Title: CagriSema improves insulin sensitivity in diet-induced obese rats

Author names and affiliations:

Rishi Handa*, Anna Secher[1], Christian L Brand[2], Kirsten Raun[1]

[*]Durham Care Organization, Ontario, Canada

[1]Global Drug Discovery, Novo Nordisk A/S, Søborg, Denmark

[2]Global Drug Discovery, Novo Nordisk A/S, Måløv, Denmark

***Presenting author:** Dr. Rishi Handa, MD, ABIM

Email: rishi@durhamcare.ca

Abstract (Word count: 250/250)

Background: CagriSema combines cagrilintide (long-acting analogue of amylin) and semaglutide (glucagon-like peptide-1) and is undergoing clinical development for obesity and type 2 diabetes treatment. In preclinical studies, CagriSema resulted in weight loss. This study aims to investigate changes in insulin sensitivity with CagriSema in diet-induced obese (DIO) rats.

Methods: DIO male rats (n=6 per group) were treated with vehicle control (VC), CagriSema [2 nmol/kg] or VC weight-matched (WM) to CagriSema by calorie-restriction. Groups were stratified by body weight (BW), fat- and fat-free mass, and instrumented for sampling after 21-days of treatment. Post-recovery (9-11 days), rats were subjected to a 180-minute hyperinsulinemic (15 pmol/kg/min) and euglycemic (~5.7 mM) clamp. Hepatic glucose production (HGP), glucose uptake (GU), and tissue-specific 2-deoxy-glucose (2DG) uptake were measured by ^{3}H-glucose and ^{14}C-2-deoxy-glucose.

Results: CagriSema-treated rats needed 10% less food intake than WM-treated rats, yet both groups lost ~10% BW, suggesting metabolic adaptation by CagriSema. Baseline plasma insulin decreased by 40% in CagriSema-treated group versus VC ($p<0.03$), suggesting increased insulin sensitivity, without effect on fasting plasma glucose. Compared to VC, in clamp glucose infusion rates (GIR) increased in CagriSema (4.2-fold, $p<0.001$) and WM (2.6-fold, $p=0.097$) and GU by 3.3-fold ($p=0.002$) and 1.6-fold (p=NS), respectively. A higher 2DG uptake in muscle was seen in CagriSema-treated compared to VC with no significant differences in HGP between groups.

Conclusion: CagriSema resulted in increased insulin sensitivity and glucose metabolism compared with VC in DIO rats; partly explained by weight loss (GIR was numerically, not significantly higher [65%, $p=0.079$] Cagrisema vs. WM).

Conflict of Interest: Dr. Rishi Handa, MD, ABIM has received research grant from Abbott, Amgen, AstraZeneca, Bausch Health, Bayer, Boehringer Ingelheim, Dexcom, HLS, Janssen, Lilly, Novartis, Novo Nordisk, Pfizer, Sanofi; serves as a consultant for Bayer, Boehringer Ingelheim, Novo Nordisk; received speakers' bureau from Abbott, Amgen, AstraZeneca, Bausch Health, Bayer, Boehringer Ingelheim, Dexcom, HLS, Janssen, Lilly, Novartis, Novo Nordisk, Pfizer, Sanofi.

Financial support: Research relating to this abstract was funded by Novo Nordisk A/S.