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012. Lowered glucose levels and exogenous insulin requirements in T2DM and T1DM patients treated with oral insulin (ORMD-0801): Phase 2, randomized, placebo-controlled evaluations

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Purpose

Consensus regarding the convenience of oral insulin, alongside the proposed therapeutic advantages of this administration route over systemic exposure, have fueled numerous attempts at design of such a formulation. Portally infused insulin brings to more rapid and pronounced suppression of hepatic glucose production and to reduced circulating peripheral insulin levels as compared to systemically administered insulin. Oral insulin deposited directly into the portal vein is expected to have similar salient effects. Oramed Ltd. has developed an oral insulin formulation (ORMD-0801), which harnesses excipients to both hinder proteolysis in the small intestine and enhance translocation of insulin across the gut epithelial lining. 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 rst-pass metabolism in the liver, before being delivered to peripheral sites of action. The PK/PD prole of ORMD-0801 is well suited for the control of fasting blood glucose due to the delayed onset of action. Therefore, Oramed is pursuing the bed-time oral administration of ORMD-0801 for the treatment of elevated fasting blood glucose in adult patients with T2DM. In parallel, the drug has been shown to minimize glucose instability when provided as an adjunct to subcutaneous insulin regimens in T1DM patients. These two prospective, randomized, placebo-controlled Phase II studies aimed to evaluate the impact of ORMD-0801 on blood glucose homeostasis in T2DM patients and to evaluate its impact on bolus insulin requirements in T1DM patients.

Methods

In a Phase 2a study, the effect of preprandial ORMD-0801 on exogenous insulin requirements was assessed in T1DM patients monitored with a continuous glucose monitor (CGM) over a 7-day double-blind treatment period. A single ORMD-0801 capsule (8 mg insulin) was administered three times daily, 45 min before meals to 15 patients, while 10 received placebo. Insulin requirements were documented and glucose levels were recorded with a blinded continuous glucose monitor. Similarly, in a Phase IIb randomized (1:1:1), double-blind, placebo-controlled, multicenter (n=33) study, 192 adult patients with T2DM, participated in a 14-day placebo run-in period, followed by a 28-day treatment period with 16 mg ORMD-0801, 24 mg ORMD-0801 or placebo, self-administered at bedtime. Glucose levels were monitored, via a blinded CGM, during the last 7 days of the run-in and treatment periods.

Results

On all treatment days, ORMD-0801-treated T1DM patients showed consistently lower fasting plasma glucose (FPG) levels as compared to baseline, peaking at -60.263.3 mg/dL on day 7, versus a mere -10.255.7 mg/dL change measured for the placebo cohort at the same time point. Reduced FPG levels directly correlated with reduced rapid-acting insulin

requirements, reaching a mean difference of -5.9 mIU/mL insulin intake between active versus placebo-treated patients on day 7. On day 7 of treatment, an equal number of hypoglycemic events (<60 mg/dL)) requiring clinical intervention was reported for each cohort. In T2DM patients, the active treatment proved safe, well-tolerated and nonimmunogenic, with no serious adverse drug-related events reported. No significant difference in incidence and types of adverse events, including hyper/hypoglycemia, was noted between cohorts. CGM data indicated a significantly smaller change from baseline in nighttime glucose levels in the pooled ORMD-0801 (1.7 mg/dL) as compared to the placebo (13.7 mg/dL, p=0.027) cohort. Mean 24-hour glucose readings remained stable among ORMD-0801-treated patients (mean difference: -0.32 mg/dL), whereas patients receiving placebo demonstrated a mean 13.26 mg/dL change from baseline in these readings (p<0.001). . Similarly, mean change from baseline in fasting (5AM7AM) and daytime (6AM-10PM) CGM glucose were significantly smaller among ORMD-0801-treated patients as compared to those treated with placebo (-0.4 mg/dL vs. 16.0 mg/d [p<0.001] and 0.9 mg/dL vs. 11.9 mg/dL [p<0.001] respectively). In parallel, the mean change from baseline in HbA1c levels in the combined ORMD-0801 cohorts (-0.01%) was significantly smaller as compared to the placebo cohort (0.2%; p=0.01), and was projected to show a 0.5% drop from baseline following 12 weeks of treatment.

Conclusions

Preprandial ORMD-0801 reduced the exogenous short-acting insulin demands required to maintain euglycemia in T1DM patients. In parallel, the active treatment led to a greater drop in FPG concentrations, when compared to placebo treatment, seemingly due to improved hepatic insulinization and subsequently normalized gluconeogenesis/glycogenolysis ratios. Similarly, ORMD-0801 treatment elicited a sustained and highly significant reduction in mean nighttime, fasting, daytime and 24-hour glucose concentrations. In both patient populations, the treatment proved safe for use and well tolerated at the tested regimen.