NCT NUMBER: NCT02536248

DRUG NAME: SITAGLIPTIN

STUDY TITLE: **EFFECTS OF SITAGLIPTIN THERAPY ON THE KINETICS OF MARKERS OF LOW-GRADE INFLAMMATION AND CELL ADHESION MOLECULES IN PATIENTS WITH TYPE 2 DIABETES**

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PROTOCOL DATE: February 12nd, 2015

EFFECTS OF SITAGLIPTIN THERAPY ON THE KINETICS OF MARKERS OF LOW-GRADE INFLAMMATION AND CELL ADHESION MOLECULES IN PATIENTS WITH TYPE 2 DIABETES

Inflammatory processes are increasingly being recognized as a critical step in the pathogenesis of both diabetes and heart disease and may constitute a biological link between the two diseases. Inflammatory cytokines increase vascular permeability, change vasoregulatory responses, increase leukocyte adhesion to endothelium, and facilitate thrombus formation by inducing procoagulant activity, inhibiting anticoagulant pathways, and impairing fibrinolysis. Leukocyte adhesion to arterial endothelial cells is thought to be an important step in the development of atherosclerosis, and adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and L-selectin, play key roles in this process. Therefore, identifying novel therapeutic approaches that would favorably affect inflammation, endothelial function, and glucose is of significant interest. We have recently demonstrated that, relative to placebo, sitagliptin treatment resulted in a significant reduction in plasma levels of various inflammatory markers and cell adhesion molecules[1]. Our results also suggest that the beneficial effects of sitagliptin on both inflammation and endothelial function are most likely mediated by an elevation in plasma GLP-1 levels and global improvement of the glucose-insulin homeostasis. However, the mechanisms underlying the beneficial effects of sitagliptin on these markers remain to be fully elucidated. The proposed study will address this key issue.

The general objective of the proposed research is to investigate how sitagliptin therapy modulates the kinetics of various inflammatory markers and cell adhesion molecules in patients with type 2 diabetes. More specifically, we will:

1. *Examine the impact of sitagliptin therapy on the in vivo kinetics of key inflammatory markers associated with an increase risk of cardiovascular disease (C-reactive protein-CRP, plasminogen, von Willebrand factor-vWF). We hypothesize that sitagliptin therapy will decrease the production rate of these markers. Preliminary results from our group show that, compared with placebo, sitagliptin decreases CRP concentrations by 25.9% (placebo: 3.75±2.37 vs. sitagliptin: 2.78±2.04 mg/L; P<0.0001) in patients with type 2 diabetes (see **Figure 1A**).*
2. *Examine the impact of sitagliptin therapy on the in vivo kinetics of the cell adhesion molecules ICAM-1 and L-selectin associated with an increase risk of cardiovascular disease. We hypothesize that sitagliptin therapy will decrease the production rate of these molecules. Preliminary results from our group show that, compared with placebo, sitagliptin decreases ICAM-1 concentrations by 6.3% (placebo: 229±46 vs. sitagliptin: 213±46 ng/mL; P=0.004) in patients with type 2 diabetes (see **Figure 1B**).*

Study Design and Methods

All the analyses proposed will be performed on plasma samples collected during a previous research project supported by Merck (IISP#39262 – see attached manuscript for further details). The study design is illustrated in **Figure 2**. Plasminogen, L-selectin, and von Willebrand factor concentrations will be measured using commercial ELISA. Protein enrichment will be assessed using liquid chromatography-multiple reaction monitoring (LC-MRM) analysis. Samples will be analysed on a ABSciex 5500QTRAP™ hybrid triple quadrupole/linear ion trap mass spectrometer equipped with an Eksigent nanoLC AS2 cHiPLC nanoflex controlled by Analyst 1.6™ and with a nanospray ionization source (ABSciex, Framingham, MA, USA). This method has been used to assess apoB-48, B-100, apoC-III, and apoE kinetics in the triglyceride-rich lipoprotein fraction in patients with type 2 diabetes (see attached manuscript). Similarly, kinetic parameters (production and fractional catabolic rates) of the various markers will be calculated using multi-compartmental modeling.

Relevance and Importance

Data generated over the course of the proposed research will lead to considerable advances in our understanding of the mechanisms underlying the beneficial effects of sitagliptin therapy on inflammation and endothelial function in patients with type 2 diabetes.

[1]Tremblay AJ, Lamarche B, Deacon CF, Weisnagel SJ, Couture P. Effects of sitagliptin therapy on markers of low-grade inflammation and cell adhesion molecules in patients with type 2 diabetes. Metabolism 2014;63(9):1141-1148.

Figure 1

Preliminary results from study IISP#39262 showing that sitagliptin therapy significantly decreases both CRP and ICAM-1 concentrations in patients with type 2 diabetes.

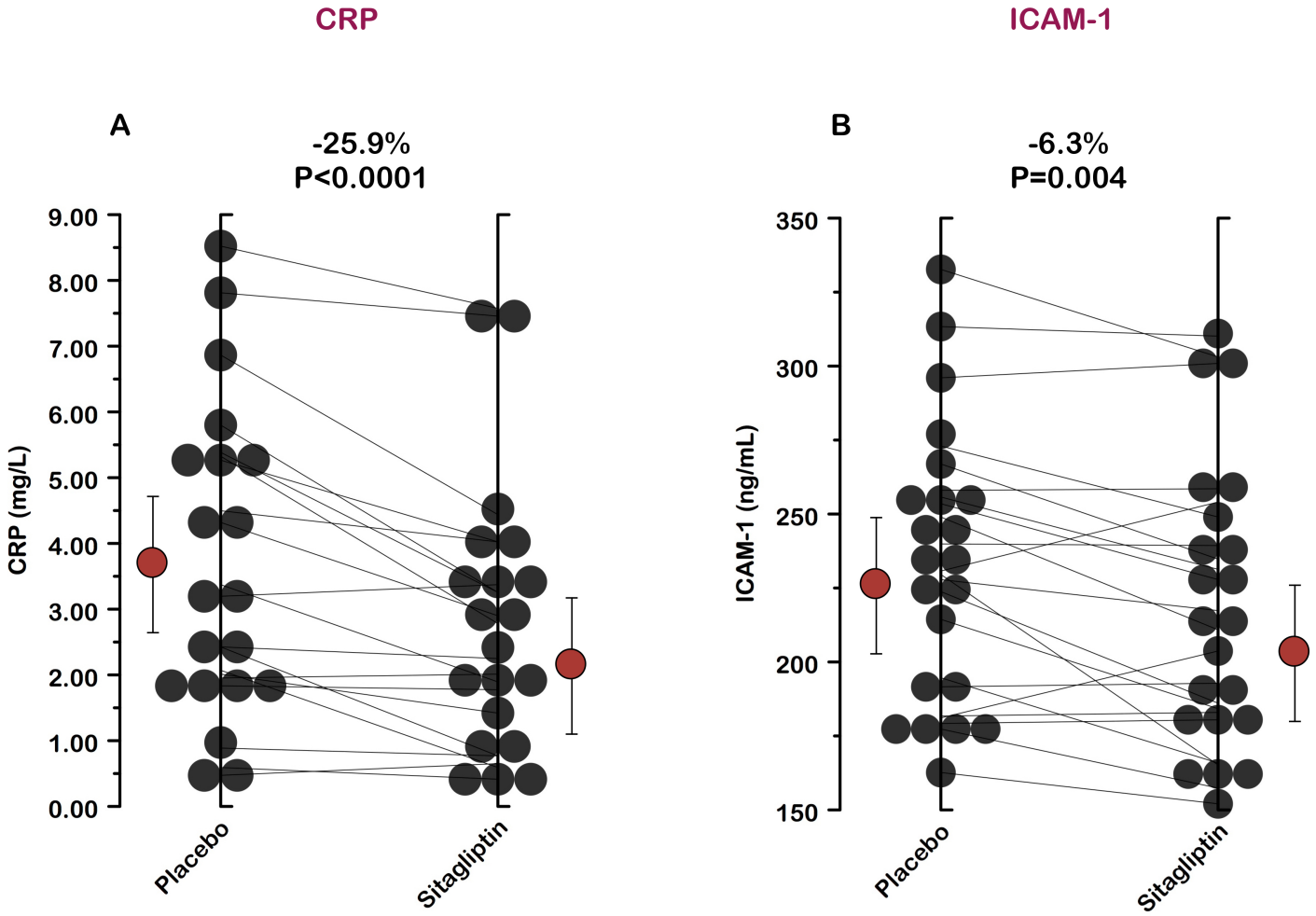

Figure 2

Design of the study IISP#39262 supported by Merck (see attached manuscript).
All analyses of the current proposal will be performed on samples already collected during the study IISP#39262