

Open -Label Study to Assess the Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Oral Insulin Formulation in Subjects with Type 2 Diabetes (T2DM)

Miriam Kidron¹, Ehud Arbit¹, Roy Eldor¹, Katrin Kessler², Herve Schwob², Christian Schrufer²
¹Diabetes Unit, Hadassah University Hospital, and Oramed Pharmaceuticals Jerusalem Israel, ²Swiss Caps, Kirchberg Switzerland

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Introduction:

Oramed Pharmaceuticals has developed an oral insulin dosage form (ORMD-0801) based on its proprietary technology. The encapsulated dosage form contains unmodified recombinant human insulin combined with adjuvants which protect the insulin from enzymatic degradation in the gastrointestinal tract and facilitate its absorption through the epithelial lining of the gut.

ORMD-0801 oral insulin formulations are currently being advanced as alternatives to parenteral insulin delivery and may offer patients a number of advantages including:

- (1) Replication of the natural route of endogenous pancreatic insulin secretion
- (2) Low risk of hypoglycemia due to first-pass hepatic extraction of the bulk of the insulin absorbed in the GIT.
- (3) Avoidance of hyperinsulinemia
- (4) As an oral drug, delivered via a preferred route of administration, ORMD-0801 may offer the opportunity to begin insulin therapy at early stages of diabetes, potentially foster more compliance and adherence among patients and consequentially improve treatment outcome.

Objectives:

- a) To assess the safety and tolerability of ORMD-0801 on its first exposure in Type 2 diabetic patients
- b) To assess the pharmacodynamics and pharmacokinetics of various ORMD-0801 formulations

Results:

All formulations were well tolerated and safe, with Formulations J and K showing most profound effects on reduction in glucose, c-peptide and rise in plasma insulin. Insulin T_{max} was observed at approximately 150 minutes post-ingestion (range: 130-200 min), where its levels returned to baseline within 30-40 minutes (Figure 1A). In parallel, T_{max} for glucose and c-peptide were observed at a mean 40 minute latency from the insulin peak (Figure 1 B-C). Glucose area under the curve (AUC)_{120-180/0-60} and AUC_{180-240/0-60} ratios were 7.5% and 7% lower in ORMD-0801-treated subjects, respectively, in comparison to placebo-treated subjects (Figure 2A, p=0.049, p=0.07, respectively). Similarly, mean c-peptide AUC_{180-240/0-60} estimations demonstrated significantly lower ratios for ORMD-0801-treated subjects (78.8%) in comparison to placebo-treated subjects (89.6%) (Figure 2B, p=0.03)

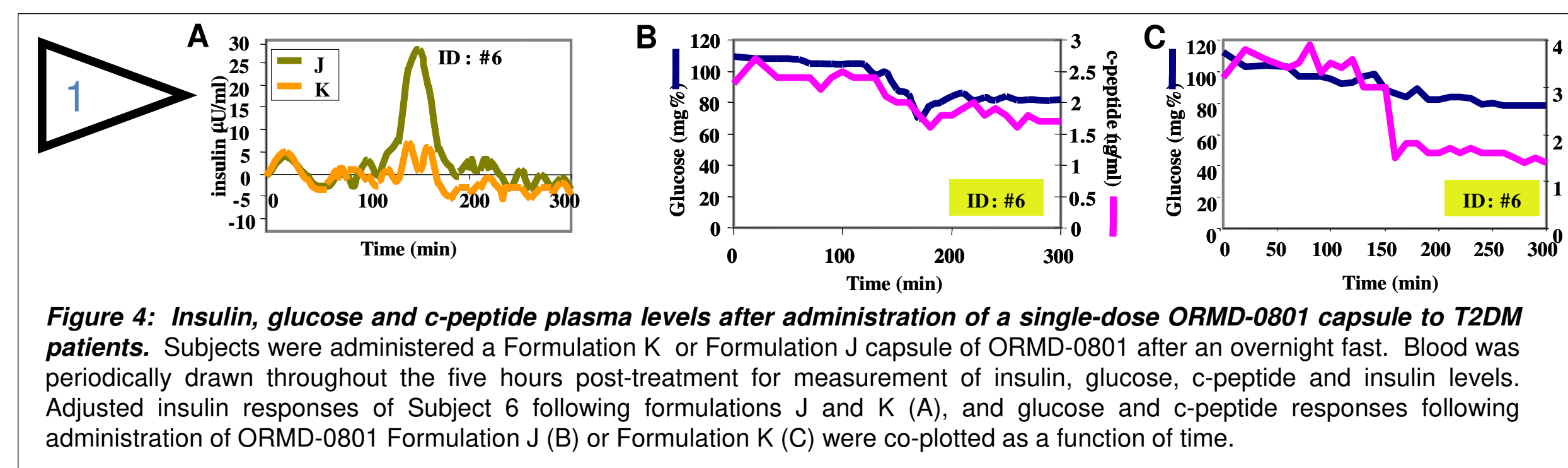


Figure 4: Insulin, glucose and c-peptide plasma levels after administration of a single-dose ORMD-0801 capsule to T2DM patients. Subjects were administered a Formulation K or Formulation J capsule of ORMD-0801 after an overnight fast. Blood was periodically drawn throughout the five hours post-treatment for measurement of insulin, glucose, c-peptide and insulin levels. Adjusted insulin responses of Subject 6 following formulations J and K (A), and glucose and c-peptide responses following administration of ORMD-0801 Formulation J (B) or Formulation K (C) were co-plotted as a function of time.

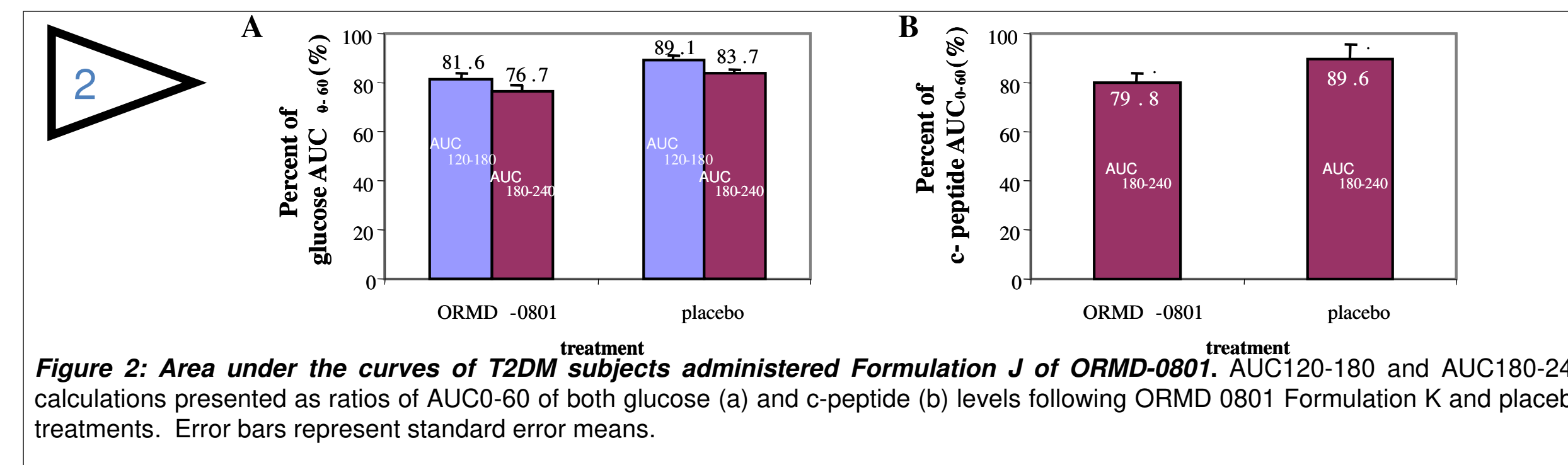


Figure 2: Area under the curves of T2DM subjects administered Formulation J of ORMD-0801. AUC₁₂₀₋₁₈₀ and AUC₁₈₀₋₂₄₀ calculations presented as ratios of AUC₀₋₆₀ of both glucose (a) and c-peptide (b) levels following ORMD 0801 Formulation K and placebo treatments. Error bars represent standard error means.

Experimental Methods:

Nine Type 2 diabetes subjects (ages: 35-69, BMI 23-30.9, HbA1c 6.5-7.9. %) , 4 diet-treated and 5 metformin-treated received a placebo capsule or one of five different ORMD-0801 formulations of oral insulin capsules on six independent visits. Sessions were separated by a 72-96 hour washout period. The formulations varied in their ratio of adjuvant per capsule, while the insulin dose remained fixed. Assayed PK and PD parameters included insulin C_{max}, T_{max}, glucose and c-peptide levels and corresponding area under the curve (AUC).

Summary and Conclusions:

- The results of this study performed in subjects with Type 2 diabetes demonstrated that ORMD-0801 oral insulin:
1. Is safe and well tolerated in this subject population.
 2. ORMD-0801 administration results in a reduction in glucose and c-peptide levels.
 3. ORMD-0801 yields unique PK and PD effects characterized by a delayed onset of action and a prolonged metabolic effect.

ORMD-0801 oral insulin may have great potential as a antihyperglycemic agent in a stand alone or in combination treatment regimen. Furthermore, ORMD-0801 may be influential at various stages of diabetes progression, namely from impaired glucose tolerance (IGT) and early stage T2DM to the more advanced disease. Future clinical studies to establish the optimal indications for ORMD-0801 oral insulin as well as its effect in heterogenous patient populations are planned.

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