Design of SAR441255, a potent unimolecular peptidic triple GLP-1/GIP/GCG receptor agonist and its effects on weight loss and glycemic control

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Unimolecular triple incretins, combining the activity of glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) and glucagon (GCG), have demonstrated reduction in body weight and improved glucose control in rodent models. We developed SAR441255, a synthetic peptide agonist of the GLP-1, GIP and GCG receptors structurally based on the exendin-4 sequence. SAR441255 displays high potency with balanced activation of all three target receptors. In animal models, metabolic outcomes were superior to results with a dual GLP-1/GCG receptor agonist. Preclinical in vivo positron emission tomography imaging demonstrated SAR441255 binding to GLP-1 and GCG receptors. In healthy subjects, SAR441255 improved glycemic control during a mixed meal tolerance test and impacted biomarkers for GCG and GIP receptor activation. Single doses of SAR441255 were well tolerated. The results demonstrate that integrating GIP activity into dual GLP-1 and GCG receptor agonism provides improved effects on weight loss and glycemic control while buffering the diabetogenic risk of chronic GCG receptor agonism.

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