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 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 first-pass metabolism in the liver, before being delivered to peripheral sites of action. The enteric-coated ORMD-0801 capsule has been shown to provide effective glucose control in both type 1 and type 2 diabetes patients.

OBJECTIVES

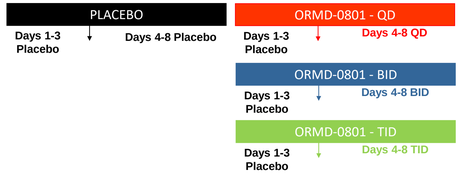
- To compare pre-treatment to end of treatment 24-hour continuous glucose monitoring (CGM) glucose levels for multiple doses of ORMD-0801 versus placebo
- To evaluate safety parameters associated with multiple doses of ORMD-0801

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 F1). 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 ORMD-0801 either once (qd), twice (bid) or three (tid) times daily. Treatment sessions were performed at ≥1-week intervals. During the treatment period, 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 pretreatment (Day 4) and at the end of treatment (Day 9).

Main inclusion criteria: Male or female; T2DM patients; ages 20-75, inclusive, HbA1c ≥7.5% and ≤10.5%, currently on a stable (≥8 weeks) metformin only, metformin + sulfonylurea, metformin + TZD, metformin + SGLT-2 inhibitor or metformin + DPP-4 inhibitor regimen.

F1



Incomplete block randomization with subjects assigned to 3 of 4 treatments in random sequence. All subjects underwent placebo treatment plus two active treatments

T4

TABLE 4. HYPER/HYPOGLYCEMIA INCIDENCE

	Placebo	ORMD-0801 (460 IU)		
		qd	bid	tid
	N=64	N=20	N=21	N=21
Total hyperglycemia events	27	15	8	12
Patients with at least one hyperglycemia event, n (%)	11 (36)	6 (30)	5 (24)	5 (24)
Total hypoglycemia events	3	2	4	5
Patients with at least one hypoglycemia event, n (%)	3 (10)	2 (10)	4 (19)	2 (10)

T1

TABLE 1. MEAN 24-HR CGM – ALL PATIENTS

	Placebo	ORMD-0801 (460 IU, qd)	ORMD-0801 (460 IU, bid)	ORMD-0801 (460 IU, tid)
	N=31	N=20	N=21	N=20
Run-In, mean (SE)	198.4 (6.2)	205.0 (4.9)	190.0 (6.0)	202.8 (9.7)
Treatment, mean (SE)	191.9 (5.1)	185.0 (7.0)	188.4 (6.9)	181.3 (7.0)
Placebo-adjusted difference, mean (SE)		-7.7 (6.3)	-4.0 (6.6)	-9.9 (7.3)
Placebo-adjusted % change, mean (SE)		-5.5 (3.2)	-3.0 (3.4)	-4.7 (3.6)

T2

TABLE 2. MEAN 24-HR CGM – HIGH BASELINE GLUCOSE PATIENTS

	Placebo	ORMD-0801 (460 IU, qd)	ORMD-0801 (460 IU, bid)	ORMD-0801 (460 IU, tid)
	N=17	N=14	N=11	N=8
Run-In, mean (SE)	205.5 (9.6)	203.0 (6.2)	194.3 (10.5)	212.8 (17.1)
Treatment, mean (SE)	200.2 (8.1)	186.3 (9.3)	192.3 (10.6)	177.8 (12.1)
Placebo-adjusted difference, mean (SE)		-12.4 (8.3)	-4.9 (10.6)	-18.4 (12.4)
Placebo-adjusted % change, mean (SE)		-7.2 (3.9)	-2.2 (5.2)	-8.5 (6.1)

T3

TABLE 3. MEAN 24-HR CGM – LOW BASELINE GLUCOSE PATIENTS

	Placebo	ORMD-0801 (460 IU, qd)	ORMD-0801 (460 IU, bid)	ORMD-0801 (460 IU, tid)
	N=14	N=6	N=10	N=12
Run-In, mean (SE)	188.2 (8.4)	211.0 (7.3)	188.3 (6.4)	195.1 (11.0)
Treatment, mean (SE)	184.3 (5.3)	192.6 (11.7)	186.9 (8.8)	176.2 (6.3)
Placebo-adjusted difference, mean (SE)		10.6 (10.3)	1.1 (7.4)	-10.4 (5.8)
Placebo-adjusted % change, mean (SE)		-0.9 (6.0)	1.1 (4.0)	-4.2 (2.9)

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 (80.6%). Mean placebo-adjusted change from baseline in 24-hour glucose (means of all run-in days vs. all treatment days) ranged from -7.65 mg/dL for qd to -9.9 mg/dL for tid, corresponding to a percent change from baseline ranging from -3.1 (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. ORMD-0801 was well tolerated and did not elicit any serious adverse 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 (≤5/group); all hypoglycemia events were mild (55-70 mg/dL).

CONCLUSIONS

Multiple-dose ORMD-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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