

# Preservation of oral insulin bioavailability using a recombinant protease inhibitor

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## BACKGROUND

Oral insulin delivery is projected to provide both physiologic and technical benefits in diabetes management, and has been the focus of rigorous research efforts in recent years. The ORMD-0801 oral insulin formulation relies on the activities of both a soybean-extracted protease inhibitor and an absorption enhancer to ensure insulin integrity and bioavailability. The unique blend of excipients both hinders proteolysis in the small intestine and enhances translocation of insulin across the gut epithelial lining. Once transported across the gut wall, the insulin is ferried to the hepatic portal vein, mimicking the natural route of endogenous pancreatic insulin, and then subjected to first-pass metabolism in the liver, before being delivered to peripheral sites of action. In efforts to establish a more cost-effective source of protease inhibitor, a recombinant Bowman-Birk inhibitor (rBBI), identical in sequence to its natural counterpart, was cloned, expressed and purified.

## OBJECTIVES

❖ To assess the efficacy of increasing concentrations of rBBI as compared to its soybean-extracted counterpart

## METHODS

The base ORMD-0801 formulation was prepared with increasing doses of good manufacturing practice (GMP)-grade rBBI (Formulations A, B and C: 25 mg, 50 mg, 75 mg rBBI, respectively) or with 25 mg rBBI along with 25 mg soybean derived trypsin inhibitor (Kunitz trypsin inhibitor [KTI]) (Formulation D). All samples contained 2 mg insulin/mL. The test ORMD-0801 formulations (1 mL) were delivered directly to the duodenum of 4 healthy, fasting pigs and the glucose-lowering effect was monitored over a 5-hour period. Blood samples were drawn periodically, to determine glucose concentrations.

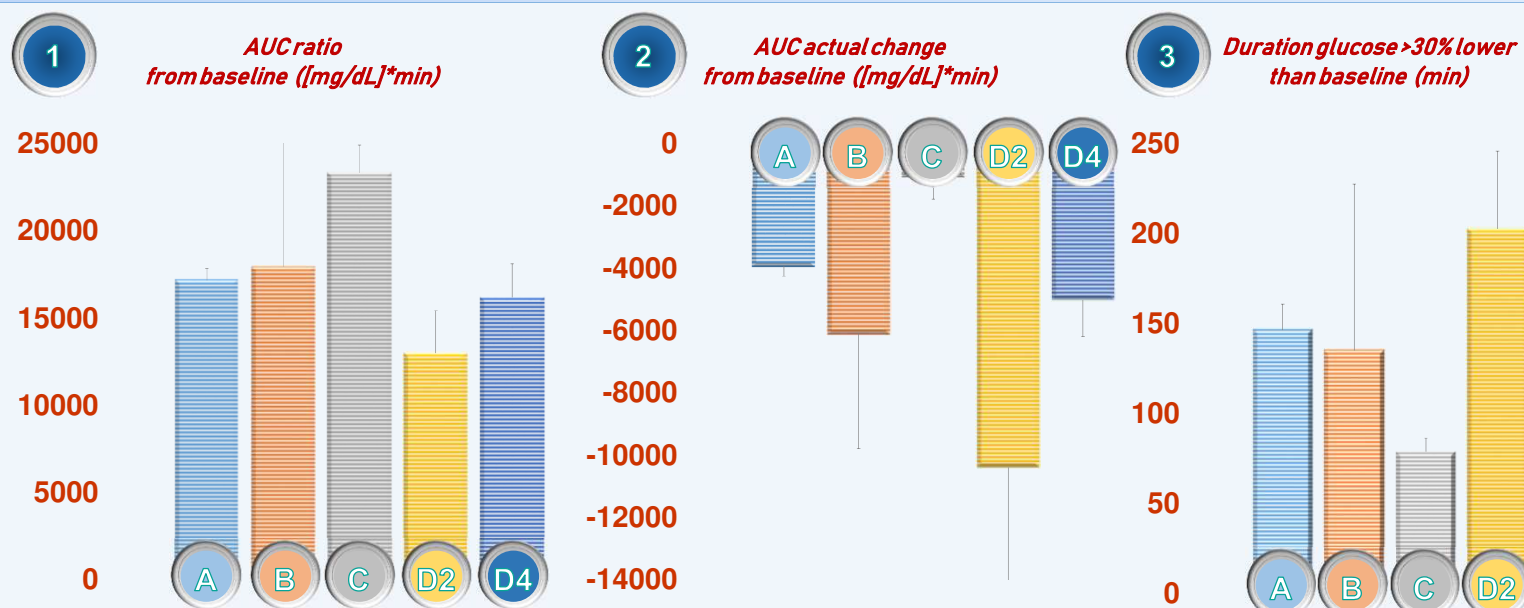
## RESULTS

Pigs treated with ORMD-0801 Formulation D experienced the greatest change from baseline serum glucose concentrations ( $-10403.0$  [mg/dL]\*min) as compared to the other tested formulations (Figure 2). In parallel, the duration of time in which glucose levels remained  $>30\%$  lower than baseline levels was considerably longer following treatment with Formulation D ( $203 \pm 43$  min) as compared to Formulations A, B or C ( $146 \pm 14$  min,  $135 \pm 93$  min and  $79 \pm 8$  min, respectively) (Figure 3). When compared to a previous study testing Formulation D prepared with 4 mg insulin (D4), a greater glucose-lowering effect was achieved with the 2 mg (D2) as compared to the 4 mg insulin dose (Figure 1-2).

## CONCLUSIONS

GMP rBBI preserves oral insulin bioavailability and exhibits a synergistic effect when mixed with KTI, reaching saturation at the tested PI:insulin ratio. Its protective effect on insulin exposed to the harsh conditions of the gastrointestinal tract will likely improve the clinical potential and value of orally delivered insulin. GMP rBBI will soon be tested in a first-in-human clinical trial to confirm its effectiveness in patients with type 1 diabetes mellitus.

### GLUCOSE-LOWERING EFFECT OF ORMD-0801 INTEGRATING rBBI



mean (SD) are presented: A, B, C, D2: n=4; D4: n=3