Glucose- and Glucagon-Lowering Effect of a Single Oral Leptin Dose in Type 1 Diabetes Patients

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Abstract: 121-LB

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BACKGROUND/OBJECTIVE

LEPTIN and T1DM

While historically thought to be involved in long-term regulation of appetite and energy expenditure, leptin is now known to regulate food absorption, mucus secretion, intestinal motility and inflammatory processes. Leptin was shown to directly inhibit glucose uptake and reduce glucagon levels and insulin requirements in NOD mice, to ameliorate hyperglycemia in a T1D mouse model, and reduce insulin requirements in patients with insulin-resistant diabetes.

Tx BARRIERS

Leptin-based drugs are currently only available in injectable forms, and suffer from a short half-life in the circulation. Oral protein-based drugs are poorly absorbable owing to their high molecular weight and hydrophilicity, and are susceptible to mechanical and enzymatic degradation along the gastrointestinal tract.

ORMD-0701

ORMD-0701 is a novel oral human leptin formulation, which integrates both a species-specific protease inhibitor that provides a protective environ for active ingredients, and a potent absorption enhancer that promotes absorption of the active ingredient across the intestinal epithelium.

OBJECTIVE

This first-in-human, placebo-controlled trial, aimed to assess the safety and short-term effects of a single ORMD-0701 dose (3 mg leptin) administered to fasting patients with T1D.

DESIGN AND INCLUSION CRITERIA

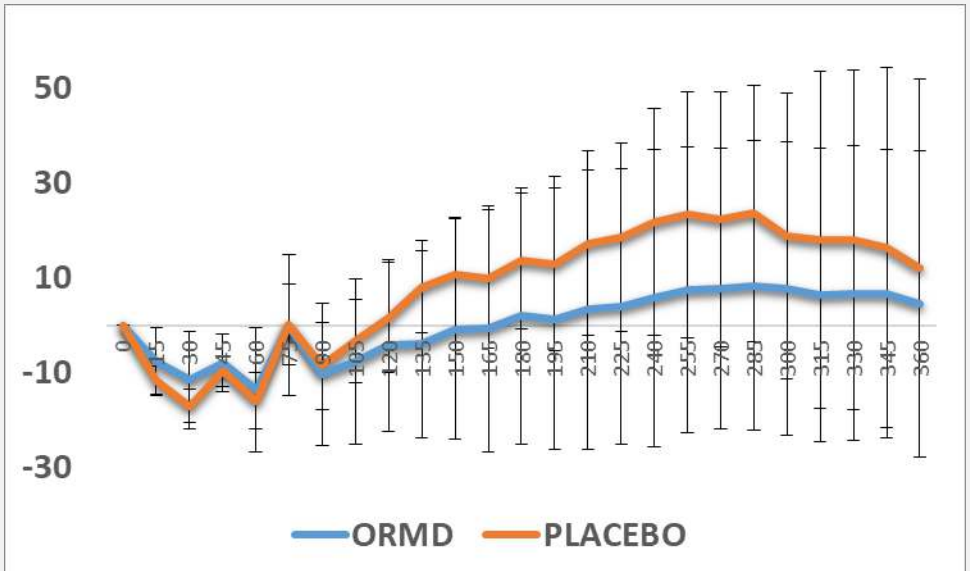
INCLUSION/EXCLUSION CRITERIA

- Adult (ages 18-50) T1DM patient
- Treated with insulin pump
- Glucose >100 mg% and <280 mg%
- No additional hypoglycemic treatments
- No gastrointestinal disease
- Informed consent

Patient Demographics and Baseline Characteristics

	PLACEBO N=3	ORMD-0701 N=7
Sex, n (%) Male	3 (100)	7 (100)
Race, n (%) White	3 (100)	7 (100)
Age, (y) Mean [Std]	29.6 (3.8)	30.7 (10.6)
BMI, (m/kg^2) Mean [Std]	25.9 (3.8)	26.5 (5.1)
Fat, (%) Mean [Std]	17.5 (6.5)	21.2 (8.3)
Time from diagnosis, (y) Mean [Std]	16.7 (5.7)	15.6 (6.7)
Diabetes meds, (n) Humolog Novorapid	 1 2	 4 3

GLUCOSE – PERCENT CHANGE FROM BASELINE



AUC Mean Change from Baseline	ORMD0701	PLACEBO
AUC_{30-120}	-0.43	0.24
AUC_{30-150}	-0.25	0.49
AUC_{30-180}	-0.06	0.66

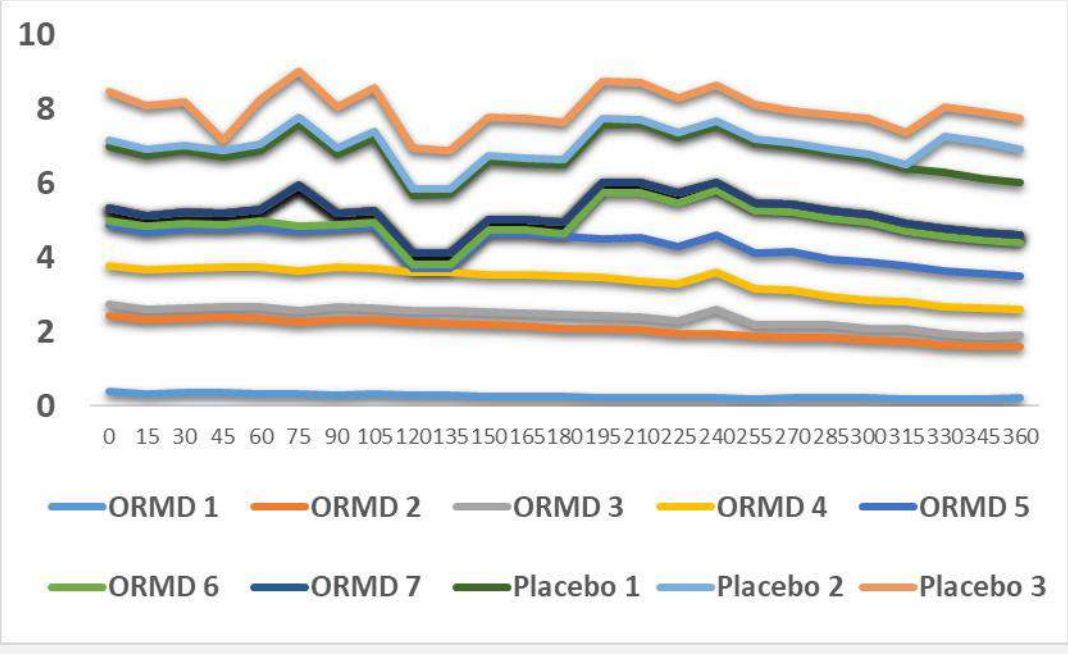
Glucose change from baseline AUC_{30-120} was -0.43 mmol*min/L in the active group versus 0.24 mmol*min/L in the placebo group.

GLUCAGON – PERCENT CHANGE FROM BASELINE

AUC Mean Change from Baseline	ORMD0701	PLACEBO
$AUC_{30\text{-}90}$	**-0.61**	**-0.39**
$AUC_{105\text{-}165}$	-0.45	-1.13
$AUC_{180\text{-}240}$	1.43	-0.95
$AUC_{255\text{-}315}$	0.63	-1.13
$AUC_{330\text{-}360}$	-0.78	-0.46

Glucagon change from baseline $AUC_{30\text{-}90}$ was -0.61 ng*min/L and -0.39 ng*min/L in the active and placebo treatment groups, respectively.

LEPTIN (NG/ML)

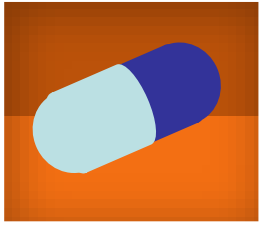


No significant changes in blood leptin levels were detected in either cohort.

CONCLUSION

A single dose of ORMD-0701 was safe and tolerable.

ORMD-0701 had a transient glucose-lowering effect.



These preliminary findings set the stage for further assessment of oral leptin and its impact on normalizing glucose levels in patients with T1DM.