteral administration and sufficient to induce insulin secretion resulting in attenuation of postmeal glucose excursions in subjects with type 2 diabetes. An E_{\max} (maximum effect) model described the relationship between GLP-1 concentration and insulin release. The variability in the E_{\max} may be due to differences in baseline glucose levels, differences resulting from genetic polymorphisms in GLP-1 receptors (GLP-1Rs), or the stage of diabetes of the patient.

Glucagon-like peptide 1 (GLP-1) is an incretin hormone secreted by intestinal L cells. GLP-1 circulates as the 7–36 and the 7–36 amide, with the amide providing the majority of the biological activity.^{1,2} GLP-1 stimulates insulin release and decreases gastric motility. GLP-1 receptor (GLP-1R) agonists are used in the treatment of type 2 diabetes.³ GLP-1Rs are also present in the heart and the central nervous system and may exert some of their gastrointestinal (GI) effects through central vagal nerve circuits.^{4,5} The current clinically available formulations are subcutaneous (s.c.) injections. New approaches to the administration of GLP-1R agonists have focused on extending the duration of agonist exposure by developing once-daily to once-weekly formulations, thereby achieving chronic continuous exposure. Chronic exposure to GLP-1 and GLP-1 analogs have been shown to desensitize the GLP-1R. Chronic central nervous system exposure has been shown to reverse the beneficial effects of GLP-1 agonists in animal models.^{6,7} No reported clinical consequences of chronic exposure have been noted to date with a GLP-1 analog administered twice a day for 30 weeks.^{8,9} Chronic administration of an extended-exposure formulation of a GLP-1

agonist has been associated with the development of medullary thyroid tumors in animals.¹⁰

Formulations that deliver GLP-1 in a normal physiologic pattern would rapidly reach peak levels soon after a meal and produce rapid rises in insulin concentrations. Patients with type 2 diabetes often have an impaired first-phase insulin response. Bolus administration of GLP-1 produces an increase in insulin concentrations in response to the intravenous administration of glucose. The insulin response to a bolus of GLP-1 was not as high as for a 3-h infusion of GLP-1 that reached the same peak concentration levels.¹¹ When patients with type 2 diabetes were given 16- or 24-h infusions of GLP-1, the overall insulin levels were lower than those produced by the shorter infusions. This suggests that chronic administration may downregulate GLP-1R response.¹²

Technosphere inhalation particles are microspheres of 2–2.5 microns in median diameter; they are composed of fumaryl diketopiperazine (FDKP) and are capable of carrying small peptides deep into the lungs. The particles dissolve rapidly at physiological pH. This drug delivery platform allows the efficient

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transport of small-molecular-weight peptides to the surface of the respiratory epithelium, where they are absorbed into the circulation. The inhalation is facilitated by a palm-sized device, the proprietary MedTone Inhaler, a breath-powered, unit-dose, dry-powder inhaler that does not require propulsion synchronization by the user. The investigational medicinal product, MKC253 (GLP-1/Technosphere) Inhalation Powder is composed of specific doses of synthetic GLP-1 (7–36 amide), a human incretin hormone, as the active agent and FDKP as a carrier to deliver GLP-1 to the deep lung through inhalation.¹³ FDKP is a pH-sensitive molecule that, under mildly acidic conditions, can self-assemble into small particles. GLP-1 is adsorbed onto these particles. The half-life of FDKP in blood, when administered to humans by inhalation, is ~3 h, and it is excreted unchanged in the urine.

The aim of these studies was to determine the pharmacokinetics of GLP-1 administered via the pulmonary route and to evaluate its effects on levels of insulin, C-peptide, blood glucose, and glucagon in healthy normal subjects and in subjects with type 2 diabetes. The effect on gastric emptying in subjects with type 2 diabetes was also evaluated.

RESULTS

Pharmacokinetics

GLP-1 as delivered by MKC253 was rapidly absorbed and produced peak concentrations in the plasma within 5 min. GLP-1 concentrations returned to baseline values within 30 min both in healthy volunteers and in subjects with type 2 diabetes (Figure 1). In healthy subjects, when GLP-1 was administered

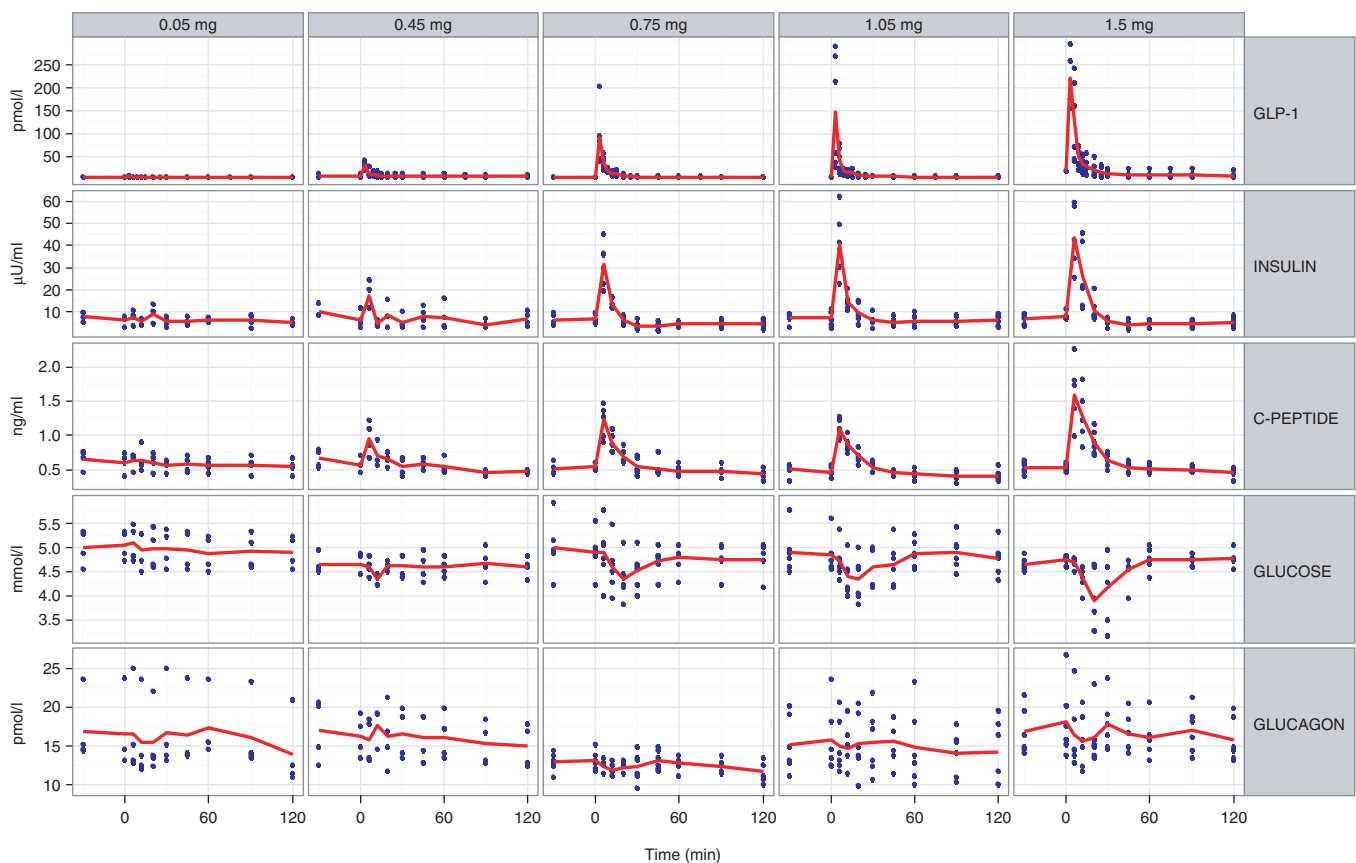


Figure 1 Study 1: GLP-1, insulin, C-peptide, glucose, and glucagon levels by dose group. The doses of 0.05, 0.45, 0.75, 1.05, and 1.5 mg are shown from left to right. All data and mean lines are shown. GLP-1, glucagon-like peptide 1.

Table 1 Summary of pharmacokinetic parameters in healthy volunteers (study 1) and in subjects with type 2 diabetes (study 2)

	Study 1			Study 2		
	Clearance	Volume	K_a	Clearance	Volume	K_a
Mean	305 l/min	1,580 l	2.62/min	188 l/min	1,650 l	1.26/min
SE	46.2 l/min	368 l	1.06/min	25.5 l/min	230 l	0.383/min
CV%	63%	92%	120%	56%	52%	89%
Error model	Log normal CV			Constant CV variance	Additive variance	
CV	24%			50%	7.97	

CV, coefficient of variance.

