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Oral Insulin (ORMD-0801) in Type 2 Diabetes Mellitus: Dose-Finding 12-Week Randomized Placebo-Controlled Study

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ABSTRACT

Aims: To assess the safety and efficacy of multiple daily doses of oral insulin (ORMD-0801) in subjects with type 2 diabetes (T2DM) over 12 weeks.

Materials and Methods: Participants with T2DM on metformin or combination oral therapy with HbA1c ≥7.5% were randomized to receive ORMD-0801 8 mg or 16 mg once (QD) or twice (BID) daily, or 32 mg QD and BID or three times (TID) daily over a 12-week period.

Results: A total of 373 subjects were randomized to active treatment or placebo (~60% male, age ~ 56 y, HbA1c 9-9.8%). Placebo-adjusted HbA1c changes from baseline to Week 12 were observed with ORMD-0801 8 mg BID (-0.65±0.33%; -7.15±3.57 mmol/mol, p=0.046). However, a significant site interaction was observed in 2 sites. After excluding these HbA1c reduction was observed with 8 mg QD (-0.81±0.37%, p=0.028, n=15), 8 mg BID (-0.82±0.37%; p=0.029, n=17), 32 mg QD (-0.54±0.26%; p=0.036, n=69) and 32 mg BID (-0.53±0.26%; p=0.042, n=68). No effect was observed with 16 mg QD (0.25±0.37%; p=0.48, n=18), BID (-0.36±0.40%; p=0.36, n=15) or 32 mg TID (-0.45±0.27%, p=0.093, n=69). CGM and serum glucose measurements showed similar trends but were not significant. ORMD-0801 was safe, well tolerated and not associated with weight gain or hypoglycemia.

Conclusions: Oral insulin (ORMD-0801) induced greater reductions in HbA1c when compared to placebo and was safe and well-tolerated in individuals with uncontrolled T2DM. The efficacy and safety findings support continued development of the 8 mg dose at bedtime, which is currently being evaluated in two Phase 3 trials.

Introduction

Since the discovery of insulin almost a century ago, scientists have aspired to develop an oral insulin product[1]. In addition to the convenience and avoidance of injections, oral insulin could provide various clinical benefits arising from its postulated portal venous system route of entry, mimicking the direct "first-pass" action of endogenously secreted insulin on the liver[2].

ORMD-0801 (ORMD) is an orally administered insulin formulation packaged in an enteric-coated capsule, which facilitates passage through the stomach and into the small intestine thereby preventing active ingredient degradation within the gastrointestinal tract. Additional features of this novel insulin formulation include soybean trypsin inhibitor which inhibits proteolysis of the active ingredient, disodium ethylene-diamine tetra-acetic acid, which facilitates translocation of insulin to the basal side of the epithelium and subsequent systemic uptake, colloidal silicone dioxide (Aerosil 200), a common stabilizer, Tween 80 which assists with emulsion and crossing of lipophilic and hydrophilic barriers and fish oil-derived omega-3 acid triglycerides to prolong shelf-life.

ORMD-0801 has been tested in 16 Phase 1 and 10 Phase 2 clinical studies involving 884 subjects in total, including healthy volunteers and individuals with type 1 diabetes [3] and type 2 diabetes. Recently, we reported the results of a phase 2A study in 188 patients with type 2 diabetes (T2DM)[4] [HbA1c: 7.82±0.88% (placebo) and 8.08±1.11% (pooled ORMD-0801 group)] randomized to receive placebo or 16 mg or 24 mg ORMD-0801, once daily, at bedtime, for 28 days. In the placebo group, mean night-time glucose levels, measured with a continuous glucose monitor (CGM) increased from baseline by 13.7±26.1 mg/dL, whereas the increase was significantly smaller in the pooled ORMD-0801 group [1.7±23.5 mg/dL (p=0.0120)]. Even with the short study duration, change from baseline HbA1c was -0.01% in the pooled ORMD-0801 group vs. +0.20% in the

placebo group (p=0.0149). No apparent dose response was observed. ORMD-0801 was well-tolerated, with similar adverse event and hypoglycemia rates as placebo.

The dose-ranging trial presented herein investigated the efficacy and safety of ORMD-0801 in a 12-week dosing regimen with initial forced escalation, in participants with T2DM inadequately controlled by oral glucose-lowering agents. The optimal doses identified have been approved by the FDA and adopted in two larger and longer, currently ongoing Phase 3 studies.

Materials and Methods

The trial protocol was approved by FDA as well as local IRBs of the participating sites and was conducted in accordance with the Declaration of Helsinki and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). (ClinicalTrials.gov identifier: NCT03467932). The trial began on May 29, 2018, and the last patient completed his last visit on February 18, 2020. All patients provided written, informed consent prior to commencement of trial-related activities.

Patient Population: Key eligibility criteria were patients with T2DM, HbA1c ≥7.5% [58 mmol/mol], on stable doses of metformin with or without up to two other oral anti-hyperglycemic medications [sulfonylurea (SU), dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium glucose cotransporter-2 inhibitors (SGLT2i), or thiazolidinediones (TZD)]. A full list of inclusion/ exclusion criteria is provided in Supplementary Table 1.

Study Design: This placebo-controlled, multicenter, randomized, double-blind trial was conducted in 40 centers (Supplementary Table 2) in the U.S.A. All subjects underwent a two-week, single-blind, placebo run-in period, during which placebo capsules containing fish oil only, were self-administered at bedtime each night, no sooner than 2 h after dinner. Outpatient glycemic levels were measured at baseline and in the last two weeks of treatment using a blinded continuous glucose meter (CGM; Dexcom G4, Dexcom Inc., San Diego, CA, USA). Subjects were separately recruited to two cohorts and were randomly assigned to one of the following treatment arms:

Cohort A: In part 1, subjects (n=272) underwent a 2-week stepwise dose-escalation period, which began with a starting ORMD-0801 dose of 16 mg (2x8 mg capsules for 1 week) (Visit 3), escalated to 24 mg (1x8 mg capsule + 1x16 mg capsule for 1 week) (Visit 4), and then to a top dose of 32 mg (2x16 mg capsules) (Visit 5 onward) ORMD-0801 or matched placebo, once (QD), twice

(BID), or three (TID) times daily in accordance with the randomization scheme. In Part 2, treatment remained at a fixed dose of 32mg ORMD-0801 (or matched placebo) QD, BID, or TID in accordance with the frequency of treatment they received in part 1, for 10 consecutive weeks. QD dosing was at bedtime (at 10 PM ± 90 minutes), BID dosing was at bedtime and 30-45 minutes prior to breakfast and TID dosing was at bedtime and 30-45 minutes prior to breakfast and lunch. During Part 2, doses were not adjusted unless clinically indicated for adverse events or hypoglycemia.

Cohort B: Cohort B was added as a protocol amendment (after study initiation) to further assess the lower ORMD-0801 dose range, and to determine whether larger doses given QD are more effective than the same total dose administered in a BID regimen. This was pursued following a blinded review of the data which found no apparent distinction between the Cohort A arms after 28 days of therapy and the 28-day data obtained in a previous study which tested lower doses of ORMD-0801 administered QD and BID[4]. Subjects (n=81) were randomized to receive 8 mg ORMD-0801 QD or BID, 16 mg (1x16 mg capsule) ORMD-0801 QD or BID, or a matched placebo for 12 consecutive weeks. Dosing times were as described above for Cohort A. Doses were not adjusted unless clinically indicated for adverse events or hypoglycemia.

Excipient-only arm: Twenty subjects enrolled at site 20, received capsules containing ORMD-0801 excipient material only (without insulin), TID in a non-randomized single blind fashion. This was an FDA request to ensure that the fish oil placebo does not have a significant effect on efficacy or safety and was considered exploratory. Results from this cohort were not intended to be combined with the primary results.

Randomization was stratified by background anti-hyperglycemic medications but not stratified by site.

Assessments: At the screening visit and visits during Day 1 and Week 10, a physical examination, blood and urine laboratory tests, and other safety assessments were performed. On these visit days, all subjects reported to the research center following a 10-hour fast and before taking morning medications. Blood and urine samples were collected and analyzed in a central laboratory.

A mixed meal tolerance test (MMTT) was conducted at the randomization visit and at Week 12 of active treatment and were always scheduled at the same time of day for each subject. The MMTT was conducted using Boost™, which contains 240 calories, 10 g protein, 37 g carbohydrate, 6 g fat and 27 vitamins and minerals, ingested over 10 min. Baseline blood levels for insulin, glucose, and c-peptide were taken 50 min and 5 min prior to the start of the meal. For subjects receiving BID or TID dosing, study medication was given 45 min before the ingestion of the meal. Additional blood samples were drawn at 60 and 120 min after the ingestion of the meal for insulin, c-peptide, and glucose.

During Week 0 (run-in) and after 10 weeks of treatment, subjects had a CGM (Dexcom G4) applied for 14 days. Subjects were instructed on how and when to calibrate the device during the collection period and were told to avoid acetaminophen usage while connected to the monitor. CGM data were blinded to both the subject and investigator and were therefore not used to determine hypoglycemia during the study.

The quality of life (QOL) Diabetes Treatment Status Questionnaire (DTSQ) was completed by subjects at Baseline, Week 2, Week 10, and end-of-study rescue visits. The tool measured satisfaction with treatment, flexibility of dosing, perception of elevated and low glycemic excursions and willingness to carry on with the randomized treatment.

Safety and tolerability were assessed on an ongoing basis by review of reported adverse events (AEs), including reports of hypoglycemia, physical examinations, 12-lead electrocardiograms (ECGs), vital signs, and clinical safety laboratory data. Patients were provided with a Freestyle™ blood glucose meter to be used to confirm hypoglycemic symptoms. All reports of clinical hypoglycemia were extracted from the patient diaries. Patients with persistent symptomatic hyperglycemia were considered for rescue therapy (addition of a protocol-approved glucose-lowering agent in accordance with standard practice) to restore adequate glycemic control.

Randomization Scheme: In Cohort A, subjects were randomized 1:1:1:1 to placebo, QD, BID, or TID ORMD-0801 32 mg. Cohort B subjects were randomized 1:1:1:1:1 to placebo, 8mg (QD, BID) or 16 mg (QD, BID) ORMD-0801. The randomization was centralized and stratified by a) SU usage and b) metformin alone vs. combination therapy.

Study Endpoints: The primary endpoint was change in HbA1c, from baseline to Week 12. Secondary endpoints included mean HbA1c change from baseline over time, fasting plasma glucose (FPG), and parameters obtained during a MMTT, including area under the curve $(AUC)_{0-60}$, AUC_{0-120}, and 2-hour post-prandial glucose.

The per-protocol analysis included all study completers with both baseline and endpoint HbA1c data as well as without any major protocol violations. Supportive secondary endpoints included changes in baseline glycemic control (determined using CGM), weight change from baseline to Week 12, proportion of subjects requiring glycemic rescue therapy during the treatment period, and treatment safety. CGM data were collected from 6 AM – 6 AM of the following day and further sub-classified into periods of daytime (6AM-10PM) and nighttime (10 PM to 6 AM). For each of the time intervals, the following parameters were derived for both the observed values and the pre-dose adjusted values: AUC, time-in-range between 70 mg/dL and 140 mg/dL, time-in-

range between 70 mg/dL and 180 mg/dL, time-below-range <70 mg/dL, and time-above-range >180 mg/dL. Results obtained from the DTSQ questionnaires were considered exploratory endpoints.

Statistical Analysis: The confirmation of efficacy of ORMD-0801 on change in HbA1c and on body weight in Cohort A was based on a Holm-Bonferroni testing strategy[5] to control the overall type 1 error for the hypotheses evaluated by the treatment policy estimand. When analyzing Cohort A and Cohort B together, a hierarchical method was used with Cohort A treatments being given higher priority than Cohort B treatments due to the difference in the number of subjects in each cohort. The order of the testing was 32 mg QD, 32 mg BID, 8 mg QD, 8 mg BID, 16 mg QD. The treatment policy was controlled for multiplicity to claim superiority and all other p-values are descriptive. The treatment policy estimand consisted of a linear mixed model using multiple imputation to handle missing Week 12 data for confirmatory endpoints. Data collected at Week 12, irrespective of premature discontinuation of trial product and initiation of rescue medication, were included in the statistical analysis. Imputation was done within groups defined by trial product and treatment status at Week 12. Both the imputation and the analysis were based on ANCOVA models.

The primary efficacy endpoint was the change from baseline in HbA1c after 12 weeks of active treatment in Cohort A patients only. Based on previous results, a drop in HbA1c of 0.6% was expected with a standard deviation of 1.2. The primary analysis was assessed by comparing the pooled BID and TID treatment data to that of the pooled placebo data. In order to achieve 80% power, 48 completers were required per treatment group. Assuming an approximate 20% dropout rate, 240 randomized subjects would yield approximately 192 completers or approximately 48 subjects per treatment group.

Since Cohort B was intended to provide supplementary information only, it was not powered to stand alone but was powered to be combined with Cohort A. For powering purposes, the combined Cohort B was given the same weight as the primary dosing cohort (Cohort A). Thus, Cohort B was to enroll 75 subjects to achieve at least 60 completers, i.e., 15 subjects enroll per cohort achieve 12 completers for each.

All measured variables and derived parameters are listed individually and, if appropriate, tabulated by descriptive statistics. For descriptive statistics, summary tables present by treatment group, summaries of sample size, arithmetic mean, standard deviation and 95% confidence intervals (if appropriate). For categorical variables summary tables include summaries of frequency counts by study group. All analyses were performed using SAS, version 9.4.

Results

Patient Disposition and Baseline Characteristics: Of the 685 patients screened, 312 patients failed screening; 20 subjects received excipient only capsules and 353 subjects were randomized to receive either active or placebo treatment (Fig. 1). All randomized subjects were included in the Safety Population. The study was completed by 85% of subjects receiving ORMD-0801 treatment and by 88% of placebo subjects. Compliance with all treatment regimens as measured by study drug accountability, over the 12-week study period was high and exceeded or close to 90% in most treatment groups (data on file). The major reason for withdrawal was participant decision. Two subjects experienced adverse events (AEs) that led to withdrawal from the study; both events were not serious and were unrelated to the study drug.

Baseline demographics and disease characteristics were similar between treatment groups and are summarized in Table 1. Most of the subjects were white males, and mean age was 55-56 years. Mean body mass index (BMI) was between 30-32 kg/m^2 (SE 4-6.1) across the cohorts and mean baseline HbA1c ranged between 8.5% [69 mmol/mol] and 9.8% [84 mmol/mol] (SE 1.1-1.8). The distribution of background diabetic medications was similar in both cohorts with approximately 32% of subjects taking metformin only and 43% of subjects taking sulfonylureas together with metformin.

Exclusion of sites 13 and 20: During the analysis of the primary outcome and as per guidance of ICH E-9 section 3.2 [6] regarding positive treatment effects in multicenter trials, we conducted an exploration of the heterogeneity of treatment effects across centers. A significant treatment-by-center interaction was noted for the observed mean changes in HbA1c at Week 12 of placebo-treated subjects at sites 13 (n=5) and 20 (n=9), which was -1.15% compared to -0.20% for the placebo-treated subjects at all the other sites. A comprehensive discussion and analysis of the

substantially different results at Sites 13 and 20 as compared to the remaining sites is provided in the attached supplementary discussion. Possible reasons for the treatment-by-center interaction could include an error in medication dispensation, a randomization error, poor adherence to study medication, unreported antihyperglycemic medication and specific patient characteristics that would result in a different response to study medication. To understand these observed differences the sites were audited and a careful review of the dispensed medication and study drug accountability in these sites was conducted but no reason for this discrepancy was found. A randomization error was also not detected. Baseline demographics and characteristics of patients at these two cohorts were similar to patients recruited at other sites (Supplementary Table 3A-B). Due to the clear treatment-by-site interaction, exclusion of sites 13 and 20 constituted the most conservative approach and is referred to as the qualified Intent-to-Treat analysis. Therefore, the 49 (14.2%) subjects who received ORMD-0801 and 14 (5.2%) placebo-treated subjects at these outlier sites, were excluded from the primary and secondary analysis. (Primary analysis results including sites 13 and 20 are presented as Supplementary Tables 4E-F).

Primary and Secondary Endpoints:

Placebo-adjusted HbA1c changes ± SE from baseline to Week 12 were statistically significant only among subjects treated with ORMD-0801 8 mg BID (-0.65±0.33%; -7.15±3.57 mmol/mol, p=0.046; Supplementary Tables 4A-B). A non-significant reduction in placebo-adjusted HbA1c change from baseline was observed in the ORMD-0801 32 mg QD, BID, TID and in the 8 mg QD and 16 mg BID arms.

When excluding sites 13 and 20, placebo-adjusted HbA1c changes ± SE from baseline to Week 12 were statistically significant among subjects treated with the ORMD-0801 8 mg QD (-0.81±0.37% ;-8.89±4.01 mmol/mol, p=0.028), 8 mg BID and (-0.82±0.37%; -8.95±4.08

mmol/mol, p=0.029), 32 mg QD (-0.54±0.26%; -5.89±2.78 mmol/mol, p=0.036) or 32 mg BID (-0.53±0.26%; -5.80±2.83 mmol/mol, p=0.042). Subjects receiving doses of ORMD-0801 16 mg QD, 16 mg BID or 32 mg TID had HbA1c changes that were comparable to the changes measured in the placebo-treated subjects [(0.25±0.37%; 2.76±3.99 mmol/mol, p=0.49) (-0.36±0.40%; -3.97±4.33 mmol/mol, p=0.36) (-0.45±0.27%; -4.89±2.90 mmol/mol, p=0.09 respectively)] (Fig. 2, Supplementary Tables 4C-D). Similar trends were observed when only the placebo-treated subjects from sites 13 and 20 were excluded (Supplementary Tables 4E-F) and in the per-protocol population analysis (Supplementary Tables 4G-H). In all cases, the 8 mg QD and 8 mg BID regimens had the largest HbA1c-lowering effect. When analyzing Cohort A alone the effect of the combined 32 mg QD and 32 mg BID vs. combined placebo was significant (p=0.021). The Holm-Bonferroni method was used to compare the 32 mg QD and 32 mg BID groups individually. However, since the p-values were greater than 0.025, testing was stopped (32mg QD ,p=0.036; 32 mg BID, p=0.042).

Fasting serum glucose levels (Supplementary Tables 5A-B) did not significantly change in any ORMD-0801 arms at Week 12. Although the change from baseline to Week 12 in glycemic parameters measured via CGM was not statistically significant, the AUC of the glucose change from baseline followed a similar pattern as the reduction of HbA1c (Supplementary Fig.1). Similarly, parameters obtained during the MMTT, including glucose, insulin and c-peptide levels (Supplementary Fig. 2) were not significantly different in ORMD-0801 arms at Week 12 (except for a significant reduction in placebo-adjusted percent change from baseline in glucose in the 32 mg arm, p= 0.0345). No difference in mean observed body weight (Supplementary Table 6A-B) or DTSQ (Supplementary Fig. 3) was observed between ORMD-0801-treated groups and placebo-treated. .

Safety: The overall incidence of adverse events and serious adverse events was similar between ORMD-0801 and placebo-treated subjects (Table 2). Most AEs were mild or moderate in severity and considered unlikely to be related to the study drug. No drug-related severe or serious AEs were reported. One subject in the excipient only arm died of a myocardial infarction, which was considered unrelated to study treatment. The most common AEs were related to infections and infestations (mostly nasopharyngitis) followed by gastrointestinal disorders (3.7% in the combined placebo group as compared with 4.4-6.7% in the active treatment groups, including diarrhea and abdominal pain). Treatment-emergent AEs (TEAEs) were observed at similar frequencies in subjects receiving placebo as in subjects receiving active treatment (data on file). TEAEs leading to drug discontinuation occurred in 1 subject each in the 32 mg BID and TID cohorts. The proportion of subjects requiring at least one glycemic rescue therapy drug was low and similar across all treatment groups (6.3% in the combined placebo arm and 6.7%, 0%, 5.9%, 6.7%, 5.9%, 7.5% and 8.7% in the 8 mg QD, 8 mg BID, 16 mg QD, 16 mg BID, 32 mg QD, 32 mg BID and 32 mg TID arm respectively).

Hypoglycemic Events: At the tested doses, ORMD-0801 was not associated with any increase in the rate of hypoglycemia when compared with placebo (Table 2). In the combined placebo group, a total of 25 events were reported, with 17 of these events occurring in 1 subject. Four subjects in the 8 mg BID group reported 16 events and one subject in the 16 mg QD group reported 20 hypoglycemic events, three of which occurred during the placebo run-in period. Six subjects in the 32 mg QD group reported 16 events, 11 of which occurred in 2 subjects. Three subjects in the 32 mg BID group reported 4 events and 6 subjects in the 32 TID mg group reported 32 events, of which 23 were reported by 1 subject. There were no events reported in the 8 mg QD group. All subjects who reported one or more hypoglycemic events took sulfonylureas as part of their diabetes

treatment regimen. All hypoglycemia events were level 1 (<70 mg/dL and ≥54 mg/dL) except for two moderate events (level 2 <54 mg/dL), which occurred in the 32 mg QD and in the 8 mg BID cohorts. None of the hypoglycemic events required intervention by another person.

Discussion

This Phase 2 study was primarily designed to identify the optimal ORMD-0801 dose and regimen in reducing HbA1c in patients with uncontrolled T2DM treated with metformin alone or in combination with other oral glucose-lowering agents as dual background therapy. The primary endpoint, reduction in HbA1c compared to a placebo group at Week 12, was achieved in most of the dose-ranging subgroups in this study. Subjects dosed with ORMD-0801 8 mg QD or BID achieved greater reductions in HbA1c (0.81% [-8.89 mmol/mol] and 0.82% [-8.95 mmol/mol], respectively). Higher doses (32 mg QD and BID) also improved HbA1c compared to placebo, yet the improvements were not dose dependent. The observed effect on lowering fasting plasma glucose and glycemic parameters measured via CGM followed similar patterns to the reductions in HbA1c. Regarding safety, the incidence of drug-related AEs was <5% at all doses, with no difference between active therapy and placebo. While hypoglycemic episodes were seen at all doses, they occurred exclusively among patients receiving background therapy with sulfonylureas. The episodes were generally mild and seen at similar frequencies in both actively treated as well as placebo-treated subjects. No severe or life-threatening hypoglycemic events were reported in any treatment group.

Overall, based on the primary and secondary efficacy outcomes, this study clearly supports 8 mg ORMD-0801 QD, at bedtime, as the most efficacious dosing schedule for the Phase 3 program, while 8 mg of ORMD-0801 BID should be further explored.

We hypothesize as the mechanism of action for orally delivered ORMD-0801, that it is absorbed by the intestinal mucosa and appears in the portal venous system, simulating the natural transport of insulin after secretion from the pancreas. Hepatic glucose production is highly sensitive to changes in insulin exposure and thus can be controlled by a minute increase in hepatic

insulinization[7-9]. Increased hepatic insulin exposure could thereby improve hepatic glucose metabolism without increasing peripheral insulin exposure[10,11]. This hepatic sensitivity to insulin exposure could, in part, explain why treatment effects on some metabolic parameters, such as fasting glucose levels were not observed. Human insulin administered directly into the portal vein is rapidly cleared[12], suggesting that the prolonged glucose-lowering effect observed here and the lack of an increase in hypoglycemic events may be the result of a secondary hepatic effect, rather than prolonged increases in plasma insulin levels. Alternatively, these observations may be related to poor absorption of ORMD-0801. However, they are consistent with the results of a previous study in which treatment with ORMD-0801 led to a prolonged glucose-lowering effect without hypoglycemia and a detectable increase in fasting serum insulin or changes in c-peptide levels[4]. In contrast, subcutaneously injected insulin is initially absorbed into the peripheral circulation without a "first-pass" hepatic effect. This in turn may lead to excessive peripheral insulin exposure and increase the risk of hypoglycemia [13].

The absence of weight gain observed in this study despite the improved glucose control, contrasts with the weight gain frequently associated with insulin administration[14-16]. This benefit paired with the apparent lack of need for dose titration and low risk of hypoglycemia represent potential positive attributes of oral insulin therapy and help differentiate it from other T2DM therapies, such as injectable insulin and sulfunylureas[14,15].

The strengths of this study include its randomized double blind, placebo-controlled design and its relatively large cohort and prolonged follow up time allowing for a full appreciation of the anti-hyperglycemic effect of ORMD-0801. The limitations of the study include the two outlier sites which were found to have aberrant results with no apparent cause. In addition, the 8 mg and 16 mg cohorts were relatively small and added as an amendment to the protocol. This may have

increased the variability of the observed results and, to some extent, may explain the apparent lack of treatment effect in the 16 mg QD arm. Alternatively, it is conceivable that the 16 mg formulation batch might have behaved differently than the 8 mg dose.

The reason for the observed lack of dose response is unclear. Peripherally injected insulin has a well-known dose response, but, little or no peripheral insulin exposure was detected with ORMD-0801. A similar phenomenon was observed in a prior study with ORMD-0801[4] in which 188 patients with T2DM were randomized to receive placebo or 16 mg or 24 mg ORMD-0801, once daily, at bedtime, for 28 days. While both doses of ORMD-0801 were efficacious, no clear dose response was observed and a numerically greater glucose-lowering effect was achieved with the lower dose. No increase in plasma insulin levels was detected. Likewise, in a small mechanistic study of euglycemic insulin clamps in 11 subjects with type 1 diabetes who received 2x8mg; 3x8mg and 1x16mg ORMD-0801 no clear dose response and no increase in peripheral insulin was noted (while a slight trend towards reduced hepatic glucose production and glucagon was observed; unpublished data).

While the most plausible explanation for this phenomenon is insufficient statistical power to discern differences between treatment groups, erratic insulin absorption and slight differences in baseline HbA1c, we propose several mechanistic reasons: **1**. a potential interaction of insulin molecules in the intestinal lumen leading to impaired insulin absorption; **2**. a potential difference in intestinal absorption of the 8 mg and 16 mg formulations (used in all the dosing regimens of doses higher than 8 mg in this study) due to different ratios of insulin and excipients in the capsule; **3**. a non-linear hepatic response to ORMD-0801 doses >8 mg, with minimal peripheral insulin exposure, which may result in “hepatic saturation” . Further mechanistic studies are ongoing to understand this phenomenon.

Development of an oral insulin product has presented many challenges over the years and ORMD-0801 appears to be the most advanced formulation of oral insulin prototypes now entering Phase 3 of development. Recently, Novo Nordisk reported discontinuation of their oral insulin formulation (Oral insulin 338, a long-acting basal insulin analogue) entering Phase 2 due to dose requirements that would not be commercially feasible[17]. Other formulations of non-injectable insulin exist and are at earlier stages of development. The NIH recently funded studies for an ingestible, self-orienting, millimeter-scale applicator (SOMA) in oral capsule form, which deploys milliposts fabricated from active pharmaceutical ingredients directly through the gastric mucosa while avoiding perforation. Tregopil (IN-105 in previous studies), another early contender now in early clinical trials, is a novel insulin analog modified for oral delivery through the addition of a single short-chain amphiphilic oligomer at the Lys-β29 residue of recombinant human insulin. Tregopil's rapid onset and absorption into the hepatic portal circulation are two key strengths that hold promise for clinical translation[18].

In conclusion, ORMD-0801 treatment in patients with poorly controlled type 2 diabetes resulted in significant reductions in HbA1c across most doses ranging from 8 mg QD to 32 mg BID without increasing hypoglycemia or weight gain and was safe and well-tolerated. The efficacy and safety findings support continued development of the 8 mg dose at bedtime, which is currently being evaluated in two Phase 3 trials authorized by the FDA. If these preliminary findings are confirmed by the phase 3 trials, ORMD-0801could become an earlier oral option for type 2 diabetes management.

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Conflict of Interest

RE: consultant for Oramed; has served on advisory panels for Oramed, Boehringer Ingelheim, Merck, Eli Lilly, Novo Nordisk, Sanofi, and Medtronic, has conducted research studies for Novo Nordisk, Sanofi and Eli Lilly and has received research support from Boehringer Ingelheim.

BF: employee of Oramed Pharmaceuticals.

AF: consultant for Acer, Acasti, Adocia, Abbott, Aerami, ALMS, Amolyt, Baker Heart and Diabetes, Berg, Biocon, Caladrius, Chiasma, CMC Magnetics, Diabeloop, Diasome, Embera Neuro, Entera, Enterin, Esperion, Fortress, Gencia, Genmab, Gila Therapeutics, Glyscend, Hagar, Hagens Berman, IM Therapeutics, Innoneo, Intarcia, IPharma, Know Labs, Linear Therapies, Lumos, MannKind, ManTech, Mars Symbioscience, Melior, Modular Medical, Northwestern, NuSirt, Oberland, Oramed, Orgenesis, Pano, Periovance, RenovoRx, Rivus, Rhythm, Serpin, SFC Fluidics, Skinject, Stalicla, Stelis, Surf Bio, Tanomed, Tolerion, Unify, Veroscience, Verthermia, Zenomics, Zucara

JN: Served on advisory panels and conducted research studies for Novartis, Merck, Boehringer Ingelheim, Eli Lilly, Sankyo, Viking, Oramed, Seres, Amgen, Gila Therapeutics and Pfizer

KH: No conflicts of interest to declare.

MK: employee of Oramed Pharmaceuticals.

JR: served on advisory panels for Applied Therapeutics, Boehringer Ingelheim, Eli Lilly, Hanmi, Intarcia, Janssen, Novo Nordisk, Oramed, Sanofi, and Zealand; and has received research support from Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Genentech, GlaxoSmithKline, Hanmi, Intarcia, Janssen, Lexicon, Merck, Novo Nordisk, Novartis, Oramed, Pfizer and Sanofi.

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Table 1. Demographics and Baseline Characteristics

	Combined Placebo (N=82)	8 mg QD (N=15)	8 mg BID (N=17)	16 mg QD (N=18)	16 mg BID (N=15)	32 mg QD (N=69)	32 mg BID (N=68)	32 mg TID (N=69)
Sex, n (%)								
Male	49 (59.8)	10 (66.7)	10 (58.8)	11 (61.1)	11 (73.3)	42 (60.9)	45 (66.2)	40 (58.0)
Female	33 (40.2)	5 (33.3)	7 (41.2)	7 (38.9)	4 (26.7)	27 (39.1)	23 (33.8)	29 (42.0)
Race, n (%)								
White	69 (84.1)	12 (80.0)	11 (64.7)	16 (88.9)	11 (73.3)	59 (85.5)	57 (83.8)	58 (84.1)
Black or African American	11 (13.4)	3 (20.0)	4 (23.5)	1 (5.6)	1 (6.7)	7 (10.1)	8 (11.8)	8 (11.6)
Ethnicity, n (%)								
Hispanic or Latino	48 (58.5)	9 (60.0)	8 (47.1)	9 (50.0)	8 (53.3)	36 (52.2)	37 (54.4)	36 (52.2)
Not Hispanic or Latino	33 (40.2)	6 (40.0)	6 (35.3)	9 (50.0)	6 (40.0)	32 (46.4)	29 (42.6)	33 (47.8)
Age (years)								
Mean ±SD	55.8±9.9	53.7±8.3	56.9±9.1	55.0±11.2	55.0±11.8	56.7±10.8	55.7±10.6	55.2±11.7
BMI (Kg/m^2) at Screening								
Mean ±SD	31.1±4.8	31.8±4.4	31.0±5.0	31.9±6.1	30.8±5.5	31.7±4.9	30.4±4.8	31.2±4.0
Baseline HbA1c								
Mean ±SE (%)	9.5±1.4	9.8±1.8	8.5±1.1	9.0±1.4	9.2±1.7	9.0±1.3	9.4±1.7	9.6±1.6
Mean ±SE (mmol/mol)	79.8±15.7	84.0±19.2	69.0±12.1	74.5±15.5	76.8±18.4	74.5±14.0	78.8±18.1	81.8±17.2
Fasting Plasma Glucose								
Mean ±SE (mg/dL)	205.6±62.4	218.4±61.9	159.6±49.7	205.6±51.9	208.1±69.3	195.2±48.2	206.8±67.9	205.5±61.4
Mean ±SE (mmol/L)	11.4±3.5	12.1±3.4	8.9±2.8	11.4±2.9	11.6±3.9	10.8±2.7	11.5±3.8	11.4±3.4
Diabetes Medication Usage (%)								
Metformin Alone	22 (26.8)	6 (40.0)	5 (29.4)	7 (38.9)	5 (33.3)	20 (29.0)	20 (29.4)	12 (17.4)
Metformin with Sulfonylureas Only	33 (40.2)	7 (46.7)	7 (41.2)	8 (44.4)	3 (20.0)	30 (43.5)	26 (38.2)	33 (47.8)

SD: standard deviation; SE: standard error

Table 2. Incidence, seriousness, and severity of safety and hypoglycemia events, by cohort

	Combined Placebo (N=82)	8 mg QD (N=15)	8 mg BID (N=17)	16 mg QD (N=18)	16 mg BID (N=15)	32 mg QD (N=69)	32 mg BID (N=68)	32 mg TID (N=69)
Number of Reported Adverse Events	82	21	9	13	15	108	56	79
Number (%) of Subjects With at Least One:								
Treatment Emergent Adverse Event (TEAE)	37 (45.1)	9 (60.0)	6 (35.3)	10 (55.6)	7 (46.7)	38 (55.1)	27 (39.7)	35 (50.7)
Severe TEAE	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (5.8)	0 (0.0)	2 (2.9)
Serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	5 (7.2)	0 (0.0)	3 (4.3)
Drug-related serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to withdrawal of study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.4)
Hypoglycemia Events								
Number Subjects Having a Hypoglycemia Event (Number of Events)	5 (25)	0 (0)	4 (16)	1 (20)	0 (0)	6 (16)	3 (4)	6 (32)
Percentage of Subjects Having a Hypoglycemia Event	6.1%	0%	23.5%	5.6%	0%	8.7%	4.4%	8.7%
Number of Mild Hypoglycemia Events	25	0	15	20	0	15	4	32
Number of Moderate Hypoglycemia Events	0	0	1	0	0	1	0	0
Number of Hypoglycemia Events Requiring Extensive Intervention or Hospitalization	0	0	0	0	0	0	0	0

Figure Legends

Figure 1. CONSORT flow diagram for the presented randomized trial. The safety population included all subjects who received at least one dose of the study drug. The intent-to-treat (ITT) population included all subjects who received at least one dose of the study drug and in whom HbA1c and /or CGM data was collected both at baseline and during treatment.

Figure 2. Placebo-adjusted change from baseline HbA1c (%) at Week 12 with increasing doses of ORMD-0801 Subjects with type 2 diabetes mellitus and on metformin therapy (≥ 1500 mg daily) were randomized to receive oral insulin (ORMD-0801) 8 mg once (QD) or twice (BID) daily, 16 mg QD or BID, 32 mg QD, BID, or three times (TID) daily, or matching placebo regimens, over a 2-week period, followed by a 10-week dose maintenance period. Least squares mean change from baseline HbA1c was measured at the end of week 12 of the study and compared to placebo for the qualified intent-to-treat population (*$p<0.05$). Error bars represent

standard error of means.