Multiple Oral Insulin (ORMD-0801) Doses Elicit a Cumulative Effect on Glucose Control in T2DM Patients

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BACKGROUND

Efforts to overcome the narrow therapeutic index of subcutaneously delivered insulin have propelled the development of orally delivered alternatives. Oramed Ltd. developed an oral insulin formulation (ORMD-0801), which harnesses exipients to both hinder proteolysis in the small intestine and enhance translocation of insulin across the gut epithelium. Once transported across the gut wall, the insulin is ferried to the hepatic portal vein, mimicking the natural route of endogenous pancreatic insulin, and then subjected to first-pass metabolism in the liver before being delivered to peripheral sites of action. The enterico-coated ORM-0801 capsule has been shown to provide effective glucose control in both type 1 and type 2 diabetes patients.

OBJECTIVES

- To compare pre-treatment to end-of treatment 24-hour continuous glucose monitoring (CGM) glucose levels for multiple doses of ORMD-0801 versus placebo
- To evaluate safety parameters associated with multiple doses of ORMD-0801

DESIGN

In this Phase IIa, randomized, double-blind, double-dummy, placebo-controlled, 3-way crossover study, 31 adult patients with T2DM were randomly assigned to specific sequences of three 10-day treatment periods (Figure 1). One period involved 8 days of placebo treatment, while the others involved a 3-day placebo run-in, followed by 5 days of treatment with 460 IU ORM-0801 either once (qd), twice (bid) or three (tid) times daily. Treatment sessions were performed at 21-street intervals. During the treatment periods, patients were confined to the unit for 8 nights. Blood glucose was continuously monitored with a CGM. Insulin and C-peptide levels were determined from blood samples collected pre-treatment (Day 0) and at the end of treatment (Day 9).

Main inclusion criteria: Male or female; T2DM patients; ages 20-75, inclusive; HbA1c 27% and <10.5%, currently on a stable (≥28 weeks) metformin only, metformin + sulfonylurea, metformin + T2D, metformin + SGLT-2 inhibitor or metformin + DPP-4 inhibitor regimen.

RESULTS

Of the 31 patients randomized to a specific treatment sequence, 30 completed the full course of treatment. Patients were of a mean age of 57.5±7.8, and most were male (61.3%) and Caucasian (60.6%). Mean placebo-adjusted change from baseline in 24-hour glucose (mean of all run-in days vs. all treatment days) ranged from -7.6 mg/dL for qd to -9.8 mg/dL tid, corresponding to a percent change from baseline ranging from -5.1 (bid) to -5.5% (qd) (Table T1). This effect was more dramatic among subjects with high glucose (>190 mg/dL) n=17 at baseline (-12.4 mg/dL, qd), -4.9 mg/dL (bid) and -18.4 (tid) as compared to those with low baseline glucose levels (10.6 mg/dL (qd), 1.1 mg/dL (bid) and 10.4 mg/dL (tid) (Tables T2-3). Of note, Day 8 readings among patients on the bid regimen, showed an unexpected deviation from day 4-7 readings, which impacted the calculated mean treatment effect. Pre-versus posttreatment and placebo versus active treatment C-peptide and insulin ratios were similar across all regimens. ORM-0801 was well tolerated and did not elicit any serious treatment effects. The vast majority of hyperglycemic events were recorded during placebo treatment (n=27), and a larger percentage of placebo-treated patients experienced at least one hyperglycemia event (Table T4). The incidence of was similar across treatment groups (55%/group); all hypoglycemia events were mild (55-70 mg/dL).

CONCLUSIONS

Multiple-dose ORM-0801 regimens safely provide for improved glucose control, which is expected to be enhanced with more extended treatment. Its impact may be of particular benefit to patients uncontrolled by current drug regimens.

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