Extended exposure to an oral insulin formulation yields decreased insulin secretion in Type II diabetes subjects

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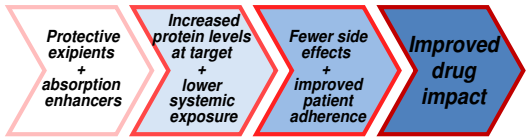
Introduction

Use of oral insulin preparations would reduce discomfort, and are likely to foster patient compliance and adherence as well as the prospects of early insulin intervention regimens in early T2DM. Of no less importance, due to their hepato-portal route of delivery, direct engagement of the liver and the significant insulin sequestration upon first-pass metabolism by this organ, such oral formulations are expected to significantly reduce risk of hypoglycemia and systemic hyperinsulinemia. Thus, Oramed Pharmaceuticals has set out to apply its oral protein-delivery platform toward development of an effective insulin capsule. The technology focuses on preventing degradation of active ingredients within the gastrointestinal tract and promoting gastrointestinal absorption.



Objectives

To evaluate the safety, tolerability and efficacy of oral insulin versus placebo, administered over a treatment period of 6 weeks in patients with Type II Diabetes Mellitus (T2DM) currently on diet alone, or diet and monotherapy with Metformin. Focus was to be placed on the incidence of nocturnal hypoglycemia.

Methods

This work was a Phase IIb multi-site, placebo-controlled, randomized, double-blind study evaluating the responses of 29 T2DM patients to ORMD-0801. Twenty one (21) volunteers received a once-daily fixed dose capsule (8 mg/capsule, 2 capsules/day) at bed-time, for a period of six weeks, while eight (8) received placebo capsules for the same period of time and under the same administration regimen. Three subjects were otherwise on diet, while 26 were on diet + Metformin (<2.5 g/day) management programs before the start of the study. Blood samples of fasting subjects were drawn on the mornings of the start of the study (wk 0) and the end of the study (wk 6) and prestudy versus poststudy insulin, C-reactive protein (CRP), c-peptide, fasting blood glucose, fructose-amine and Hb1Ac levels were compared. Safety and tolerability were assessed by monitoring adverse events (AEs), hypoglycemia, vital signs, laboratory biochemical markers and subject physical wellbeing.

Results

The 6-week ORMD-0801 treatment regimen proved safe and tolerable, with no reports of serious AEs throughout the study period. No cumulative effects of extended exposure to ORMD-0801 were observed, and only two mild hypoglycemic events were recorded in patient diaries (Table 1).

Event	Severity	Action	Outcome	Notes
Hypoglycemia	Mild	Dose not changed	Recovered	Blood sugar: 12.0 mmol/L
Hypoglycemia	Unknown	Unknown	Unknown	Hypoglycemic on clinical symptoms
Constipation	Mild	Dose not changed	Not recovered	
Diarrhea and skin rash	Mild	Dose not changed	Recovered	
Diarrhea	Mild	Dose not changed	Recovered	
Increased bowel movement	Mild	Not applicable	Recovered	

*** No adverse events were reported for the placebo cohort**

Efficacy evaluations were performed on blood samples of 21 patients on oral insulin and 8 patients on placebo. Mean decreases in insulin and CRP levels were found to be statistically significant following the 6-week, once-daily ORMD-0801 treatment period, when compared to the placebo group (Figure 1A). In contrast, placebo-treated subjects demonstrated elevated insulin and CRP levels at the end of the treatment period. These findings suggest that bed-time ORMD-0801 lowers ambient glucose levels possibly by restraining hepatic glucose output overnight. Such action then yields decreased requirements for endogenous insulin secretion, offering temporary beta-cell relief. Moreover, the percentage of subjects demonstrating clinically relevant reductions in insulin, c-peptide, FBG and Hb1Ac levels was consistently higher in the ORMD-0801 cohort, when compared to the placebo, with maximal variances measured for the number of CRP and fructose-amine responders, followed by c-peptide and insulin responders (Figure 1B).

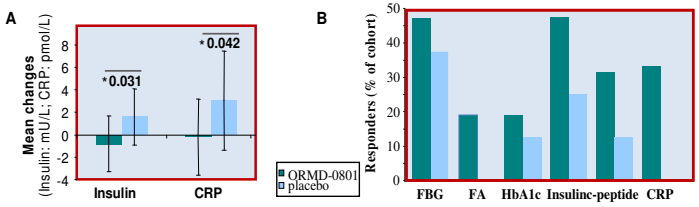


Figure 1. Plasma marker responses and percent responders to a six-week, daily oral ORMD-0801 regimen T2DM patients were treated once daily with a 16 mg insulin ORMD-0801 formulation or placebo capsule. Blood samples drawn at the start of the study and after a 6-week treatment period were tested for marker levels. **A**. Mean changes (±SD) in plasma and CRP levels between the samples of days 0 and samples taken after the 6-wk treatment period are presented. p-values are depicted above each set of bars. **B.** Subjects demonstrating a decrease of ≥ 0.5 mmol/L in FBG, ≥40 µmol/L fructose-amine (FA), ≥ 0.6% Hb1Ac, ≥ 1 mU/L insulin, ≥ 100 pmol/L c-peptide or ≥ 1 mg/L CRP were considered responders for that specific marker. The number of responders for each tested marker is presented as the percent of the total number of subjects analyzed for the given parameter.

- SAFE
- TOLERABLE
- NO ADVERSE CUMULATIVE EFFECTS
- GRADUAL RECTIFICATION OF INSULIN PROFILES

Conclusions

The reported results allay the concern that bed-time oral insulin will cause hypoglycemia. Furthermore, the results substantiate the overall safety and tolerability of ORMD-0801 and demonstrate a relevant clinical impact of ORMD-0801 at the tested dose. The small sample size and placebo effect, thoroughly described in the literature for diabetes management studies, contributed to the often insignificant outcomes in baseline vs. post-treatment marker levels. However, this first analysis of long-term exposure to ORMD-0801, proved its safety and tolerability, and will lay the foundation for further testing in larger populations.

For More Information: www.oramed.com

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