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CagriSema: Emerging Data on a New Treatment Option for Patients with Diabetes

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Abstract

A combination medication of cagrilintide and semaglutide (CagriSema), an amylin analogue and a glucagon-like peptide-1 receptor agonist (GLP-1 RA), is in phase II studies for the treatment of type 2 diabetes mellitus (T2DM). The long-acting effects of both medications offer a unique option for those in need of glycemic reductions in addition to weight loss. While to date, the combination medication has shown promising results in both overweight/obesity and T2DM, the phase III REDEFINE program plans to further evaluate cagrilintide with semaglutide for benefits in people with other chronic disease states such as cardiovascular disease. This review serves to present a summary of the emerging data for cagrilintide with semaglutide as it relates to T2DM.

Keywords: Cagrilintide; Semaglutide; CagriSema; Pharmacological Treatment; Glucose Cotransporter-2; Cardiovascular Disease

Abbreviations: CGM: Continuous Glucose Monitor; TIR: Time In Range; FPG: Fasting Plasma Glucose; SGLT2i: Sodium Glucose Cotransporter-2 Inhibitors; RAMP(1-3): Receptor Activity Modifying Proteins 1,2,3; ADA: American Diabetes Association; CDC: Control and Prevention

Introduction

Obesity is commonly recognized as a risk factor for the development, progression and potential worsening of many chronic conditions, such as hypertension, hyperlipidemia and type 2 diabetes (T2DM). The prevalence of chronic disease, for example diabetes and cardiovascular disease, continues to increase over time, impacting patients and the healthcare system overall [1]. The Center for Disease Control and Prevention (CDC) estimates the current prevalence of obesity in adults at 41.9% of the US population, while diabetes prevalence is estimated at 11.3% [2,3]. When analyzing the correlation between obesity and diabetes, it becomes clear that these disease states directly impact each other. The American Heart Association reports that obesity contributes to approximately 30-53% of new diabetes cases in the US each year [4]. Current literature supports recommendations associated with weight loss and the prevention and progression of T2DM. Hamman et al. demonstrated that regardless of race, ethnicity, sex and/or age, weight loss reduces the incidence of diabetes [5]. For people with diabetes, weight loss contributes to improvement in glycemic control and insulin sensitivity [6-8]. Furthermore, there is evidence to suggest there is improvement in blood pressure and cholesterol management coupled with weight loss [7]. Better control of associated cardiovascular disease states may lead to an overall reduction in macrovascular complications connected to T2DM. Given the vast number of cases of diabetes and obesity and the correlation between them, the American Diabetes Association (ADA) has placed emphasis on recommendations for lifestyle behavior changes and weight loss for the prevention and progression of T2DM [9,10]. In view of all available data and current recommendations from the ADA, pharmacological treatment options that target both weight loss and T2DM greatly impact patients. CagriSema (cargrilintide/semaglutide) is a unique combination option that may help reduce medication burden while targeting glycemic control and weight loss.

Mechanism of Action

CagriSema is a long-acting combination medication consisting of semaglutide and cargrilintide. Semaglutide is an incretin mimetic that binds to and activates GLP-1 receptors to perform numerous actions including but not limited to glucose dependent insulin production, decrease glucagon secretion, and suppression

of hepatic gluconeogenesis [11]. Cagrilintide is a long-acting amylin analogue that targets amylin receptors, to exert the same intended effects as amylin, and calcitonin receptors, specifically receptor activity modifying proteins 1,2,3 (RAMP 1-3) [12]. Amylin, a pancreatic hormone belonging to the calcitonin family of peptides, is co-secreted with insulin in order to delay gastric emptying and suppress postprandial release of glucagon [13]. It also acts within the brain to regulate appetite and satiation through activation in the area postrema and nucleus of the solitary tract of the hindbrain [14]. CagriSema's multi targeted approach via GLP-1 and amylin/calcitonin receptor activation leads to synergistic delay in gastric emptying, suppression of glucagon release, and regulation of satiety.

Clinical Studies

While CagriSema has been studied in the overweight/obesity disease space and proven weight loss benefits, investigation in people with T2DM is ongoing. A phase Ib, randomized, placebo-controlled study evaluated the combination of semaglutide and cagrilintide with regards to weight management. Participants were randomized to receive cagrilintide subcutaneously (SQ) once weekly at the following doses 0.16, 0.30, 0.60, 1.2, 2.4 or 4.5 mg with semaglutide 2.4 mg SQ once weekly or placebo in a 3:1 ratio. Overall, the combination of cagrilintide and semaglutide was well tolerated, exhibited a positive effect in body weight reduction and demonstrated a reduction in glycemic parameters [15]. The results of this study provided foundational evidence to further evaluate the efficacy of the combination medication in patients with T2DM and overweight/obesity. The phase II study included people with T2DM on metformin with or without sodium glucose cotransporter-2 inhibitors (SGLT2i) and body mass index (BMI) of at least 27 kg/m2. Participants were randomized 1:1:1 to receive either cagrilintide 2.4 mg SQ with semaglutide 2.4 mg SQ once weekly, cagrilintide 2.4 mg SQ once weekly, or semaglutide 2.4 mg SQ once weekly [16].

The study was completed with positive results for the fixed dose combination of cagrilintide and semaglutide. Of the 92 total participants included, those randomized to receive cagrilintide with semaglutide showed a larger reduction in HbA1c of 2.18% and body weight reduction of 15.6% compared to those who received semaglutide (1.79%, 5.1%) or cagrilintide alone (0.93%, 8.1%) [16,17]. Additionally, continuous glucose monitor (CGM) data were evaluated including time in range (TIR), CGM-measured glucose, and fasting plasma glucose (FPG). Percent TIR was highest with the combination cagrilintide and semaglutide at 88.9% compared to semaglutide alone (76.2%) and cagrilintide alone (71.7%). Cagrilintide with semaglutide showed significantly greater mean CGM-measured glucose reductions compared with semaglutide alone or cagrilintide alone (-3.6, -2.4, and -1.3 mmol/L mean change from baseline respectively). Cagrilintide with semaglutide also showed a significant reduction in FPG compared to cagrilintide alone with estimated mean change from baseline -3.3 vs -1.7 mmol/L respectively; of note, semaglutide showed a mean change from baseline in FPG of -2.5 mmol/L. Gastrointestinal adverse events were most commonly reported during the dose escalation phase and were mild to moderate in severity [16].

With a favorable safety profile and clinically relevant reductions in body weight and glycemic variables, investigation of semaglutide with cagrilintide will continue. The phase III programme, REDEFINE, plans to further explore the effects of cagrilintide with semaglutide on patients with overweight/obesity. These studies are currently recruiting people with overweight and obesity with or without T2DM where weight loss with CagriSema will be evaluated for a longer period of time and in a larger patient population (REDEFINE 1 NCT05567796, REDEFINE 2 NCT05394519, REDEFINE 3 NCT05669755). One of the studies in this programme, REDEFINE 2, will measure weight loss with a primary outcome of relative change in body weight through week 68. The study is recruiting 1200 participants with T2DM and BMI greater than or equal to 27 kg/m2. Participants will be randomized 1:1 to receive cagrilintide 2.4 mg SQ with semaglutide 2.4 mg SQ or placebo once weekly. The study's estimated completion date is December 2024 [18]. REDEFINE 1 and REDEFINE 3 will evaluate the combination of cagrilintide and semaglutide in people with overweight/obesity and obesity with cardiovascular disease respectively. REDEFINE 1 plans to include 3400 participants with a primary outcome of change in body weight. The participants will be randomized to receive cagrilintide 2.4 mg SQ with semaglutide 2.4 mg SQ once weekly or placebo. The estimated completion date is October 2026 [19]. REDEFINE 3 will include approximately 4000 participants with obesity and established cardiovascular disease. Participants will be randomized to receive placebo or the combination of cagrilintide 2.4 mg SQ once weekly with semaglutide 2.4 mg SQ once weekly. The primary outcome is time to first occurrence of MACE with an estimated study completion in May 2027 [20].

Conclusion

Reductions in body weight and HbA1c in the phase II study show promise for the combination of cagrilintide with semaglutide for patients with T2DM. Future studies of the combination medication will be important for determining its place in therapy for those with a need for glycemic reductions and the added benefit of weight loss.

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