# Antisense Mediated Lowering of Plasma Apolipoprotein C-III by Volanesorsen Improves Dyslipidemia and Insulin Sensitivity in Type 2 Diabetes

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# Presenter Disclosure Information

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Perelman School of Medicine at the University of Pennsylvania

**FINANCIAL DISCLOSURE:**

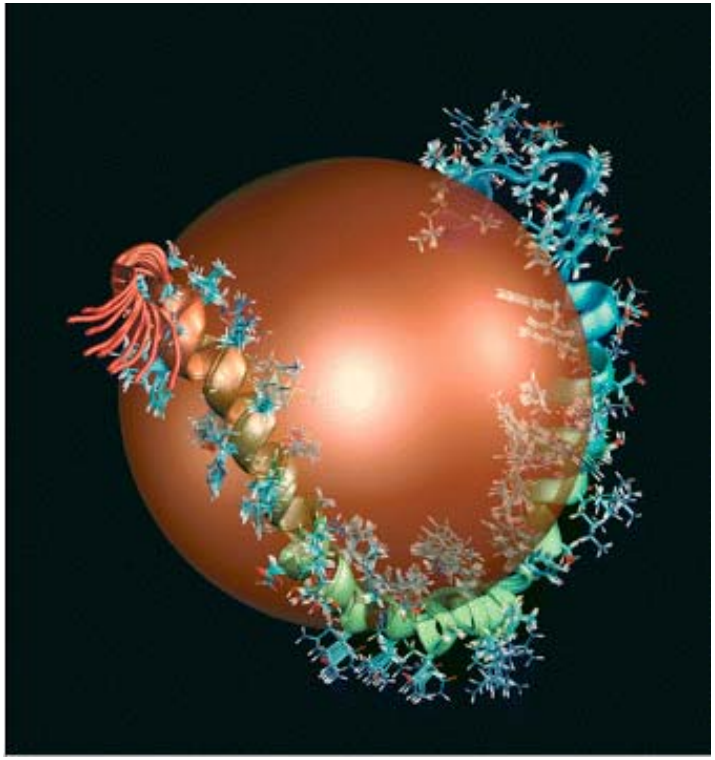
I am the local PI of a project sponsored by Ionis

I once served on an ad hoc advisory board for Ionis

**UNLABELED/UNAPPROVED USE:**

**Volanesorsen is an investigational drug**

# Targeting Apolipoprotein C-III (ApoC-III) A Novel Cardiometabolic Target



**ApoC-III in a complex with an SDS micelle as derived by NMR**

- **ApoC-III is a 79 amino acid glycoprotein synthesized principally in the liver**
  - Associated with apoB-containing lipoproteins and HDL
- **Plays a key role in determining serum triglyceride levels**
  - Potent inhibitor of lipoprotein lipase (LPL)-catalyzed lipolysis of triglyceride rich lipoproteins
    - Inhibits LPL activation by apoC-II
  - Inhibits hepatic lipase which also plays an important role in the conversion of dense VLDL to IDL
  - Inhibits receptor-mediated uptake of lipoprotein remnant uptake by the liver
- **Genetically validated target**
  - Loss of function mutations in ApoC-III exhibit a favorable lipid profile, reduced CHD and increased longevity
- **ApoC-III and triglycerides are independent risk factors for cardiovascular disease**
  - Elevated apoC-III levels also associated with metabolic syndrome, diabetes and inflammation

# Volanesorsen Treatment Significantly Reduced ApoC-III Levels in Patients with HTG

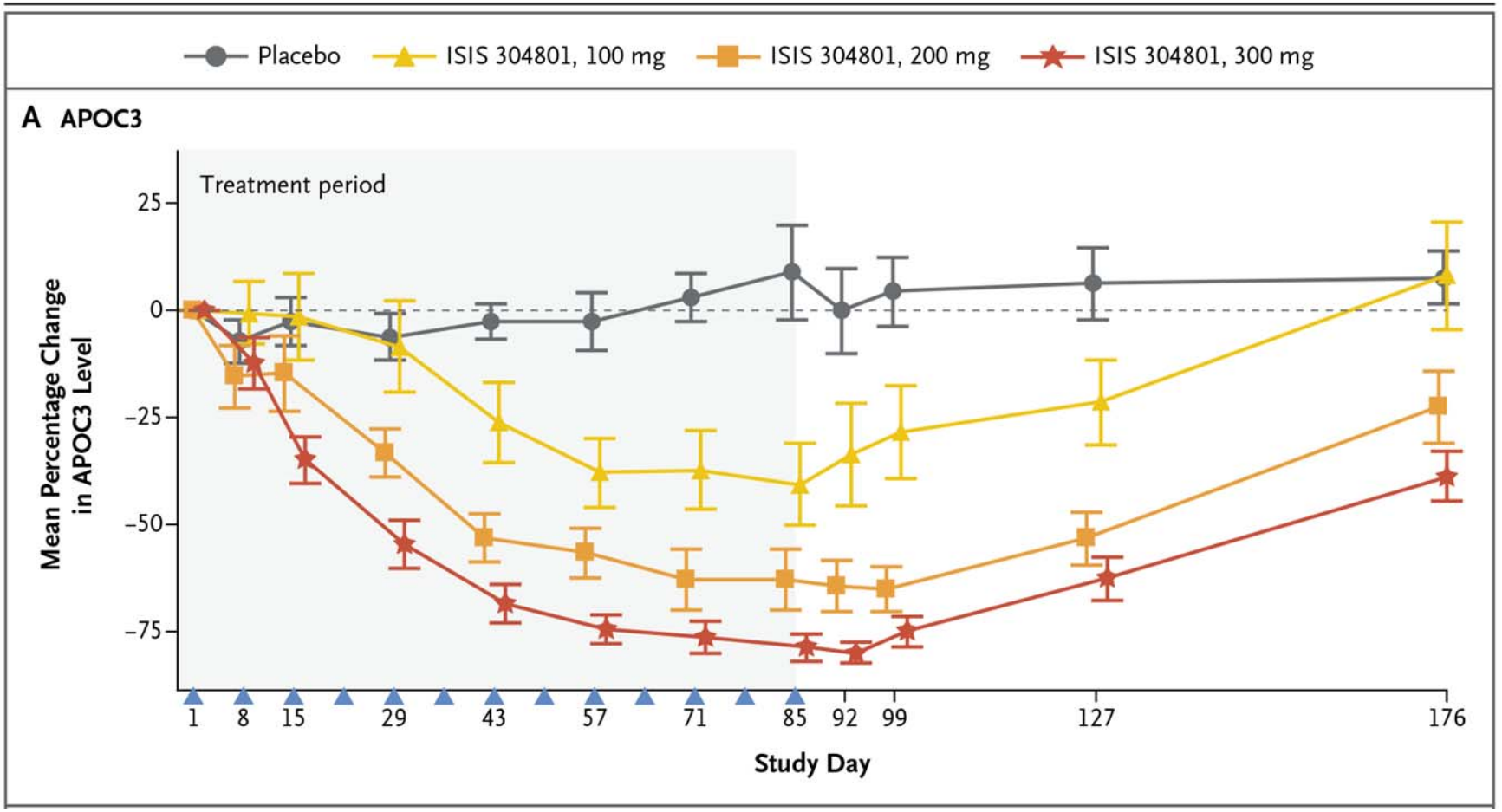
ORIGINAL ARTICLE

## Antisense Inhibition of Apolipoprotein C-III in Patients with Hypertriglyceridemia

Daniel Gaudet, M.D., Ph.D., Veronica J. Alexander, Ph.D., Brenda F. Baker, Ph.D., Diane Brisson, Ph.D., Karine Tremblay, Ph.D., Walter Singleton, M.D., Richard S. Geary, Ph.D., Steven G. Hughes, M.B., B.S., Nicholas J. Viney, B.Sc., Mark J. Graham, M.S., Rosanne M. Crooke, Ph.D., Joseph L. Witztum, M.D., John D. Brunzell, M.D.,* and John J.P. Kastelein, M.D., Ph.D.

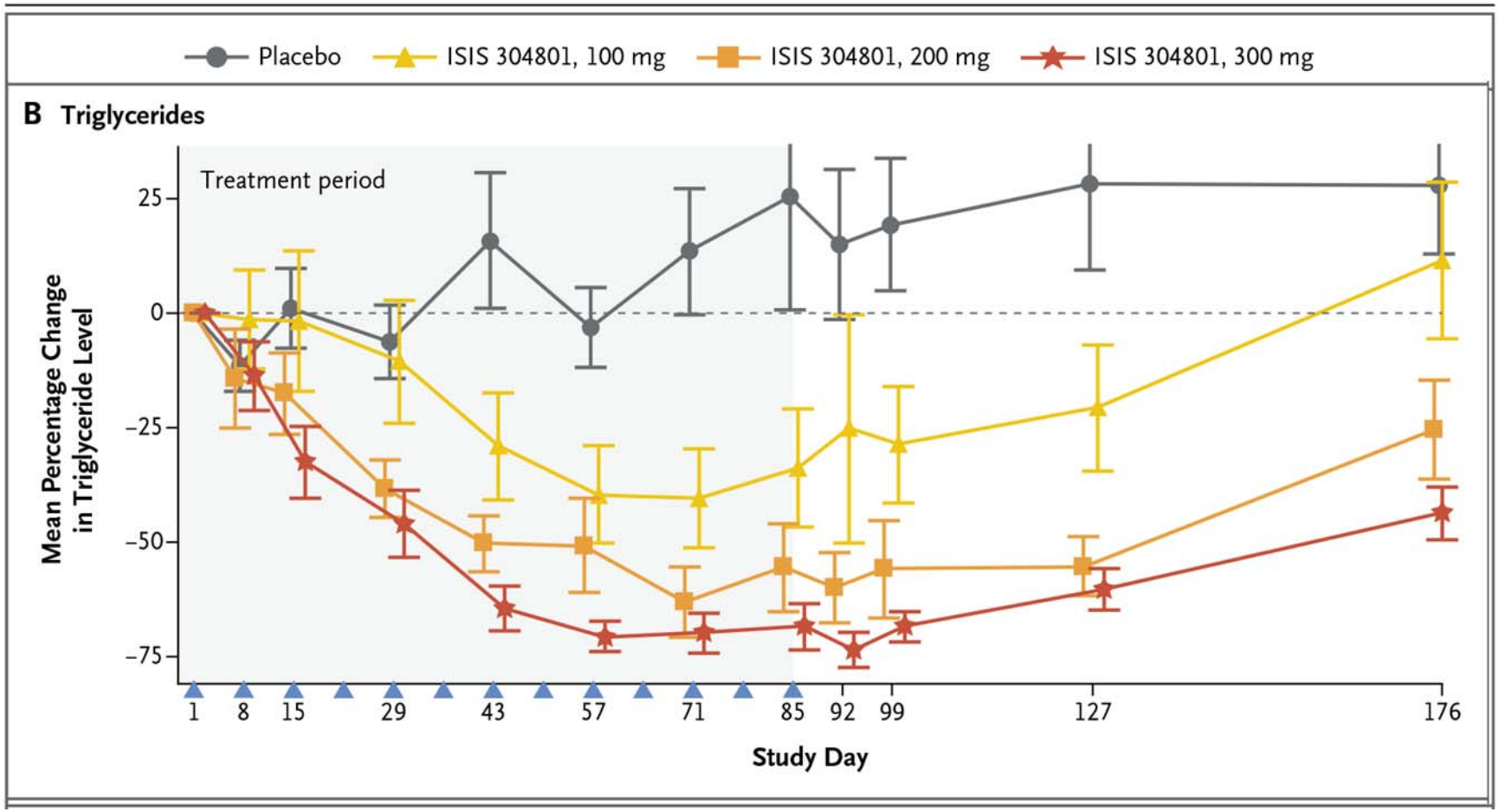
Gaudet et al. NEJM 2015

# Volanesorsen Treatment Significantly Reduced ApoC-III (Mean % Change)



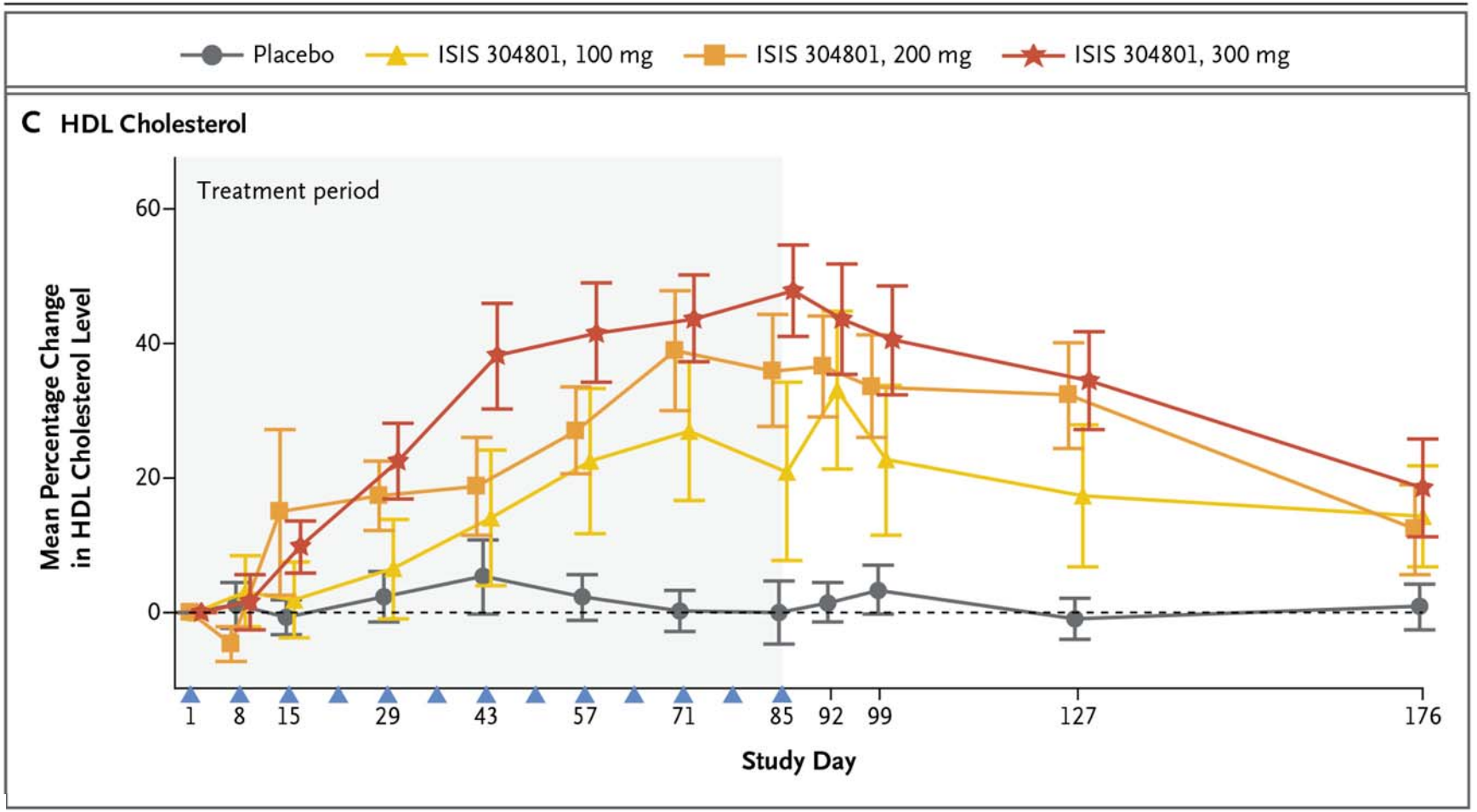

Gaudet et al. NEJM 2015

# Volanesorsen Treatment Significantly Reduced TG Levels (Mean % Change)




Gaudet et al. NEJM 2015

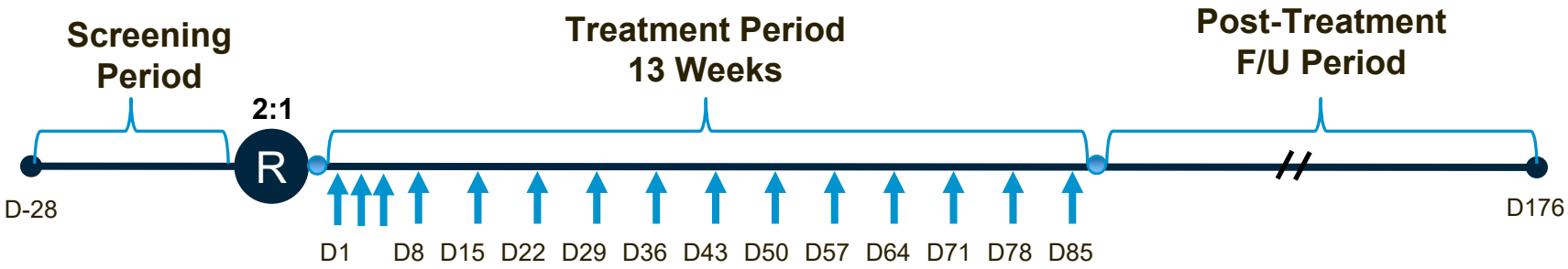
# Volanesorsen Treatment Significantly Increased HDL-C (Mean % Change)




Gaudet et al. NEJM 2015

# Study Design

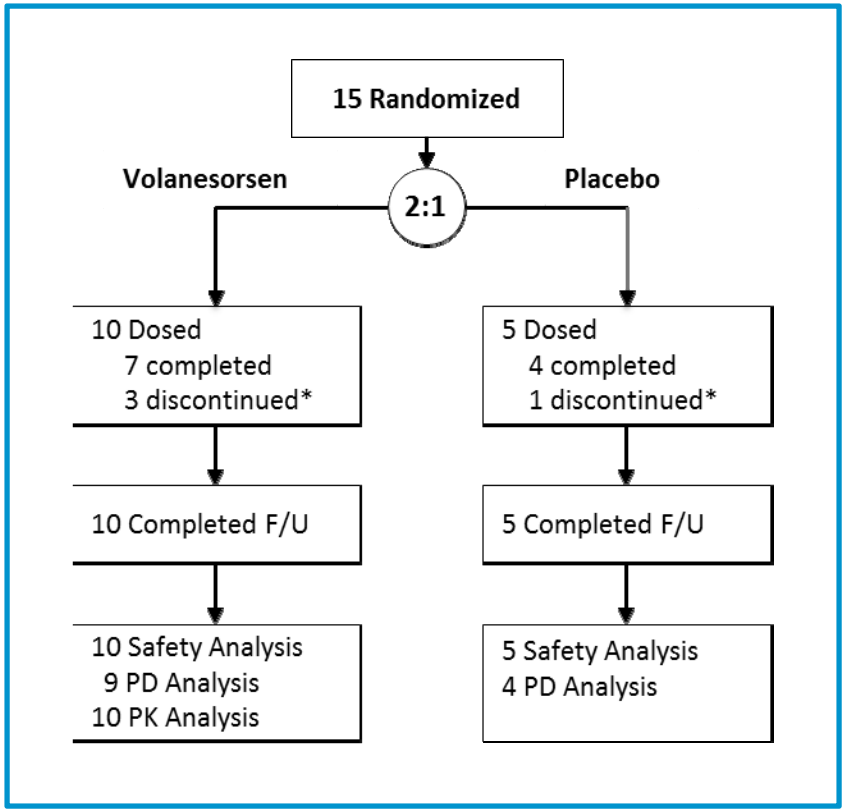
- Objectives
  - To determine the pharmacodynamic effect of volanesorsen, vs placebo, on apoC-III levels
  - To assess the effects of volanesorsen on whole-body insulin sensitivity and other markers of glycemic control
  - To assess the safety and tolerability to volanesorsen
- Key Eligibility Criteria
  - Adult, 18 to 65 years old
  - Triglycerides >200 mg/dL and <500 mg/dL, and HbA1c >7.0% and <9.0%
  - Diagnosed with Type 2 diabetes (≥6 months)
  - On a stable dose of metformin ≥1,000 mg/day




Two-step Hyperinsulinemic-Euglycemic Clamp procedure

# Patient Baseline Characteristics & Flow through Study

| | Placebo | Volanesorsen |
|---|---|---|
| N | 5 | 10 |
| Gender, F:M | 3:2 | 8:2 |
| Age, years | 55.0 (10.0) | 57.2 (6.4) |
| BMI, kg/m$^2$ | 32.5 (4.9) | 33.4 (4.4) |
| Glucose, mg/dL | 180.2 (31.3) | 180.9 (29.3) |
| HbA1c, % | 7.6 (0.3) | 8.0 (0.7) |
| TG, mg/dL | 215.2 (48.6) | 266.3 (75.2) |



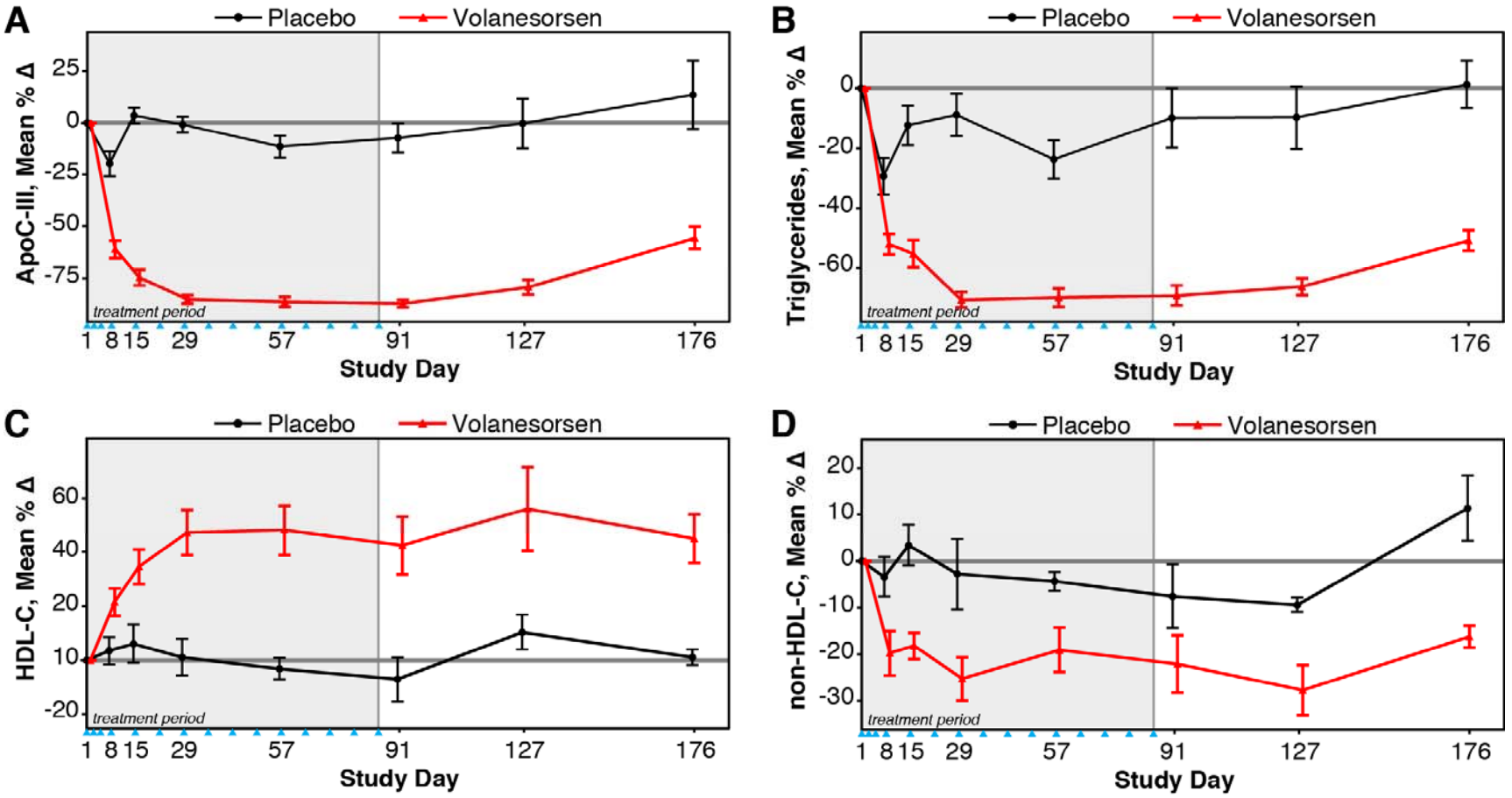
# Effect of Volanesorsen on Lipid & Lipoprotein Levels & Glycemic Control

| Lipids & Lipoproteins | Placebo | Volanesorsen |
|---|---|---|
| N | 4 | 9 |
| ApoC-III, mg/dL | | |
| Baseline | 11.7 (2.3) | 13.9 (4.4) |
| Day 91 | 11.1 (3.4) | 1.7 (0.6) |
| % Change | -7.3% (14.0) | -87.5% (5.4)* |
| Triglycerides, mg/dL | | |
| Baseline | 223.0 (52.3) | 260.1 (77.0) |
| Day 91 | 202.8 (71.1) | 75.9 (18.6) |
| % Change | -9.9% (19.9) | -69.1% (10.1)* |
| HDL-C, mg/dL | | |
| Baseline | 38.9 (6.6) | 41.1 (7.7) |
| Day 91 | 36.5 (11.4) | 57.8 (13.3) |
| % Change | -7.2% (16.5) | +42.5% (32.2)* |

| Glycemic Control | Placebo | Volanesorsen |
|---|---|---|
| N | 4 | 9 |
| Glycated Albumin, % | | |
| Baseline | 15.6 (0.5) | 16.2 (1.7) |
| Delta Day 91 | 0.7 (1.6) | -1.7 (1.2)* |
| Delta Day 176 | 1.8 (1.8) | -2.1 (2.4) |
| Fructosamine, μM | | |
| Baseline | 244.3 (4.2) | 273.8 (31.0) |
| Delta Day 91 | 14.5 (33.2) | -38.7 (22.5)* |
| Delta Day 176 | 47.8 (22.5) | -11.6 (22.6)* |
| HbA1c, % | | |
| Baseline | 7.8 (0.2) | 7.9 (0.6) |
| Delta Day 91 | 0.50 (0.62) | -0.27 (0.50) |
| Delta Day 176 | 0.78 (0.71) | -0.44 (0.39)* |

Data shown are the mean (SD). Pharmacodynamic analysis is based on the per-protocol population (patients who received at least nine doses of study drug; had a valid baseline total apoC-III measure and at least one post-baseline measure; and did not have any significant protocol deviations that would be expected to bias the patients' assessments.
* $p<0.05$, Wilcoxon Rank Sum Test

# Sustained Effect of Volanesorsen on Lipids & Lipoproteins Over Time



# Volanesorsen Treatment Improves Whole-body Insulin Sensitivity

| Insulin Sensitivity Index Ratio | Placebo (n=5) | Volanesorsen (n=8) | Group Comparison |
|---|---|---|---|
| Day 1 | 0.0206 (0.0074) | 0.0129 (0.0043) | |
| Day 92 | 0.0186 (0.0063) | 0.0182 (0.0046) | |
| %Change | -7.0% (25.1%) | +50.3% (48.6%) | +57.3% (41.6%) |
| P-Value | 0.4458 | 0.0000 | 0.0003* |

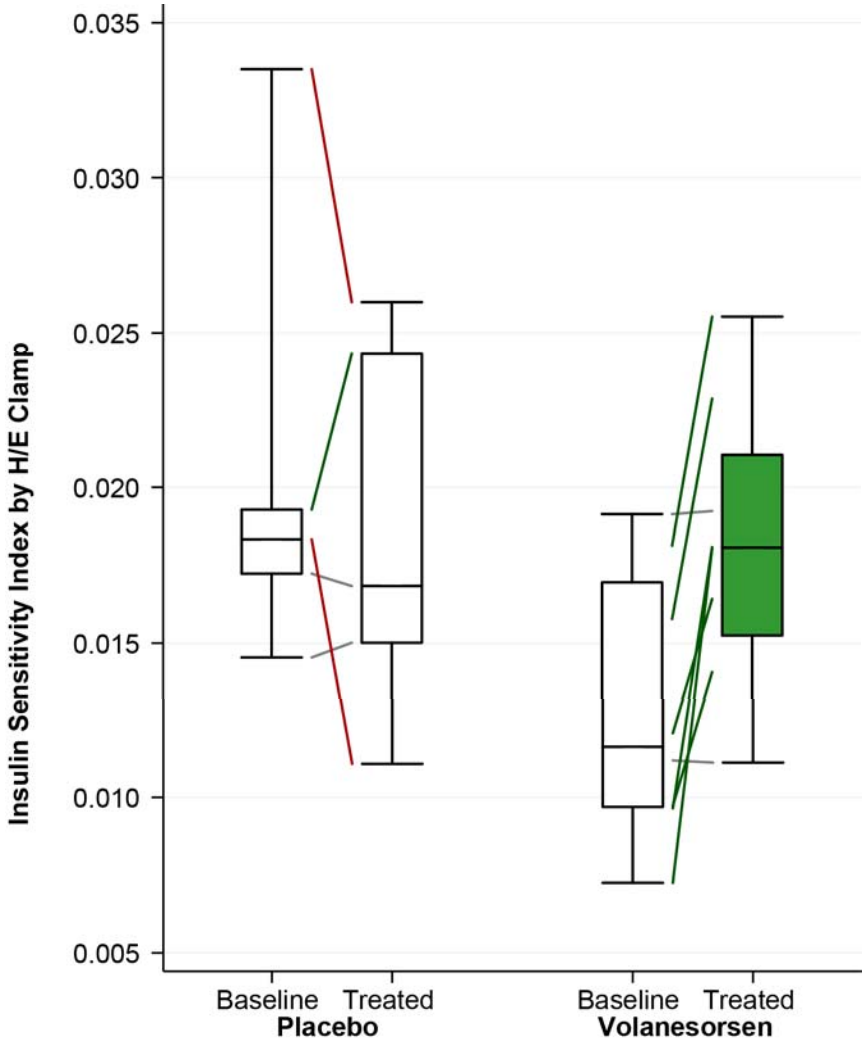
Results shown are the unadjusted values for patients who had valid clamp data (N=13).
P-values were derived from the mixed effect regression analysis.

- $p<0.05$ for % change group comparison by Wilcoxon Rank Sum test

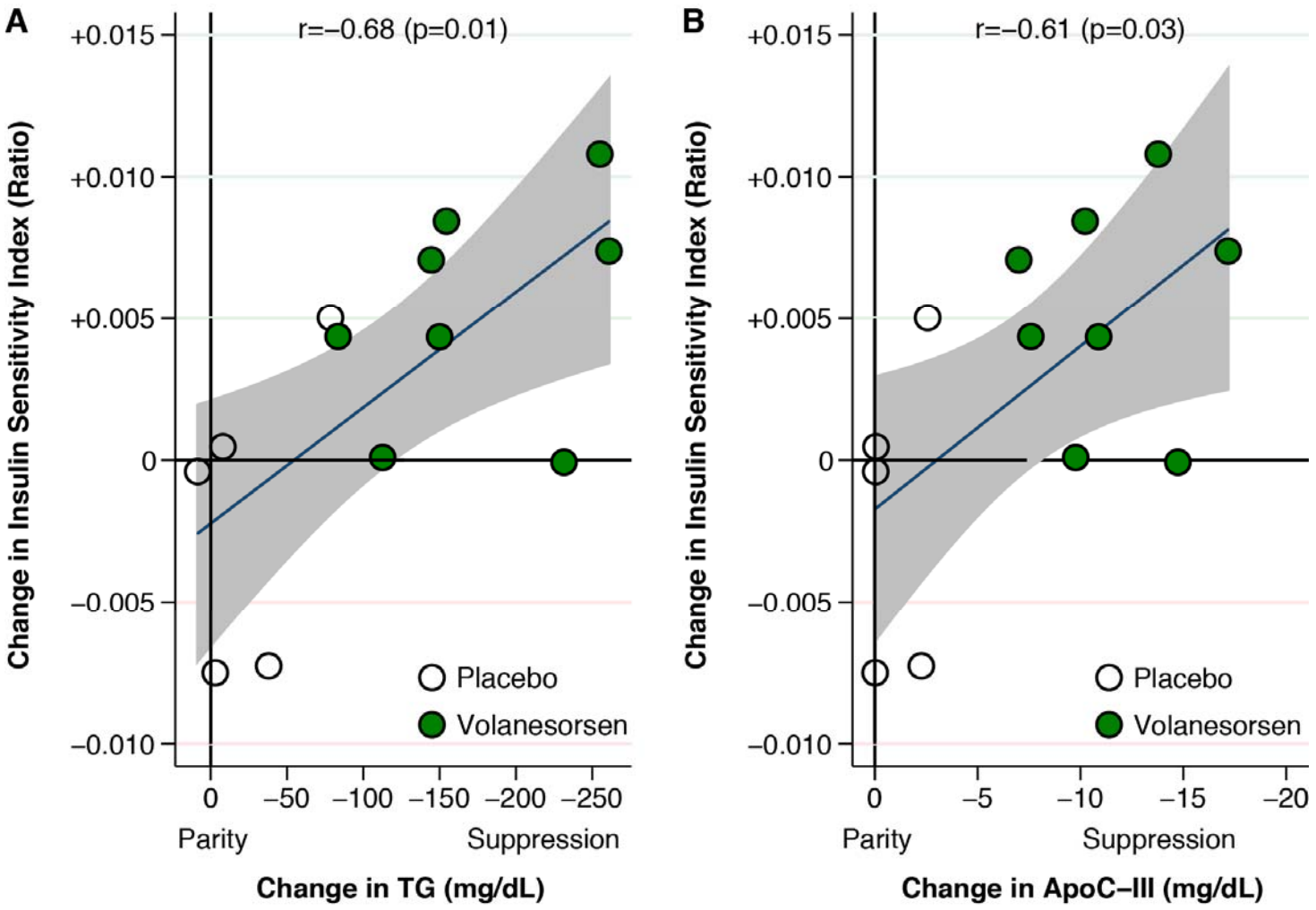
2-step clamp: Step 1 low-dose insulin (30 mU/m$^2$/min), Step 2 high-dose insulin (150 mU/m$^2$/min)

$$SI_{clamp} = \frac{\text{mean(GIR)}_{Step2} - \text{mean(GIR)}_{Step1}}{\left[\text{mean(I)}_{Step2} - \text{mean(I)}_{Step1}\right] \times \left[\text{mean(BG)}_{Steps1\&2}\right]}$$

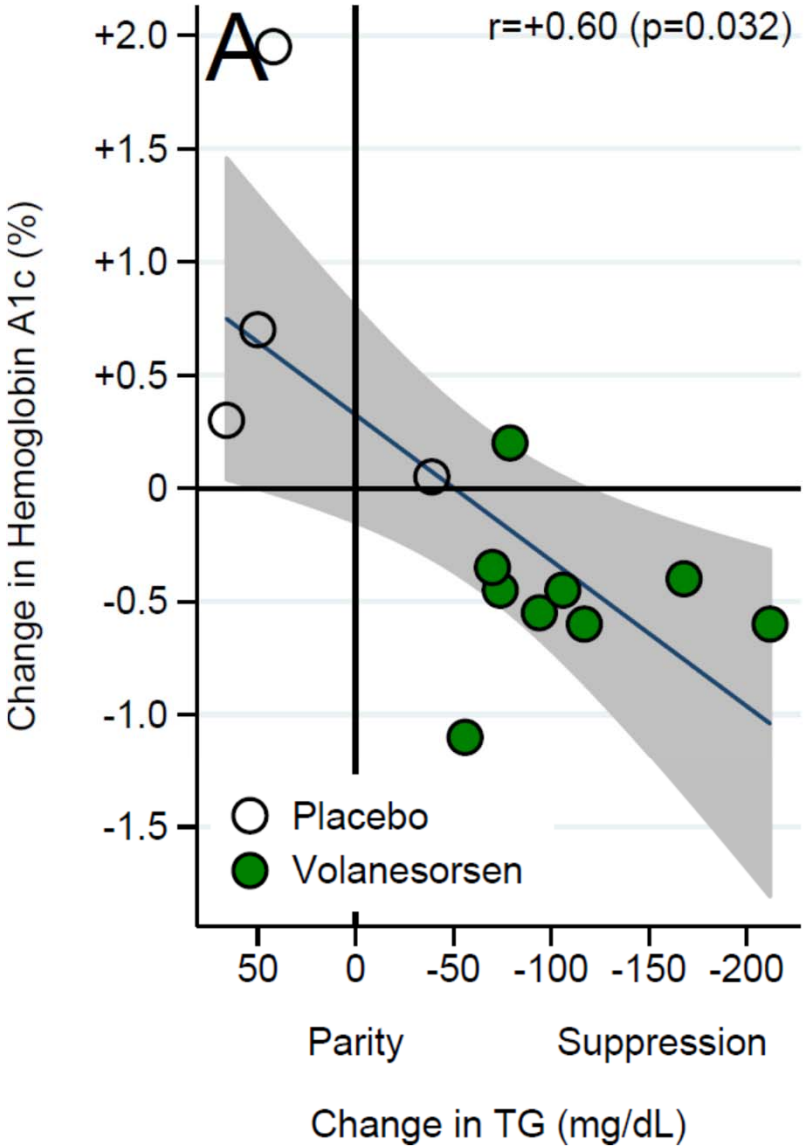
# Volanesorsen Treatment Improves Whole-body Insulin Sensitivity

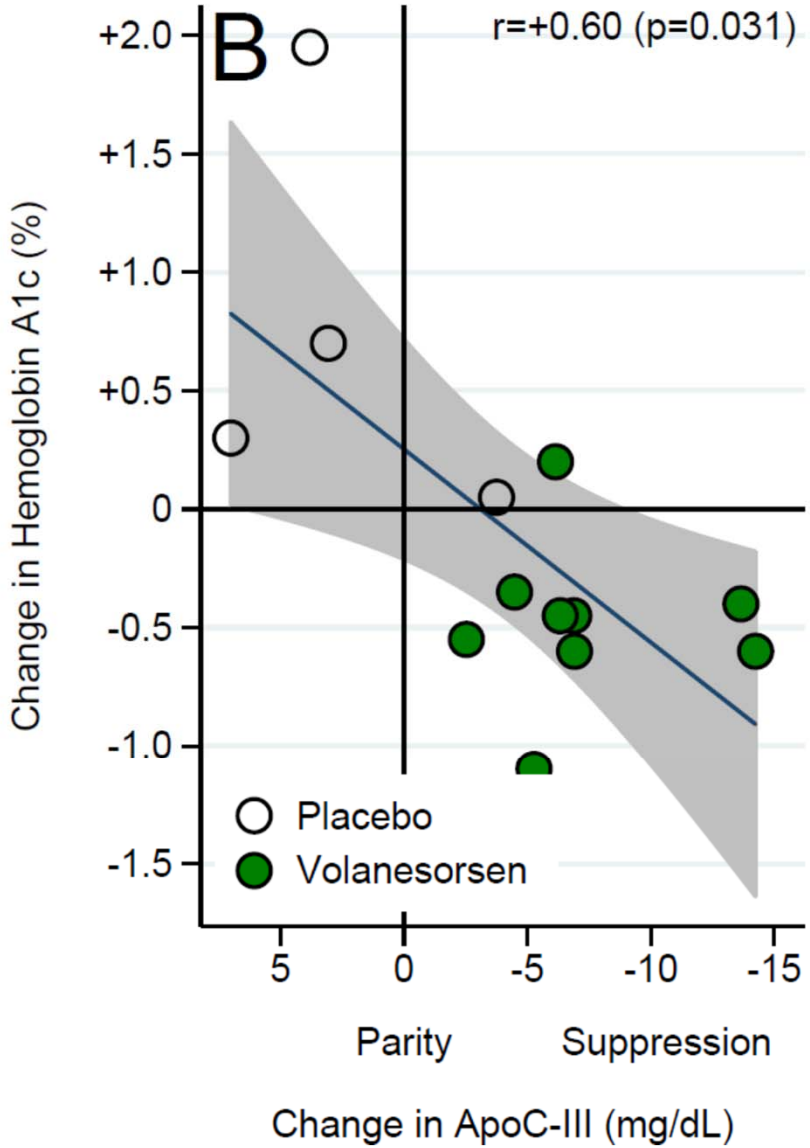


# Improved Insulin Sensitivity Correlates with Suppression of ApoC-III and TG Levels



# Improved HgbA1c Correlates with Suppression of ApoC-III and TG Levels



# Summary of Safety & Tolerability

- No deaths
- One SAE of syncope occurred in the post-treatment f/u period considered unlikely related to volanesorsen
- Majority of AEs (98%) were mild in severity
- No dose discontinuations due to an adverse event
- No clinically relevant changes in serum chemistries, hematology, urinalysis, ECG or vital signs

# Conclusions

**Inhibition of apoC-III with a second generation antisense oligonucleotide in patients with T2D**

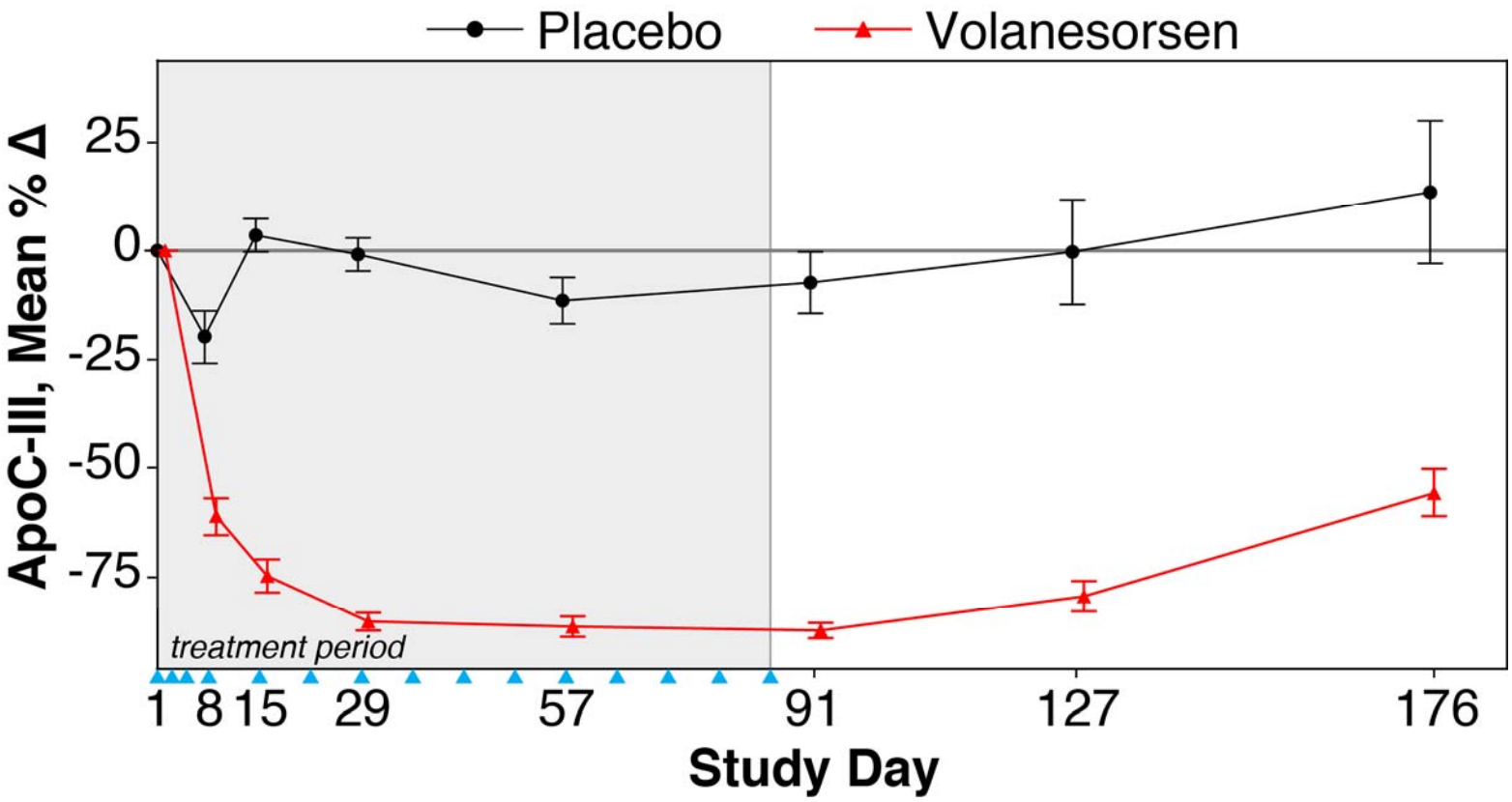
- Improved their atherogenic dyslipidemia
- Improved whole-body insulin sensitivity and clinical integrative markers of glucose handling
- Further studies are needed to clarify whether TG suppression through apoC-III inhibition could complement diabetes management

# Acknowledgements

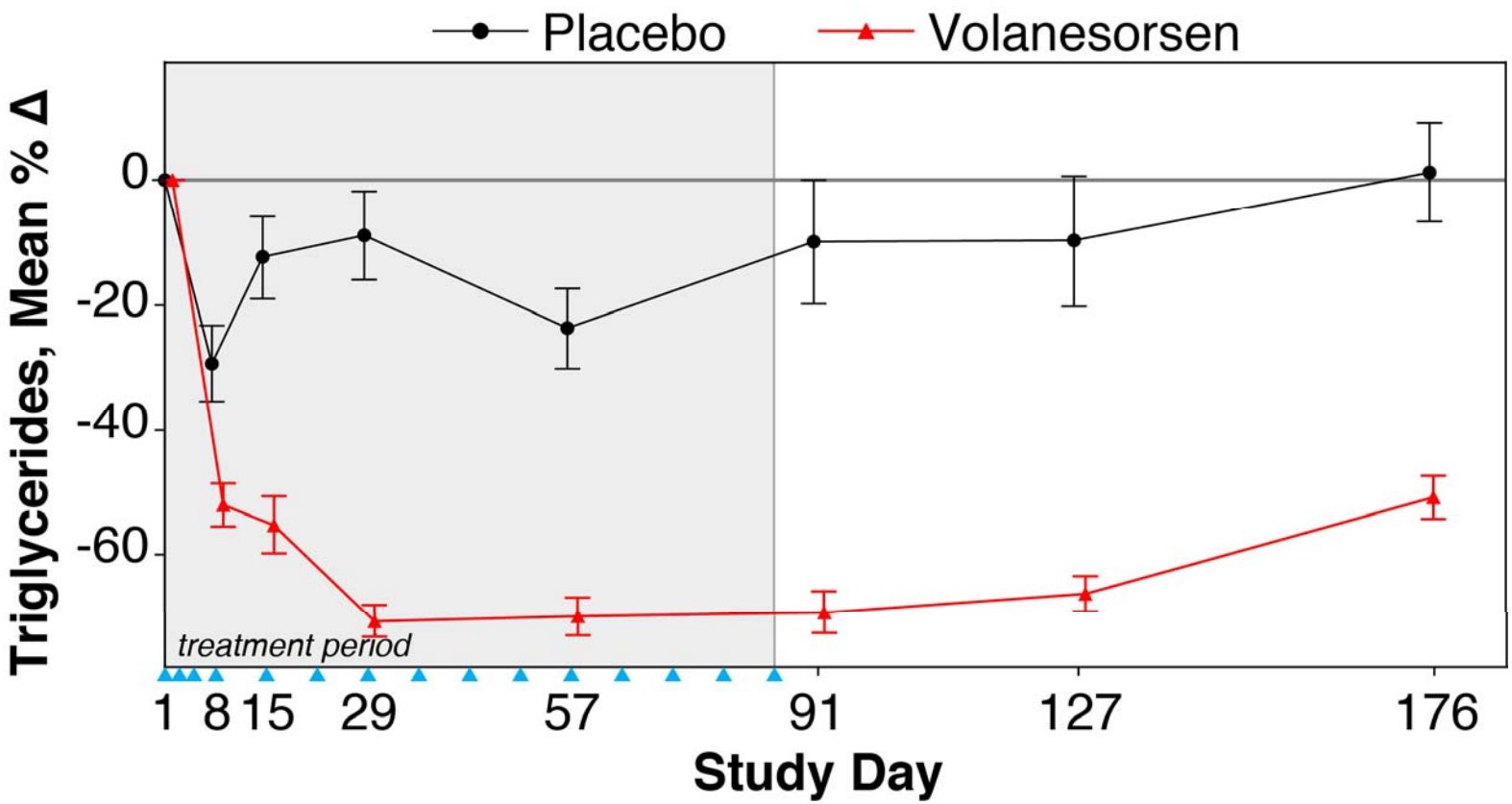

- Study Investigators and Staff at Profil Institute of Clinical Research
- Funding by Ionis Pharmaceuticals, Inc.

# Backup

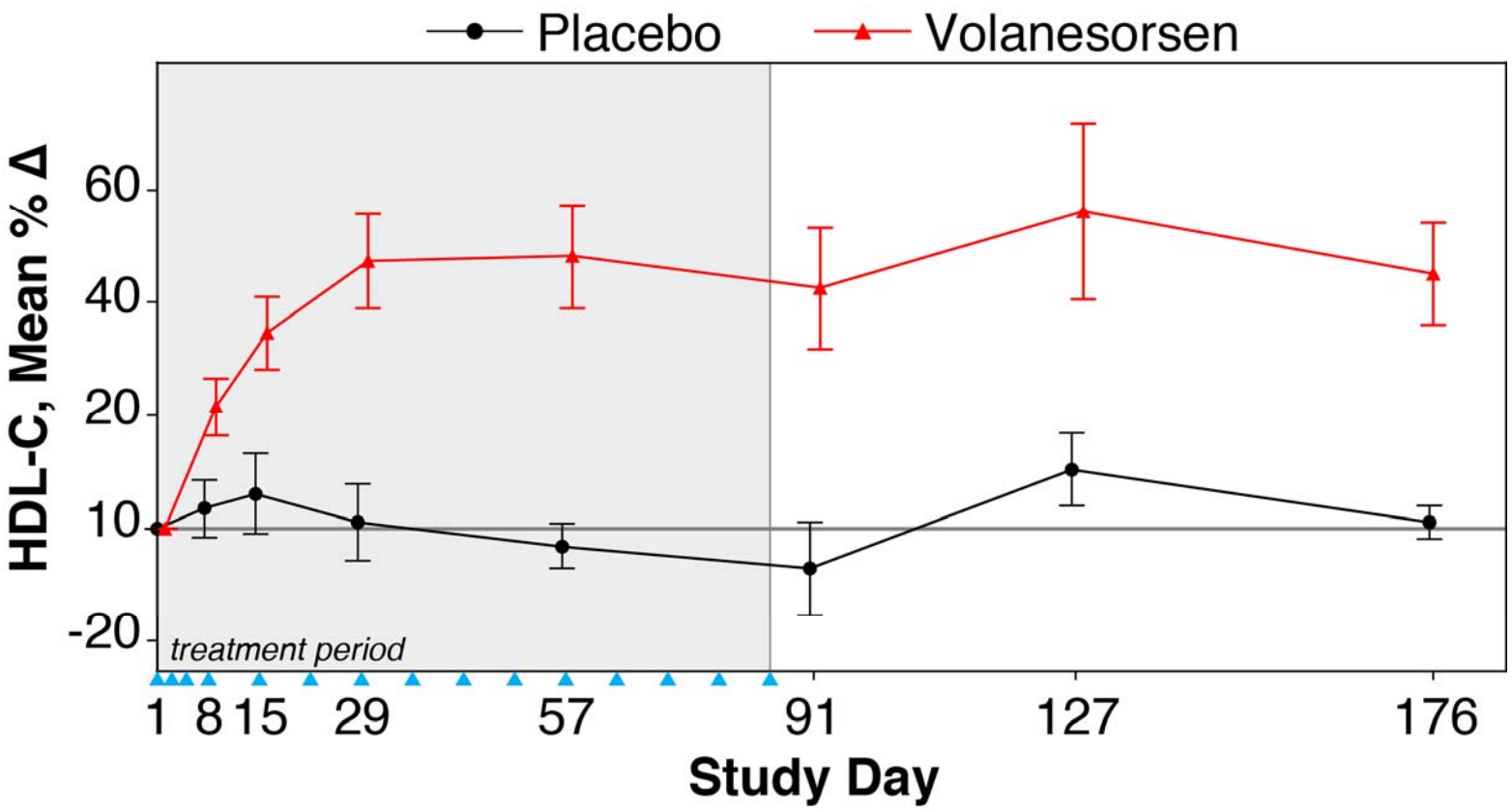
# ApoC-III


Placebo
Volanesorsen
ApoC-III, Mean % Δ
25
0
-25
-50
-75
treatment period
1
8
15
29
57
91
127
176
Study Day

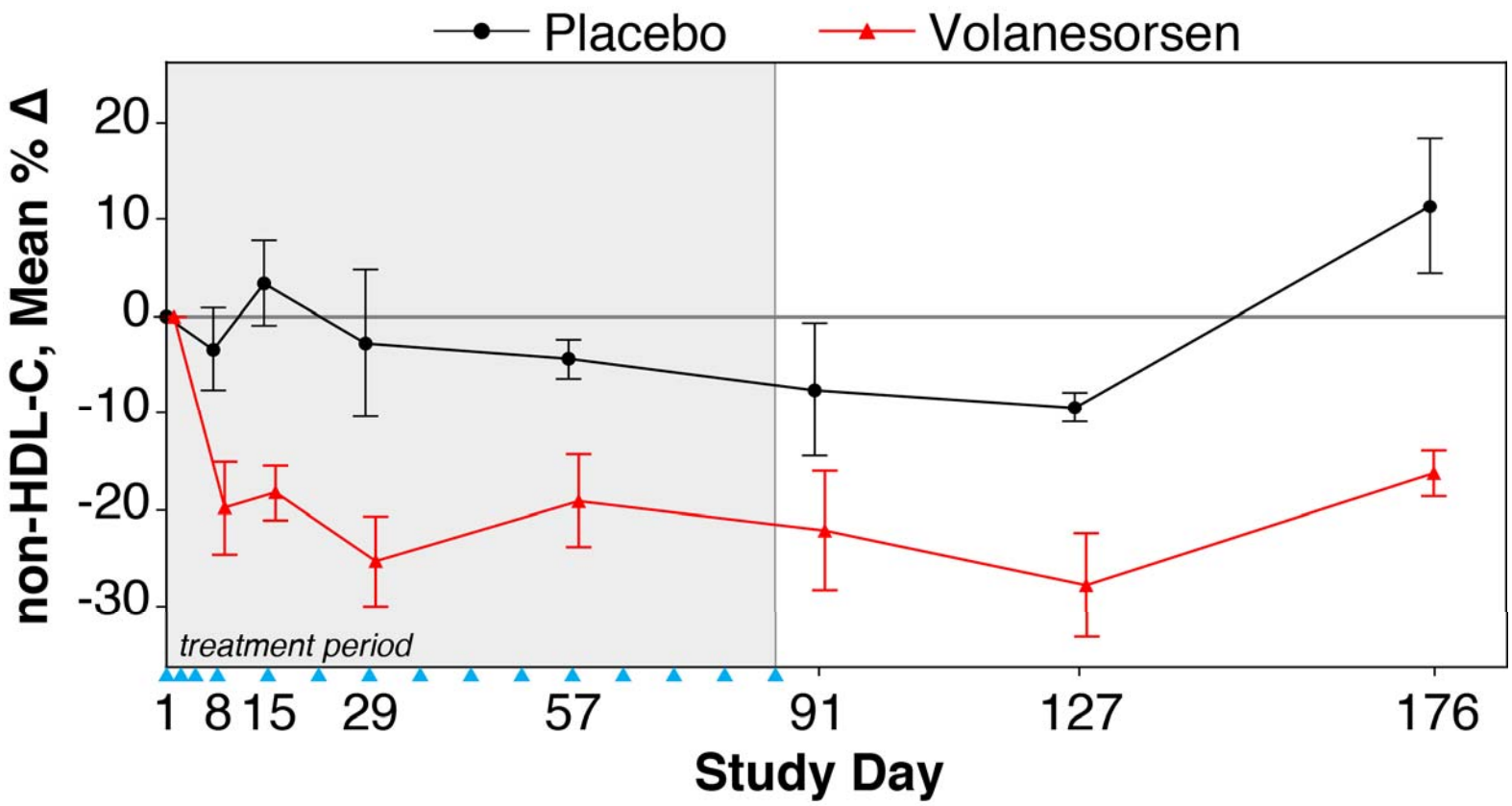
# Triglycerides



# HDL-C


Placebo
Volanesorsen
HDL-C, Mean % Δ
60
40
20
10
-20
treatment period
1
8
15
29
57
91
127
176
Study Day

# Non-HDL-C


Placebo
Volanesorsen
non-HDL-C, Mean % Δ
20
10
0
-10
-20
-30
treatment period
1
8
15
29
57
91
127
176
Study Day