A triple agonist of glucagon, GIP, and GLP-1 receptors as a novel therapeutic option for the treatment of heart failure with preserved ejection fraction. Effects on diastolic dysfunction, arrhythmogenesis, and quality of life.

Heart failure (HF) is a progressive disease that leads to chronic disability and ultimately death. It is the most common and costly cause of hospitalization in patients over 65 years of age. Approximately 60 million people worldwide suffer from HF. Currently, the most prevalent form of HF is heart failure with preserved ejection fraction (HFpEF), where the primary issue is diastolic dysfunction of the myocardium. This type of HF predominantly affects older adults, individuals with type II diabetes, hypertension, and those who are overweight or obese, occurring more frequently in women than in men. The number of HFpEF patients is rapidly increasing due to aging populations and the obesity epidemic, while therapeutic options for these patients remain limited.

The only treatment currently recommended by the European Society of Cardiology (ESC) are sodium-glucose cotransporter 2 (SGLT2) inhibitors. Randomized clinical trials (DELIVER, EMPEROR-PRESERVED) have demonstrated that SGLT2 inhibitors reduce a composite endpoint comprising cardiovascular death or HF hospitalization. However, these trials did not show a significant reduction in mortality when considered independently, as seen in heart failure with reduced ejection fraction (HFrEF). This underscores the urgent need to intensify therapy for HFpEF patients. According to the updated 2023 ESC guidelines, treating comorbidities, including obesity, is recommended for HFpEF patients. Given that approximately 80% of HFpEF patients are overweight or obese—a condition that exacerbates hypertension, lipid disorders, and type 2 diabetes—treating obesity in these patients has become a significant challenge.

Currently, incretin peptide analogs, GLP-1 and GIP, have shown favorable effects in patients with type 2 diabetes and obesity, as well as improved quality of life in HFpEF patients. The newest drug in this class, retatrutide, which activates receptors for GLP-1, GIP, and glucagon, has demonstrated superior glycemic control and greater weight reduction compared to GLP-1 and GIP analogs in clinical studies. However, no studies have yet been designed to evaluate the use of retatrutide in HFpEF patients. Providing evidence for the efficacy of adding retatrutide as an additional therapy alongside SGLT2 inhibitors in patients with HFpEF, and identifying the mechanisms underlying its beneficial effects, could contribute to the design of clinical trials testing this therapeutic option.

The aim of this project is to investigate the effects of the glucagon/GLP-1/GIP receptor agonist retatrutide, the SGLT2 inhibitor dapagliflozin, and their combination on key elements of HFpEF pathophysiology that determine prognosis and quality of life. These include the severity of diastolic dysfunction, arrhythmogenic susceptibility, and physical and cognitive performance. The study will be conducted in a cardiometabolic rat model of HFpEF (obese ZSF-1 rats), recognized as the model most accurately reflecting the course of this disease in humans. Both male and female animals will be used to evaluate sex-dependent differences in disease progression and treatment efficacy.

We hope that the findings of this proposed project will contribute to the development of more effective, personalized treatments for HFpEF, improving prognosis and quality of life for both male and female patients.