Effects of Canagliflozin Versus Glimepiride on Adipokines, Inflammatory Biomarkers, and Chemokines in Patients With Type 2 Diabetes Mellitus

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Disclosure Information: W. Timothy Garvey, MD

- Advisory boards for Merck, Alexion, Novo Nordisk, Janssen, Eisai, Vivus, and Takeda
- Research support from Merck, AstraZeneca, Weight Watchers, Pfizer, Novo Nordisk, Elcelyx, and Lexicon

Introduction

- Type 2 diabetes mellitus (T2DM) and obesity are pro-inflammatory states associated with increased risk of cardiovascular disease and premature death[1-3]
- Chronic hyperglycemia and obesity can lead to impaired adipose tissue function, characterized by altered production of adiposity-related hormones, as well as cytokines and chemokines that promote inflammation, endothelial dysfunction, and oxidative stress[4-8]
- Canagliflozin (CANA), a sodium glucose co-transporter 2 inhibitor, lowers the renal threshold for glucose and increases urinary glucose excretion, resulting in a mild osmotic diuresis and a net caloric loss[9,10]

1. Belalcazar LM, et al. *Arterioscler Thromb Vasc Biol*. 2011;31(7):1689-1695.
2. Berg AH, Scherer PE. *Circ Res*. 2005;96(9):939-949.
3. Van Gaal LF, et al. *Nature*. 2006;444(7121):875-880.
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5. Fasshauer M, Blüher M. *Trends Pharmacol Sci*. 2015;36(7):461-470.
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Introduction (cont)

- In a 52-week, Phase 3 study in patients with T2DM on background metformin, CANA 300 mg demonstrated superiority in lowering HbA1c versus glimepiride (GLIM) and provided greater body weight reduction, primarily via loss of fat mass[1]
- In the current analysis, we examined the effects of CANA versus GLIM on select adipokines, inflammatory biomarkers, and chemokines that have been associated with impaired tissue function, insulin resistance, and cardiovascular disease

1. Cefalu WT, et al. *Lancet*. 2013;382(9896):941-950.

Objective

- To assess the effects of CANA 300 mg versus GLIM on serum levels of select biomarkers
  - Adipokines:
    - Leptin
    - Adiponectin
  - Pro-inflammatory cytokines:
    - Interleukin-6 (IL-6)
    - Tumor necrosis factor-α (TNFα)
    - C-reactive protein (CRP)
  - Chemokines:
    - Plasminogen activator inhibitor-1 (PAI-1)
    - Vascular cell adhesion molecule-1 (VCAM-1)
    - Monocyte chemoattractant protein-1 (MCP-1)

Serum Samples

- This post hoc, exploratory analysis was conducted using serum samples from 200 randomly selected patients from the overall study[1] (100 patients each in the CANA 300 mg and GLIM groups) who completed 52 weeks of treatment without rescue therapy (~20% of patients from each group in the overall study)
  - The samples were collected from a Phase 3, randomized, double-blind, active-controlled study in patients with T2DM inadequately controlled on metformin
  - CANA 300 mg was selected for this analysis due to its greater efficacy compared with CANA 100 mg and likely greater effects on biomarkers

1. Cefalu WT, et al. *Lancet*. 2013;382(9896):941-950.

Endpoints/Assessments

- Change from baseline in HbA1c and body weight was evaluated at Week 52
- Change from baseline in serum leptin, adiponectin, leptin/ adiponectin ratio, CRP, PAI-1, VCAM-1, and MCP-1 at Week 52 was assessed based on measurements from a multiplex assay (Myriad RBM, Austin, TX)
- Change from baseline in serum IL-6 and TNFα at Week 52 was assessed based on ultra-high–sensitivity assays performed using technology from Simoa-Quanterix (Lexington, MA)

Statistical Analyses

- Pairwise comparisons of mean change from baseline in HbA1c, body weight, PAI-1, VCAM-1, and MCP-1 were performed using an analysis of covariance (ANCOVA) model, with treatment, antihyperglycemic agent adjustment period, and country as fixed effects and the corresponding baseline value as a covariate
  - Least squares (LS) mean differences and 2-sided 95% confidence intervals (CIs) were estimated for comparisons of CANA and GLIM
- Nonparametric Hodges-Lehmann estimates were calculated for differences in the medians for leptin, adiponectin, leptin/adiponectin ratio, IL-6, TNFα, and CRP; distribution-free CIs were based on the Wilcoxon rank sum test[1]
- Correlations between change from baseline in serum leptin, adiponectin, leptin/adiponectin ratio, IL-6, TNFα, and CRP and change from baseline in clinical parameters (eg, HbA1c, body weight) were calculated within each group

1. Hollander M, Wolfe DA. *Nonparametric Statistical Methods*. 2nd ed. New York, NY: John Wiley & Sons, Inc.; 1999.

Baseline Demographic and Disease Characteristics

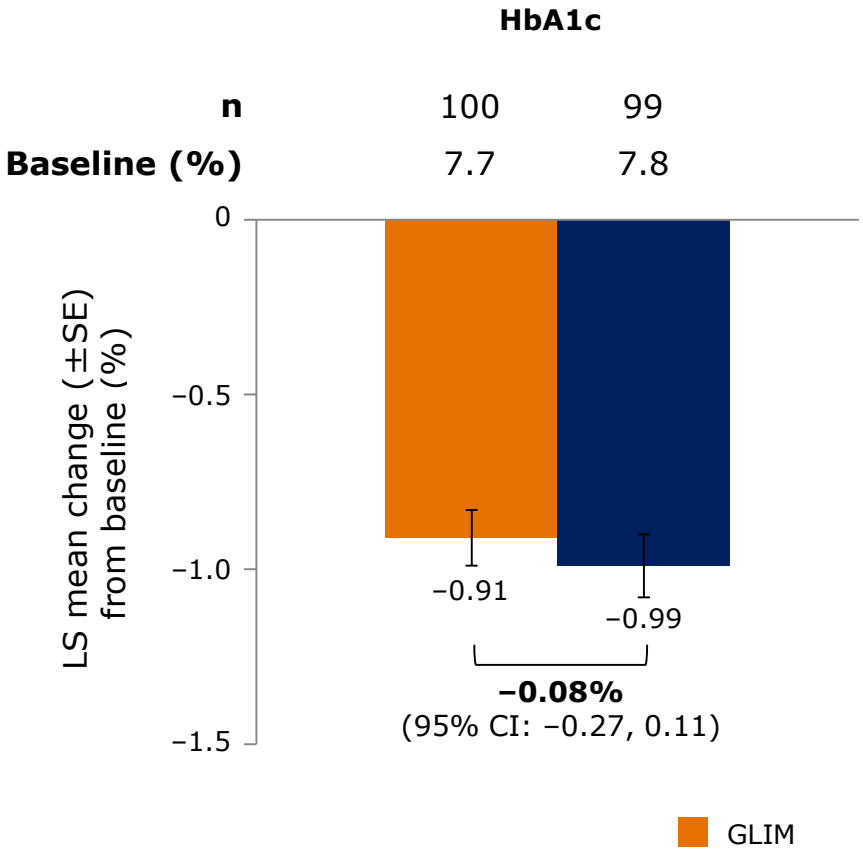
- Baseline characteristics were generally balanced between groups and were consistent with the overall population[1]

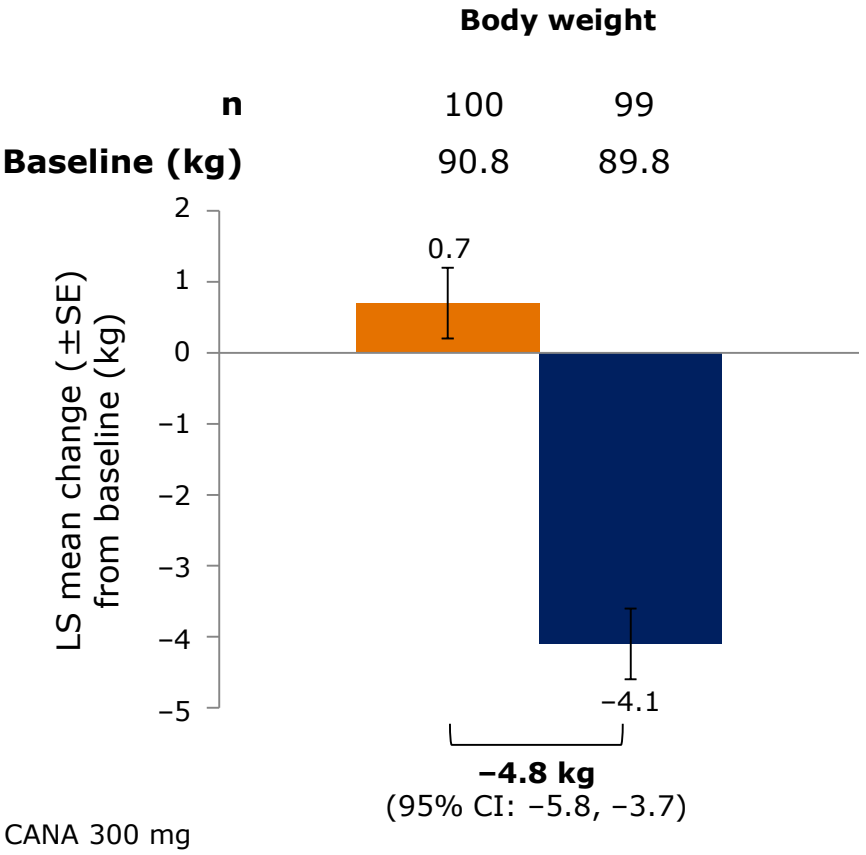
Characteristic*	GLIM (n = 100)	CANA 300 mg (n = 100)
Age, y	57.5 (8.6)	58.5 (9.0)
Male, %	55	48
Race, %		
White	80	87
Black	5	5
Asian	7	1
Other†	8	7
Ethnicity, %		
Hispanic/Latino	10	12
Not Hispanic/Latino	90	88
Body weight, kg	90.9 (17.6)	90.2 (16.8)
BMI, kg/m^2	31.7 (5.0)	32.5 (4.7)
Waist circumference, cm	105.4 (11.0)	107.3 (12.9)
HbA1c, %	7.7 (0.8)	7.8 (0.9)
T2DM duration, y	6.8 (4.9)	7.5 (6.0)
eGFR (creatinine), mL/min/1.73 m^2	86.7 (16.5)	91.6 (18.1)

BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation.
*Data are mean (SD) unless otherwise indicated.
†Includes American Indian or Alaska Native, multiple, and other.

1. Cefalu WT, et al. *Lancet*. 2013;382(9896):941-950.

Change From Baseline in HbA1c and Body Weight at Week 52





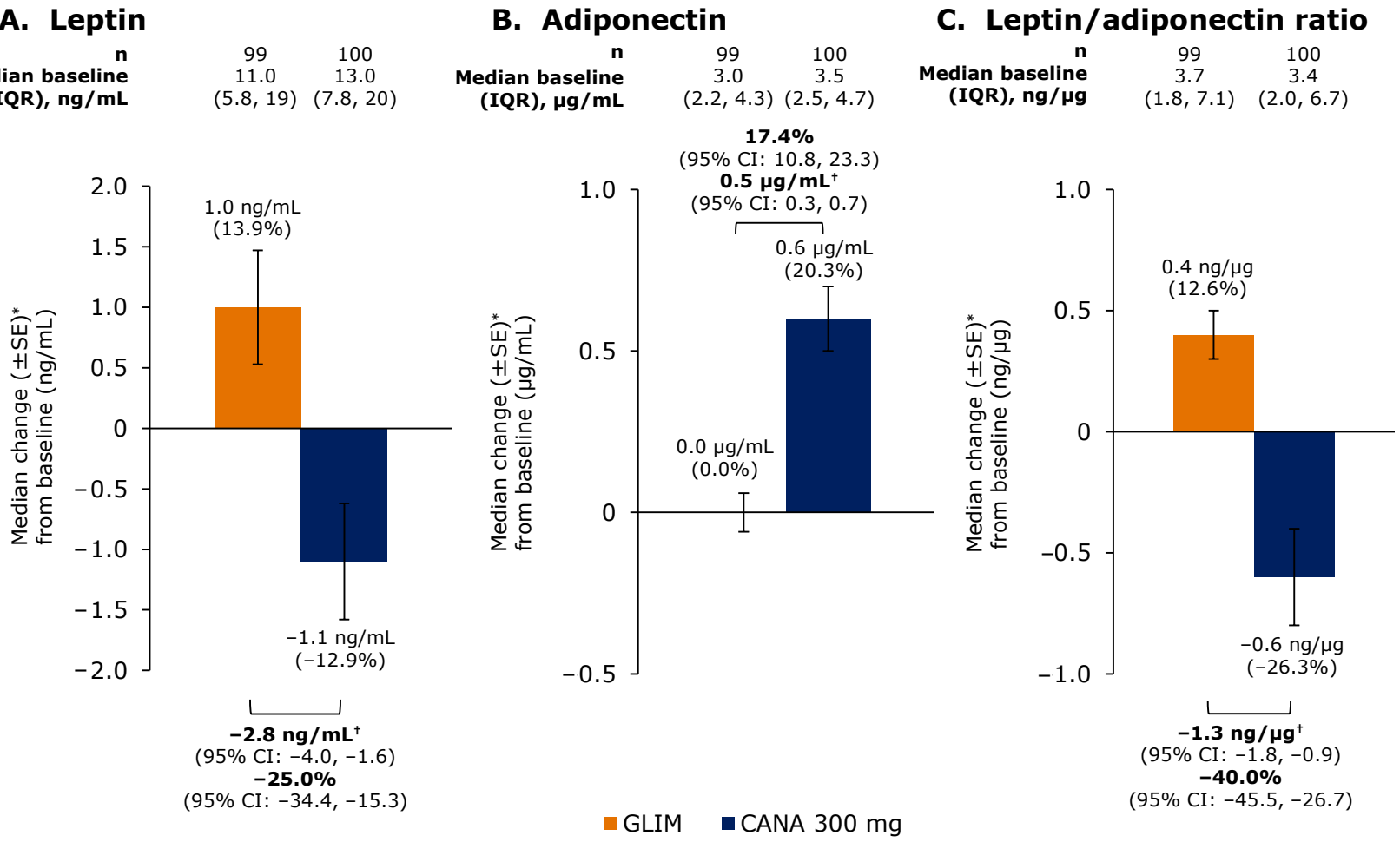
GLIM CANA 300 mg

- Changes in HbA1c and body weight were consistent with those seen in the overall population[1]

SE, standard error.

1. Cefalu WT, et al. *Lancet*. 2013;382(9896):941-950.

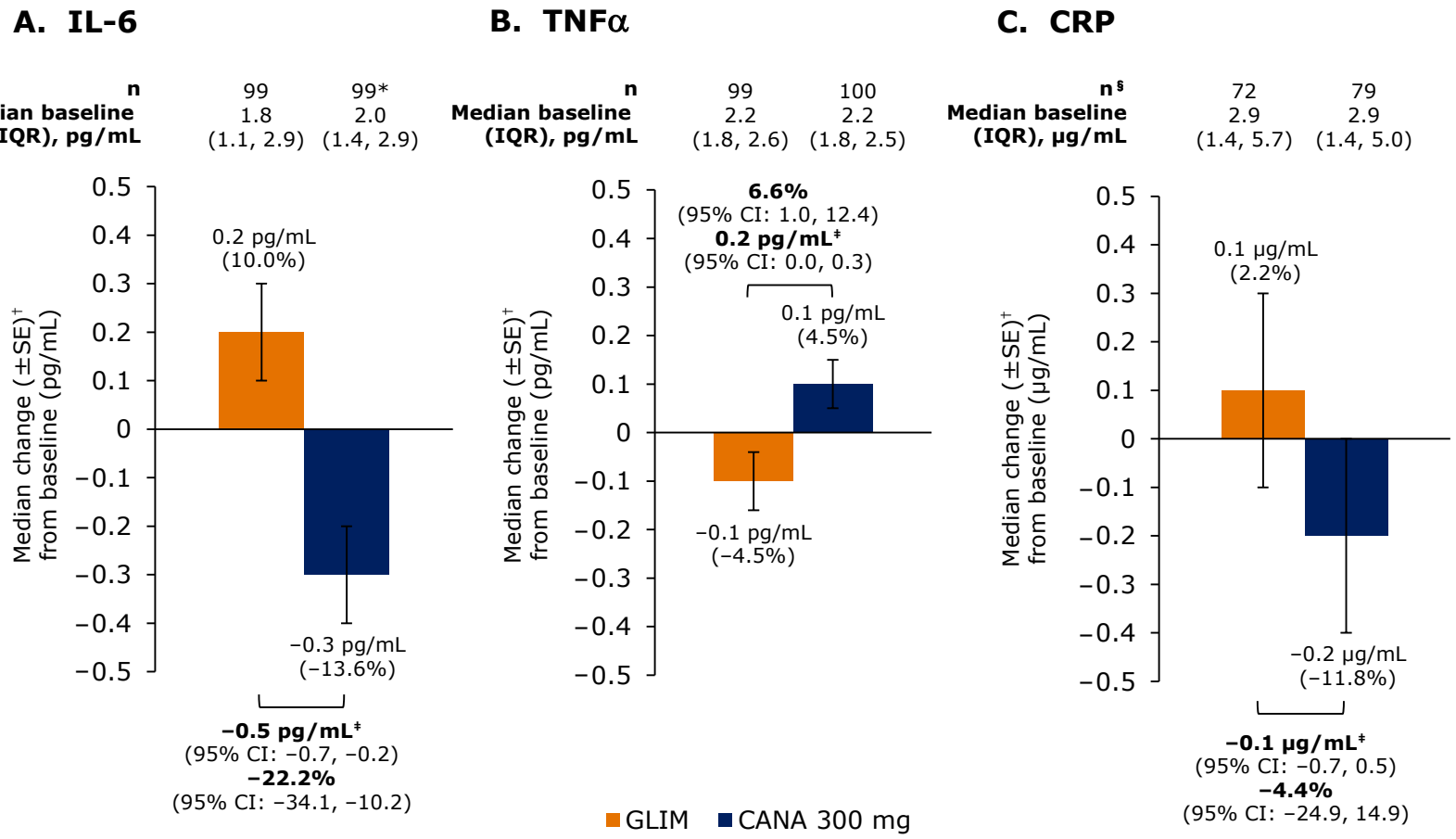
Change From Baseline in Serum Adipokines at Week 52



- Change in leptin and change in body weight showed meaningful correlation ($r \geq 0.35$)
- Change in adiponectin not correlated with change in HbA1c, body weight, or lipids (not shown)

*The SE for the median was estimated using the bootstrap technique by simulating repeated samples for each biomarker and treatment group.
†Data are nonparametric Hodges-Lehmann median estimates; 95% CIs were estimated based on the Wilcoxon rank sum test.

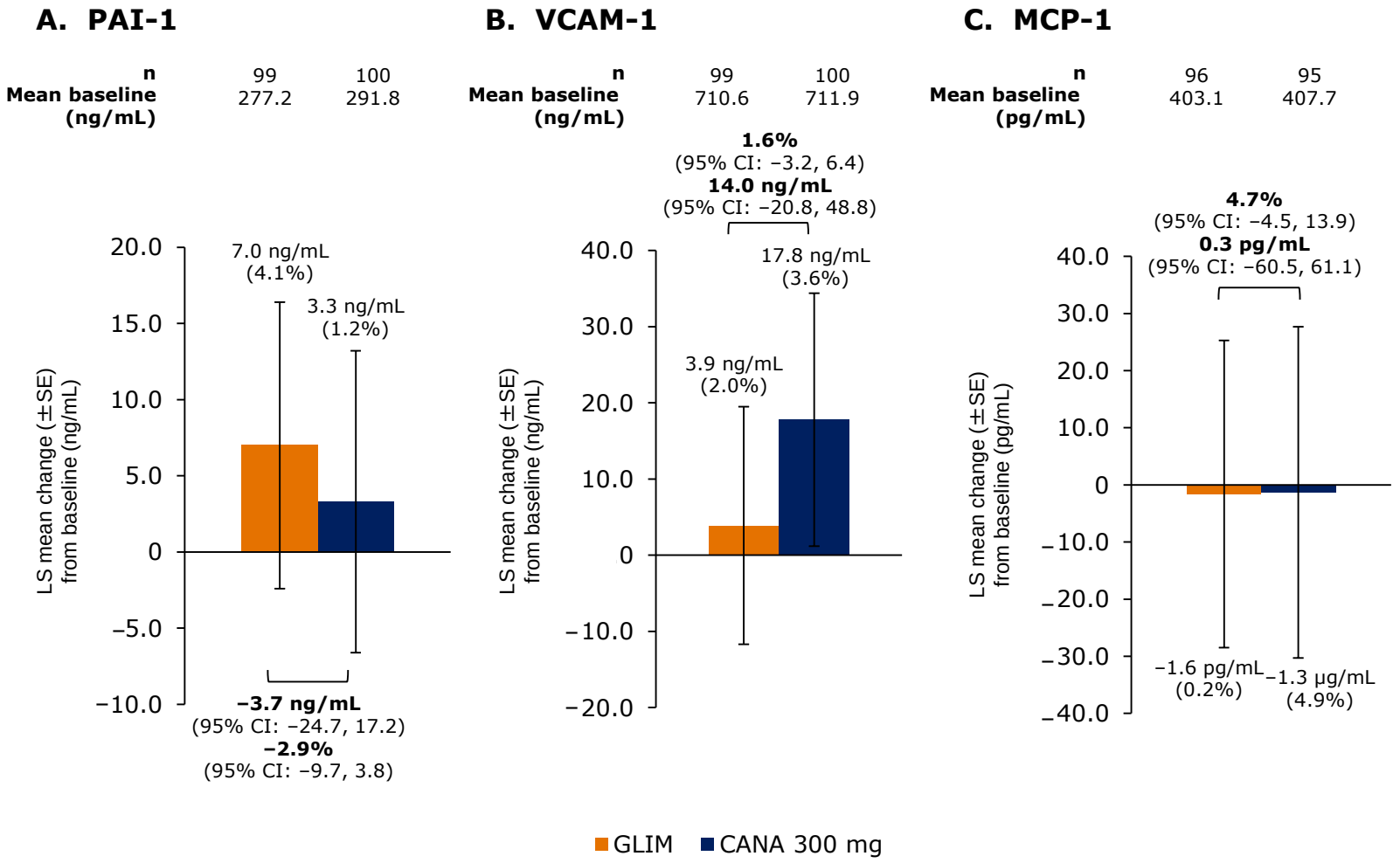
Change From Baseline in Serum Inflammatory Biomarkers at Week 52



- Change in IL-6, TNFα, or CRP not correlated with change in HbA1c, body weight, or lipids (not shown)

IQR, interquartile range; SE, standard error.
*Excludes 1 patient with outlier values at baseline and Week 52.
†The SE for the median was estimated using the bootstrap technique by simulating repeated samples for each biomarker and treatment group.
‡Data are nonparametric Hodges-Lehmann median estimates; 95% CIs were estimated based on the Wilcoxon rank sum test.
§Excludes patients with CRP >10 µg/mL or with a ≥5-fold change from baseline.

Change From Baseline in Serum Chemokines at Week 52



Summary

- CANA 300 mg demonstrated reductions in serum leptin and IL-6 and an increase in adiponectin versus GLIM in patients with T2DM
- CANA 300 mg was associated with a small increase in serum TNFα and had neutral effects on other biomarkers
- The CANA-related changes in leptin, adiponectin, and IL-6 were independent of glycemic benefit, and the changes in adiponectin and IL-6 were independent of weight loss
- These collective results suggest that CANA may improve adipose tissue function, which may have favorable effects on cardiometabolic health[1-3]
- Direct evidence of the effects of CANA on cardiovascular outcomes will be available upon completion of the ongoing CANVAS Program, including the CANagliflozin cardioVascular Assessment Study (CANVAS; ClinicalTrials.gov Identifier: NCT01032629) and CANVAS-R (Renal endpoints; NCT01989754)[4-6]

1. Berg AH, Scherer PE. *Circ Res*. 2005;96(9):939-949.
2. Van Gaal LF, et al. *Nature*. 2006;444(7121):875-880.
3. Paneni F, et al. *Curr Atheroscler Rep*. 2014;16(7):419.
4. Neal B, et al. *Am Heart J*. 2013;166(2):217-223.
5. Neal B, et al. *Diabetes Obes Metab*. 2017;19(3):387-393.
6. Neal B, et al. *Diabetes Obes Metab*. 2017. doi: 10.1111/dom.12924.

Acknowledgments

- This analysis was supported by Janssen Scientific Affairs, LLC

- Editorial support was provided by Alaina Mitsch, PhD, of MedErgy, and was funded by Janssen Global Services, LLC

- Canagliflozin has been developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation

Backup

Correlation Coefficients for Changes in Serum Adipokines and Clinical Parameters at Week 52*

Parameter	Treatment	HbA1c, %	Body weight, kg
Adiponectin, µg/mL	CANA 300 mg	0.0143	−0.1448
	GLIM	−0.0467	**0.2744**
Leptin, ng/mL	CANA 300 mg	0.0975	**0.4054**
	GLIM	−0.1657	**0.3518**
Leptin/adiponectin ratio, ng/µg	CANA 300 mg	**0.2547**	**0.4178**
	GLIM	0.0368	**0.2746**
IL-6, pg/mL	CANA 300 mg	0.0614	0.1079
	GLIM	−0.1291	0.1133
TNFα, pg/mL	CANA 300 mg	0.0746	−0.0539
	GLIM	−0.0770	0.0513
CRP, µg/mL	CANA 300 mg	**0.2411**	0.1213
	GLIM	−0.0538	0.0680

*Bold indicates statistically significant correlations (P <0.05).

- Change in leptin and change in body weight showed meaningful correlation (r ≥0.35)
- Changes in adiponectin, IL-6, TNFα, and CRP were not correlated with change in HbA1c, body weight, or lipids (not shown)