

Response to Inhaled GLP-1 is Dependent on Baseline Glucose

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ABSTRACT

Background and aims: MKC253 is GLP-1 adsorbed to Technosphere[®] microparticles for oral inhalation. This report presents data from two studies: MKC253-001 evaluated the effect of MKC253 under fasting conditions in healthy subjects, and MKC253-002 evaluated MKC253 in subjects with type 2 diabetes. **Material and methods:** In MKC253-001, six healthy subjects received GLP-1 1.5 mg. In MKC253-002, 15 subjects with type 2 diabetes received GLP-1 1.5 mg, and five subjects with type 2 diabetes received Technosphere[®] placebo. All subjects were nonsmokers with normal lung function. **Results:** In healthy subjects, MKC253 produced a transient decrease in glucose of 0.8 mmol/L. Minimum levels occurred approximately 15 min after inhalation of MKC253. Following the decrease, glucose returned to baseline levels by 1 h. The duration of response was much longer than the half-life of GLP-1 (~2 min). Response to GLP-1 in subjects with type 2 diabetes depended on baseline glucose. Of the 15 subjects in MKC253-002 who received GLP-1, 11 had baseline glucose > 9 mmol/L and four had baseline glucose < 9 mmol/L. Subjects with baseline glucose < 9 mmol/L had a mean maximum decrease of 0.75 mmol/L. The time to reach the minimum was about 0.5 h. Although glucose values recovered, they did not return to baseline levels after 4 h. Subjects with baseline glucose > 9 mmol/L had a 1.2 mmol/L decrease in glucose. The duration of response was longer—the minimum occurred 45 min after inhalation, with no return from the minimum levels. Placebo subjects had no change in glucose over the first 2 h after inhalation. **Conclusion:** It has been shown previously that inhalation of MKC253 produces a sharp spike in plasma insulin. This rapid pulse of insulin can produce a long-lasting decline in plasma glucose in fasting subjects with type 2 diabetes.

INTRODUCTION

This report compares the responses to inhalation of MKC253 in fasting healthy adults with those in fasting subjects with type 2 diabetes mellitus (T2 DM). Data from two separate trials with MKC253, MKC253-001 and MKC253-002, are included.

MKC253 is GLP-1 7-36 amide adsorbed onto Technosphere[®] microparticles (15% w/w) for oral. Technosphere[®] microparticles are suitable for adsorption of many polypeptides allowing administration by oral inhalation.

MATERIALS AND METHODS

The primary objective of the MKC253-001 trial was to determine the safety and tolerability of MKC253 in fasting healthy adult male subjects by monitoring the physiological and pharmacological responses to 5 ascending doses of MKC253: 0.05, 0.45, 0.75, 1.05, and 1.5 mg GLP-1. Each subject received a single dose of MKC253. This report contains data only from the 1.5 mg GLP-1 dose level.

The primary objective of the MKC253-002 trial was to evaluate the effect of MKC253 on postprandial glucose concentrations in subjects with T2 DM following a standardized meal. In this trial, MKC253 was also to be administered to all 20 subjects while they were fasting. The trial design was amended so that the last 5 subjects were given Technosphere[®] Inhalation Powder (Technosphere[®] microparticles with no GLP-1) to serve as a vehicle control.

The complete MKC253-002 trial consisted of 4 phases:

- Screening followed by a 2-week washout of all OADs.
- Treatment 1 on Day 1: open-label administration of MKC253 or Technosphere[®] Inhalation Powder (T Inhalation Powder) to fasting subjects (data reported in this poster).
 - 15 fasted subjects: 1.5 mg dose of GLP-1 as MKC253 Inhalation Powder with continued fasting after dosing until 4 hours postdose.
 - 5 fasted subjects: TIP with continued fasting after dosing until 4 hours postdose.
- Treatments 2-5 on Days 3, 5, 7, and 9 were varying regimens of MKC253 or exenatide prior to a meal challenge (data reported in Poster 778 - Inhaled GLP-1 and exenatide: different effects on pancreatic and gastric activity following a single dose in type 2 diabetes mellitus).
- Follow-up 8-14 days after last treatment.

Subjects

MKC253-001

Key inclusion criteria included:

- Healthy, nonsmoking males 18 to < 45 years of age.
- PE, medical history, clinical chemistry, and urinalysis normal at screen.
- FPG < 110 mg/dL (6.1 mmol/L).
- Body mass index (BMI) < 30 kg/m².
- PFTs: FEV₁/FVC > NHANES III Lower Limit of Normal.
 - FEV₁ > 80% of predicted (NHANES III).
 - FVC > 80% of predicted (NHANES III).
 - DL_{CO} (uncorrected for Hb) > 80% of predicted (Miller).

Key exclusion criteria included:

- History of chronic obstructive pulmonary diseases (COPD).
- Use of any prescription medications within 90 days prior to screening.

MATERIALS AND METHODS (CONT'D)

MKC-253-002

Key inclusion criteria included:

- Nonsmoking male or female subjects 18 to 70 years old with T2 DM.
- Stable regimen of diet and exercise and/or metformin and/or a sulfonylurea or meglitinide or alpha glucosidase inhibitor – no dose adjustments for 8 weeks. One or both oral agents had to be greater than half the maximal allowable dose.
- HbA1c > 6.2 to < 8.5%; fasting C-peptide > 0.5 ng/mL.
- FPG < 13.5 mmol/L on last 3 days of the washout period.
- Body Mass Index (BMI) < 32 kg/m².
- PFTs: FEV₁/FVC > Lower Limit of Normal (predicted NHANES III).
 - FEV₁ > 70% predicted (NHANES III).
 - TLC > 80% Predicted (ITS).
 - DL_{CO} (uncorrected for Hb) > 70% predicted (Miller).

Key exclusion criteria included:

- Treatment with TZDs, DPP-IV inhibitors, pramlintide acetate, and/or exenatide.
- Symptomatic GI disease that could predispose to nausea and/or vomiting.
- Significant improvement in pre- to postbronchodilator spirometry (defined as an increase of 12% AND 200 mL in either FVC or FEV₁).
- History of COPD.

Criteria for Evaluation (both studies):

Plasma GLP-1, Glucose, C-peptide, and insulin

Safety endpoints: Incidence and severity of AEs, changes from screening in vital signs, clinical laboratory tests, PFTs, ECGs, and physical examinations.

Statistical Methods (both studies):

Per Protocol (PP) Population was defined as all subjects who had received a dose of Study medication, had sufficient concentration-time data to calculate the primary PK and PD parameters, and were deemed to be protocol-compliant. All PK and PD analyses were conducted on the PP Population.

RESULTS

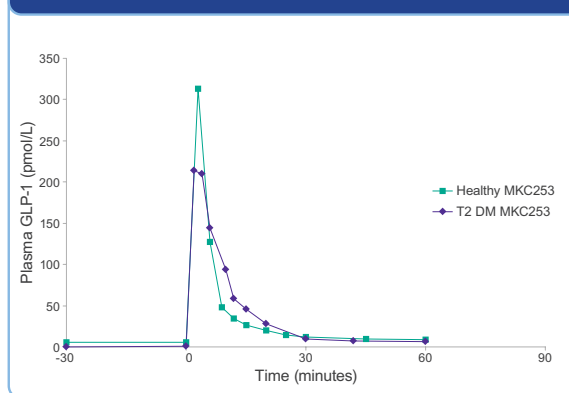
All subjects in both studies were nonsmokers with normal lung function. The severity of diabetes in subjects enrolled in Study MKC-253-002 tended to decrease over the enrollment period because of the difficulty of finding subjects with stable T2 DM who could be safely washed out of their antidiabetic medications.

Plasma GLP-1

In both fasting healthy subjects and in fasting subjects with T2 DM, administration of MKC253 produced an extremely rapid rise in plasma GLP-1.

- In healthy subjects, the peak plasma GLP-1 was 315 pmol/L at 3 minutes.
- In subjects with T2 DM, peak plasma levels of 214 pmol/L and 209 pmol/L were seen at 2 and 4 minutes, respectively.
- In the 5 subjects with T2 DM given T Inhalation Powder, all samples were below the lower limit of quantitation of the assay used, and the data are not shown.
 - In the MKC-253-001 trial all subjects had reached the maximum plasma GLP 1 at the first sampling point (3 minutes). Sampling time was modified in the MKC-253-002 trial, and samples were taken at 2, 4, and 6 minutes.
 - The variability in the absorption and metabolism of GLP-1 is such that any differences between the healthy subjects and the subjects with T2 DM are not felt to be meaningful.

Figure 1. Plasma GLP-1 Following MKC253 Inhalation

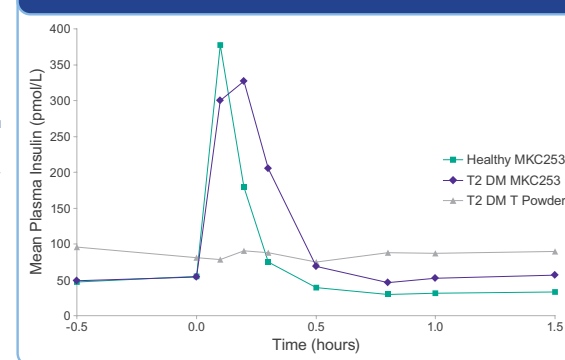


RESULTS (CONT'D)

Plasma Insulin and Glucagon

- The amount of insulin released following inhalation of MKC253 was almost identical in subjects with T2 DM and in healthy volunteers.
- The peak insulin release corresponded with the kinetics of GLP-1 absorption, occurring slightly later and lasting for a slightly longer period in the subjects with T2 DM than in the healthy subjects.
- The mean peak insulin concentration was 377 pmol/L in the healthy subjects and 326 pmol/L in the subjects with T2 DM. In the subjects who received T Inhalation Powder, there was no change in plasma insulin levels throughout the observation period.
- MKC253 administration produced slight short-duration decreases in plasma glucagon in both healthy subjects and in subjects with T2 DM.
- In healthy subjects, plasma glucagon dropped from 18.2 to 16.8 pmol/L, and in subjects with T2 DM, it decreased from 19 to 16.8 pmol/L. In both groups, the plasma glucagon response was transitory.

Figure 2: Insulin Response to MKC253 Inhalation



Glucose Response

- Although the insulin response to MKC253 was similar in healthy subjects and in subjects with T2 DM, the glucose responses differed markedly. This can be better seen as change from baseline in FPG.
 - In healthy subjects, plasma glucose decreased about 0.8 mmol/L from 4.7 mmol/L to 3.9 mmol/L by 20 minutes after administration of MKC253.
 - In subjects with T2 DM, the initial drop in plasma glucose was 1.1 mmol/L, from 10.8 to 9.7 mmol/L.
 - Subjects with T2 DM receiving TIP had no change in glucose over the first 2 hours after inhalation.
 - In both healthy subjects and in subjects with T2 DM, the duration of response was much longer than the t_{1/2} of GLP-1 (< 2 minutes).
- In healthy subjects, glucose returned to baseline levels by 1 hour, but in subjects with T2 DM there was no return towards baseline glucose.
 - In subjects with T2 DM receiving MKC253, plasma glucose remained at 9.8 mmol/L for 2 hours postdosing. Between 2 and 4 hours postdosing, the plasma glucose fell by another 1.5 mmol/L.
 - In subjects with T2 DM receiving T Inhalation Powder, there was no change in plasma glucose over the initial 2 hours postdosing, but from 2-4 hours postdose their glucose fell in parallel with glucose in the subjects receiving MKC253.

Figure 3: Change in Plasma Glucose Following MKC253

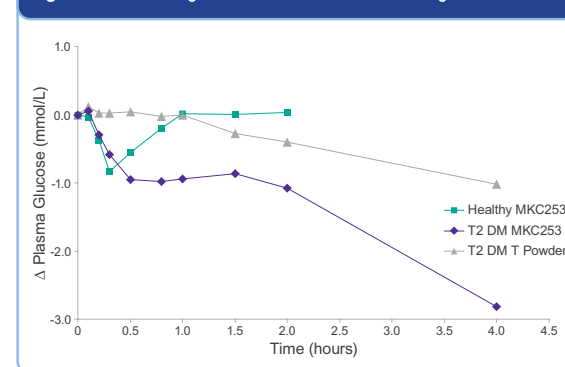
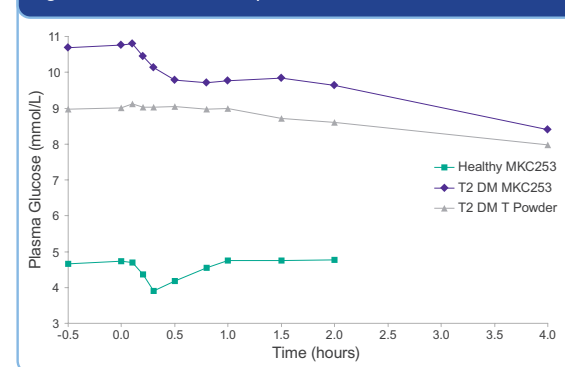
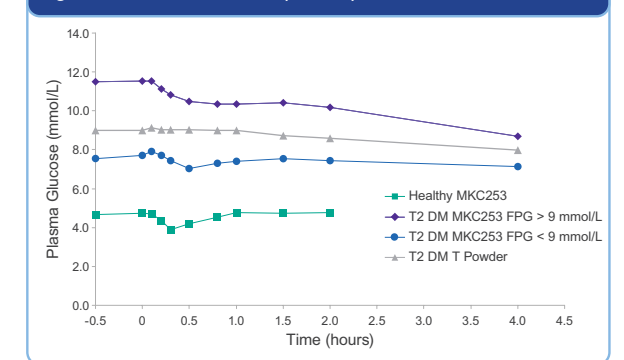


Figure 4: Glucose Response to MKC253 Inhalation



RESULTS (CONT'D)

Figure 5: Glucose Response by Baseline FPG



Subjects with T2 DM were stratified by baseline FPG posthoc to see if there were differences in response based on FPG. Of the 15 subjects who received MKC253, 4 had FPG < 9 mmol/L at baseline and 11 had FPG > 9 mmol/L.

- Decreases in plasma glucose were larger among the subjects with FPG > 9mmol/L.
- There was some return towards baseline glucose levels in the subjects with FPG < 9mmol/L.
- Review of the GLP-1 and insulin data showed that the 4 subjects with FPG < 9 mmol/L had peak GLP-1 levels at least as high as the rest of the population, but that the release of insulin was less than half of that of the overall population.
- In this small sample of 4 subjects, it is unclear whether the difference in response is due to an underlying difference based on FPG (as suggested by the partial return to baseline glucose) or due to differences in the release of insulin in this sample of "poor responders."

CONCLUSIONS

Inhalation of MKC253 produces a sharp spike in plasma insulin and a slight decrease in plasma glucagon. Although the amount of insulin released in subjects with T2 DM was almost identical to that seen in healthy subjects, the glucose responses differed substantially.

Fasting healthy subjects showed a rapid return to baseline glucose levels. This is an expected homeostatic response. In contrast, the subjects with high fasting glucose values had a marked and sustained decrease in plasma glucose. There was no tendency for the plasma glucose values to autoregulate to their pretreatment levels, and there was a total decrease in glucose levels of 2.5 mmol/L over the 4 hours of observation. Subjects with T2 DM and FPG < 9 mmol/L showed an intermediate response after receiving MKC253.

Subjects who did not receive MKC253, but fasted for a similar period of time showed a decrease in plasma glucose of approximately 1 mmol/L over the course of observation.

The difference in the duration of the response cannot be explained by differences in glucagon secretion. In both healthy subjects and subjects with T2 DM, there was a small decrease in glucagon secretion consistent with that known to occur with GLP-1 administration. However, there was no compensatory increase in glucagon secretion following the glucose decrease in either group of subjects. Subjects receiving T Inhalation Powder showed no changes in glucose, insulin, or glucagon. Changes in insulin sensitivity have been noted with injected GLP-1, and these changes could differentially affect subjects with T2 DM. However, these effects are thought to occur only with longer-term administration of GLP-1 (Zander et al. *Lancet*. 2002;359: 824–30).

The etiology for the difference in response is unknown but suggests that, in subjects with T2 DM, GLP-1 may contribute to glucose regulation by mechanisms that involve neither insulin nor glucagon.