Supplementary Material

Cognitive Effects of the BET Protein Inhibitor Apabetalone: A Prespecified MoCA Analysis Nested in the BETonMACE Randomized Controlled Trial

Supplementary Table 1. The Shift Table shows how patients with baseline MoCA scores of ≤ 21, 25 – 22, and ≥ 26, respectively, shift groups from baseline to last observation captured according to MoCA subgroup and assigned treatment group. Data are presented as n (%).

| Placebo MoCA Baseline | Last Observation Captured |
|-----------------------|---------------------------|
|                       | ≤ 21 | 25 – 22 | ≥ 26 |
| ≤ 21                  | 28 (62%) | 16 (35%) | 1 (2%) |
| 25 – 22               | 13 (19%) | 28 (41%) | 28 (41%) |
| ≥ 26                  | 3 (3%) | 16 (16%) | 82 (81%) |

| Apabetalone MoCA Baseline | Last Observation Captured |
|--------------------------|---------------------------|
|                         | ≤ 21 | 25 – 22 | ≥ 26 |
| ≤ 21                    | 13 (43%) | 14 (46%) | 3 (10%) |
| 25 – 22                 | 8 (15%) | 26 (47%) | 21 (38%) |
| ≥ 26                    | 5 (6%) | 17 (20%) | 63 (74%) |

MoCA, Montreal Cognitive Assessment
**Supplementary Table 2.** Least Squares (LS) mean change in MoCA domain scores from baseline to last observation captured according to MoCA subgroup and assigned treatment group. Data are presented as LS means (standard error).

| LS mean change in MoCA domain scores from baseline to LOC | Patients with MoCA ≥ 26 by Assigned Treatment Group | Patients with MoCA 25 – 22 by Assigned Treatment Group | Patients with MoCA ≤ 21 by Assigned Treatment Group |
|----------------------------------------------------------|----------------------------------------------------|----------------------------------------------------|----------------------------------------------------|
|                                                          | Placebo (n=101) Apabetalone (n=85) P | Placebo (n=69) Apabetalone (n=55) P | Placebo (n=45) Apabetalone (n=30) P |
| Abstraction (/2)                                          | -0.1 (0.0) -0.1 (0.0) 0.5 | -0.1 (0.1) 0.0 (0.1) 0.5 | 0.1 (0.1) 0.4 (0.1) 0.1 |
| Delayed Recall (/5)                                       | -0.1 (0.1) -0.3 (0.1) 0.4 | 0.4 (0.2) 0.4 (0.2) 0.9 | 0.4 (0.2) 1.0 (0.3) 0.099 |
| Language: Repeat (/2)                                     | 0.0 (0.0) -0.1 (0.1) 0.3 | 0.1 (0.1) 0.0 (0.1) 0.3 | -0.1 (0.1) 0.2 (0.1) 0.2 |
| Language: Fluency (/1)                                    | 0.0 (0.0) -0.1 (0.0) 0.054 | 0.1 (0.1) 0.1 (0.1) 0.7 | 0.1 (0.1) 0.2 (0.1) 0.2 |
| Naming (/3)                                               | 0.0 (0.0) 0.0 (0.0) 0.7 | 0.0 (0.0) 0.0 (0.0) 0.8 | 0.0 (0.1) 0.0 (0.1) 1.0 |
| Orientation (/6)                                          | -0.1 (0.1) 0.0 (0.1) 0.8 | -0.2 (0.1) 0.1 (0.1) 0.03 | 0.2 (0.1) 0.3 (0.2) 0.8 |
| Attention: Read List of Digits (/2)                       | 0.0 (0.0) -0.1 (0.0) 0.4 | 0.0 (0.1) -0.1 (0.1) 0.7 | 0.0 (0.1) 0.2 (0.1) 0.2 |
| Attention: Read List of Letters (/1)                      | -0.1 (0.0) -0.1 (0.0) 0.5 | 0.0 (0.0) 0.0 (0.0) 1.0 | 0.0 (0.1) 0.1 (0.1) 0.2 |
| Attention: Serial 7 Subtraction Starting At 100 (/3)      | -0.1 (0.1) -0.2 (0.1) 0.5 | 0.1 (0.1) 0.2 (0.1) 0.7 | 0.3 (0.1) 0.3 (0.2) 1.0 |
| Visuospatial or Executive (/5)                            | 0.0 (0.1) -0.2 (0.1) 0.1 | -0.1 (0.1) 0.0 (0.2) 0.6 | 0.1 (0.2) 0.3 (0.2) 0.2 |

p-values were calculated using ANCOVA statistical analysis to compare change in MoCA domain scores from baseline to last observation captured between apabetalone-treated patients and placebo with baseline MoCA domain scores serving as a covariate and treatment arm as a factor. p-values of <0.05 are considered statistically significant. p-values of <0.1 are considered to have trending significance. MoCA, Montreal Cognitive Assessment.
**Supplementary Table 3.** Biochemical parameters at baseline and median across all time points with apabetalone or placebo treatment groups. Data are presented as median (quartile 1-quartile 3).

|                     | Patients with MoCA ≥ 26 by Assigned Treatment Group | Patients with MoCA 25 – 22 by Assigned Treatment Group | Patients with MoCA ≤ 21 by Assigned Treatment Group |
|---------------------|---------------------------------------------------|--------------------------------------------------------|-----------------------------------------------|
|                     | Placebo (n=101) Apabetalone (n=85) p               | Placebo (n=69) Apabetalone (n=55) p                     | Placebo (n=45) Apabetalone (n=30) p           |
| **HbA1c**           |                                                   |                                                        |                                               |
| Baseline (%)        | 7.1 (6.3 – 8.3)                                   | 6.9 (6.3 – 7.9)                                       | 7.0 (6.1 – 7.9)                               |
| Follow up (%)       | 7.2 (6.4 – 8.1)                                   | 7.0 (6.5 – 7.9)                                       | 7.1 (6.3 – 8.1)                               |
| Percent change (%)  | 0.0 (-5.0 – 7.2)                                  | 2.0 (-3.0 – 9.4)                                      | 1.7 (-3.6 – 10.3)                            |
| Serum Glucose       |                                                   |                                                        |                                               |
| Baseline (mg/dL)    | 129.7 (104.7 – 161.2)                             | 136.0 (116.9 – 165.4)                                | 131.8 (109.9 – 172.0)                        |
| Follow up (mg/dL)   | 141.8 (116.6 – 166.1)                             | 114.1 (119.3 – 127.8)                                | 140.7 (115.3 – 168.8)                        |
| Percent change (%)  | -0.9 (-11.2 – 31.4)                               | 3.3 (-8 – 20.6)                                      | 3.8 (-9.0 – 16.6)                            |
| Total Cholesterol   |                                                   |                                                        |                                               |
| Baseline (mg/dL)    | 128.8 (109.0 – 155.8)                             | 126.8 (104.8 – 150.4)                                | 128.0 (106.7 – 149.7)                        |
| Follow up (mg/dL)   | 128.0 (108.3 – 150.4)                             | 125.7 (110.2 – 140.2)                                | 124.1 (107.5 – 148.1)                        |
| Percent change (%)  | -1.9 (-11.7 – 9.3)                                | 0.4 (-13.1 – 15.3)                                   | 1.7 (-11.6 – 12.0)                           |
| LDL Cholesterol     |                                                   |                                                        |                                               |
| Baseline (mg/dL)    | 61.9 (46.8 – 82.4)                                | 62.6 (44.9 – 85.8)                                   | 64.2 (49.5 – 84.7)                           |
| Follow up (mg/dL)   | 57.6 (46.4 – 78.1)                                | 56.8 (44.1 – 72.7)                                   | 59.0 (46.8 – 78.1)                           |
| Percent change (%)  | -3.9 (-18.2 – 19.9)                               | -5.5 (-29.3 – 20.0)                                  | 0.0 (-18.3 – 16.0)                           |
| HDL Cholesterol     |                                                   |                                                        |                                               |
| Baseline (mg/dL)    | 34.4 (31.7 – 39.1)                                | 33.3 (29.8 – 36.7)                                   | 34.0 (31.3 – 37.5)                           |
| Follow up (mg/dL)   | 37.1 (33.3 – 42.9)                                | 38.7 (33.6 – 44.1)                                   | 37.1 (33.4 – 42.2)                           |
| Percent change (%)  | 8.4 (-1.0 – 20.5)                                 | 16.9 (4.0 – 30.2)                                    | 11.2 (-1.1 – 20.5)                           |
| Triglycerides       |                                                   |                                                        |                                               |
| Baseline (mg/dL)    | 193.6 (128.4 – 207.3)                             | 145.3 (121.3 – 191.3)                                | 147.0 (102.7 – 174.5)                        |
| Follow up (mg/dL)   | 146.1 (117.8 – 170.1)                             | 132.0 (107.2 – 178.0)                                | 132.1 (100.5 – 167.0)                        |
| Percent change (%)  | -8.4 (-25.0 – 11.0)                               | -7.1 (-25.7 – 10.9)                                  | 0.63 (-6.7 – 25.0)                            |
| Alkaline Phosphatase|                                                   |                                                        |                                               |
| Baseline (U/L)      | 76.0 (61.0 – 91.0)                                | 76.0 (64.0 – 88.0)                                   | 76.0 (61.0 – 94.0)                           |
| Follow up (U/L)     | 74.5 (60.9 – 90.5)                                | 67.0 (55.0 – 78.0)                                   | 74.0 (63.0 – 95.0)                           |
| Percent change (%)  | 0.0 (-9.0 – 10.6)                                 | -10.6 (-20.5 – 3.4)                                  | -1.1 (-12.0 – 6.8)                           |
|                  | Alanine Aminotransferase | Total Bilirubin | hsCRP | NLR |
|------------------|--------------------------|-----------------|-------|-----|
| **Baseline (U/L)** | 20.0 (15.8 – 28.0)      | 10.1 (7.8 – 13.8) | 1.1 (0.6 – 2.3) | 2.4 (2.1 – 3.3) |
|                  | 19.0 (15.0 – 26.0)      | 9.9 (7.5 – 12.9)  | 2.8 (1.7 – 5.5) | 2.8 (2.1 – 3.3) |
|                  | 19.0 (15.0 – 27.0)      | 9.2 (7.4 – 13.9)  | 1.0 (0.4 – 2.7) | 2.9 (2.2 – 3.6) |
|                  | 17.0 (13.5 – 22.5)      | 9.4 (7.9 – 11.6)  | 2.3 (1.3 – 4.4) | 2.9 (2.2 – 3.8) |
|                  | 18.0 (14 – 25.0)        | 9.9 (8.5 – 13.8)  | 4.4 (3.2 – 8.4) | 2.5 (2.2 – 3.2) |
|                  | 20.0 (13.0 – 27.0)      | 9.6 (6.1 – 13.8)  | 2.2 (0.8 – 5.1) | 3.0 (2.1 – 3.9) |
| **Follow up (U/L)** | 19.0 (15.0 – 25.0)      | 10.3 (8.4 – 13.0) | 1.3 (0.7 – 4.6) | 2.3 (1.9 – 2.7) |
|                  | 20.0 (15.0 – 26.0)      | 11.4 (8.9 – 14.4) | 2.4 (1.2 – 4.4) | 2.5 (2.1 – 3.3) |
|                  | 18.0 (13.0 – 24.0)      | 10.7 (7.3 – 14.1) | 0.7 (0.5 – 1.7) | 2.4 (1.9 – 2.9) |
|                  | 18.0 (14.5 – 23.3)      | 11.4 (8.6 – 14.2) | 1.5 (0.9 – 4.8) | 2.7 (1.8 – 3.1) |
|                  | 18.0 (14.0 – 22.0)      | 9.9 (7.8 – 13.2)  | 4.5 (2.1 – 5.7) | 2.2 (1.7 – 2.6) |
|                  | 17.3 (14.3 – 22.9)      | 10.1 (7.7 – 13.3) | 4.2 (1.4 – 7.2) | 2.6 (2.2 – 3.2) |
| **Percent change (%)** | -4.1 (-25.0 – 9.3)      | 2.8 (-9.3 – 15.1) | 0.2 (<0.0001)  | -11.1 (-26.0 – 0.6) |
|                  | 3.8 (-13.9 – 25.3)      | 16.4 (2.2 – 39.9) | 3.5 (-7.3 – 19.3) | -13.5 (-27.0 – 2.6) |
|                  | **0.01**                | **-0.0001**      | **0.08**   | **-0.76** |
|                  | 5.0 (-16.2 – 31.4)      | **-0.02**        | 0.0 (-18.8 – 27.9) | **-0.72** |
|                  | **0.02**                | **-4.0 (-25.0 – 13.6)** | 12.8 (-1.8 – 26.0) | 0.16 |
|                  | **0.0**                 | **-32.5 (-49.4 – 54.5)** | 39.3 (-24.0 – 93.7) | **0.41** |
|                  | **39.3**                | **-5.3 (-28.1 – 10.6)** | **0.36** | **0.41** |

MoCA, Montreal Cognitive Assessment; HbA1c, hemoglobin A1C; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; NLR, neutrophil-lymphocyte ratio.

p-values comparing groups were calculated using Wilcoxon tests for continuous variables. p-values of <0.05 are considered statistically significant.
Supplemental Statistical Analysis Plan

Resverlogix Corp.

Protocol Number: RVX222-CS-015

A Phase III multi-center, double-blind, randomized, parallel group, placebo-controlled clinical trial in high-risk type 2 diabetes mellitus (T2DM) subjects with coronary artery disease (CAD) to determine whether bromodomain extraterminal domain (BET) inhibition treatment with RVX000222 increases the time to major adverse cardiovascular events (MACE)

Final

Supplemental Statistical Analysis Plan: Cognition

Date: September 13, 2019

Prepared by: Jeffrey Cummings, MD, Neurologist, Cleveland Clinics, and Jan Johansson, MD, Resverlogix on behalf of BETonMACE Clinical Steering Committee.

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**Background**

BETonMACE is a pivotal phase 3 trial in 2,425 post-ACS patients with diabetes and low HDL cholesterol levels. The primary objective of the trial is to assess the effect of randomization to apabetalone 100 mg bid vs. placebo on 3P-MACE (CV-death, non-fatal MI, stroke). Patients are randomized to apabetalone: placebo 1:1 across 13 countries and 195 sites. Based on collecting 250 3P-MACE events BETonMACE has an 80% power to detect a 30% lowering of events at a p<0.05 level. Further details can be found in the design manuscript that was recently accepted for publication in American Heart Journal (Supplementary Figure 1) [1].

In addition, there are pre-specified subpopulations where the treatment effects of apabetalone will be further evaluated. In the 70 and older population effects on cognition will be assessed as outlined below.

The BETonMACE formal *Statistical Analysis Plan* (hereafter, “main SAP”) was initially submitted to FDA on Sept 1, 2018 with clarifying amendment submitted June 2019. The current version is *Final Version 3.0, dated 10 June 2019*.

In BETonMACE the Montreal Cognition Assessment (MoCA) (see Supplementary Figure 2 below) covering 7 cognition domains is being performed in patients that are 70 years and older at time of randomization. In the main SAP submitted to FDA, a pre-specified assessment for cognition is included as an exploratory endpoint, i.e., change in MoCA score within and between treatment group in those with MoCA ≤ 25 at randomization.

In BETonMACE, MoCA was performed at baseline in 19% (n= 469) of the population. Of those, approximately 52% (n=246) had a baseline MoCA score ≤ 25 suggesting potentially compromised cognition. Given that BETonMACE participants have type 2 diabetes, low HDL cholesterol, and recent ACS, the assumption is that their dementia is largely attributable to vascular
cognitive impairment (VCI). MoCA is collected at baseline, 12 months, and 24 months, as well as at the last visit on treatment (LVT). Average duration of study participation in BETonMACE is 27 months. The size of the MoCA subpopulation and follow-up duration are consistent with those in phase 3 Alzheimer’s disease (AD) trials, although AD trials differ in other aspects including having a more comprehensive battery of cognition assessments.

An exploratory objective in the main SAP is to evaluate Health-Related Quality of Life (HRQOL) as measured using the EQ-5D-5L questionnaire. Change in Health-Related Quality of Life (HRQOL) during the study is also measured using the EQ-5D-5L. Analyses will summarize EQ-5D-5L scale and subscale scores at each visit and change from baseline at each visit. This SAP seeks to understand how MoCA and EQ-5D-5L potentially co-vary over time and with treatment.

**Objectives**

This BETonMACE Cognition supplemental SAP is generated to create pre-specified metrics for the evaluation cognition and quality of life including the following 4 main objectives:

a) To follow change in composite MoCA and its 7 domains over time to assess effects of randomization to apabetalone 100 mg bid vs. placebo, specifically to determine if apabetalone vs. placebo prevents or slows down cognitive decline in post-ACS patients with diabetes and low HDL cholesterol that are 70 and older at time of randomization.

b) To determine if MoCA correlates with PD biomarkers, both at baseline and with respect to changes from baseline. The hypothesis is that the underlying cause poor MoCA in this population is linked to pathophysiology of the vascular bed. Consistency between low MoCA score, PD biomarkers of CV risk would support that hypothesis. Furthermore, assess if a low MOCA score or decrease in MOCA predicts broad total CV events.
Additional exploratory analyses of individual MoCA domains vs. PD biomarkers, as well as the association between event rates and MoCA will be conducted.

c) To determine if change in MoCA correlates with change in EQ-5D-5L scale. Analyses of MoCA domains and EQ-5D-5L subscale scores will also be conducted.

d) To determine if an effect of apabetalone vs. placebo on MoCA/cognition impairment is related to pathophysiology of cognitive impairment. Specifically, plasma biomarkers will be assessed for evidence of neurodegenerative processes including Alzheimer’s disease that might co-exist with vascular pathophysiology, and a potential difference in the effect of treatment on MoCA between pathophysologies will be assessed.

Objective (a): MoCA Total and Domain Scores over Time

Baseline characteristics (demographics and clinical chemistry, see example Supplementary Table 4) of:

a) MoCA population vs. non-MoCA vs. all BETonMACE patients
b) Comparison 70 and older population with and without MoCA
c) MoCA population apabetalone vs. placebo

Treatment effect:

We will summarize MoCA scores by randomized treatment at baseline, month 12, month 24, and last visit on treatment (LVT), as well as changes from baseline at month 12, 24, and LVT. We will also produce summaries for “last value captured” (LVC) defined as the last post-baseline value obtained (provided it is at least 9 months post-baseline).

We will fit a linear mixed effects model of post-baseline MoCA scores by treatment with an effect for timepoint and baseline covariates including baseline MoCA scores and key demographic
variables (sex, age, systolic BP, smoking status, LDL-C, HDL-C, hsCRP, eGFR, ALP, NLR, and statin); additional contingency variable covariates (see Supplementary Appendix) may be added following archive sample analysis. From this model, estimates and 95% confidence intervals for MoCA change from baseline to 12 and to 24 months will be calculated by treatment group, and treatment group differences will be tested.

Similar exploratory analyses of the 7 MoCA subdomains (see Fig. 1) will be conducted.

Objective (b): Association of MoCA change to serum PD biomarkers

We will assess correlations between MoCA and serum PD biomarkers (ALP, NLR, hsCRP, and contingency markers):

- Baseline MoCA compared to baseline PD biomarker
- Change in MoCA from baseline to month 12 compared to baseline PD biomarker
- Change in MoCA from baseline to month 12 compared to change in PD biomarker from baseline to month 12

Analyses of the relationship of treatment effect on MoCA by ApoE carrier status (if available), age, and sex that are standard for cognitive datasets will also be performed [2].

We will also conduct a multivariate analysis of change in MoCA from baseline to month 12 with covariates to include treatment, age, sex, statin, change in ALP, NLR, hsCRP, and contingency markers. We will conduct additional exploratory analyses of a similar nature using MoCA domains.

Finally, we will conduct an exploratory analysis of the association between CV events (narrow and broad MACE) and baseline MoCA using a Cox model with treatment, baseline MoCA (continuous and categorically as > 25 vs. ≤ 25 and > 25 vs. ≤ 25 – 22 vs. ≤ 21), and their interaction.
Objective (c): Association of MoCA with EQ-5D-5L

Associations between MoCA and EQ-5D-5L will be assessed using the same analyses as those used to assess MoCA/PD associations in part (b).

A linear model will be used to associate change in MoCA score with concomitant change in EQ-5D-5L score by randomized treatment; the model will include effects for change in EQ-5D-5L score, treatment, and their interaction.

Exploratory analyses similar to those above will also be conducted for MoCA domains and EQ-5D-5L subscales.

Objective (d): Characterization of vascular vs. mixed (vascular and Alzheimer’s disease) origin behind low MoCA score at baseline and assess the relationship of vascular vs. mixed origin for apabetalone treatment response

Apabetalone does not cross the blood brain barrier and the hypothesis is that apabetalone effects are vascular in nature. However, the neurovascular biology is complex with peripheral-central interplay-effects poorly understood including that of signaling, BBB transportation and neurovascular configuration/architecture. Thus, apabetalone effects on Alzheimer’s disease cannot be excluded and need to be tested empirically. BETonMACE provides an opportunity to do so.

Analyses of the relationship of treatment effect on MoCA by ApoE carrier status, age, and sex that are standard for cognitive datasets will also be performed [2].

One objective is to see if apabetalone’s effects on MoCA is better or worse in vascular cognitive impairment vs. mixed (vascular and AD) pathology. AD pathology contribution to
vascular dementia will be arbitrarily defined by a single AD plasma biomarker or combination of AD biomarkers, see below.

Single biomarkers for AD origin are defined based on: a) presence of $APOE4$ genotype, b) plasma $A\beta_{42/40}$ ratio below established cut-off value [3], c) NfL above median, d) plasma YKL-40 above median. (Exclusive vascular origin populations are derived from the complementary population to the AD defined one).

Combination biomarkers for AD origin are patients with any of; a) presence of $APOE4$ genotype, b) plasma $A\beta_{42/40}$ ratio below $\leq 25^{th}$ percentile, c) NfL $\geq 75^{th}$ percentile, d) plasma YKL-40 $\geq 75^{th}$ percentile.

Exclusive vascular origin will be defined as not meeting the above criteria, i.e., the complementary group.

We will fit a linear mixed effects model of MoCA at post-baseline timepoints with main effects for treatment, origin category, and their interaction; additional covariates will include baseline MoCA and other baseline covariates as described in objective (a).

Additional exploratory analyses for MoCA domains will also be conducted.
SUPPLEMENTARY REFERENCES

[1] Ray KK, Nicholls SJ, Ginsberg HD, Johansson JO, Kalantar-Zadeh K, Kulikowski E, Toth PP, Wong N, Cummings JL, Sweeney M, Schwartz GG (2019) Effect of selective BET protein inhibitor apabetalone on cardiovascular outcomes in patients with acute coronary syndrome and diabetes: Rationale, design, and baseline characteristics of the BETonMACE trial. *Am Heart J* 217, 72–83.

[2] Cummings J, Ritter A, Zhong K (2018) Clinical trials for disease-modifying therapies in Alzheimer’s disease: a primer, lessons learned, and a blueprint for the future. *J Alzheimers Dis* 64, S3-S22.

[3] Palmqvist S, Janelidze S, Stomrud E, Zetterberg H, Karl J, Zink K, Bittner T, Mattsson N, Eichenlaub U, Blennow K, Hansson O (2019) Performance of fully automated plasma assays as screening tests for alzheimer disease-related β-amyloid status. *JAMA Neurol* 76, 1060–1069.
*Contingency analysis, e.g., statistical calculations following biomarker analysis from archive samples.*

If MoCA is improved by apabetalone treatment, then we plan to analyze plasma biomarkers to better understand the mechanism of action underpinning the treatment effect. Is treatment more or less efficient in the CVD patients that have vascular dementia or mixed (vascular and Alzheimer’s) dementia?

Is a treatment effect on MoCA score dependent on baseline biomarker values of AD and non-AD biomarkers? Is a MoCA score treatment effect associated with change in an AD or non-AD biomarker. The suggestion is to measure AD biomarkers from plasma archive samples at times of MoCA testing, i.e., at randomization, 12 and 24 months.

Variables of importance include:

a) apoE isoform analysis, at a minimum apoE4 (prevalence 20%) vs. non apoE4 (prevalence 80%)
b) plasma Neurofilament light (NfL) (tubular damage)
c) plasma YKL-40 (neuroinflammation)
d) plasma Aβ42/40 ratio (Bateman, Nakamura method or similar)
e) proteomics assessment will try to link plasma biomarkers to MoCA and to apabetalone treatment effect in:

- Biased confirmatory approach using customized panel assessing exploratory positive findings from phase 2 studies including amyloid beta A4 protein, gelsolin, Annexin A1, serum amyloid b component, brain derived neurotropic factor, CHIP/STUB1, LRP1, Insulin Degrading Enzyme, Neprolysin, Thrombospondin 1 within and between groups.
An unbiased proteomics approach (for example SomaLogics).

Baseline and treatment change will be included in the analysis described above.

Comment about power calculation for future studies: Apabetalone treatment effect vs. placebo from baseline to last value captured (>9 months after baseline) in patients with baseline MoCA score \( \leq 25 \) or \( \leq 21 \) population may be the best for assessing natural course of decline (placebo group) and calculating “effect size” of apabetalone treatment (apabetalone active group) for powering of future phase 2-3 cognition trials.

For missing values use Mixed-Effect Model Repeated Measure (MMRM) model rather than last-value-carried-forward.
**Supplementary Table 4.** Baseline demographics, all patients doing MoCA exam vs. those with MoCA score > 25 vs. ≤ 25.

|                       | All Patients Randomized | Cognition Subgroup | Patients Randomized with Baseline MoCA > 25 | Patients Randomized with Baseline MoCA ≤ 25 | Patients with MoCA > 25 vs. Patients with MoCA ≤ 25 |
|-----------------------|-------------------------|--------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|
|                       | N  | %    | N  | %    | N  | %    | N  | %    | p   |
| **Number of Participants** | 2,425 | 469 | 223 | 246 | -   |
| Age (y) (median) (min, max) | 62 (31, 88) | 73 (69, 88) | 73 (70, 88) | 74 (69, 86) | 0.13 * |
| Sex (male) | 1,806 | 74.5% | 300 | 64.0% | 144 | 64.6% | 156 | 63.4% | 0.85 |
| Caucasian | 2,115 | 87.2% | 417 | 88.9% | 211 | 94.6% | 206 | 83.7% | **0.0002** |
| Education (≤12 y) | - | - | 360 | 76.8% | 162 | 72.6% | 198 | 80.5% | **0.05** |
| MoCA Score (mean) (SD) | - | - | 24.4 (4.1) | 27.7 (1.4) | 21.4 (3.4) | -<0.0001 * |
| **Domains (mean scores) (SD)** |  |  |  |  |  |
| Visuospatial / Executive Function (/5) | - | - | 3.8 (1.2) | 4.3 (0.8) | 3.3 (1.3) | -<0.0001 * |
| Naming (/3) | - | - | 2.9 (0.4) | 3.0 (0.1) | 2.8 (0.5) | -<0.0001 * |
| Attention (Digits, Letters, Subtraction) (/6) | - | - | 4.7 (1.4) | 5.5 (0.8) | 4.0 (1.5) | -<0.0001 * |
| Language (Repetition, Fluency) (/3) | - | - | 2.1 (0.9) | 2.6 (0.7) | 1.6 (0.9) | -<0.0001 * |
| Abstraction (/2) | - | - | 1.7 (0.6) | 1.9 (0.4) | 1.5 (0.7) | -<0.0001 * |
| Memory (Recall) (/5) | - | - | 2.8 (1.6) | 3.8 (1.1) | 1.9 (1.4) | -<0.0001 * |
| Orientation (/6) | - | - | 5.8 (0.7) | 6.0 (0.2) | 5.7 (0.9) | -<0.0001 * |
| **Index ACS Event** |  |  |  |  |  |
| ACS / MI | 1,787 | 73.7% | 327 | 69.7% | 150 | 67.3% | 177 | 72.0% | 0.31 |
| Unstable Angina | 625 | 25.8% | 139 | 29.6% | 70 | 31.4% | 69 | 28.0% | 0.48 |
| History of PCI | 1,930 | 79.6% | 343 | 73.1% | 173 | 77.6% | 170 | 69.1% | **0.05** |
| **Medical History** |  |  |  |  |  |
| Diabetes History (median years) (IQR) | 6.7 (10.8) | 9.8 (12.7) | 10.0 (13.6) | 9.7 (11.4) | 0.81 * |
| History of taking Diabetes Medication: Yes (%) | 2,322 | 95.8% | 445 | 94.9% | 212 | 95.1% | 233 | 94.7% | 1.00 |
| History of taking Diabetes Medication: No (%) | 103 | 4.2% | 24 | 5.1% | 11 | 4.9% | 13 | 5.3% | 0.62 |
| HbA1c ≥6.5% at Visit 1 | 1,770 | 73.0% | 317 | 67.6% | 148 | 66.4% | 169 | 68.7% | 0.31 * |
| BMI (kg/m²) (median) (IQR) | 29.6 (6.6) | 28.7 (6.3) | 28.7 (5.8) | 28.6 (6.6) | 0.03 |
| Hypertension | 2,144 | 88.4% | 445 | 94.9% | 217 | 97.3% | 228 | 92.7% | 0.13 |
| Tobacco Use | 313 | 12.9% | 30 | 6.4% | 10 | 4.5% | 20 | 8.1% | 0.57 |
| Prior Stroke / TIA | 184 | 7.6% | 55 | 11.7% | 24 | 10.8% | 31 | 12.6% | 0.57 |
### Concomitant Statins:

| Statin       | N   | %   | N   | %   | N   | %   |
|--------------|-----|-----|-----|-----|-----|-----|
| Atorvastatin | 1,245 | 51.3% | 232 | 49.5% | 111 | 49.8% | 121 | 49.2% | 0.93 |
| Rosuvastatin | 1,180 | 48.7% | 237 | 50.5% | 112 | 50.2% | 125 | 50.8% |

### Diabetes Mellitus Medications:

| Medication          | N   | %   | N   | %   | N   | %   |
|---------------------|-----|-----|-----|-----|-----|-----|
| Insulin             | 907 | 37.4% | 157 | 33.5% | 68  | 30.5% | 89  | 36.2% | 0.20 |
| Diabetes Medications (Excluding Insulins): | 2,139 | 88.2% | 407 | 86.8% | 194 | 87.0% | 213 | 86.6% |
| Metformin           | 1,954 | 80.6% | 355 | 75.7% | 172 | 77.1% | 183 | 74.4% | 0.52 |
| Sulfonylureas       | 699  | 28.8% | 152 | 32.4% | 68  | 30.5% | 84  | 34.1% | 0.43 |
| GLP-1 Agonists      | 79   | 3.3%  | 6   | 1.3%  | 1   | 0.4%  | 5   | 2.0%  | 0.22 |
| DPP-4 Inhibitors    | 292  | 12.0% | 58  | 12.4% | 25  | 11.2% | 33  | 13.4% | 0.49 |
| SGLT2 Inhibitors    | 290  | 12.0% | 28  | 6.0%  | 14  | 6.3%  | 14  | 5.7%  | 0.85 |

### Cardiovascular Disease Medications:

| Medication          | N   | %   | N   | %   | N   | %   | N   | %   | N Median (IQR) | p    |
|---------------------|-----|-----|-----|-----|-----|-----|-----|-----|----------------|------|
| ACE Inhibitors      | 1,764 | 72.7% | 319 | 68.0% | 162 | 72.6% | 157 | 63.8% | 0.05 |
| ARBs                | 709  | 29.2% | 157 | 33.5% | 67  | 30.0% | 90  | 36.6% | 0.14 |
| Beta-Blockers       | 2,193 | 90.4% | 428 | 91.3% | 203 | 91.0% | 225 | 91.5% | 0.87 |
| Anti-Platelet Agents| 2,396 | 98.8% | 460 | 98.1% | 217 | 97.3% | 243 | 98.8% | 0.32 |
| DAPT                | 2,116 | 87.3% | 393 | 83.8% | 185 | 83.0% | 208 | 84.6% | 0.71 |

### Clinical Chemistry:

| Parameter          | N   | Median (IQR) | N   | Median (IQR) | N   | Median (IQR) | N   | Median (IQR) | p    |
|--------------------|-----|--------------|-----|--------------|-----|--------------|-----|--------------|------|
| ALP† (U/L)         | 2,424 | 78 (30)      | 469 | 76 (30)      | 223 | 76 (30)      | 246 | 77 (31)      | 0.63 * |
| eGFR (mL/min/1.73m²)| 2,413 | 99 (51)      | 467 | 70 (29)      | 223 | 71 (32)      | 244 | 70 (28)      | 0.21 * |
| Albumin (g/dL)     | 2,413 | 4.3 (0.4)    | 467 | 4.2 (0.4)    | 223 | 4.2 (0.4)    | 244 | 4.2 (0.5)    | 0.04 * |
| LDL-C (mg/dL)      | 2,413 | 33 (7.0)     | 467 | 34 (6.0)     | 223 | 34 (7.0)     | 244 | 34 (6.0)     | 0.47 * |
| ApoA-1† (mg/dL)    | 483   | 118 (20)     | 91  | 121 (22)     | 47  | 117 (25)     | 44  | 122 (14)     | 0.34 * |
| hsCRP* (mg/dL)     | 493   | 2.81 (4.95)  | 94  | 2.46 (5.19)  | 48  | 1.82 (3.45)  | 46  | 3.16 (5.68)  | 0.28 * |
| Fibrinogen† (mg/dL)| 471   | 385 (136)    | 91  | 387 (118)    | 47  | 388 (110)    | 44  | 386 (142)    | 0.75 * |
| HbA1c (%)          | 2,369 | 7.3 (2.3)    | 456 | 7.0 (1.8)    | 216 | 7.0 (1.8)    | 240 | 7.1 (2.1)    | 0.38 * |
| Platelets (10⁹/L)  | 2,295 | 249 (94)     | 442 | 237 (93)     | 208 | 243 (95)     | 234 | 231 (89)     | 0.56 * |
| NLR (ratio)        | 2,313 | 2.57 (1.37)  | 445 | 2.76 (1.52)  | 209 | 2.68 (1.54)  | 236 | 2.87 (1.55)  | 0.54 * |

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MoCA, Montreal Cognitive Assessment; ACS, acute coronary syndrome; MI, myocardial infarction; PCI, percutaneous coronary intervention; HbA1c, hemoglobin A1C; BMI, Body mass index; TIA, transient ischemic attack; GLP1, glucagon-like peptide 1; DPP-4, dipeptidyl peptidase; SGLT2, sodium-glucose cotransporter 2; ACE, angiotensin-converting enzyme; ARB, Angiotensin II receptor blocker; DAPT, dual anti-platelet therapy; ALP, alkaline phosphatase;
eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ApoA-1, apolipoprotein A-1, hsCRP, high-sensitivity C-reactive protein; NLR, neutrophil-lymphocyte ratio.
Continuous variables are presented as mean (standard deviation [SD]) or median (interquartile range [IQR]). Categorical variables are presented as n (%).
p-values comparing groups at baseline were calculated using Wilcoxon tests for continuous variables (*) and fisher exact tests for categorical variables. p-values of <0.05 are considered statistically significant
†results from visit 2/week 0, whereas all other values are from visit 1/screening
Supplementary Figure 1. Design of the BETonMACE study.

**BETonMACE Study Design**

**Indication:** Secondary CVD prevention in T2DM patients with low HDL-C at high-risk for MACE

IP: 100 mg RVX002222 or Placebo BID

![Diagram describing the study design with phases such as Screening, Randomization, BID Treatment, and End of Study/Follow-up.](image)

**Patient Population:** T2DM & high risk CAD treated with high intensity statin therapy and with a low level of HDL-C
Supplementary Figure 2. MoCA specific domains (max score 30 or 31 if <12 years education)

### MONTREAL COGNITIVE ASSESSMENT (MOCA)

**Version 7.1 Original Version**

| VISUOSPATIAL / EXECUTIVE | NAME: | Education: | Sex: | Date of birth: | DATE: |
|-------------------------|-------|------------|------|---------------|-------|
| Copy cube              |       |            |      |               |       |
| Draw CLOCK (Ten past eleven) | (3 points) |            |      |               |       |

**NAMING**

- Rhinoceros
- Lion
- Camel

**MEMORY**

Read a list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

| Face | Velvet | Church | Daisy | Red |
|------|--------|--------|-------|-----|
|      |        |        |       | No points |

**ATTENTION**

Read a list of digits (1 digit/sec). Subject has to repeat them in the forward order

- 21854

Subject has to repeat them in the backward order

- 742

Read a list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

- FBACMNAAJKLBAFAKDEAAAJMOMAAB

**LANGUAGE**

Repeat: I only know that John is the one to help today. [

The cat always hid under the couch when dogs were in the room. [

Fluency: Name maximum number of words in one minute that begin with the letter F

- 11 words

**ABSTRATION**

Similarity between e.g. banana - orange = fruit

- Train - Bicycle

- Watch - Ruler

**DELAYED RECALL**

Has to recall words with no cue

**ORIENTATION**

- Date
- Month
- Year
- Day
- Place
- City

© Z. Nasreddine MD

Administered by: ________________________________

[www.mocatest.org](http://www.mocatest.org) Normal ≥ 26 / 30

Add 1 point if ≤ 12 years old
Supplementary Figure 3. Montreal Cognitive Assessment (MoCA) subdomains distribution in patients with total score > 25, < 25 – 22, and ≤ 21.