Efficacy and safety of 28-day treatment with oral insulin (ORMD-0801) in patients with type 2 diabetes mellitus - A randomized placebo-controlled trial

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Conflicts of interest

RE is a principal investigator/coinvestigator in clinical trials being conducted at the Sourasky Medical Center for Novo Nordisk, Inc., Sanofi Inc., is on a consultant and on the advisory board at Oramed Pharmaceuticals, Merck & Co., Inc., Sanofi, AstraZeneca, Novo Nordisk Inc., Boehringer Ingelheim Pharmaceuticals and is a shareholder at Oramed Pharmaceuticals. MK is an employee at and shareholders at Oramed Pharmaceuticals Jerusalem, Israel. JN is at employee of Orange County Research Center, Tustin, California, USA. KH is an employee at Integrium, LLC, Tustin, California, USA. JN was Principal Investigator in this Oramed-sponsored study.

ABSTRACT

Aims

To assess the safety and efficacy of oral insulin (ORMD-0801) in type 2 diabetes (T2DM) patients.

Materials and methods

After a 2-week washout of other medications, adult metformin-treated patients with T2DM, were randomized to receive placebo or 16 mg or 24 mg ORMD-0801, once daily, at bedtime, for 28 days. The mean change from baseline weighted mean night-time glucose levels was determined from two nights of continuous glucose monitoring (CGM) recordings during the placebo run-in and last week of treatment.

Results

In total, 188 patients [HbA1c: 7.82±0.88% (placebo) and 8.08±1.11% (pooled ORMD-0801 group)] were enrolled. In the placebo group, mean night-time 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)]. Glycemic control parameters (24-hour, fasting and daytime CGM glucose) also displayed smaller increases with ORMD-0801 vs. placebo. Change from baseline HbA1c was -0.01% in the pooled ORMD-0801 group vs. +0.20% in the placebo group (p=0.0149). ORMD-0801 was well-tolerated, with similar adverse event and hypoglycemia rates as placebo.

Conclusions

In patients with T2DM, bedtime ORMD-0801 curbed increases in night-time glycemia, 24-hour glycemia and HbA1c, without increasing risk of hypoglycaemia, or safety events as compared to the control arm.

Keywords: ORMD-0801, oral insulin, continuous glucose monitoring, randomized controlled trial

Introduction

Subcutaneously administered insulin is the cornerstone of diabetes therapy, conferring a highly potent antihyperglycemic effect. Insulin is available in formulations with different pharmacokinetic (PK) and pharmacodynamic (PD) profiles (e.g., rapid, regular, intermediate, long-acting, or combinations of these), which are used to tailor treatment regimens to patient needs[1]. Regardless of its characteristics, subcutaneously administered insulin requires daily injections and frequent blood glucose monitoring, and is associated with weight gain and a narrow therapeutic index, with an increased risk of hypoglycemia.

ORMD-0801 is an oral formulation of recombinant human insulin[2-4]. Its oral polypeptide delivery system contains excipients that facilitate uptake by inhibiting proteolysis in the small intestine and improving translocation of peptides across the gut epithelial lining, into the systemic circulation. The oral insulin capsules have been tested in four small Phase II studies, (two in patients with type 2 diabetes, and two in patients with type 1 diabetes), which have suggested that ORMD-0801 is well tolerated and can reduce plasma glucose and c-peptide levels. Treatment of uncontrolled T1DM patients with the oral insulin capsules for ten consecutive days, resulted in an overall reduction in blood glucose levels, with a 24.4% lower frequency of >200 mg/dL glucose readings[5].

Here, we report the results of the largest Phase II placebo-controlled study conducted with ORMD-0801 to date, which aimed to assess the safety and efficacy of the addition of ORMD-0801 (16 mg insulin or 24 mg insulin) to metformin for 28 consecutive days, in 180 patients with type 2 diabetes.

Materials and Methods

Subjects

Adult patients with type 2 diabetes, defined according to American Diabetes Association guidelines[6], aged 20-75 years, body mass index (BMI) 25-40kg/m^2, who were on stable treatment with metformin (immediate release (IR); ≥1500 mg/day) for at least 2 weeks and had HbA1c 6.5-10% (48–86 mmol/mol) at the screening visit, were eligible to enter the study. Patients naïve to antidiabetic therapy and with HbA1c ≥7.5% (58 mmol/mol) were started on metformin IR and titrated to a maintenance dose of ≥1,500 mg daily for two weeks. Patients on metformin IR monotherapy <1,500 mg daily and with HbA1c ≥7.0% (53 mmol/mol) were titrated to and then maintained on ≥1,500 mg metformin IR daily, for two weeks. Patients on antidiabetic monotherapy with a drug other than metformin IR and with HbA1c 6.5-9.5% (48–80 mmol/mol), discontinued their current drug and were put on or titrated to ≥1,500 mg metformin IR daily, which they took daily for the two-week stabilization period. Patients on metformin IR plus one additional antidiabetic drug (excluding insulin), with HbA1c 6-9.5% (42–80 mmol/mol) discontinued the other drug and continued with metformin IR ≥1,500 mg only for the two weeks of stabilization. Key exclusion criteria included: history of type 1 diabetes mellitus, fasting blood glucose >260 mg/dL at the end of Day -7 before treatment initiation, presence of any clinically significant endocrine disease, history of use of insulin for more than one week in the preceding six months, any use of insulin in the six weeks preceding randomization, serum creatinine >1.4mg/dl in males, >1.3mg/dl in females and history of gastrointestinal disorders with the potential to interfere with drug absorption.

Study Design

This was a 28-day, multicenter, Phase IIb, randomized, double-blind, placebo-controlled, parallel-group study, preceded by a ≥14-day washout/medication stabilization period and a

14-day, single-blind, placebo run-in period (Supplementary Figure 1). Patients were screened across 32 study centers and enrolled at 30 sites (ClinicalTrials.gov identifier: NCT02496000). The trial began on July 23, 2015 and the last patient completed his last visit on March 30, 2016. The study protocol was approved by the local institutional review boards and the study conformed with the Declaration of Helsinki. All participating patients provided written, informed consent. The data were analysed by KH.

After the washout/metformin stabilization period, patients entered a 2-week, single-blind, placebo run-in period, and were monitored with a continuous glucose monitor (CGM) during the last seven days. Patients demonstrating adequate compliance during the placebo run-in period (≥80%, based on pill count) were randomized 1:1:1 to receive placebo, ORMD-0801 16 mg insulin (2x8 mg capsules) or ORMD-0801 24 mg insulin (3x8 mg capsules) for 28 consecutive days.

Doses of ORMD-0801 were determined based on safety and efficacy information obtained from previously completed clinical trials. In one study, bedtime administration of ORMD-0801 16 mg, for 6 weeks, in patients with T2DM (21 patients receiving ORMD-0801 and 8 receiving placebo treatment) was found to be safe and well tolerated (unpublished). In another study, the safety, pharmacokinetics and pharmacodynamics of ORMD-0801 16 mg and 24 mg evaluated in patients with T2DM (NCT01889667; unpublished), were safe and well tolerated. More specifically, treatment with 16mg ORMD-0801 for 8 consecutive days resulted in a mean inter-cohort difference of -32.31 mg/dL night-time glucose readings obtained by continuous glucose monitoring. Similar trends were noted for both daytime and fasted morning glucose levels.

Patients were instructed to take the study medication at bedtime, at least two hours after the evening meal, and to refrain from caloric intake for 6 hours after dosing. Patients were again connected to a CGM during the last 7 days of treatment. Clinic visits were conducted on

Days 1, 22 and 29, during which fasting blood samples were collected to measure fasting plasma glucose (FPG), morning fasting serum insulin, c-peptide, triglycerides, HbA1c and c-reactive protein (CRP). Drug safety was assessed throughout the study period, by monitoring adverse events, vital signs, hypoglycemic events, cardiovascular events, clinical laboratory measures and physical findings. Potential immunogenicity of ORMD-0801 was assessed by comparing levels of anti-insulin antibodies in blood samples collected on Days 1 and Day 29 of the treatment period. Patients, investigators, and the sponsor remained blinded to the treatment identity during the 28-day treatment period.

Endpoints

The primary efficacy endpoint was the mean change from baseline (run-in period) in weighted mean night-time glucose levels in Week 4 of treatment (pooled active treatment data), determined from two nights (defined as the 6-hour period following treatment) of CGM recordings. Means and percent change from baseline of pooled ORMD-0801 treatment groups and the placebo treatment group were compared. The pooling of the two active groups was pre-specified due to statistical power considerations (detailed below). Secondary efficacy endpoints were the effect of each ORMD-0801 dose (24 mg insulin and 16 mg insulin), on weighted mean night-time glucose levels, the effect of ORMD-0801 (24 mg insulin, 16 mg insulin and pooled) on other parameters extracted from CGM recordings (mean 24-hour glucose, mean daytime (6AM to 10PM) glucose, and mean fasting (5-7AM) glucose), and on mean fasting plasma glucose, morning fasting serum insulin, c-peptide, triglycerides and HbA1c.

The CGM was applied for 7 days, in order to obtain at least two days in which 80% of the glucose measurements were accurately collected. Efficacy assessments using CGM data were based on the results from the two last days of the assessment period (run-in or active treatment), unless technical difficulties precluded calculation of the weighted mean glucose

levels. In this case, the last two days with at least 80% of the expected number of measurements were used.

Safety endpoints included the number (%) of patients with treatment-emergent adverse events (AEs) (defined as any AE that started after the first dose of study medication was administered or that increased in severity or frequency after dosing). Events of hyperglycemia and hypoglycemia were of particular interest in this study, and were verified through glucose readings from the CGM or by patient diary records.

Method of Assigning Patients to Treatment Groups

Instructions regarding blinding procedures were provided to the Investigator to ensure that the study blind was maintained at the study site. No stratification procedures were used for assigning patients to specific treatment groups. The randomization code was held by an unblinded pharmacist at Integrium and was not supplied to individuals who were involved in the conduct of the study or other study-related activities.

Statistical Analysis

From historical data, it was assumed that both 16 mg and 24 mg ORMD-0801 would induce a ≥10% treatment change in mean nighttime glucose levels as compared to placebo, with a common standard deviation of 18.2%. A significance level of 0.05 was used. The sample size calculations ensured that the primary analysis had 80% power to detect a difference between the pooled active treatment groups and placebo. Hence, fifty-three (53) completed patients per treatment group were to provide 90% power using a one-way analysis of variance model. Assuming a <10% dropout rate during the short study period, 180 patients (approximately 60 patients per treatment group) were needed.

The primary endpoint was analyzed using a one-way analysis of variance (ANOVA) model. To reduce the variability introduced by the extreme outliers that are often present in diabetes studies using CGM data, the 80% trimmed data (data excluding the 10% highest and lowest

values for each treatment group) were analyzed. The trim was predefined in the statistical analysis plan and performed in a blinded manner prior to database lock. The trends seen in the 80% trimmed data were also present when the outliers were included; thus, only the trimmed data are presented.

The efficacy population was the intent-to-treat (ITT) population. The primary analysis was of mean observed change from baseline weighted mean night-time glucose levels. Imputation methods including last observation carried forward (LOCF) or mixed-effect model for repeated measurements (MMRM), were predefined but were not necessary for CGM analysis since no data were missing. For HbA1c and fasting plasma glucose, data were missing for one subject and an LOCF imputation was performed.

The safety population included all patients who received at least one treatment with the study drug.

Results

Patient Disposition and Baseline Characteristics

Of the 188 enrolled patients, 179 completed the study. In the placebo group, one patient withdrew consent and one was lost to follow-up (Supplementary Figure 2, Table 1 and Supplementary Table S1). In the ORMD-0801 16 mg group, two patients withdrew consent, two were withdrawn due to non-compliance and one was lost to follow up. In the ORMD-0801 24 mg group, one patient was lost to follow-up and one was withdrawn due to protocol violation. Baseline demographics were generally similar between treatment groups (Table 1). Patients receiving placebo or active treatment were of a mean age of 58.6 years and 57.6 years, respectively. There were more females in the placebo population (54.7%) than in the population receiving ORMD-0801 (41.1%). Mean HbA1c was 7.82±0.88% (62±10 mmol/mol) in the placebo cohort and 8.08±1.11% (65±12 mmol/mol) in the active cohort and mean FPG was 156.1±46.4 mg/dL (placebo) or 164.72±49.80 mg/dL (active). In total, 56.3% of placebo-treated patients and 38.7% of the active-treated patients were on at least one medication at the screening visits (42.2% and 22.5%, respectively on sulfonylurea and/or 12.5% and 9.7%, respectively on metformin); 1 patient in the placebo cohort and 3 patients in the ORMD-0801 cohorts were taking a thiazolidinedione.

Efficacy

An increase from baseline weighted mean night-time CGM readings was observed in the last week of treatment in both the placebo and pooled active arms, but was significantly smaller in patients treated with ORMD-0801 as compared to placebo (mean percent change 2.0±14.8% and 8.5±16.3%, respectively, p=0.0268; mean absolute changes 1.7±23.5 mg/dL and 13.7±26.1 mg/dL, respectively; p=0.0120) (Table 2 and Figure 1 and Supplementary Figure 3; non-trimmed data is represented in Supplementary Table S4). The mean percent change and absolute changes from baseline in weighted mean night-time CGM increased to a

significantly lesser extent in patients treated with 16 mg insulin ORMD-0801 vs. placebo (-1.3±11.6% and 8.5±16.3%, respectively; p = 0.0052; -3.7±18.9 mg/dL and 13.7±26.1 mg/dL, respectively; p = 0.0020) but not in those treated with 24 mg insulin ORMD-0801 vs. placebo.

Mean percent and absolute changes from baseline 24-hour CGM recordings were significantly greater in the placebo vs. the pooled ORMD-0801 group (8.0±10.2% vs. 0.2±9.8%; p<0.0001; 13.3±17.5 mg/dL vs. -0.3±16.0 mg/dL; p <0.0001). Subgroup analysis of subjects who discontinued prior medication but maintained metformin (placebo n=29; pooled ORMD-0801 n=35) and subjects on metformin monotherapy prior to initiation of ORMD-0801 (placebo n=26; pooled ORMD-0801 n=67) showed a similar trend with no clear washout effect (Supplementary Table S2). Mean percent and absolute changes from baseline fasting CGM glucose were higher in the placebo group vs. the combined ORMD-0801 group (10.8±13.9% vs. 1.1±17.1%; p= 0.0012; 16.0±20.8 mg/dL vs. -0.4±21.9 mg/dL; p<0.0001). Similarly, mean percent and absolute changes in baseline daytime CGM recordings were higher in the placebo group vs. the combined ORMD-0801 group (7.0±10.1% vs. 1.1±10.8%; p = 0.0030; 11.9±17.2 mg/dL vs. 0.9±17.9 mg/dL; p = 0.0010) (Table 2). HbA1c slightly decreased (-0.01±0.5%) during ORMD-0801 treatment, while it increased by 0.20±0.5% in the placebo group (p = 0.0149; LOCF imputation accounting for one missing subject: ORMD-0801 -0.02±0.5%, placebo 0.20±0.5%, p=0.0123) (Table 3).

Mean change from baseline fasting plasma glucose was greater in the placebo as compared to the combined ORMD-0801 group, although the difference was not statistically significant (8.9±26.2 mg/dL vs. 2.3±38.2 mg/dL; p=0.238; LOCF imputation accounting for one missing subject: ORMD-0801 9.3±26.1 mg/dL vs. placebo 2.1±38.0 mg/dL; p=0.198) (Table 3). No intercohort differences were found in the post-treatment morning fasting serum insulin, morning fasting c-peptide, alkaline phosphatase, ALT, AST, total bilirubin, LDH, total

protein or fasting morning triglyceride levels. No change in CRP, or change in weight were noted across cohorts (Table 3). Three subjects in the placebo group tested positive for anti-insulin antibodies on Day 29 (mean 11.1 ± 12.6 kU/L) and two subjects tested positive on day 43 (17.2 ± 18.1). In the 24mg ORMD-0801 cohort, 2 subjects tested positive for anti-insulin antibodies on day 29 (7.35 ±1.9 kU/L) and day 43 (6.3 ±1.8).

Safety

The proportion of patients with one or more AEs was similar across treatment groups (Supplementary Table S3). Two subjects in the placebo group suffered from continuous constipation that was recorded as related to treatment. One patient in the ORMD-0801 16 mg group experienced a severe AE of cerebral vascular accident in the left basal ganglia, which was considered unrelated to the study medication. In total, only four treatment-emergent hyperglycemic events were reported in four patients, (one in the placebo group and three in the ORMD-0801 16 mg group; Supplementary Table S4). One patient in each group experienced a hypoglycemic event, none of which were nocturnal (Supplementary Table S5).

Discussion

In patients with type 2 diabetes and inadequate glycemic control with metformin alone, oral administration of a single evening dose of encapsulated human insulin in the form of ORMD-0801 for 28 days, was safe and resulted in a modest but statistically significant anti-hyperglycemic effect, which was maintained throughout the 24 hours post-administration. While in the placebo arm glucose levels generally increased during the study, in the treatment arms, the increase was significantly smaller. The observed increase in plasma glucose levels in the placebo arm may have been the effect of the short washout phase implemented in this study (2 weeks). This phenomenon has been previously seen in other clinical trials which included medication washout. For example, in a study of sitagliptin monotherapy, despite a 10-week medication washout, HbA1c levels increased over 24 weeks by 0.18% [7]. Similarly in a study comparing vildagliptin to placebo in Japanese patients with T2DM, after a 2-4-week washout and placebo run-in, HbA1c levels in the placebo group increased from a mean 8.01% at baseline to 8.34% at week 12[8]. However, as seen in Supplementary Table S2, the results were not clearly different between patients who required a washout prior to randomization as compared to those who did not.

It remains to be determined how the anti-hyperglycemic effect of ORMD-0801 was maintained throughout the day. In light of observations reported for recombinant human insulin injected directly into the portal vein[9], it has been speculated that ORMD-0801 is absorbed from the small intestine into the portal venous system, and rapidly cleared by the liver, leaving no insulin reservoirs or depots. The prolonged glycemic effect may be the result of a local effect of ORMD-0801 on hepatic glucose production. The liver plays a crucial role in glucose homeostasis[10], where increases in porto-hepatic insulin concentrations have been shown to directly reduce gluconeogenesis and glycogenolysis without a clear peripheral effect[11-13]. In a study by Luci et al., a short-term increase in insulin, simulating first-phase

insulin release, measured during intraduodenal glucose infusion given on the background of a pancreatic clamp, resulted in a significant improvement of the glycemic profile for as long as four hours. Prevention of the first-phase insulin secretion with somatostatin, resulted in continuous hepatic glucose production, despite hyperglycemic and hyperinsulinemic conditions[14]. Therefore, short-term exposure of the liver to insulin introduced through the portal circulation, may trigger prolonged suppression of hepatic gluconeogenesis and glycogenolysis.

No clear dose-response was observed with ORMD-0801 16 mg vs. 24 mg (Table 2) i.e., the minimally effective dose of ORMD-0801 in this study was 16mg at bedtime. Unlike injected insulin which has a narrow therapeutic index, a 50% increase in the administered ORMD-0801 dose did not increase the anti-hyperglycemic efficacy or raise incidence of hypoglycemia and other insulin-related adverse events. This may be due to a lack of sufficient pharmacokinetic differentiation between the studied doses; further dose escalating studies are underway.

At the tested doses, ORMD-0801 was as well tolerated as placebo and was not associated with any serious AEs or hypoglycemia. Moreover, no change from baseline in any liver functions and only a slight reduction in triglyceride levels was noted in the active treatment arms. In contrast, treatment with peglispro, a hepatic-preferential insulin, was reportedly associated with higher liver fat, triglycerides and alanine aminotransferase (ALT) levels, including a higher frequency of elevation of ALT >/=3 times the upper limit of normal, but without severe, acute drug-induced liver injury[15]. This effect was hypothesized to be secondary to the predominantly hepatic effect of the drug and subsequent failure to suppress peripheral lipolysis[16] or perhaps a unique attribute of the attached polyethylene glycol polymer [17].

Recently, Halberg et al. reported the results of an 8-week randomized controlled trial in which 50 patients with type 2 diabetes were treated with a basal oral insulin preparation, I338, or with insulin glargine[18]. The glycemic efficacy and the rate of hypoglycemia were similar between the two groups[18]. Thus, while I338 seemed to be as efficacious as injected insulin, it did not differ with regards to the narrow therapeutic index of insulin and the risk of hypoglycemia. In contrast, ORMD-0801 was not associated with an increase in hypoglycemia. This was likely due to the difference in the HbA1c-lowering effect observed across the two studies, although a difference in the mechanism of action of ORMD-0801 may have also been responsible for this. Numerous approaches to create oral insulin have been reported in recent years, but to the best of our knowledge, all are in early preclinical or clinical stages of development (including utilization of microparticles, microcapsules and microspheres, use of protease inhibitors, lipid nanocarriers, protein-stabilized multiple emulsion with permeation enhancers, nanocomposite system of organoclay/glycol chitosan/Eudragit((R))S100, inclusion complex based on N-acetyl-L-cysteine and arginine-modified hydroxypropyl-beta-cyclodextrin, virus-mimicking polyelectrolyte complexes, Zein-based nanocarriers amongst others)[19-27].

The strengths of the present study included its randomized, double-blind design, and relatively large sample size. Its limitations included the short washout period, the relatively short exposure period and lack of ORMD-0801 dose titration. Future studies will address these limitations with longer exposure periods and multiple daily dosing regimens.

In conclusion, ORMD-0801 administered at bedtime resulted in a modest but statistically significant anti-hyperglycemic effect without increasing the incidence of hypoglycaemia or adverse events or inducing changes in liver function, when compared to placebo.

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References

1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2015;38(1):140-149.
2. Eldor R, Kidron M, Arbit E. Open-label study to assess the safety and pharmacodynamics of five oral insulin formulations in healthy subjects. *Diabetes Obes Metab.* 2010;12(3):219-223.
3. Arbit E, Kidron M. Oral insulin: the rationale for this approach and current developments. *J Diabetes Sci Technol.* 2009;3(3):562-567.
4. Arbit E, Kidron M. Oral Insulin Delivery in a Physiologic Context: Review. *J Diabetes Sci Technol.* 2017;11(4):825-832.
5. Eldor R, Arbit E, Corcos A, Kidron M. Glucose-reducing effect of the ORMD-0801 oral insulin preparation in patients with uncontrolled type 1 diabetes: a pilot study. *PLoS One.* 2013;8(4):e59524.
6. Standards of Medical Care in Diabetes-2017: Summary of Revisions. *Diabetes Care.* 2017;40(Suppl 1):S4-S5.
7. Aschner P, Kipnes MS, Lunceford JK, et al. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care.* 2006;29(12):2632-2637.
8. Kawamori R, Inagaki N, Araki E, et al. Linagliptin monotherapy provides superior glycaemic control versus placebo or voglibose with comparable safety in Japanese patients with type 2 diabetes: a randomized, placebo and active comparator-controlled, double-blind study. *Diabetes Obes Metab.* 2012;14(4):348-357.
9. Gualandi-Signorini AM, Giorgi G. Insulin formulations--a review. *Eur Rev Med Pharmacol Sci.* 2001;5(3):73-83.
10. Edgerton DS, Lautz M, Scott M, et al. Insulin's direct effects on the liver dominate the control of hepatic glucose production. *J Clin Invest.* 2006;116(2):521-527.
11. Edgerton DS, Kraft G, Smith M, et al. Insulin's direct hepatic effect explains the inhibition of glucose production caused by insulin secretion. *JCI Insight.* 2017;2(6):e91863.
12. Maheux P, Chen YD, Polonsky KS, Reaven GM. Evidence that insulin can directly inhibit hepatic glucose production. *Diabetologia.* 1997;40(11):1300-1306.
13. Edgerton DS, Cardin S, Emshwiller M, et al. Small increases in insulin inhibit hepatic glucose production solely caused by an effect on glycogen metabolism. *Diabetes.* 2001;50(8):1872-1882.
14. Luzi L, DeFronzo RA. Effect of loss of first-phase insulin secretion on hepatic glucose production and tissue glucose disposal in humans. *Am J Physiol.* 1989;257(2 Pt 1):E241-246.
15. Jacober SJ, Prince MJ, Beals JM, et al. Basal insulin peglispro: Overview of a novel long-acting insulin with reduced peripheral effect resulting in a hepato-preferential action. *Diabetes Obes Metab.* 2016;18 Suppl 2:3-16.
16. Riddle MC. Lessons From Peglispro: IMAGINE How to Improve Drug Development and Affordability. *Diabetes Care.* 2016;39(4):499-501.
17. Munoz-Garach A, Molina-Vega M, Tinahones FJ. How Can a Good Idea Fail? Basal Insulin Peglispro [LY2605541] for the Treatment of Type 2 Diabetes. *Diabetes Ther.* 2017;8(1):9-22.
18. Halberg IB, Lyby K, Wassermann K, Heise T, Zijlstra E, Plum-Morschel L. Efficacy and safety of oral basal insulin versus subcutaneous insulin glargine in type 2

diabetes: a randomised, double-blind, phase 2 trial. *Lancet Diabetes Endocrinol.* 2019;7(3):179-188.
19. Wong CY, Al-Salami H, Dass CR. Microparticles, microcapsules and microspheres: A review of recent developments and prospects for oral delivery of insulin. *Int J Pharm.* 2018;537(1-2):223-244.
20. Drucker DJ. Advances in oral peptide therapeutics. *Nat Rev Drug Discov.* 2020;19(4):277-289.
21. Poudwal S, Misra A, Shende P. Role of lipid nanocarriers for enhancing oral absorption and bioavailability of insulin and GLP-1 receptor agonists. *J Drug Target.* 2021:1-14.
22. Kaur I, Nallamothu B, Kuche K, Katiyar SS, Chaudhari D, Jain S. Exploring protein stabilized multiple emulsion with permeation enhancer for oral delivery of insulin. *Int J Biol Macromol.* 2021;167:491-501.
23. Lee SH, Back SY, Song JG, Han HK. Enhanced oral delivery of insulin via the colon-targeted nanocomposite system of organoclay/glycol chitosan/Eudragit((R))S100. *J Nanobiotechnology.* 2020;18(1):104.
24. Li S, Liang N, Yan P, Kawashima Y, Sun S. Inclusion complex based on N-acetyl-L-cysteine and arginine modified hydroxypropyl-beta-cyclodextrin for oral insulin delivery. *Carbohydr Polym.* 2021;252:117202.
25. Liu C, Xu H, Sun Y, Zhang X, Cheng H, Mao S. Design of Virus-Mimicking Polyelectrolyte Complexes for Enhanced Oral Insulin Delivery. *J Pharm Sci.* 2019;108(10):3408-3415.
26. Martinez-Lopez AL, Gonzalez-Navarro CJ, Vizmanos JL, Irache JM. Zein-based nanocarriers for the oral delivery of insulin. In vivo evaluation in Caenorhabditis elegans. *Drug Deliv Transl Res.* 2021.
27. Iyer H, Khedkar A, Verma M. Oral insulin - a review of current status. *Diabetes Obes Metab.* 2010;12(3):179-185.

Figure Legends

Figure 1. Percent mean change from baseline glucose at 4 weeks. Efficacy assessments using continuous glucose monitoring 80% trimmed data, were based on the readings from the two last days during the assessment period (run-in or active treatment), unless technical difficulties precluded calculation of the weighted mean glucose levels. In this case, the last two days with at least 80% of the expected number of measurements were used. Error bars represent standard error of means. **A. Night time glucose:** Night time was defined as 6 hours after dosing; * p=0.0268. **B. 24-hour glucose**. 24-hours were defined as 6AM to 6AM the following day; ** p<0.0001. **C. Fasting glucose:** Fasting was defined as the time period between 5AM to 7AM; **** p=0.0012. **D. Daytime glucose:** Daytime was defined as 6AM to 10PM; † p=0.003.

Table 1. Demographics and Baseline Characteristics by Treatment Group

	Placebo (N=64)	ORMD-0801 16 mg (N=61)	ORMD-0801 24 mg (N=63)	ORMD-0801 pooled (N=124)
Age (Mean ± SD)	58.6±9.2	57.9±8.0	57.3±8.8	57.6±8.4
Men, n (%)	29 (45.3)	39 (63.9)	34 (54.0)	73 (58.9)
Race, n (%)				
White	53 (82.8)	50 (82.0)	55 (87.3)	105 (84.7)
Black or African American	7 (10.9)	8 (13.1)	4 (6.3)	12 (9.7)
Asian	2 (3.1)	2 (3.3)	2 (3.2)	4 (3.2)
Native Hawaiian or Other Pacific Islander	2 (3.1)	1 (1.6)	0 (0)	1 (0.8)
Other	0(0)	0(0)	2 (3.2%)	2 (1.6)
Ethnicity N (%)				
Hispanic or Latino	31 (48.4)	32 (52.5)	36 (57.1)	68 (54.8)
Non-Hispanic or Latino	33 (51.6)	29 (47.5)	27 (42.9)	56 (45.2)
HbA1c	7.9 (0.9)	7.97 (0.9)	8.04 (0.9)	8.01 (0.9)
Fasting blood glucose (mg/dL)	166.03 (41.4)	169.57 (49.7)	162.60 (39.7)	165.9 (44.6)
Subject on ≥1 medication N (%)	36 (56.3)	24 (39.3	24 (38.1)	48 (38.7)
Metformin	8 (12.5)	6 (9.8)	6 (9.5)	12 (9.6)

Sitagliptin	1 (1.6)	0 (0.0)	3 (4.8)	3 (2.4)
Glimepiride	12 (18.8)	4 (6.6)	5 (7.9)	9 (7.3)
Glipizide	14 (21.9)	11 (18.0)	5 (7.9)	16 (12.9)
Glyburide	1 (1.6)	1 (1.6)	2 (3.2)	3 (2.4)
Pioglitazone	1 (1.6)	2 (3.3)	1 (1.6)	3 (2.4)

Table 2. Glucose readings at baseline and after 4 weeks of treatment as obtained from continuous glucose monitoring - 80% trimmed data - ITT population‡

	Placebo (N=58)	ORMD-0801 16mg (N=54)	ORMD-0801 24mg (N=60)	ORMD-0801 pooled (N=114)
Mean nighttime glucose (mg/dL), mean± SD				
N	46	44	47	91
Run-in period	171.4 ± 43.3	173.1 ± 36.6	164.1 ± 43.9	168.4 ± 40.5
Treatment period	185.1 ± 52.7	169.4 ± 33.9	170.7 ± 49.1	170.1 ± 42.2
Change (mg/dL)	13.7 ± 26.1	-3.7 ± 19.0	6.6 ± 26.4	1.7 ± 23.5
p-value†	--	0.0020	0.2118	0.0117
Change (%)	8.5 ± 16.3	-1.3 ± 11.6	5.1 ± 16.9	2.0 ± 14.8
p-value†	--	0.0052	0.3091	0.0268
Mean 24-hour glucose (mg/dL), mean± SD				
N	44	44	46	90
Run-in period	173.5 ± 37.5	173.8 ± 35.9	163.7 ± 35.9	168.6 ± 35.9
Treatment period	186.7 ± 40.8	171.8 ± 36.3	164.9 ± 38.2	168.3 ± 37.2
Change (mg/dL)	13.3 ± 17.5	-2.0 ± 14.5	1.3 ± 17.3	-0.3 ± 16.0
p-value†	--	<0.0001	0.0008	<0.0001
Change (%)	8.0 ± 10.2	-0.8 ± 8.0	1.2 ± 11.2	0.2 ± 9.8
p-value†	--	<0.0001	0.0016	<0.0001
Mean fasting glucose (mg/dL), mean ± SD				
N	46	45	47	92

Run-in period	159.0 ± 33.0	155.4 ± 38.2	152.0 ± 29.7	153.7 ± 33.9
Treatment period	175.0 ± 37.4	155.1 ± 33.9	151.5 ± 35.3	153.3 ± 34.5
Change (mg/dL)	16.0 ± 20.8	-0.3 ± 22.0	-0.5 ± 22.0	-0.4 ± 21.9
p-value†	--	0.0005	0.0003	<0.0001
Change (%)	10.8 ± 13.9	2.1 ± 18.7	0.2 ± 15.5	1.1 ± 17.1
p-value†	--	0.0115	0.0018	0.0012
Mean daytime glucose (mg/dL), mean ± SD				
N	44	43	46	89
Run-in period	178.2 ± 41.2	174.4 ± 41.2	166.4 ± 34.2	170.3 ± 37.7
Treatment period	190.1 ± 44.7	174.9 ± 39.9	167.7 ± 35.8	171.2 ± 37.8
Change (mg/dL)	11.9 ± 17.2	0.5 ± 18.7	1.2 ± 17.4	0.9 ± 17.9
p-value†	--	0.0034	0.0052	0.0010
Change (%)	7.0 ± 10.1	1.0 ± 10.5	1.2 ± 11.2	1.1 ± 10.8
p-value†	--	0.0094	0.0100	0.0030

† Analysis performed comparing to placebo using either a one-way analysis of variance (ANOVA) or a one-way analysis of variance (ANOVA) model on the ranks (Kruskal-Wallis Test) depending on the normality of the residuals.

‡ Efficacy assessments using CGM data were based on the readings from the two last days during the assessment period (run-in or active treatment), unless technical difficulties precluded calculation of the weighted mean glucose levels. In this case, the last two days with at least 80% of the expected number of measurements were used. Nighttime- 6 hours after dosing; 24-hour- 6AM to 6AM; fasting- 5AM to 7AM; daytime- 6AM to 10PM.

Table 3. Measures at baseline and after 4 weeks of treatment - ITT‡ population

	Placebo (N=58)	ORMD-0801 16mg (N=54)	ORMD-0801 24mg (N=60)	ORMD-0801 pooled (N=114)
HbA1c (%)				
N	58	53	59	113
Baseline mean ± SD	7.9 ± 0.9	7.97 ±0.9	8.04 ± 0.9	8.01 ± 0.9
Day 29- End of treatment mean ± SD	8.1 ± 1.0	8.0 ± 1.0	8.0 ± 1.0	8.0 ± 1.0
Change, mean ± SD	0.2 ± 0.5	0 ± 0.5	-0.0 ± 0.6	-0.0 ± 0.5
p-value†		0.0515	0.0232	0.0149
Fasting blood glucose (mg/dL)				
N	57	53	60	113
Baseline mean ± SD	166.03 ±41.4	169.57 ± 49.7	162.60 ± 39.7	165.9 ± 44.6
Day 29- End of treatment mean ± SD	174.7 ± 46.8	170.4 ± 52.0	166.3 ± 48.5	168.2 ± 50.0
Change from baseline, mean ± SD	8.9 ± 26.2	0.65 ± 43.4	3.72 ± 33.2	2.3 ± 38.2
p-value†		0.216	0.4234	0.2376
Morning fasting serum insulin (pmol/L)				
N	58	52	60	112
Baseline mean ± SD	130.32± 87.3	117.53 ± 110.8	118.0 ± 78.4	117.78 ± 94.8
Day 29- End of treatment mean ± SD	125.5 ± 82.3	114.4 ± 75.7	114.9 ± 72.9	114.7 ± 73.9
Change, mean ± SD	-4.82 ± 55.0	-5.32 ± 107.3	-3.65 ± 54.3	-4.4 ± 83.0
p-value†		0.9726	0.9327	0.9777

Morning fasting C-peptide (nmol/L)				
N	58	52	60	112
Baseline mean ± SD	0.89 ± 0.4	0.84 ± 0.5	0.84 ± 0.4	0.84 ±0.4
Day 29- End of treatment mean ± SD	0.9 ± 0.4	0.9 ± 0.4	0.8 ± 0.3	0.9 ±0.4
Change, mean ± SD	-0.0 ±0.3	0.0 ±0.4	-0.0 ± 0.3	-0.0 ± 0.3
p-value†		0.7044	0.8629	0.7475
Morning fasting triglycerides (mmol/L)				
N	58	53	60	113
Baseline mean ± SD	1.86 ± 1.0	1.8 ± 1	1.78 ± 0.8	1.79 ±0.9
Day 29- End of treatment mean ± SD	2.0 ± 1.1	1.9 ± 1.0	1.9 ± 0.9	1.9 ± 0.9
Change, mean ± SD	0.1 ± 0.7	0.1 ± 0.7	0.1 ± 0.7	0.1 ± 0.7
p-value†		0.6647	0.975	0.8127
Weight (kg)				
N	58	54	60	114
Baseline mean ± SD	86.70 ± 16.6	90.78 ± 16.1	86.82 ± 19.8	88.70 ±18.1
Day 29- End of treatment mean ± SD	86.2 ± 16.5	90.5 ± 16.4	86.8 ± 19.7	88.5 ± 18.2
Change, mean ± SD	-0.5 ± 1.6	-0.29 ± 1.6	-0.0 ± 1.6	-0.2 ± 1.6
p-value†		0.3995	0.0889	0.1431
Alkaline Phosphatase (U/L)				
N	62	59	63	
Baseline mean ± SD	88.5 ± 25.7	89.5 ± 25.6	88.0 ± 24.8	
Day 29- End of treatment	83.5 ± 24.8	89.6 ± 26.7	82.7 ± 22.6	

mean ± SD			
Change, mean ± SD	-4.9 ± 13.6	-0.1 ± 15.2	-5.2 ± 12.4
p-value†		0.0546	0.9168
ALT (U/L)			
N	62	59	62
Baseline mean ± SD	29.3 ± 15.9	28.7 ± 11.2	30.1 ± 12.7
Day 29- End of treatment mean ± SD	32.6 ± 19.1	32.0 ±14.7	30.7 ± 16.0
Change, mean ± SD	3.6 ± 10.0	3.0 ± 10.7	0.7 ± 10.0
p-value†		0.7689	0.1221
AST (U/L)			
N	62	59	62
Baseline mean ± SD	24.4 ± 9.2	24.3 ± 7.9	25.0 ± 9.6
Day 29- End of treatment mean ± SD	25.8 ± 11.1	26.4 ± 12.5	25.4 ± 11.4
Change, mean ± SD	1.5 ± 6.8	1.9 ± 11.3	0.5 ± 7.8
p-value†		0.8355	0.4941
Bilirubin, total (mg/dL)			
N	62	59	63
Baseline mean ± SD	0.5 ± 0.2	0.6 ± 0.3	0.5 ± 0.3
Day 29- End of treatment mean ± SD	0.5 ± 0.3	0.6 ± 0.4	0.5 ± 0.3
Change, mean ± SD	0.0 ± 0.1	-0.0 ±0.2	-0.0 ± 0.2
p-value†		0.1033	0.2253
Systolic blood pressure (mmHg)			

N	63	60	63	
Baseline mean ± SD	126.5 ± 13.8	128.1 ± 14.2	123.8 ± 12.9	
Day 29- End of treatment mean ± SD	125.8 ± 13.7	129.0 ± 16.0	124.8 ± 14.8	
Change, mean ± SD	-0.6 ± 11.5	0.9 ± 11.3	1.0 ± 11.8	
p-value†		0.4859	0.441	
Diastolic blood pressure (mmHg)				
N	63	60	63	
Baseline mean ± SD	77.8 ± 9.4	76.8 ± 7.7	76.8 ± 8.8	
Day 29- End of treatment mean ± SD	77.5 ± 8.5	77.2 ± 8.4	75.8 ± 8.6	
Change, mean ± SD	-0.2 ± 7.4	0.2 ± 8.1	-1.1 ± 7.2	
p-value†		0.7758	0.5193	
C-Reactive Protein (mg/L)				
N	57	53	57	110
Baseline mean ± SD	6.55 ±10.7	3.90 ± 3.9	4.46 ± 4.6	4.19 ±4.3
Day 29- End of treatment mean ± SD	6.26 ± 6.4	4.04 ± 4.1	5.61 ± 7.5	4.85 ± 6.2
Change, mean ± SD	-0.28 ± 9.9	0.15 ± 4.1	1.15 ± 6.8	0.67 ± 5.7
p-value†		0.7624	0.3045	0.4438

†Analysis performed comparing to placebo using a one-way analysis of variance (ANOVA) model.

‡ ITT- intention to treat

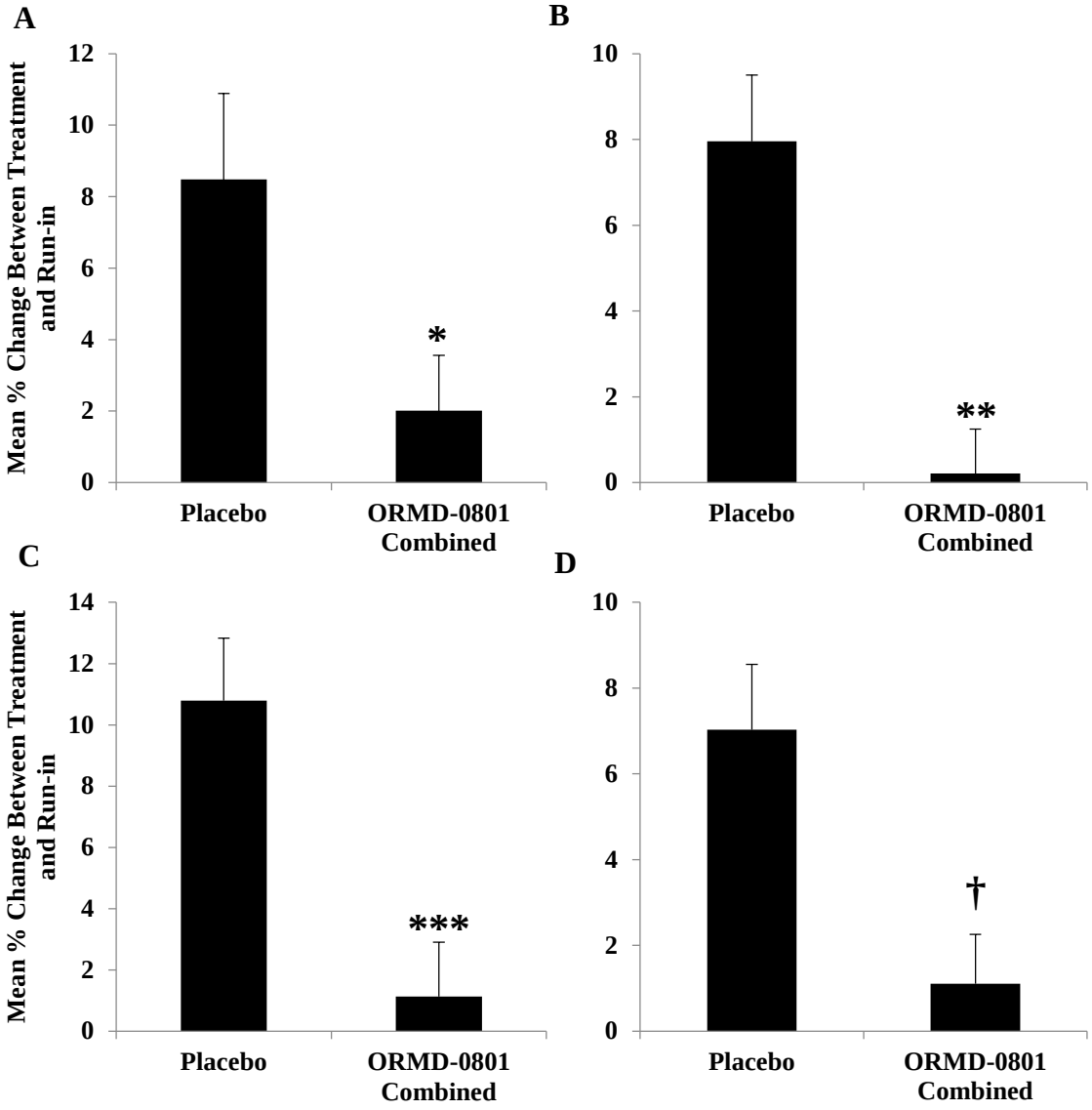

Figure 1.