



# PULMONARY ADMINISTRATION OF GLP-1 (GLP-1 TECHNOSPHERE® POWDER) I: KINETICS

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## ABSTRACT

**Background and Aims:** GLP-1 enhances insulin release and regulates both glucagon release and gastrointestinal motility. MKC253 is GLP-1 (15% by weight) adsorbed to Technosphere® microparticles for administration using the MedTone® Inhaler. Technosphere® microparticles dissolve rapidly in the lung, providing a drug delivery platform for pulmonary administration of protein and peptide drugs. **Material and Methods:** The safety, tolerability, pharmacokinetics, and pharmacodynamics of MKC253 were evaluated in a first-in-human single-dose, open-label, dose-escalation trial in 26 healthy adult males. Five doses of MKC253 were tested in fasted subjects: 4 subjects received 0.05 and 0.45 mg GLP-1 and 6 subjects received 0.75, 1.05, and 1.5 mg of GLP-1. **Results:** All doses of MKC253 were well tolerated. No nausea or vomiting was reported. GLP-1 was rapidly absorbed; peak concentrations were achieved at the first post-dose sampling time (3 minutes). Mean peak concentrations of Active GLP-1 were > 300 pmol/L at the 1.5 mg dose, and 2 subjects achieved concentrations above the quantitation limit of the assay (500 pmol/L). The half-life of GLP-1 was about 2 minutes. Despite high levels of DPP-IV in the lungs, the levels of GLP-1 following MKC253 inhalation were equivalent to those achieved with intravenous bolus administration of 50 µg and are more than 10X those reached following physiological postprandial release. GLP-1 plasma concentrations increased dramatically at doses above 0.75 mg, suggesting that DPP-IV degradation has been limited. **Conclusions:** Pulmonary administration of MKC253 produces high circulating GLP-1 concentrations without nausea and vomiting.

## INTRODUCTION

In 1987, Kreyman et al demonstrated that, in humans, the release of 2 gastrointestinal polypeptides, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), was responsible for greater endogenous insulin release following oral glucose ingestion as compared to intravenous infusion (the "incretin effect").<sup>1</sup> Nauck et al showed that the incretin effect was decreased in patients with type 2 diabetes.<sup>2</sup> Since that time, the incretin defect in type 2 diabetes has been shown to be primarily due to reduced GLP-1 secretion. Two therapeutic modalities involving GLP-1, exenatide and DPP-IV inhibition, have been approved for treatment of type 2 diabetes. Both of these modalities have durations of action which extend far beyond the natural incretin effect seen physiologically. Additionally, exenatide must be administered via subcutaneous injection. For these reasons, we proposed to test whether native GLP-1 administered via oral inhalation could achieve physiological concentrations in plasma and whether we could elicit physiological or pharmacological effects by this route.

The objectives of this study were to determine the safety and tolerability of ascending doses of MKC253 (GLP-1/Technosphere® Inhalation Powder) in healthy adult males. Secondary objectives were to evaluate changes in pulmonary function, pharmacokinetic (PK) parameters of GLP-1, and effects on clinical laboratory variables (pharmacodynamics, PD), including plasma glucose, insulin, and glucagon. This poster will address the pharmacokinetic response to MKC253 administration. The PD response is addressed in Poster 868.

Native GLP-1 was formulated with fumaryl diketopiperazine (FDKP) and polysorbate 80 (Technosphere® Inhalation Powder) to produce an inhalable dry powder for pulmonary administration via a MedTone® C inhaler. Five dosage strengths of GLP-1 (7-36) amide (0.05 mg, 0.45 mg, 0.75 mg, 1.05 mg, and 1.5 mg) 15% w:w GLP-1:FDKP powder were prepared and were blended with blank Technosphere® Inhalation Powder qs to 10 mg (final total cartridge load). This single-dose trial used an open-label, ascending dose design. Each of 5 cohorts of subjects underwent 3 visits:

- Visit 1 – Screening
- Visit 2 – Treatment
- Visit 3 – Follow-up: 8-14 days after Visit 2

Each cohort received a single dose of MKC253 at the treatment visit. Cohort 1 (4 subjects) received 0.05 mg GLP-1, Cohort 2 (4 subjects) received 0.45 mg GLP-1, Cohort 3 (6 subjects) received 0.75 mg GLP-1, Cohort 4 (6 subjects) received 1.05 mg GLP-1, and Cohort 5 (6 subjects) received 1.5 mg GLP-1.

The 0.05 mg dose of GLP-1 was expected to produce no physiological or pharmacological effects and was planned as a no-effect dose cohort. Cohorts 2 through 5 were dosed only after the safety and tolerability data for the prior dose had been reviewed by the Principal Investigator (PI) and the Sponsor. A half-hour dosing lag time was implemented between subjects in each cohort to ensure subject safety. The dosing was planned to be halted if 3 or more subjects within a cohort experienced severe nausea and/or vomiting, when the maximum dose was reached, or at the discretion of the PI.

Blood samples were drawn at protocol-specified time points for determination of Active GLP-1 (7-36 amide), Total GLP-1 (7-36 amide + 9-36 amide), FDKP, glucagon, glucose, insulin, and C-peptide determination. Pharmacodynamic data are presented in Poster 868. The Active GLP-1 assay was validated to be GLP compliant and had a validated range of quantification of 3 to 500 pmol/L. Although specified in the protocol, measurement of Total GLP-1 could not be carried out as planned. A C-terminal directed RIA assay was used for this measurement, and the method could not be validated for adequate dilutions of the samples. The upper limit of quantification (ULOQ) for this assay was 130 pmol/L.

## RESULTS

Administration of all GLP-1 doses tested resulted in increased plasma levels of GLP-1, except for the 0.05 mg dose (Figure 1).

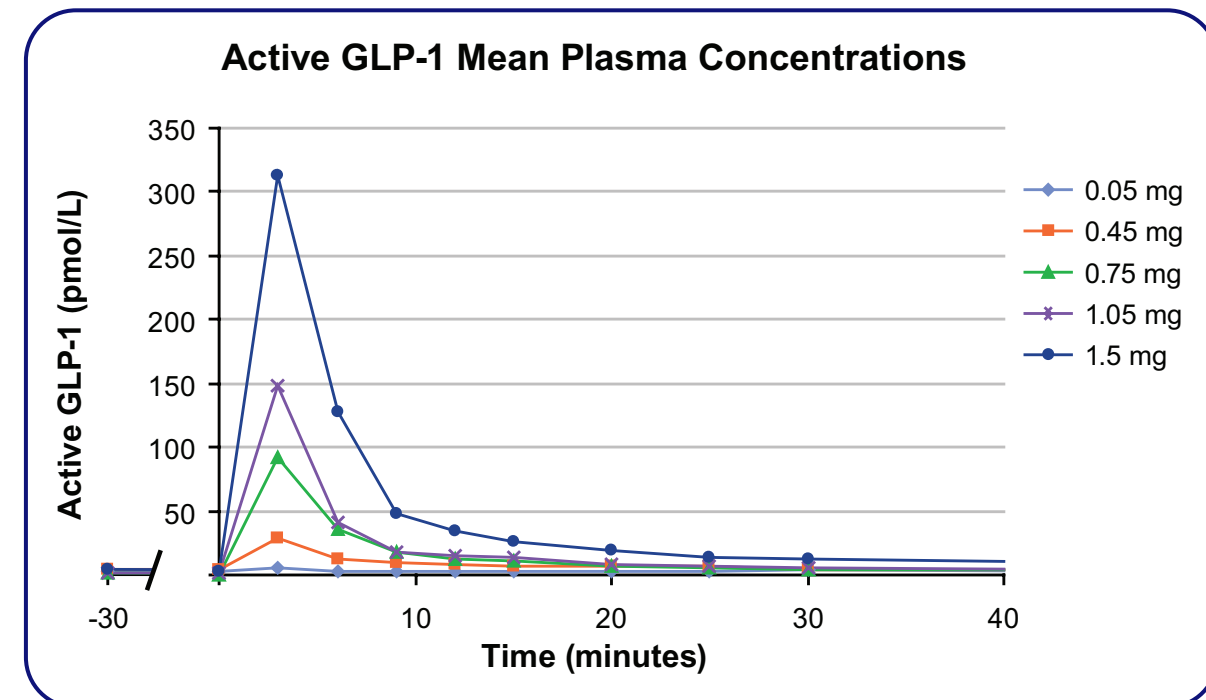


Figure 1. Mean Active GLP-1 Plasma Concentration Following Inhalation of MKC253 at Different Doses of GLP-1

The individual blood concentration curves for the 1.5 mg dose of GLP-1 are presented in Figure 2. For 2 subjects in this dose group, the peak values of GLP-1 exceeded the limit of quantitation of the assay (500 pmol/L). A value of 500 pmol/L was used to compute the mean peak concentration shown in Figures 1 and 2 and used in the PK computations in Table 1 (far right).

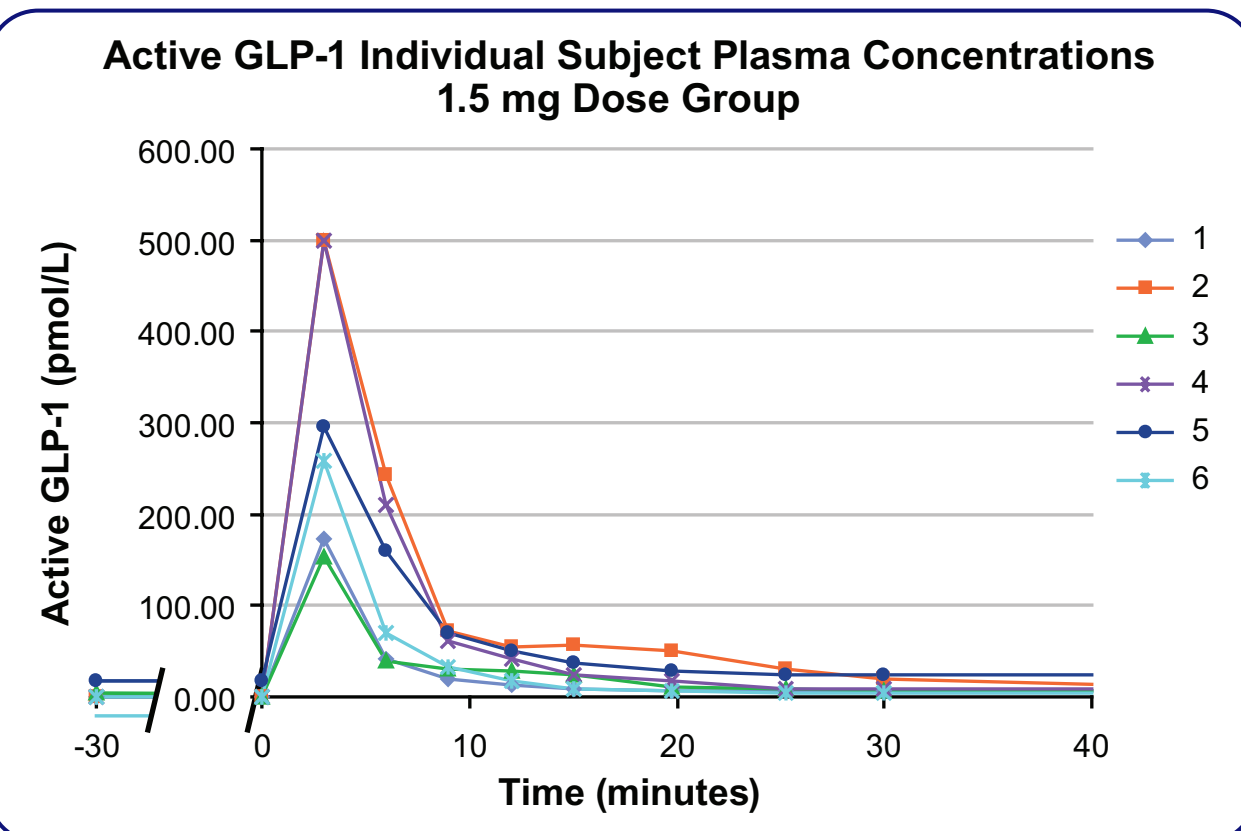


Figure 2. Individual Subject Plasma Concentration Profile of Active GLP-1 Following Inhalation of MKC253 with 1.5 mg GLP-1

For all subjects, the peak circulating concentrations were seen at the first time point tested (3 minutes). The half-life of GLP-1 when given by pulmonary administration was consistent with that seen when given via intravenous bolus, 1-2 minutes. Because of the very rapid kinetics of GLP-1, the peak concentration was almost certainly missed.

Despite this underestimation of the C<sub>max</sub> values in the 1.5 mg dose group, the increase in C<sub>max</sub> with increasing dose of GLP-1 (Figure 3) appears to be more than dose proportional.

Figure 4 shows the mean GLP-1 totals, using the 130 pmol/L for all values which exceeded the ULOQ. While the 2 highest dose groups cannot be distinguished on a C<sub>max</sub> basis, the number of values above the ULOQ is greater for the 1.5 mg GLP 1 dose group than for the 1.05 mg dose group (Figure 4).

The PK parameters for Active GLP-1 and for FDKP, the raw material that comprises Technosphere® particles, are presented in Table 1. The measures of exposure (C<sub>max</sub> and AUC) for Active GLP-1 increased with increasing dose of MKC253. FDKP was only analyzed in the 1.05 and 1.5 mg GLP-1 dose groups. The total amount of Technosphere® Inhalation Powder (FDKP) administered was similar in both groups, and the FDKP exposure was also similar.

## RESULTS (CONT'D)

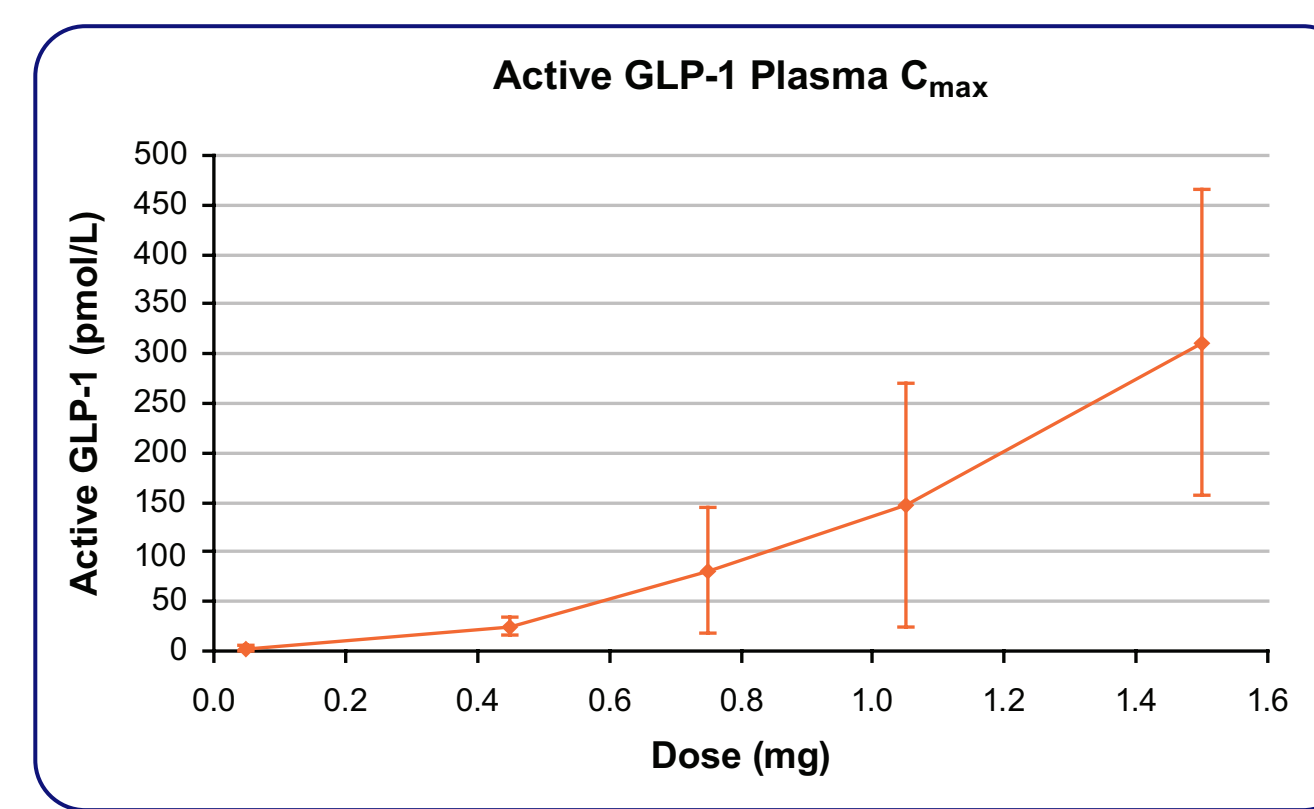


Figure 3. Mean (± SD) Active GLP-1 C<sub>max</sub> Following Inhalation of MKC253 at Different Doses of GLP-1

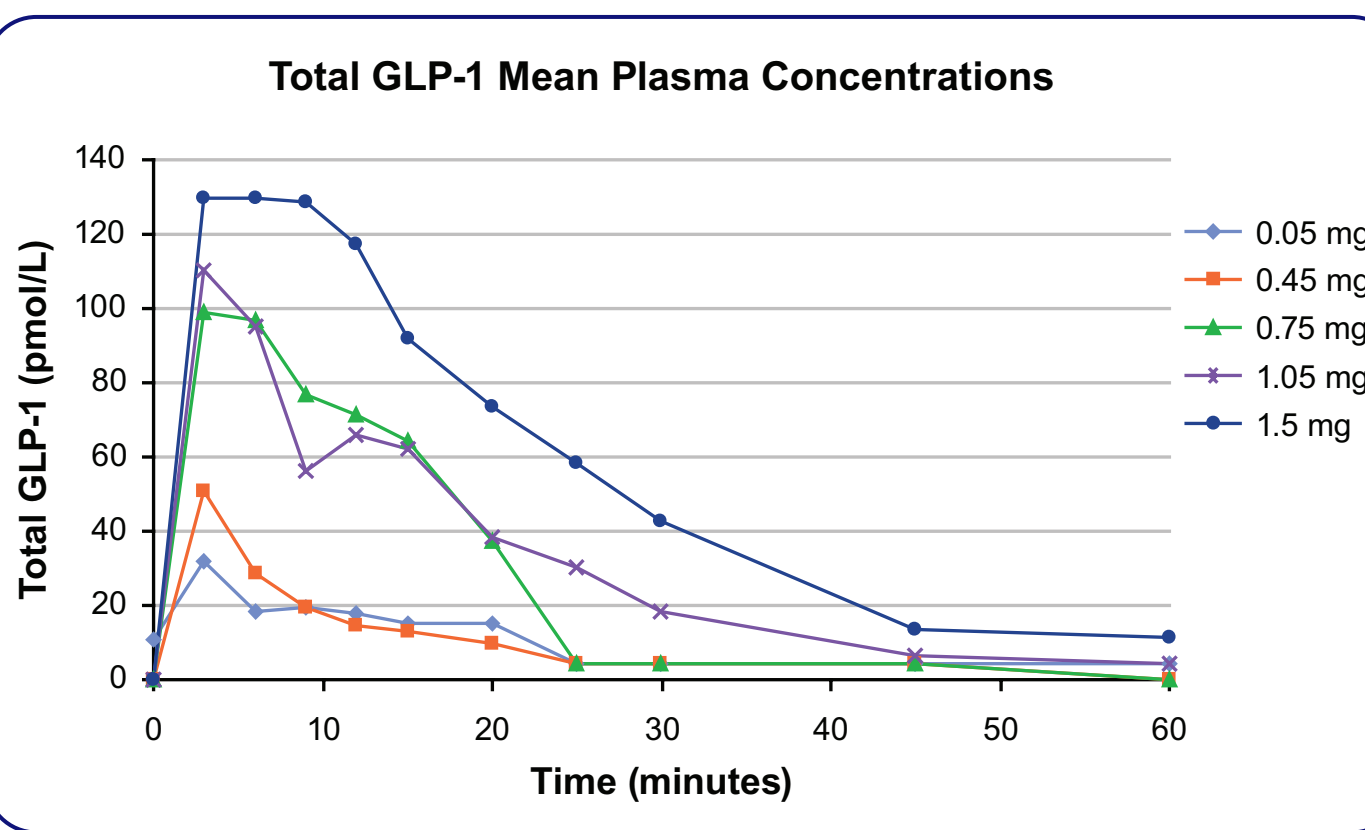


Figure 4. Mean Total GLP-1 Plasma Concentration Following Inhalation of MKC253 at Different Doses of GLP-1

In healthy individuals, physiological postprandial venous plasma concentrations of Active GLP-1 are reported to be in the 10-20 pmol/L range.<sup>4</sup> These concentrations were achieved with the 0.45 mg GLP-1 dose. Succeeding doses of GLP-1 achieved peak plasma concentrations which were substantially higher than physiological peak venous concentrations. However, because the half-life of GLP-1 is so short, plasma concentrations of Active GLP-1 fell to the physiological range by the 9-minute time point. Although the peak concentrations are much higher than those seen physiologically in the venous circulation, there is evidence that local concentrations of GLP-1 may be much higher than those seen systemically.

In normal subjects, fasting concentrations of Total GLP-1 are in the 10-25 pmol/L range and rise to 25-45 pmol/L following a meal. Although the Total GLP-1 C<sub>max</sub> and AUC could not be calculated due to limitations of the assay, plasma concentrations of Total GLP-1 clearly remained above 40 pmol/L for 20 minutes in the 0.75 mg and 1.05 mg dose groups and for more than 30 minutes in the 1.5 mg dose group. This may be important because a recent study has shown that high levels of GLP-1 (9-36) amide may suppress hepatic glucose production in obese individuals.<sup>5</sup>

## RESULTS (CONT'D)

Table 1. Mean (SD) Pharmacokinetic Parameters for Active GLP-1 and FDKP Following the Inhalation of MKC253 in Fasted Healthy Subjects

PK Parameters	GLP-1 Dose				
	0.05 mg	0.45 mg	0.75 mg	1.05 mg	1.50 mg
<b>Active GLP-1</b>					
AUC <sub>0-120</sub> (min*pmol/L)	ND	n = 1 355	n = 6 880 (196)	n = 4 1378 (634)	n = 6 2685 (1284)
C <sub>max</sub> (pmol/L)	n = 4 2.828 (2.4507)	n = 4 24.6 (8.73)	n = 6 81.2 (63.4)	n = 6 148 (123)	n = 6 311 (154)
t <sub>max</sub> (min)	n = 4 3.00 (3.00, 3.00)	n = 4 3.00 (3.00, 4.02)	n = 6 3.00 (3.00, 6.00)	n = 6 3.00 (3.00, 4.98)	n = 6 3.00 (3.00, 3.00)
t <sub>1/2</sub> (min)	n = 1 6.15	n = 3 3.00 (0.835)	n = 6 5.5000 (2.97)	n = 6 3.65 (1.88)	n = 6 3.94 (1.79)
<b>FDKP</b>					
AUC <sub>0-480</sub> (min*pmol/L)	NA	NA	NA	n = 6 22169 (4767)	n = 6 25595 (5924)
C <sub>max</sub> (pmol/L)	NA	NA	NA	n = 6 184 (56.9)	n = 6 210 (53.8)
t <sub>max</sub> (min)	NA	NA	NA	n = 6 4.50 (3.00, 25.0)	n = 6 6.00 (3.00, 20.0)
t <sub>1/2</sub> (min)	NA	NA	NA	n = 6 127 (11.6)	n = 6 124 (15.6)

Within the limits of the assay, the Active GLP-1 exposure (C<sub>max</sub> and AUC) increased with dose of GLP-1 administered as MKC253 by the inhalation route. There are indications of this being greater than dose proportional, but the sample size is too small to draw conclusions. The peak concentrations obtained at the highest dose (1.5 mg GLP-1) were, in some cases, above the limit of quantification for the assay, 500 pmol/L. Due to the short half-life, the levels of Active GLP-1 were not sustained. However, meaningful changes were produced in physiological metabolic variables, including plasma insulin, glucagon, and glucose (see Poster 868). Most surprising was the lack of nausea, vomiting, or feelings of unease which have been consistently reported in prior trials in large percentages of subjects receiving GLP-1 at doses which produced similar plasma levels as those reported here.<sup>3</sup> Exposure to FDKP was similar in both of the 2 highest dose groups consistent with similar amounts of Technosphere® in the dosing cartridges.

The ability to deliver physiologically active amounts of GLP-1 via pulmonary administration suggests that therapeutically effective doses of GLP-1 may be achieved in coordination with meals (prandial administration). Although the duration of the effect of GLP-1 on glucose was relatively short, the subjects in this trial were fasted normal volunteers with intact homeostatic regulatory mechanisms. The response in patients with type 2 diabetes who have elevated fasting glucose may be more prolonged, since counterregulatory mechanisms may be altered in these patients.

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