

Inhaled GLP-1 and Exenatide: Different Effects on Pancreatic and Gastric Activity Following a Single Dose in Type 2 Diabetes Mellitus

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ABSTRACT

Background and aims: MKC253 is GLP-1 adsorbed onto Technosphere[®] microparticles for oral inhalation. A single MKC253 dose in healthy, normal volunteers produced high circulating concentrations of GLP-1 (10 min) with a dose-dependent insulin release, a reduction in fasting plasma glucose, and no nausea or vomiting. This double-blind, double-dummy, placebo-, and active-control crossover trial compared the effects of MKC253 (1.5 mg) and sc injection of exenatide (EXE; 10 µg) on postprandial glucose (PPG) excursions, postprandial insulin, gastric emptying, and GLP-1 pharmacokinetics. **Materials and methods:** Included were 20 nonsmoking subjects with type 2 diabetes mellitus (HbA1c 6.2%-8.5%) on a stable oral antidiabetic regimen. Subjects received five treatments 2 days apart. All received MKC253 or inhaled placebo (InhP) while fasting. EXE or sc placebo (SCP) was given 15 min premeal, and MKC253 or InhP was given premeal (Pre) or 30 min postmeal (Post). Subjects received in randomized order: SCP + MKC253 Pre + InhP Post; SCP + MKC253 Pre + MKC253 Post; EXE + InhP Pre + InhP Post; or SCP + InhP Pre + InhP Post. Gastric emptying was measured by absorption of ¹³C-octanoate from a 575 kcal standardized meal. **Results:** MKC253 produced a rapid spike in insulin. Mean maximum insulin concentration occurred < 10 min after dosing and fell sharply thereafter. Mean peak insulin was 60 µU/mL. Mean pharmacokinetics of insulin release closely tracked mean GLP-1 kinetics. The insulin response following EXE was slower and less pronounced. In fasting subjects with baseline glucose < 9 mmol/L, MKC253 produced a mean maximal decrease in glucose of 0.75 mmol/L about 30 min after inhalation. Subjects with baseline glucose > 9 mmol/L had a 1.2 mmol/L decrease in glucose ~45 min after inhalation. MKC253 reduced PPG excursions. Compared with InhP, MKC253 Pre decreased PPG by ≥ 1 mmol/L for > 1 h and MKC253 Pre + Post decreased PPG for > 3 h. Reductions were longer than that predicted by a GLP-1 half-life of < 2 min. MKC253 had little or no effect on gastric emptying. In contrast, EXE also reduced PPG but acted by delaying gastric emptying. More than 90% of ¹³C-octanoate ingested was unabsorbed 4 h after the meal compared with < 60% with MKC253. After EXE injection, the insulin response to meal challenge was much smaller than with MKC253. Only 1 of 20 subjects reported nausea with MKC253 vs rates > 66% from literature with injected GLP-1. **Conclusion:** Both MKC253 and EXE reduce PPG excursions, but appear to do so by different mechanisms.

INTRODUCTION

GLP-1 Technosphere[®] Inhalation Powder (MKC253) consists of microparticles (2.5 µ median diameter) composed of specified amounts of glucagon-like peptide-1 (7-36) amide (GLP-1) and fumaryl diketopiperazine (FDKP), an inert novel excipient. The pulmonary delivery of the resulting dry powder is facilitated by the MedTone[®] Inhaler. This system enables the delivery of MKC253 powder to the deep lungs and then release of the GLP-1 by dissolution with passive diffusion into the systemic circulation.

In response to oral ingestion of food, GLP-1 inhibits gastric emptying, enhances glucose-stimulated insulin secretion, and lowers blood glucose by mechanisms that include suppression of glucagon secretion. While the secretion of GLP-1 is decreased in type 2 diabetes, clinical trials have shown that GLP-1 can enhance glucose stimulated insulin secretion and lower postprandial blood glucose levels in those patients.

Several of the actions of GLP-1, including reduction in gastric emptying, increased satiety, and suppression of inappropriate glucagon secretion seem to be linked to the burst of GLP-1 released as meals begin. Supplementing this early surge in GLP-1 with MKC253 might produce dynamic effects which would outlast the increase in the circulating levels of the hormone.

The current study was performed to test the safety and pharmacological response of repeated, single dose administrations of MKC253, placebo or active comparator (exenatide) in subjects with type 2 diabetes.

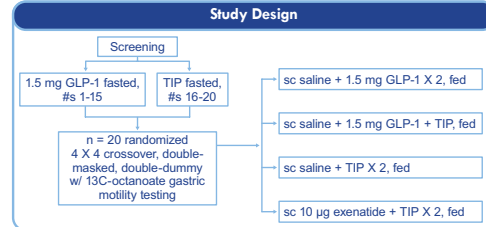
MATERIALS AND METHODS

Study Population

This was a partially double-blind, randomized trial in 20 non-smoking female or male T2DM subjects with normal pulmonary function; 18-70 yrs; BMI ≤ 32 kg/m²; stable antidiabetic regimen X 8 wks; HbA1c 6.2 – 8.5%; fasting C-peptide ≥ 0.5 ng/mL. The study was approved by the local ethics committee, and all subjects gave their written informed consent prior to study start.

On Day 1, subjects received Treatment 1 of 1.5 mg dose MKC253 (15 subjects) or TIP (Technosphere[®] Inhalation Powder) (5 subjects) in an open-label fashion, and remained fasted until 4 hours post-dose. Treatments 2-5 included a meal containing a single dose of ¹³C-octanoate. Subjects were randomized for Treatments 2-5, which they received on days 3, 5, 7, and 9 in the sequence as assigned in the randomization schedule in a double-blind, double-dummy fashion.

| Treatment | Timing Relative to Meal | | |
|-----------|-------------------------|-------------------|--------|
| | -15 | Immediately prior | 30 |
| 2 | sc saline | MKC253 | MKC253 |
| 3 | sc saline | MKC253 | TIP |
| 4 | sc saline | TIP | TIP |
| 5 | exenatide | TIP | TIP |



Blood samples were collected serially to measure plasma GLP-1, exenatide, C-peptide and glucose. The following PK parameters were derived using noncompartmental analysis using WinNonlin v 5.2 (Pharsight Corporation, Mountain View, CA): observed peak analyte concentration (C_{max}), time to peak analyte (t_{max}), and analyte exposure as measured by the area under the analyte concentration-time curve from time 0 until t minutes post-dose (AUC_{0-t}), calculated by the linear-trapezoidal method.

Breath test samples were obtained for ¹³C assessment in expired air to measure gastric emptying. Breath samples were collected every 15 minutes for 4 hours after the meal was eaten in 10 minutes or less. Time of gastric emptying (t_{1/2} and t_{lag}) was determined from the percent dose recovered/hour and cumulative percent dose curves.

RESULTS

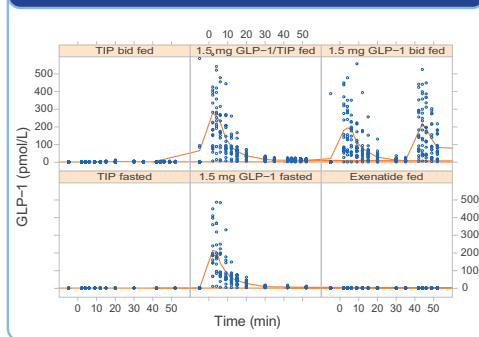
Twenty subjects were enrolled and dosed. One subject discontinued from the study on Treatment Day 5 due to inflammation of the cannula site with an infiltrate and fever that required treatment with antibiotics, but was included in all analyses for treatments completed prior to discontinuation. For another subject, no GLP-1 was detectable following the preprandial inhalation for treatment sc saline/MKC253/GLP-1. Therefore, no C_{max} and t_{max} could be calculated for the preprandial inhalation, and for both inhalations combined, the PK parameters were also not calculated.

Pharmacokinetics

The median GLP-1 t_{max} was 4 minutes after each inhalation, indicating rapid absorption following each administration of MKC253. The mean t_{1/2} for GLP-1 ranged from 6.0 to 6.9 minutes. The AUC₀₋₅₂ following pre- and postprandial inhalation was approximately twice as large as following a single inhalation.

| Parameter | Class or Statistic | Safety and Per Protocol Population (N = 20) |
|--------------------------------------|--------------------|---|
| Race (n [%]) | Caucasian | 20 (100%) |
| Gender (n [%]) | Female | 1 (5%) |
| | Male | 19 (95%) |
| Age (y) | Mean (SD) | 60 (9) |
| | Median (min, max) | 63 (40, 69) |
| Weight (kg) | Mean (SD) | 86.4 (11.8) |
| | Median (min, max) | 87.8 (65.0, 119.1) |
| Height (m) | Mean (SD) | 1.78 (0.07) |
| | Median (min, max) | 1.78 (1.66, 1.97) |
| Body mass index (kg/m ²) | Mean (SD) | 27.2 (2.6) |
| | Median | 27.6 (23.2, 31.4) |

Figure 1. Mean and Observed GLP-1 Concentrations by Treatment



| | MKC253 (n = 15) | Both Inhalations Combined (n = 19) ^b | Preprandial Inhalation (n = 19) ^b | Postprandial Inhalation (n = 19) ^b | Saline/ MKC253/ T Inhalation Powder (n = 19) ^b |
|-------------------------------------|-----------------|---|--|---|---|
| AUC ₀₋₅₂ (pM·min) | 2277 (1354) | 5045 (3265) | ND | ND | 3434 (2244) |
| C _{max} (pM) | 234.5 (128.7) | 330.2 (209.3) | 271.4 (219.5) | 235.5 (155.9) | 344.2 (232.7) |
| t _{max} (min) ^a | 4 (2, 6) | 4 (2, 49) | 4 (2, 6) | 44 (42, 49) | 4 (2, 6) |
| t _{1/2} (min) | 6.87 (3.2) | 6.0 (1.19) | ND | ND | 6.1 (1.24) |

Abbreviations: ND = not determined
a. Median (min, max)
b. n = 19 due to dropout

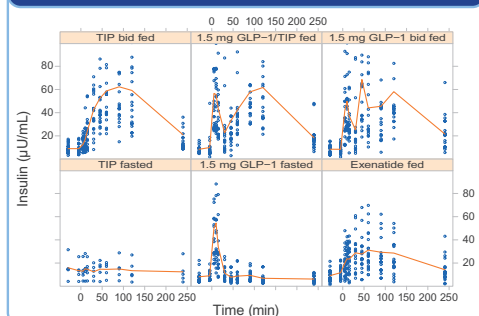
Following exenatide injection, an approximately 1.7 fold increase in mean exenatide concentrations was reported at 120 minutes after dosing, which further increased to approximately 2 times baseline values at 240 minutes after dosing. A median t_{max} of 240 minutes and a mean C_{max} of 0.678 ng/mL were observed for exenatide.

Insulin

Preprandial inhalation of MKC253 resulted in an insulin t_{max} of 9 minutes after dosing when fasted, followed by a rapid decline until 30 minutes post-dose. Thereafter, insulin increased gradually to a maximum mean value similar to the placebo treatment (61.69 µU/mL at 120 minutes after dosing). Addition of postprandial inhalation of MKC253 to the treatment resulted in 2 transient peaks in insulin concentrations, each lasting approximately 30 minutes after inhalation.

Except for the earliest time points, mean insulin concentrations were much lower following exenatide treatment than following placebo treatment or MKC253 treatment. The maximum excursion from baseline was 53% lower than following placebo treatment and 64% lower than following sc saline/GLP-1/GLP-1 treatment.

Figure 2. Mean and Observed Insulin Concentrations by Treatment



| | MKC253 (Day 1) (n = 15) | Saline/ MKC253/ T Inhalation Powder (n = 19) | Saline/ MKC253/ T Inhalation Powder (n = 19) | Saline/ T Inhalation Powder/ T Inhalation Powder (n = 20) | Exenatide/ T Inhalation Powder/ T Inhalation Powder (n = 20) |
|---|-------------------------|--|--|---|--|
| AUC ₀₋₂₄₀ (µU·h/mL) | 29.6 (17.3) | 290.2 (53.9) | 91.7 (53.0) | 98.5 (52.4) | 55.3 (31.0) |
| Maximum excursion from Baseline (µU/mL) | 49.2 (38.5) | 77.0 (53.1) | 76.2 (60.9) | 59.5 (33.8) | 27.8 (21.6) |

RESULTS

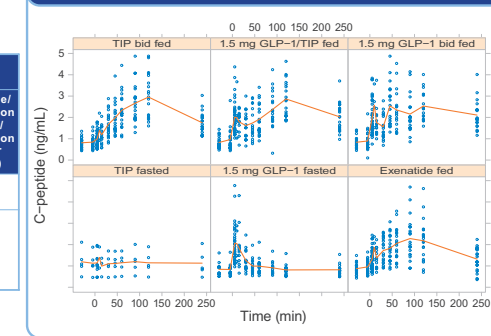
C-peptide

Following MKC253 inhalation with continued fasting (Treatment Day 1), mean C-peptide concentrations peaked at 2.13 nmol/L 9 minutes after dosing. A rapid initial decline in mean concentrations until 46 minutes after dosing was followed by a much slower decline. There was no change in C-peptide concentrations after TIP dosing when fasted.

Following a meal and treatment with sc saline/TIP/TIP, mean plasma C-peptide concentrations increased gradually to a maximum of 2.95 nmol/L 120 minutes after start of the breakfast.

MKC253 inhalation resulted in transient peaks in mean C-peptide concentrations during the first 30 to 60 minutes after each inhalation. Mean maximum values similar to those for placebo treatment were reached. The mean C-peptide AUC₀₋₁₂₀ values were similar to those observed following placebo treatment and approximately 10% higher than following exenatide treatment.

Figure 3. Mean C-peptide Concentrations by Treatment



| | MKC253 (Day 1) (n = 15) | Saline/ MKC253/ T Inhalation Powder (n = 19) | Saline/ MKC253/ T Inhalation Powder (n = 19) | Saline/ T Inhalation Powder/ T Inhalation Powder (n = 20) | Exenatide/ T Inhalation Powder/ T Inhalation Powder (n = 20) |
|--|-------------------------|--|--|---|--|
| AUC ₀₋₁₂₀ (nmol·h/L) | 2.29 (0.86) | 4.16 (1.49) | 4.14 (1.37) | 4.23 (1.45) | 3.80 (1.47) |
| Maximum excursion from Baseline (nmol/L) | 1.35 (0.76) | 2.24 (0.86) | 2.11 (0.83) | 2.14 (0.84) | 1.53 (0.89) |

Glucose

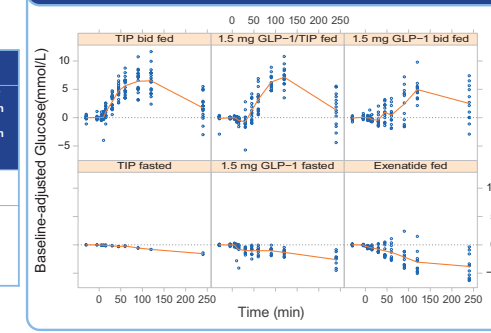
Following MKC253 with continued fasting (Treatment Day 1), by 30 minutes after dosing mean fasting blood glucose were decreased on average 0.95 mmol/L. Thereafter mean glucose concentrations remained relatively suppressed until approximately 90 minutes after dosing.

Following a meal and sc saline/TIP/TIP, mean plasma glucose concentrations increased from 9.90 mmol/L at baseline to a maximum of 16.55 mmol/L 120 minutes after start of the breakfast. Preprandial MKC253 postponed the initial rise of plasma glucose; instead an initial slight decrease in mean plasma glucose concentrations was observed, until 30 minutes after dosing, with a rapid increase in mean plasma glucose levels thereafter, to a similar maximum mean value as for placebo treatment.

Addition of postprandial inhalation of MKC253 to the treatment resulted in a further delay in rise of plasma glucose, and maximum mean glucose concentrations reached at 120 minutes after dosing were somewhat lower than for placebo treatment.

Following exenatide treatment, the postprandial glucose increase was completely abolished, and mean glucose concentrations decreased compared to values obtained before dosing. The mean AUC₀₋₂₄₀ for postprandial glucose was 29.77 mmol·h/L. Compared to placebo treatment, the postprandial glucose exposure was decreased by approximately 48%.

Figure 4. Baseline Adjusted Glucose by Treatment



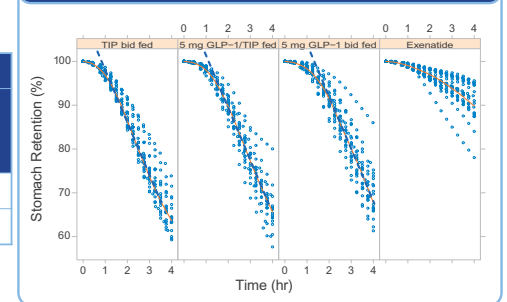
| | Saline/ MKC253/ T Inhalation Powder (n = 19) | Saline/ MKC253/ T Inhalation Powder (n = 19) | Saline/ T Inhalation Powder/ T Inhalation Powder (n = 20) | Exenatide/ T Inhalation Powder/ T Inhalation Powder (n = 20) |
|--|--|--|---|--|
| AUC ₀₋₂₄₀ (mmol·h/L) | 49.6 (10.2) | 53.3 (9.9) | 57.4 (11.7) | 29.8 (6.7) |
| Maximum excursion from Baseline (mmol/L) | 5.6 (2.0) | 7.2 (1.6) | 7.1 (1.9) | 0.2 (0.7) |

RESULTS (CONT'D)

Gastric Emptying

A slightly higher t_{lag} and a similar t_{1/2} were observed following preprandial MKC253 compared to placebo. Gastric emptying was somewhat delayed following pre- and postprandial MKC253 with a slight increase in mean t_{lag} (23% longer) and mean t_{1/2} (15% longer) compared to placebo. Exenatide treatment resulted in a large effect on gastric emptying: mean t_{lag} was 73% longer and mean t_{1/2} was 126% longer compared to placebo.

Figure 5. Gastric Motility Breath Test - Small increase in emptying lag time with MKC253; greater change in rate with exenatide



| | Saline/ MKC253/ T Inhalation Powder (n = 19) | Saline/ MKC253/ T Inhalation Powder (n = 19) | Saline/ T Inhalation Powder/ T Inhalation Powder (n = 20) | Exenatide/ T Inhalation Powder/ T Inhalation Powder (n = 20) |
|------------------------|--|--|---|--|
| t _{lag} (min) | 199.7 (59.0) | 170.2 (35.8) | 161.9 (45.5) | 279.5 (99.4) |
| t _{1/2} (min) | 270.6 (95.0) | 229.9 (59.8) | 234.9 (80.2) | 530.0 (231.9) |

Safety Conclusions

MKC253 Inhalation Powder was well tolerated in a group of 20 subjects with type 2 diabetes. Except for 2 TEAEs of moderate intensity following exenatide/TIP/TIP treatment (cannula site inflammation considered not related, and nausea considered probably related to the study medication), all TEAEs were mild in intensity.

Of the 17 subjects (85.0%) that experienced TEAEs assessed as possibly or probably related, 16 subjects (80.0%) had TEAEs related to the respiratory system, mainly cough (15 subjects, 75.0%).

There were no clinically significant changes in pulmonary function from screening to follow-up. Inhalation of MKC253 or TIP did not produce any clinically significant acute change in FEV₁, FVC, or FEV₁/FVC ratio. There were no clinically significant changes in clinical laboratory, 12-lead ECG, vital signs, or physical examination.

CONCLUSIONS

GLP-1 was rapidly absorbed after inhalation of MKC253, with a median t_{max} of 4 minutes post-dose. Thereafter, GLP-1 plasma concentrations decreased rapidly in a multiexponential manner, with a mean initial phase t_{1/2} of approximately 6 to 7 minutes. The AUC₀₋₅₂ following pre- and postprandial inhalation was approximately twice as high as the AUC₀₋₅₂ following a single inhalation.

Inhalation of 1.5 mg GLP-1 as MKC253 with continued fasting resulted in a decrease in mean fasting blood glucose by 30 minutes after dosing. Mean insulin concentrations peaked 9 minutes after dosing and returned to baseline values by 30 minutes. C-peptide concentrations showed a similar response as insulin, but the effect appeared to be slightly prolonged compared to the insulin response (up to 90 minutes after dosing).

Following preprandial inhalation of GLP-1 as MKC253, the mean postprandial glucose AUC₀₋₂₄₀ was approximately 7% lower than following placebo treatment. Following pre- and postprandial inhalation of MKC253, the decrease was approximately 14% (49.55 mmol·h/L). Following each MKC253 inhalation, a transient peak in insulin and C-peptide concentrations was observed, with a delay in rise of plasma glucose concentrations. However, the resulting effect on glucose AUC₀₋₂₄₀ was limited. Following pre- and postprandial inhalation, a small effect on gastric emptying was observed, with no clear effect following preprandial inhalation only.

Following preprandial treatment with 10 µg exenatide, the mean postprandial glucose AUC₀₋₂₄₀ was approximately 48% lower compared to placebo treatment. The postprandial increase in plasma glucose was completely abolished, and mean glucose concentrations decreased below baseline values. Gastric emptying was delayed: compared to placebo treatment, mean t_{lag} was 73% longer and mean t_{1/2} was 126% longer.

MKC253 has provided us with novel scientific data, inviting additional investigation with this agent.