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

Apabetalone			Last Observation Captured		
			≤ 21	**25 – 22**	**≥ 26**
MoCA	**Baseline**	≤ 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)	7.4 (6.5 – 8.3)		7.0 (6.4 – 8.5)	7.2 (6.2 – 9.0)	
Follow up (%)	7.2 (6.4 – 8.1)	7.0 (6.5 – 7.9)		7.1 (6.3 – 8.1)	7.3 (6.7 – 8.2)		6.7 (6.4 – 7.8)	7.1 (6.4 – 8.3)	
Percent change (%)	0.0 (-5.0 – 7.2)	2.0 (-3.0 – 9.4)	0.54	1.7 (-3.6 – 10.3)	2.6 (-6.2 – 9.0)	0.78	-0.8 (-7.4 – 5.1)	1.8 (-8.4 – 6.8)	0.49
Serum Glucose									
Baseline (mg/dL)	129.7 (104.7 – 161.2)	136.0 (116.9 – 165.4)		131.8 (109.9 – 172.0)	137.6 (112.1 – 186.3)		130.6 (100.2 – 171.0)	134.7 (104.5 – 180.8)	
Follow up (mg/dL)	141.8 (116.6 – 166.1)	141.1 (119.3 – 172.8)		140.7 (115.3 – 168.8)	142.1 (120.3 – 175.5)		131.3 (106.1 – 166.6)	135.0 (110.9 – 172)	
Percent change (%)	-0.9 (-11.2 – 31.4)	3.3 (-8 – 20.6)	0.94	3.8 (-9.0 – 16.6)	2.2 (-16.6 – 18.5)	0.47	4.9 (-18.6 – 20.7)	2.9 (-12.8 – 23.7)	0.88
Total Cholesterol									
Baseline (mg/dL)	128.8 (109.0 – 155.8)	126.8 (104.8 – 150.4)		128.0 (106.7 – 149.7)	124.5 (104.0 – 144.4)		131.5 (107.9 – 150.8)	115.2 (97.0 – 134.9)	
Follow up (mg/dL)	128.0 (108.3 – 150.4)	125.7 (110.2 – 140.2)		124.1 (107.5 – 148.1)	126.8 (114.7 – 144.4)		133.8 (108.1 – 156.2)	120.1 (109.6 – 140.5)	
Percent change (%)	-1.9 (-11.7 – 9.3)	0.4 (-13.1 – 15.3)	0.70	1.7 (-11.6 – 12.0)	2.5 (-5.1 – 16.5)	0.39	3.3 (-10.3 – 16.3)	2.4 (-4.8 – 22.9)	0.55
LDL Cholesterol									
Baseline (mg/dL)	61.9 (46.8 – 82.4)	62.6 (44.9 – 85.8)		64.2 (49.5 – 84.7)	67.3 (47.4 – 81.8)		61.3 (51.7 – 81.8)	53.6 (41.8 – 69.2)	
Follow up (mg/dL)	57.6 (46.4 – 78.1)	56.8 (44.1 – 72.7)		59.0 (46.8 – 78.1)	58.8 (48.7 – 75.1)		60.5 (46.9 – 84.7)	55.5 (47.8 – 74.4)	
Percent change (%)	-3.9 (-18.2 – 19.9)	-5.5 (-29.3 – 20.0)	0.25	0.0 (-18.3 – 16.0)	-4.7 (-19.4 – 14.5)	0.77	-3.7 (-25.6 – 24.1)	-0.6 (-18.4 – 20.8)	0.62
HDL Cholesterol									
Baseline (mg/dL)	34.4 (31.7 – 39.1)	33.3 (29.8 – 36.7)		34.0 (31.3 – 37.5)	32.9 (30.0 – 37.1)		34.4 (30.9 – 38.7)	33.6 (29.5 – 36.3)	
Follow up (mg/dL)	37.1 (33.3 – 42.9)	38.7 (33.6 – 44.1)		37.1 (34.0 – 42.2)	40.2 (33.1 – 46.0)		37.5 (35.5 – 42.5)	40.6 (36.8 – 44.5)	
Percent change (%)	8.4 (-1.0 – 20.5)	16.9 (4.0 – 30.2)	**0.004**	11.2 (-1.1 – 20.5)	19.2 (9.5 – 30.7)	**0.02**	12.5 (2.7 – 25.6)	16.9 (8.0 – 28.3)	0.15
Triglycerides									
Baseline (mg/dL)	162.1 (128.4 – 207.3)	145.3 (121.3 – 191.3)		147.0 (102.7 – 174.5)	143.5 (112.0 – 184.7)		155.0 (131.1 – 191.3)	124.9 (102.3 – 177.6)	
Follow up (mg/dL)	146.1 (117.8 – 170.1)	132.0 (107.2 – 178.0)		123.1 (100.5 – 167.0)	140.4 (107.6 – 163.6)		140.4 (102.5 – 195.2)	120.7 (97.4 – 161.0)	
Percent change (%)	-8.4 (-25.0 – 11.0)	-7.1 (-25.7 – 10.9)	0.63	-6.7 (-25.0 – 9.4)	-3.4 (-20.7 – 20.7)	0.30	-6.5 (-23.8 – 13.3)	-5.1 (-14.7 – 7.3)	0.72
Alkaline Phosphatase									
Baseline (U/L)	76.0 (61.0 – 91.0)	76.0 (64.0 – 88.0)		76.0 (61.0 – 94.0)	74.0 (60.5 – 84.5)		73.0 (65.0 – 95.0)	82.5 (65.8 – 101.8)	
Follow up (U/L)	74.5 (60 – 90.5)	67.0 (55.0 – 78.0)		74.0 (63.0 – 95.0)	65.0 (55.0 – 73.0)		70.0 (61.0 – 92.0)	75.0 (60.3 – 94.9)	
Percent change (%)	0.0 (-9.0 – 10.6)	-10.6 (-20.5 – -3.4)	**<0.0001**	-1.1 (-12.0 – 6.8)	-13.7 (-19.9 – -3.9)	**0.001**	-5.3 (-11.5 – 2.2)	-10.2 (-18.6 – -5.1)	**0.03**

Alanine Aminotransferase									
Baseline (U/L)	20.0 (15.8 – 28.0)	19.0 (15.0 – 26.0)		19.0 (15.0 – 27.0)	17.0 (13.5 – 22.5)		18.0 (14 – 25.0)	20.0 (13.0 – 27.0)	
Follow up (U/L)	19.0 (15.0 – 25.0)	20.0 (15.0 – 26.0)		18.0 (13.0 – 24.0)	18.0 (14.5 – 23.3)		18.0 (14.0 – 22.0)	17.3 (14.3 – 22.9)	
Percent change (%)	-4.1 (-25.0 – 9.3)	3.8 (-13.9 – 25.3)	**0.01**	-5.6 (-20.0 – 9.1)	5.0 (-16.2 – 31.4)	**0.02**	-4.0 (-25.0 – 13.6)	0.0 (-28.6 – 20.0)	0.77
Total Bilirubin									
Baseline (umol/L)	10.1 (7.8 – 13.8)	9.9 (7.5 – 12.9)		9.2 (7.4 – 13.9)	9.4 (7.9 – 11.6)		9.9 (8.5 – 13.8)	9.6 (6.1 – 13.8)	
Follow up (umol/L)	10.3 (8.4 – 13.0)	11.4 (8.9 – 14.4)		10.7 (7.3 – 14.1)	11.4 (8.6 – 14.2)		9.9 (7.8 – 13.2)	10.1 (7.7 – 13.3)	
Percent change (%)	2.8 (-9.3 – 15.1)	16.4 (2.2 – 39.9)	**<0.0001**	3.5 (-7.3 – 19.3)	13.3 (-5.4 – 32.2)	0.08	0.0 (-18.8 – 27.9)	12.8 (-1.8 – 26.0)	0.16
hsCRP									
Baseline (mg/L)	1.1 (0.6 – 2.3)	2.8 (1.7 – 5.5)		1.0 (0.4 – 2.7)	2.3 (1.3 – 4.4)		4.4 (3.2 – 8.4)	2.2 (0.8 – 5.1)	
Follow up (mg/L)	1.3 (0.7 – 4.6)	2.4 (1.2 – 4.4)		0.7 (0.5 – 1.7)	1.5 (0.9 – 4.8)		4.5 (2.1 – 5.7)	4.2 (1.4 – 7.2)	
Percent change (%)	6.8 (-27.2 – 211.7)	-28.4 (-57.8 – 62.7)	0.22	-25.2 (-42.3 – 70.7)	-34.9 (-43.5 – 19.4)	0.76	-32.5 (-49.4 – 54.5)	39.3 (-24.0 – 93.7)	0.41
NLR									
Baseline (ratio)	2.4 (2.1 – 3.3)	2.8 (2.2 – 3.7)		2.9 (2.2 – 3.6)	2.9 (2.2 – 3.8)		2.5 (2.2 – 3.2)	3.0 (2.1 – 3.9)	
Follow up (ratio)	2.3 (1.9 – 2.7)	2.5 (2.1 – 3.3)		2.4 (1.9 – 2.9)	2.7 (1.8 – 3.1)		2.2 (1.7 – 2.6)	2.6 (2.2 – 3.2)	
Percent change (%)	-11.1 (-26.0 – 0.6)	-13.5 (-27.0 – 2.6)	0.85	-16.3 (-28.4 – 3.7)	-14.8 (-28.2 – 3.7)	0.98	-10.9 (-29.5 – 3.0)	-5.3 (-28.1 – 10.6)	0.36

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:

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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 randomization 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 pathophysiologies 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 scors 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. $\leq 25 – 22$ 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 $A\beta_{42/40}$ 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 ≤ 25 or ≤ 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.

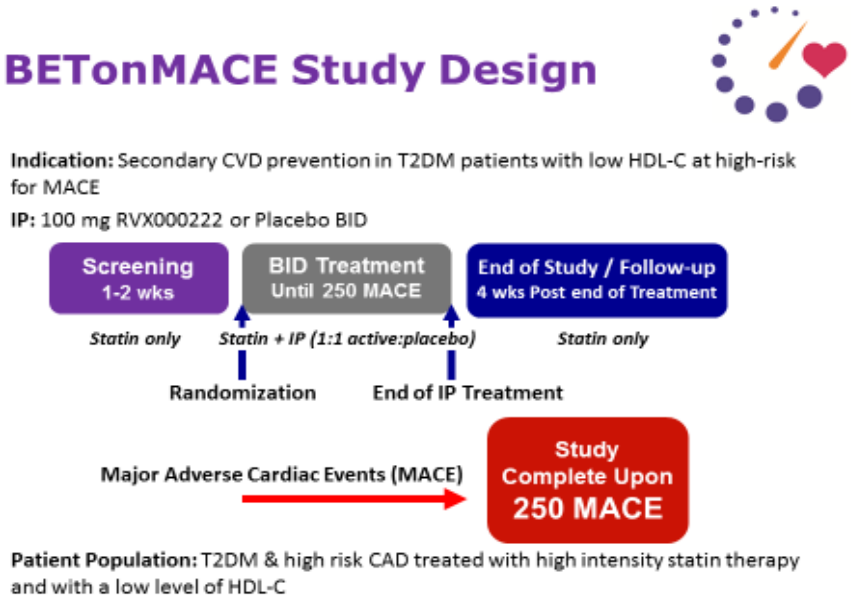
	All Patients Randomized		Cognition Subgroup		Patients Randomized with Baseline MoCA > 25		Patients Randomized with Baseline MoCA ≤ 25		Patients with MoCA > 25 vs. Patients with MoCA ≤ 25 p
	N	%	N	%	N	%	N	%	
Number of Participants	2,425		469		223		246		-
Age (y) (median) (min, max)	62 (31, 88)		73 (69, 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%	
HbA1c ≥6.5% at Visit 1	1,770	73.0%	317	67.6%	148	66.4%	169	68.7%	0.62
BMI (kg/m^2) (median) (IQR)	29.6 (6.6)		28.7 (6.3)		28.7 (5.8)		28.6 (6.6)		0.31 *
Hypertension	2,144	88.4%	445	94.9%	217	97.3%	228	92.7%	**0.03**
Tobacco Use	313	12.9%	30	6.4%	10	4.5%	20	8.1%	0.13
Prior Stroke / TIA	184	7.6%	55	11.7%	24	10.8%	31	12.6%	0.57

Concomitant Statins:									
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:									
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%	1.00
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:									
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:	**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/1.73m^2)	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)	2,395	65 (36)	465	64 (35)	223	63 (34)	242	64 (36)	0.73 *
HDL-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 (10^9/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 *

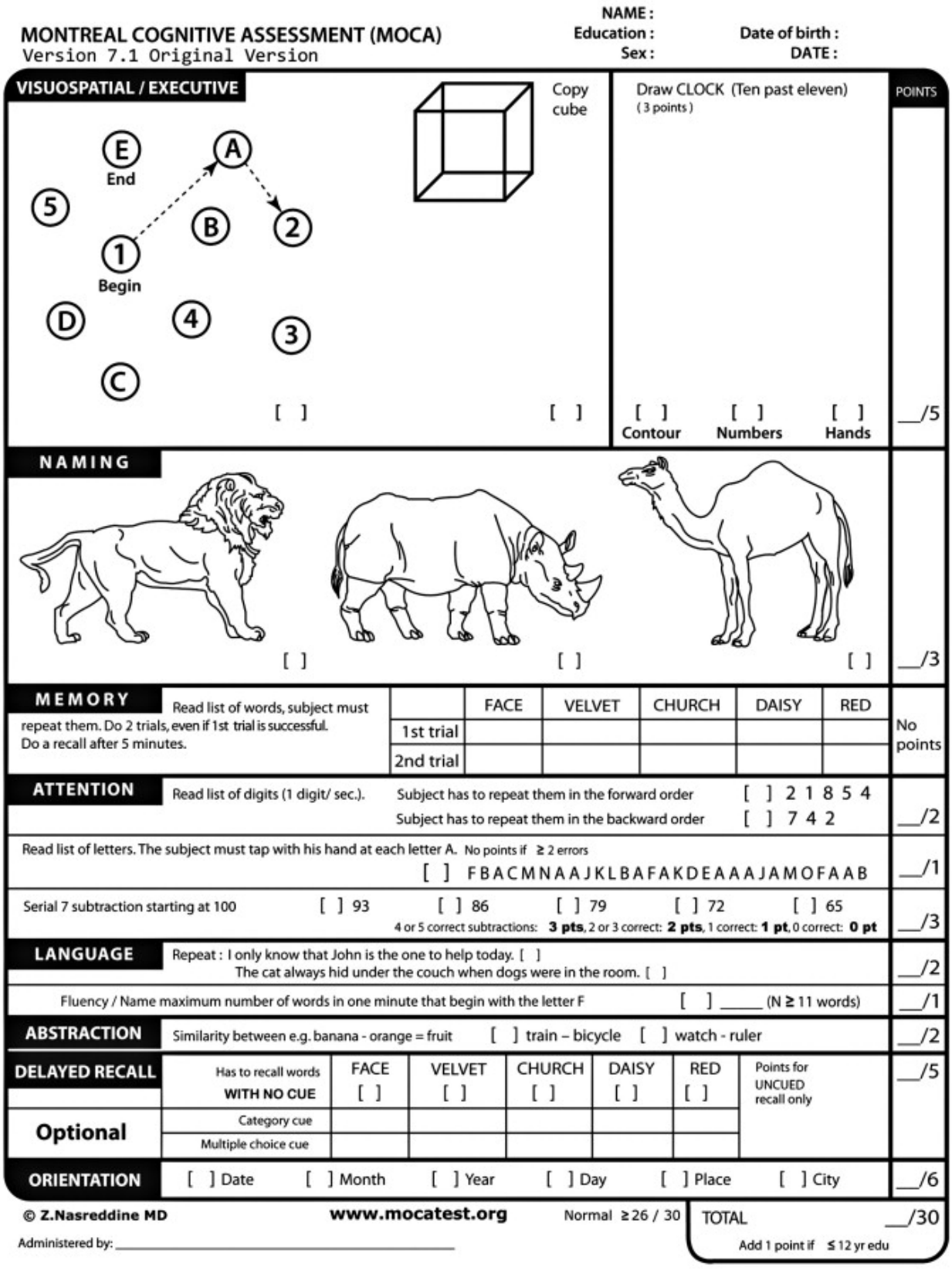
MoCA, Montreal Cognitive Assessment; ACS, acute coronary syndrome; MI, myocardial infarction; PCI, percutaneous coronary intervention; HbA1c, hemoglobin A1C; BMI, Body mass index; TIA, transient ischemic attack; GLP1, glucagon-like peptide 1; DPP-4, dipeptidyl peptidase; SGLT2, sodium-glucose cotransporter 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.



Supplementary Figure 2. MoCA specific domains (max score 30 or 31 if <12 years education)



Supplementary Figure 3. Montreal Cognitive Assessment (MoCA) subdomains distribution in patients with total score > 25, < 25 – 22, and ≤ 21.