# Open Label Study to Assess the Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Five Oral Insulin Formulations in Healthy Subjects

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## Introduction:

An estimated 246 million people worldwide are affected by diabetes (T2DM). With a further 7 million people developing diabetes each year, that number is expected to reach 380 million by 2025. Despite the availability of many different types of medications to treat T2DM, less than one half of patients reach target glycosylated hemoglobin ($HbA_{1c}$) levels. Because of this high prevalence and the difficulty patients experience reaching targets for glycemic control, research of new agents to improve the management of T2DM are actively pursued. Over the past few years, a number of new medications have been approved for clinical use. With the exception of the DPP-IV inhibitors, none of the recently approved diabetes medications are administered orally.

Oramed is developing an oral dosage form of insulin based on its proprietary drug delivery technology, which facilitates the absorption of peptides and proteins across biological membranes. Preclinical studies in dogs and clinical studies in healthy volunteers have shown that when insulin given orally in a prototypical formulation, and combined with Oramed's drug delivery agents is absorbed, reduces glucose levels and decreases c-peptide levels. The objective of this study, part of a formulation optimization study, was to assess the safety, pharmacokinetic (PK) and pharmacodynamic (PD) profiles of five oral insulin formulations in healthy subjects. The formulations consisted of 1 capsule containing 8 mg of insulin and 5 different concentration of Oramed's absorption enhancing agents.

## Methods:

Eight healthy male volunteers (mean age 26 years, BMI 24 kg/m²) participated in this 5-period, cross-over study. Subjects were dosed after an overnight fast and each consecutive visit was separated by a 72 to 96 hours washout period. The formulations consisted of 1 capsule containing 8 mg of insulin and 5 different concentration of Oramed's absorption enhancing agents. Individual blood samples (29 totals) for PK/PD analysis were collected up to 5 hours post-dose. Pharmacodynamic effects were assessed by measuring the effects of the formulation on glucose, insulin and c-peptide.

## Results:

Administration of an oral form of insulin in the fasted state demonstrated a significant decrease in c-peptide levels in all formulations (16%-92%) as well as reduction in blood glucose (7%-32%). All of the formulations were well tolerated by the volunteers, and no serious adverse events have been reported. A lead formulation was identified.

## Discussion:

Oral delivery of proteins and peptide drugs remains a major challenge because of their unique physico-chemical and biologic properties. Oramed's proprietary technology has been demonstrated to effectively deliver these molecules in preclinical and early clinical studies. In the current study 5 different formulations were assessed, and all were found to be safe and showed a salutary PD profile. The most apparent effects observed were on c-peptide and glucose. C-peptide co-secreted in equimolar concentration with insulin from the β-cell is not metabolized by the liver and thus reflects accurately the effects of exogenous insulin administration. The pharmacokinetics and pharamcodynamics of this specific enteric coated formulation are characterized by a delayed absorption and onset of action and effect (Figs 3,4).

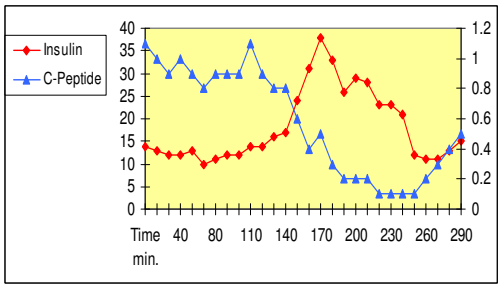


Fig 1. Representative case: Demonstrates an inverse correlation of insulin and C-peptide.

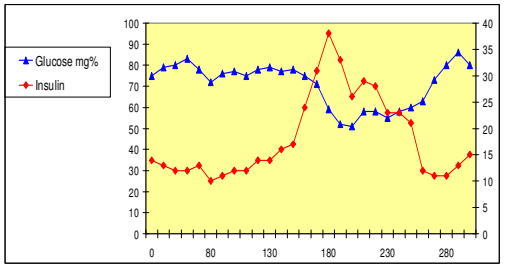


Fig 2. Same case as above: Demonstrates an inverse correlation of insulin and glucose.

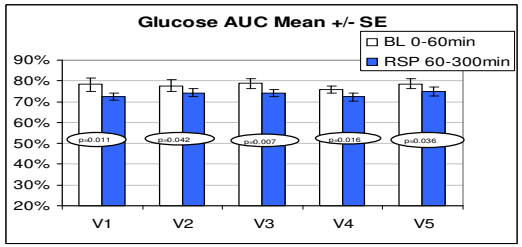


Fig 3. Mean glucose AUC. Delayed reduction observed across the five formulations.

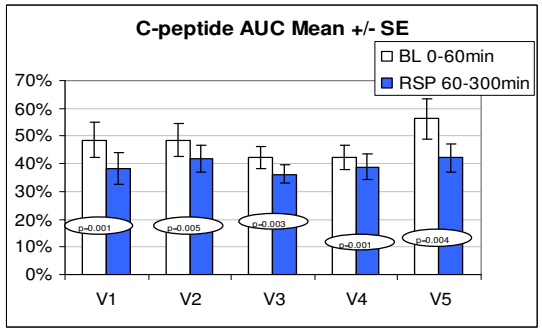


Fig 4. Mean C-peptide AUC. Reduction (delayed) observed across the five formulations.

## Conclusions:

The results of this study in healthy volunteers showed that insulin combined with Oramed's drug delivery enhancers and formulated in a capsule dosage form is absorbed and results in plasma glucose reduction, c-peptide decrease and insulin increase. The Pk and Pd of the current formulation suggests a potential clinical utility in IGT and early stage T2DM as a supplement to endogenous insulin. Supplementing endogenous insulin is likely to reduce the burden of the "overtaxed" β-cells as suggested by the observed consistent reduction in c-peptide in this study, and allow for β-cell "sparing".

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