Single-Blind, Placebo-Controlled, Dose-Ranging Trial of Oral HDV-Insulin in Patients With Type 2 Diabetes Mellitus

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Abstract

The addition of oral instead of SC insulin to oral type 2 diabetes treatment in patients with suboptimal glycemic control closely mimics normal insulin physiology and represents a significant advance. The dose-response of postprandial glycemia to add-on, pre-meal oral hepatic-directed vesicle-insulin (HDV-I) was evaluated using a 3 test meal/day model. Six adult type 2 diabetes patients, aged 56±7 years, with HbA_{1c} 8.6±2.0%, and BMI of 27.6±3.6 kg/m^2, on oral antidiabetic therapy with suboptimal glycemic control were enrolled and received treatment in a single-blind, placebo-controlled, dose-escalating trial. Each dosing day was preceded by overnight euglycemic low-dose insulin infusion stopped 1 hour prior to dosing. Each patient received their on-going oral antidiabetic therapy plus add-on single doses of oral HDV-I capsules each day 30 min before breakfast (Time 0 min), lunch and dinner as follows: Day 1 – placebo capsules; Day 2 – 0.05 U/kg; Day 3 – 0.1 U/kg; Day 4 – 0.2 U/kg; and Day 5 – 0.4 U/kg. Venous blood sampling was performed according to a prespecified schedule from 30 min before breakfast dosing to 4.5 hours after the dinner dose (-30 to 810 min). Postprandial blood glucose (PPG) AUC and incremental AUC were determined for each dose of oral HDV-I treatment and compared with placebo. Safety was assessed by adverse events and clinical laboratory tests.

Treatment / Dose (n=6)	Blood Glucose AUC for -30 to 810 min (mg.min/dl)		Incremental Glucose AUC for -30 to 810 min (mg.min/dl)	
	Mean ± SD	p-Value vs. placebo	Mean ± SD	p-Value vs. placebo
Placebo	145515 ± 41528	NA	41495 ± 34046	NA
Oral HDV-I 0.05 U/kg	126323 ± 41168	0.0073	24823 ± 33347	0.0002
Oral HDV-I 0.1 U/kg	122855 ± 43912	0.0110	20461 ± 39996	0.0023
Oral HDV-I 0.2 U/kg	124490 ± 41769	0.0067	29430 ± 35498	0.0216
Oral HDV-I 0.4 U/kg	125735 ± 37216	0.0069	31514 ± 25270	0.0352

All 4 oral HDV-I doses statistically significantly lowered mean and incremental PPG AUC compared to placebo with an increase in effect from the 0.05 U/kg to a peak effect at the 0.1 U/kg dose, followed by a lesser but significant effect at the 0.2 and 0.4 U/kg doses. The 0.05 U/kg dose was associated with the least effect in the dose range studied. Only 3 adverse events unrelated to oral HDV-I treatment were observed. In conclusion, add-on oral HDV-I in the dose range 0.05 to 0.4 U/kg significantly lowers PPG excursions compared to placebo with a peak effect at the 0.1 U/kg dose consistent with previous results of oral HDV-I use in type 2 diabetics. Oral HDV-I was safe and well tolerated.

Background

Hepatic-directed vesicles-insulin (HDV-Insilin or HDV-I) in injectable (subcutaneous = SC) and orally administered forms, is an investigational liposomal (<150 nm diameter) insulin drug delivery system (Diasome Pharmaceuticals, Conshohocken, PA) designed to provide insulin in a manner that more closely mimics the normal physiological delivery of insulin in patients with type 1 or type 2 diabetes mellitus. Based on the results of studies conducted in various animal models of diabetes, and in Phase II clinical trials in patients with diabetes which have demonstrated significantly improved glycemic control during an oral glucose tolerance test (OGTT) and diabetic meals, HDV-I is expected to provide enhanced blood glucose control with a lower risk of hypoglycemic episodes at much lower doses compared to conventional insulin therapy. This study was designed to characterize the dose-response of postprandial blood glucose to oral HDV-I and thereby establish a minimum effective dose in patients with type 2 diabetes mellitus.

OBJECTIVES

- To determine the dose response of postprandial plasma glucose to escalating doses (increased daily) of oral HDV-I given as single doses before breakfast, lunch and dinner, in addition to the diabetes mellitus patient's regular oral antidiabetic therapy
- To compare the daily glucodynamic profile of oral HDV-I over the treatment days.
- Secondary objectives were to evaluate the safety, tolerability, and efficacy of the test materials.

Subjects & Methods

This was a single-blind, placebo-controlled, dose-ranging trial of oral HDV-I in patients with type 2 diabetes mellitus. Included were six adult patients with a current diagnosis of type 2 diabetes mellitus, aged 18 – 65 years, currently managed with oral antidiabetic drugs (OAD) for at least 3 months, with BMI of ≤38 kg/m^2, glycosylated hemoglobin levels (HbA_{1c}) of ≥8 to ≤12%, c-peptide levels of >3 ng/ml and a fasting blood glucose (FBG) level of ≤200 mg/dl.

Preparatory Period: Following Screening for the study, each eligible type 2 diabetes patient arrived at the metabolic ward (study center) the evening before the Treatment Period. The subjects were admitted to the metabolic ward and placed on an overnight regular insulin drip so that the morning FBG was approximately 100 mg/dl. The intravenous insulin was withdrawn one hour before beginning the Treatment Period. The subjects were maintained on their usual oral antidiabetic therapy during the test day.

Treatment Period: During the Treatment Period (one day per dosing group), all patients were treated with placebo capsules on Day 1, oral HDV-I on Day 2 (0.05 U/kg), oral HDV-I on Day 3 (0.1U/kg), oral HDV-I on Day 4 (0.2U/kg) and oral HDV-I on Day 5 (0.4 U/kg). Each morning, the subjects were taken off the insulin drip and administered the treatments 1 hour later at each individual's daily dose based on the body weight in kg and then given a 60 g carbohydrate breakfast at 30 to 45 minutes after receiving the oral HDV-I, and the add-on single doses of oral HDV-I were repeated 30 to 45 min before lunch and dinner on each day. Peripheral venous blood was sampled according to a pre-specified schedule from 30 min before breakfast dosing to 4.5 hours after dinner (-30 to 810 min). Glucose levels were measured from each blood sample.

Data Management & Statistical Methods: The primary efficacy parameter was comparison of postprandial glycemic control between the doses of oral HDV-I and placebo. The criteria for determining the maximum effective dose was the dose at which no further meaningful reduction in the postprandial plasma glucose AUC occurred when compared with the prior day's AUC. The criteria for determining the minimum effective dose was the dose at which the majority of patients demonstrated a meaningful reduction in incremental glucose AUC lowering from Day 1. Based on the plasma concentration data for glucose, the following non-compartmental model-independent pharmacokinetic parameter was determined for each treatment, based on scheduled sampling times: $AUC_{0\rightarrow t}$ [mg x h x ml^{-1}] for glucose: area under the plasma concentration-time curve from the time of dosing to the time t of the last quantifiable concentration following dosing calculated using the linear trapezoidal rule. Other secondary efficacy and safety parameters were: Comparison of blood glucose AUCs; Comparisons of incremental glucose AUCs; and tolerability and patient acceptance of oral HDV-I compared with reference materials.

Results

Table 1. Patient Demographics and Baseline Characteristics

Characteristic / Parameter	Male (n = 3)	Female (n = 3)	Total (n = 6)
Age (years) Mean ± SD	56.0 ± 9.5	56.3 ± 6.1	56.2 ± 7.2
Weight (kg) Mean ± SD	78.8 ± 15.1	82.0 ± 11.5	80.4 ± 12.1
Height (cm) Mean ± SD	166.7 ± 4.7	165.7 ± 7.1	166.2 ± 5.4
Body Mass Index (kg/m^2) Mean ± SD	28.2 ± 3.8	26.9 ± 4.1	27.6 ± 3.6
Gender n (%)	3 (50.0%)	3 (50%)	6 (100%)
Ethnic Group Hispanic Caucasian	3 (100%) 0 (0.0%)	2 (66.7%) 1 (33.3%)	5 (83.3%) 1 (16.7%)
HbA_{1c} (%) Mean ± SD	8.4 ± 2.8	8.8 ± 1.5	8.6 ± 2.0
Baseline (Fasting) Blood Glucose (mg/dl) Mean ± SD	118.3 ± 14.7	127.0 ± 21.1	122.7 ± 16.9

Results

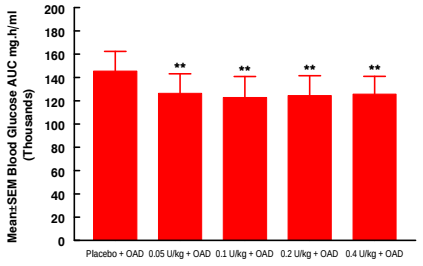

Figure 1. Mean ± SEM Blood Glucose AUC Values By Treatment and Dose. Asterisks indicate significant differences (** = p≤0.01 in each case) of mean blood glucose AUC versus the corresponding value for the Placebo + OAD treatment. AUC = area under the plasma glucose concentration-time curve; OAD = oral antidiabetic drug.

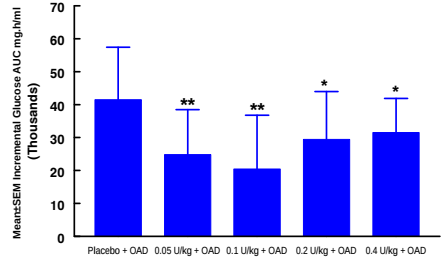

Figure 2. Mean ± SEM Incremental Glucose AUC Values By Treatment and Dose. Asterisks indicate significant differences (** = p≤0.01 and * = p<0.05, in each case) of mean incremental glucose AUC versus the corresponding value for the Placebo + OAD treatment. AUC = area under the plasma glucose concentration-time curve; OAD = oral antidiabetic drug.

Results

Comments Figure 1: All 4 doses of add-on oral HDV-I showed statistically significant reductions in mean blood glucose AUC compared to placebo (ps0.0110 each; Figure 1). The reductions in mean blood glucose AUC increased in magnitude from the 0.05 U/kg dose to a maximum at the 0.1 U/kg dose. Thereafter, there was a lesser magnitude but statistically significant reduction in blood glucose AUC with increase in dose to the 0.2 and 0.4 U/kg doses. Between the doses of Oral HDV-I, pairwise comparisons between the mean blood glucose AUC values obtained revealed no statistically significant differences between any of the 4 doses.

Comments Figure 2: The results obtained for the incremental glucose AUC were similar to those obtained for blood glucose AUC. All 4 doses of Oral HDV-I showed statistically significant reductions in mean incremental glucose AUC compared to placebo (ps0.0352 each; Figure 2). The reductions in mean incremental glucose AUC increased in magnitude from the 0.05 U/kg dose to a maximum at the 0.1 U/kg dose. Thereafter, there was a lesser magnitude but statistically significant reduction in incremental glucose AUC with increase in dose to the 0.2 and 0.4 U/kg doses.

In pairwise comparisons between the different doses of Oral HDV-I, a statistically significant difference was only obtained between the 0.10 and 0.20 U/kg dose comparison (p = 0.0059) for mean incremental glucose AUC values. In addition, the results of the pairwise comparisons between 0.05 versus 0.4 U/kg (p = 0.0772) and 0.10 versus 0.4 U/kg (p = 0.0687) approached but did not achieve statistical significance. There were no significant differences between the mean incremental glucose AUC values in the remaining pairwise comparisons.

Table 2. Adverse Events By Subjects, Study Day of Occurrence and Treatment

Subject Number	Adverse Event (Verbatim Term)	Relationship to Study Drug	Study Day of Start of Adverse Event	Treatment When Adverse Event Started
002	Headache	Unrelated	Day 1	Placebo
	Itching to area under left ear	Unrelated	Day 1	Placebo
	Left forearm IV infiltrate	Unrelated	Day 5	Oral HDV-I 0.4 U/kg
	Right forearm IV infiltrate	Unrelated	Day 5	Oral HDV-I 0.4 U/kg
	Right forearm IV site tenderness	Unrelated	Day 5	Oral HDV-I 0.4 U/kg
011	Headache	Unrelated	Day 1	Placebo
014	Hyperglycemia	Unrelated	Day 1	Placebo

Comments: There were no unexpected adverse events, serious adverse events or deaths during the study.

Conclusions

- Add-on single doses of oral HDV-I 0.05 - 0.4 U/kg to oral antidiabetic therapy statistically significantly lowered postprandial blood glucose AUC and incremental glucose AUC compared to placebo in type 2 diabetes mellitus patients.
- The peak effect of oral HDV-I in lowering postprandial blood glucose occurred at 0.1U/kg with significant but lesser magnitude of effect at 0.2 U/kg followed by 0.4 U/kg.
- The minimum effective dose of oral HDV-I in the dosage range studied was 0.05 U/kg.
- Oral HDV-I in the dosage range 0.05 to 0.4 U/kg was generally safe and well tolerated.

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