

BET-Inhibition with Apabetalone in Post-ACS Patients with Diabetes: Design and Baseline Characteristics of the BETonMACE Trial



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Background

Diabetes (DM) is associated with increased risk of macro/microvascular disease and cognitive decline. Inflammation and heightened vascular calcification may be contributing factors. Bromodomain and extraterminal (BET) proteins coordinate gene transcription and modify the transcriptional response to hyperglycemia, and inflammation. Apabetalone competitively and selectively inhibits binding between BET proteins and acetyllysine marks on histone tails: normalizing transcriptional profiles to physiological levels. Post-hoc analysis of Phase 2 trials with apabetalone show improved renal function in the chronic kidney disease (CKD) subgroups. Furthermore, treatment showed a 55% reduction in CVD events with more pronounced benefit among patients with DM, low HDL-cholesterol (HDL-C) and high sensitivity C-reactive protein (hsCRP).

Methods

The double-blind, placebo controlled Phase 3 BETonMACE trial is testing the hypothesis that apabetalone 100 mg b.i.d., added to standard of care, reduces major adverse cardiovascular events (MACE: CV death, non-fatal myocardial infarction or stroke) in patients with DM, acute coronary syndrome (ACS) within the preceding 7-90 days, low HDL-C (<40 mg/dL in men; <45 mg/dL in women). CKD was defined as eGFR 30 to 59 mL/min/1.7m², and was included as a predefined subgroup. The trial will continue until at least 250 MACE, providing 80% power to detect a 30% reduction. Secondary endpoints include changes in eGFR in patients with baseline eGFR 30 to 59 mL/min/1.7m², inflammatory markers, lipids, and ALP as a measure of BET inhibition. In addition the Montreal Cognition Assessment (MoCA) test was performed in patients ≥70 years of age at baseline and annually.

Results

Enrollment of 2,425 patients across 13 countries and 195 centers is now complete. Baseline characteristics [median (IQR)] include LDL-C 65.0 (49.0 – 85.0) mg/dL, HDL-C 33.0 (30.0 – 37.0) mg/dL, HbA1c 7.3 (6.4 – 8.7) %, hsCRP 2.8 (1.2 – 6.2) mg/L, mean blood pressure 129/76 mmHg, and CKD in 262 patients (10.8%). Background care was based on guideline recommendations. Diabetes medications include metformin (77%), insulin (32%), sulfonylureas (25%), DPP4 inhibitors (6.5%), SGLT2 inhibitors (5.0%) and GLP1 receptor agonists (2.1%). The CKD subpopulation differed significantly from the total population with regard to age (71 vs. 62 y. o.), male sex (58% vs. 75%), history of hypertension (92% vs. 88%), history of stroke (9.9% vs. 7.6%), and current smokers (6.5 % vs. 13%). In the 70 year and older (n=469, 19%) subpopulation, 53% (n=246) showed a baseline MoCA score <26, suggesting cognitive impairment.

Summary

The BETonMACE trial is testing the hypothesis that selective BET-inhibition with apabetalone, added to established, evidence-based treatment, reduces MACE in high-risk patients with DM, recent ACS, and low HDL-C. The study will also assess apabetalone's effect on renal function and cognition.

BETonMACE Baseline Characteristics

Sex (male) 1,806 74.5% 152 58.0% 1,654 76.5% <0.0001 Caucasian 2,115 87.2% 213 81.3% 1,902 87.9% 0.002 MoCA (≥70 yrs) 469 19.3% 147 56.1% 322 14.9% <0.0001 MoCA <26 246 52.5% 80 54.4% 166 51.6% 0.56 Index ACS Event: 3 1,787 73.7% 197 75.2% 1,590 73.5% 0.56 Unstable Angina 625 25.8% 63 24.0% 562 26.0% 0.50 History of PCI 1,930 79.6% 191 72.9% 1,739 80.4% 0.004	Clinical Characteristic	All Patients Randomized		(eGFR <6	CKD (eGFR <60 mL/min/1.73 m ²) Subgroup		Non-CKD O mL/min/1.73 m ²) Population	CKD Subgroup vs. Non-CKD Population p-value
Sex (male) 1,806 74.5% 152 83.7% 1,806 76.5% 0.002 Caucasian 2,115 87.7% 23 81.3% 1,902 87.9% 6.002 MoCA 270 yrs) 489 19.3% 81.3% 15.4% 166 51.6% 6.0001 Index ACS / will 71.6% 52.5% 80 54.4% 166 51.6% 0.56 MCS ACS Index 1.787 73.7% 63 2.40% 552 2.00% 0.50 History of PCI 1.930 73.5% 63 2.40% 552 2.00% 0.50 History of PCI 1.930 73.5% 63 2.40% 552 2.00% 0.50 History of PCI 1.930 73.5% 63 2.40% 552 2.00% 0.004 History of DM Medication: Note (5) 2.23 2.53% 2.21 1.00 2.75% 1.13 2.5% 0.08 Hyar tension 2.14 8.87% 2.40 9.10% 1.9		N	%	N	%	N	%	(Chi-Squared X ² Test)
Caucasian 2,115 87.9% 213 81.3% 1,902 87.9% 0.002 MoCA PCO vrs1 469 19.3% 167 56.1% 322 14.9% <0.0001	Age (yrs) (median) (min, max)	2,425	62 (31, 88)	262	71 (44, 88)	2,163	61 (31, 88)	< 0.0001*
MOCA (270 yrs) MoCA ~26 469 19.3% 147 56.1% 322 14.9% < 0.06 MoCA ~26 246 52.5% 80 54.4% 166 51.6% 0.56 Index ACS Event: ACS / MI 1,787 73.7% 197 75.2% 1,590 73.5% 0.56 History of PCI 1,930 79.6% 191 72.9% 1,739 80.4% 0.004 Medical History 1,180 yr of DM Medication: Yes (%) 2,301 95.8% 251 95.8% 2,000 94.8% 0.08 History of DM Medication: Yes (%) 2,301 95.8% 251 95.8% 2,000 94.8% 0.08 History of DM Medication: Yes (%) 1,24 4.2% 111 4.2% 113 5.2% 0.08 History of DM Medication: Yes (%) 1,24 4.2% 111 4.2% 113 5.2% 0.08 BMI (kg/m²) [median) (los) 2.2 1,44 2.8 4.2 4.0 1,590 38.0% 0.09	Sex (male)	1,806	74.5%	152	58.0%	1,654	76.5%	< 0.0001
MoCA <26 246 52.5% 80 54.4% 166 51.6% 0.56 Index ACS Feent: ACS / MI 1,787 73.7% 197 75.2% 1,590 73.5% 0.56 Mistable Angina 625 25.8% 63 24.0% 562 26.0% 0.50 History of PCI 1,930 79.6% 191 72.9% 1,739 80.4% 0.004 Medical History 0.008 6.7 (2 ≥ 13.0) 10.2 (3.8 − 18.0) 6.5 (2.1 − 12.4) 0.0001** 6.5 (2.1 − 12.4) 0.0001** 6.6 (2.2 − 13.0) 10.2 (3.8 − 18.0) 6.5 (2.1 − 12.4) 0.0001** 6.5 (2.1 − 12.4) <0.0001**	Caucasian	2,115	87.2%	213	81.3%	1,902	87.9%	0.002
Index ACS Event:	MoCA (≥70 yrs)	469	19.3%	147	56.1%	322	14.9%	< 0.0001
ACS / MI Unstable Angina 625 25.8% 63 24.0% 562 26.0% 0.50 History of PCI 1,930 79.6% 191 77.9% 1,739 80.4% 0.004 Medical History (median years) (IQR) History of DM Medication: Yes (Ys) History of DM Medication: No (Ys) History of DM Medication: No (Ys) History of IQM Medication: No (Ys) Histo	MoCA <26	246	52.5%	80	54.4%	166	51.6%	0.56
Unstable Angina 625 25.8% 63 24.0% 562 26.0% 0.50 History of PCI 1,930 79.6% 191 72.9% 1,739 80.4% 0.004 Medical History Diabetes History (median years) (IQR) 6.7 ⟨2.2−13.0⟩ 10.2 ⟨3.8−18.0⟩ 6.5 ⟨2.1−12.4⟩ <0.0001**	Index ACS Event:							
History of PCI 1,930 79.6% 191 72.9% 1,739 80.4% 0.00d 1 Medical History Diabetes History (median years) (IQR) History of DM Medication: Yes (%) History of DM Medication: No (%) 124 4.2% 11 4.2% 113 5.2% 0.86 BMI (Ikg/m²) (median) (IQR) 29.6(26.7-33.2% 190 72.5% 1,580 73.0% 0.86 BMI (Ikg/m²) (median) (IQR) 29.6(26.7-33.2% 190 27.3(24.5-30.1) 30.0(27.0-33.6) 4.00001* Hypertension 2,144 88.4% 240 91.6% 1,904 88.0% 0.09 Tobacco Use Hypertension 2,144 88.4% 240 91.6% 1,904 88.0% 0.001 Tobacco Use Prior Stroke / TIA 184 7.6% 26 9.9% 158 7.3% 0.13 Concomitant Statins Actoryastatin 1,120 48.7% 121 46.2% 1,059 49.0% 0.40 Cardiovascular Disease Medications: ACE Inhibitors ARBS 883 24.0% 82 31.3% 501 23.2% 0.004 ARBS Beta-Blockers Anti-Platelet Agents 2,146 88.5% 232 88.5% 1,104 88.5% 0.98 Anti-Platelet Agents 2,246 88.5% 232 88.5% 1,191 88.5% 0.98 Anti-Platelet Agents 02,798 86.0% 226 86.3% 1,914 88.5% 0.98 DAPT 2,086 86.0% 251 99.6% 2,131 98.5% 0.15 DAPT 3,086 86.0% 250 99.6% 2,131 98.5% 0.15 DAPT 3,086 86.0% 261 99.6% 2,131 98.5% 0.15 DAPT 3,086 86.0% 261 99.6% 2,131 98.5% 0.15 DAPT 3,086 86.0% 260 99.6% 2,131 98.5% 0.004 DAPT 3,086 86.0% 260 99.6% 2,131 98.5% 0.005 DAPT 3,086 86.0% 260 99.6% 260 99.6% 2,131 98.5% 0.005 DAPT 3,086 86.0% 260 99.6% 260 99.6% 2,131 98.5% 0.005 DAPT 3,086 86.0% 2.000 99.6% 2,131 98.5% 0.005 DAPT 3,086 86.0% 2.000 99.6% 2.000 99.6% 2.000 99.6% 2.000 99.6% 2.000 99.6% 2.000 99.6% 2.000 99.6% 2	ACS / MI	1,787	73.7%	197	75.2%	1,590	73.5%	0.56
Medical History Diabetes History (median years) (IQR) Diabetes History (median years) (IQR) 6.7 (2.2 − 13.0) 10.2 (3.8 − 18.0) 6.5 (2.1 − 12.4) <0.0001* History of DM Medication: Yes (%) History of DM Medication: Yes (%) History of DM Medication: No (%) 124 4.2% 11 4.2% 113 5.2% 0.48 History of DM Medication: No (%) History of DM Medication: No (%) History of DM Medication: No (%) 124 1.770 73.0% 190 72.5% 1,580 73.0% 0.86 BMI (kg/m²) (median) (IQR) 29.6 (26.7 − 33.2) 27.3 (24.5 − 30.1) 30.0 (27.0 − 33.6) <0.0001*	Unstable Angina	625	25.8%	63	24.0%	562	26.0%	0.50
Diabetes History (median years) (IQR)	History of PCI	1,930	79.6%	191	72.9%	1,739	80.4%	0.004
History of DM Medication: Yes (%) History of DM Medication: No (%) History of DM Medication No (%) History of DM History of DM History No (%)	Medical History							
History of DM Medication: No (%)	Diabetes History (median years) (IQR)	6.7	' (2.2 – 13.0)	10	0.2 (3.8 – 18.0)	6.5	5 (2.1 – 12.4)	< 0.0001 *
History of DM Medication: No (%)	History of DM Medication: Yes (%)	2,301	95.8%	251	95.8%	2,050	94.8%	0.40
BMI (kg/m²) (median) (IQR) 29.6 (26.7 − 33.2) 27.3 (24.5 − 30.1) 30.0 (27.0 − 33.6) < 0.0001 * Hypertension 2,144 88.4% 240 91.6% 1,904 88.0% 0.09 Tobacco Use Prior Stroke / TIA 184 7.6% 26 9.9% 158 7.3% 0.03 Concomitant Statins Atorvastatin 1,245 51.3% 141 53.8% 1,104 51.0% 0.40 Rosuvastatin 1,180 48.7% 121 46.2% 1,059 49.0% 0.40 Cardiovascular Disease Medications: 1,684 69.4% 162 61.8% 1,522 70.4% 0.005 ARBs 583 24.0% 82 31.3% 501 23.2% 0.004 Anti-Platelet Agents 2,146 88.5% 232 88.5% 1,914 88.5% 0.98 DAPT 2,086 86.0% 26 99.6% 2,131 98.5% 0.15 Dabetes Medications: 1,522 70.4% 0.27 55.	History of DM Medication: No (%)	124	4.2%	11	4.2%	113	5.2%	0.48
Hypertension	HbA1c ≥6.5% at Visit 1	1,770	73.0%	190	72.5%	1,580	73.0%	0.86
Tobacco Use 313 12.9% 17 6.5% 296 13.7% 0.001 Prior Stroke / TIA 184 7.6% 26 9.9% 158 7.3% 0.13 Concomitant Statins Atorvastatin 1,245 51.3% 141 53.8% 1,104 51.0% 0.40 Rosuvastatin 1,180 48.7% 121 46.2% 1,059 49.0% 0.40 Cardiovascular Disease Medications: ACE Inhibitors 1,684 69.4% 162 61.8% 1,522 70.4% 0.005 ARBs 583 24.0% 82 31.3% 501 23.2% 0.004 Beta-Blockers 2,146 88.5% 232 88.5% 1,914 88.5% 0.98 Anti-Platelet Agents 2,392 98.6% 261 99.6% 2,131 98.5% 0.15 DAPT 2,086 86.0% 226 86.3% 1,860 86.0% 0.91 Diabetes Mellitus Medications: 1,864	BMI (kg/m²) (median) (IQR)	29.6	5 (26.7 – 33.2)	27.	.3 (24.5 – 30.1)	30.0) (27.0 – 33.6)	< 0.0001 *
Prior Stroke / TIA 184 7.6% 26 9.9% 158 7.3% 0.13 Concomitant Statins Atorvastatin Rosuvastatin 1,245 51.3% 141 53.8% 1,104 51.0% 0.40 Cardiovascular Disease Medications: ———————————————————————————————————	Hypertension	2,144	88.4%	240	91.6%	1,904	88.0%	0.09
Concomitant Statins Atorvastatin 1,245 51.3% 141 53.8% 1,104 51.0% 0.40 Rosuvastatin 1,180 48.7% 121 46.2% 1,059 49.0% 0.40 Cardiovascular Disease Medications: ACE Inhibitors 1,684 69.4% 162 61.8% 1,522 70.4% 0.005 ARBs 583 24.0% 82 31.3% 501 23.2% 0.004 Beta-Blockers 2,146 88.5% 232 88.5% 1,914 88.5% 0.98 Anti-Platelet Agents 2,392 98.6% 261 99.6% 2,131 98.5% 0.15 DAPT 2,086 86.0% 226 86.3% 1,860 86.0% 0.91 Diabetes Mellitus Medications: Insulin 769 31.7% 90 34.4% 679 31.4% 0.33 Diabetes Medications (Ex. Insulins): 2,072 85.4% 208 79.4% 1,864 86.2% 0.0001	Tobacco Use	313	12.9%	17	6.5%	296	13.7%	0.001
Atorvastatin Rosuvastatin 1,245 51.3% 141 53.8% 1,104 51.0% 0.40 Cardiovascular Disease Medications: ACE Inhibitors 1,684 69.4% 162 61.8% 1,522 70.4% 0.005 ARBs 583 24.0% 82 31.3% 501 23.2% 0.004 Beta-Blockers 2,146 88.5% 232 88.5% 1,914 88.5% 0.98 Anti-Platelet Agents 2,392 98.6% 261 99.6% 2,131 98.5% 0.15 DAPT 2,086 86.0% 226 86.3% 1,860 86.0% 0.91 Diabetes Mellitus Medications: Insulin 769 31.7% 90 34.4% 679 31.4% 0.33 Diabetes Medications (Ex. Insulins): 2,072 85.4% 208 79.4% 1,864 86.2% 0.003 Metformin 1,866 76.9% 169 64.5% 1,697 78.5% <0.0001	Prior Stroke / TIA	184	7.6%	26	9.9%	158	7.3%	0.13
Rosuvastatin 1,180 48.7% 121 46.2% 1,059 49.0% 0.40 Cardiovascular Disease Medications: ACE Inhibitors 1,684 69.4% 162 61.8% 1,522 70.4% 0.005 ARBs 583 24.0% 82 31.3% 501 23.2% 0.004 Beta-Blockers 2,146 88.5% 232 88.5% 1,914 88.5% 0.98 Anti-Platelet Agents 2,392 98.6% 261 99.6% 2,131 98.5% 0.15 DAPT 2,086 86.0% 226 86.3% 1,860 86.0% 0.91 Diabetes Mellitus Medications: Insulin 769 31.7% 90 34.4% 679 31.4% 0.33 Diabetes Medications (Ex. Insulins): 2,072 85.4% 208 79.4% 1,864 86.2% 0.003 Metformin 1,866 76.9% 169 64.5% 1,697 78.5% <0.0001	Concomitant Statins							
Rosuvastatin 1,180 48.7% 121 46.2% 1,059 49.0% Cardiovascular Disease Medications: ACE Inhibitors 1,684 69.4% 162 61.8% 1,522 70.4% 0.005 ARBs 583 24.0% 82 31.3% 501 23.2% 0.004 Beta-Blockers 2,146 88.5% 232 88.5% 1,914 88.5% 0.98 Anti-Platelet Agents 2,392 98.6% 261 99.6% 2,131 98.5% 0.15 DAPT 2,086 86.0% 226 86.3% 1,860 86.0% 0.91 Diabetes Melitus Medications: Insulin 769 31.7% 90 34.4% 679 31.4% 0.33 Diabetes Medications (Ex. Insulins): 2,072 85.4% 208 79.4% 1,864 86.2% 0.003 Metformin 1,866 76.9% 169 64.5% 1,697 78.5% <0.0001	Atorvastatin	1,245	51.3%	141	53.8%	1,104	51.0%	0.40
Cardiovascular Disease Medications: 1,684 69.4% 162 61.8% 1,522 70.4% 0.005 ARBs 583 24.0% 82 31.3% 501 23.2% 0.004 Beta-Blockers 2,146 88.5% 232 88.5% 1,914 88.5% 0.98 Anti-Platelet Agents 2,392 98.6% 261 99.6% 2,131 98.5% 0.15 DAPT 2,086 86.0% 226 86.3% 1,860 86.0% 0.91 Diabetes Mellitus Medications: Insulin 769 31.7% 90 34.4% 679 31.4% 0.33 Diabetes Medications (Ex. Insulins): 2,072 85.4% 208 79.4% 1,864 86.2% 0.003 Metformin 1,866 76.9% 169 64.5% 1,697 78.5% <0.0001	Rosuvastatin	1,180	48.7%	121	46.2%	·		0.40
ARBs 583 24.0% 82 31.3% 501 23.2% 0.004 Beta-Blockers 2,146 88.5% 232 88.5% 1,914 88.5% 0.98 Anti-Platelet Agents 2,392 98.6% 261 99.6% 2,131 98.5% 0.15 DAPT 2,086 86.0% 226 86.3% 1,860 86.0% 0.91 Diabetes Mellitus Medications: Insulin 769 31.7% 90 34.4% 679 31.4% 0.33 Diabetes Medications (Ex. Insulins): 2,072 85.4% 208 79.4% 1,864 86.2% 0.003 Metformin 1,866 76.9% 169 64.5% 1,697 78.5% <0.0001	Cardiovascular Disease Medications:							
Beta-Blockers 2,146 88.5% 232 88.5% 1,914 88.5% 0.98 Anti-Platelet Agents 2,392 98.6% 261 99.6% 2,131 98.5% 0.15 DAPT 2,086 86.0% 226 86.3% 1,860 86.0% 0.91 Diabetes Mellitus Medications: Insulin 769 31.7% 90 34.4% 679 31.4% 0.33 Diabetes Medications (Ex. Insulins): 2,072 85.4% 208 79.4% 1,864 86.2% 0.003 Metformin 1,866 76.9% 169 64.5% 1,697 78.5% < 0.0001	ACE Inhibitors	1,684	69.4%	162	61.8%	1,522	70.4%	0.005
Anti-Platelet Agents 2,392 98.6% 261 99.6% 2,131 98.5% 0.15 DAPT 2,086 86.0% 226 86.3% 1,860 86.0% 0.91 Diabetes Mellitus Medications: Insulin 769 31.7% 90 34.4% 679 31.4% 0.33 Diabetes Medications (Ex. Insulins): 2,072 85.4% 208 79.4% 1,864 86.2% 0.003 Metformin 1,866 76.9% 169 64.5% 1,697 78.5% <0.0001	ARBs	583	24.0%	82	31.3%	501	23.2%	0.004
DAPT 2,086 86.0% 226 86.3% 1,860 86.0% 0.91 Diabetes Mellitus Medications: Insulin 769 31.7% 90 34.4% 679 31.4% 0.33 Diabetes Medications (Ex. Insulins): 2,072 85.4% 208 79.4% 1,864 86.2% 0.003 Metformin 1,866 76.9% 169 64.5% 1,697 78.5% <0.0001	Beta-Blockers	2,146	88.5%	232	88.5%	1,914	88.5%	0.98
Diabetes Mellitus Medications: 769 31.7% 90 34.4% 679 31.4% 0.33 Diabetes Medications (Ex. Insulins): 2,072 85.4% 208 79.4% 1,864 86.2% 0.003 Metformin 1,866 76.9% 169 64.5% 1,697 78.5% < 0.0001	Anti-Platelet Agents	2,392	98.6%	261	99.6%	2,131	98.5%	0.15
Insulin 769 31.7% 90 34.4% 679 31.4% 0.33 Diabetes Medications (Ex. Insulins): 2,072 85.4% 208 79.4% 1,864 86.2% 0.003 Metformin 1,866 76.9% 169 64.5% 1,697 78.5% < 0.0001	DAPT	2,086	86.0%	226	86.3%	1,860	86.0%	0.91
Diabetes Medications (Ex. Insulins): 2,072 85.4% 208 79.4% 1,864 86.2% 0.003 Metformin 1,866 76.9% 169 64.5% 1,697 78.5% < 0.0001	Diabetes Mellitus Medications:							
Metformin 1,866 76.9% 169 64.5% 1,697 78.5% < 0.0001 Sulfonylureas 608 25.1% 73 27.9% 535 24.7% 0.27 DPP-4 Inhibitors 157 6.5% 30 11.5% 127 5.9% 0.001 SGLT2 Inhibitors 122 5.0% 7 2.7% 115 5.3% 0.06	Insulin	769	31.7%	90	34.4%	679	31.4%	0.33
Sulfonylureas 608 25.1% 73 27.9% 535 24.7% 0.27 DPP-4 Inhibitors 157 6.5% 30 11.5% 127 5.9% 0.001 SGLT2 Inhibitors 122 5.0% 7 2.7% 115 5.3% 0.06	Diabetes Medications (Ex. Insulins):	2,072	85.4%	208	79.4%	1,864	86.2%	0.003
DPP-4 Inhibitors 157 6.5% 30 11.5% 127 5.9% 0.001 SGLT2 Inhibitors 122 5.0% 7 2.7% 115 5.3% 0.06	Metformin	1,866	76.9%	169	64.5%	1,697	78.5%	< 0.0001
SGLT2 Inhibitors 122 5.0% 7 2.7% 115 5.3% 0.06	Sulfonylureas	608	25.1%	73	27.9%	535	24.7%	0.27
	DPP-4 Inhibitors	157	6.5%	30	11.5%	127	5.9%	0.001
GLP-1 Agonists 51 2.1% 2 0.8% 49 2.3% 0.11	SGLT2 Inhibitors	122	5.0%	7	2.7%	115	5.3%	0.06
	GLP-1 Agonists	51	2.1%	2	0.8%	49	2.3%	0.11

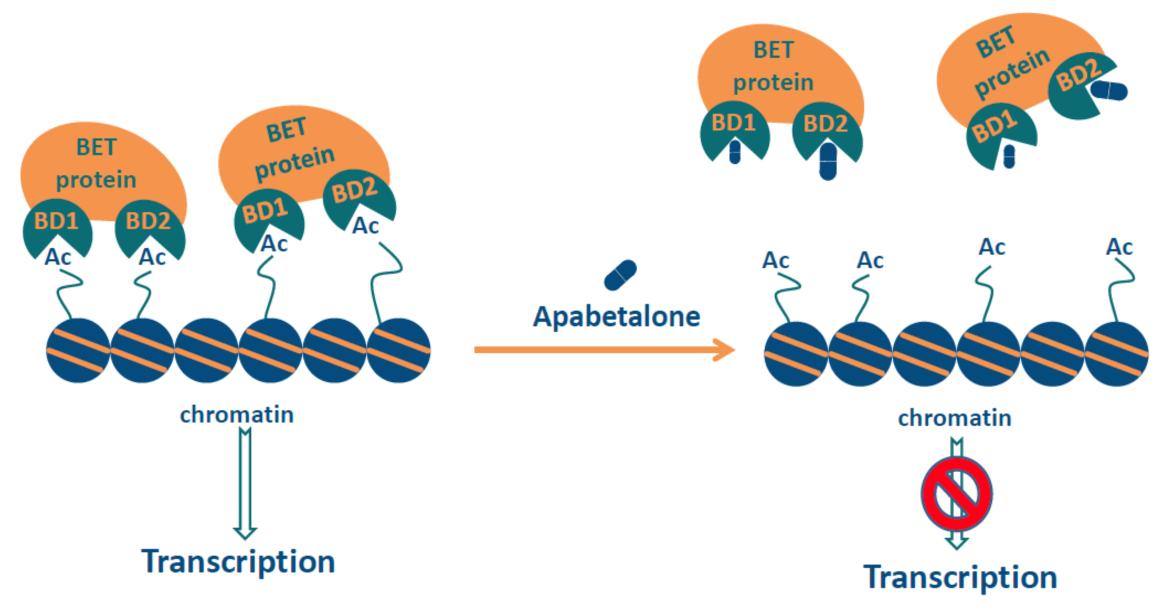
Clinical Chemistry		Median (IQR)		Median (IQR)		Median (IQR)	
ALP† (U/L)	2,424	78 (64 – 94)	262	80 (64 – 97)	2,162	77 (64 – 94)	0.07
eGFR (mL/min/1.73m ²)	2,413	99 (76 – 127)	262	49 (41 – 55)	2,151	104 (84 – 131)	< 0.0001
Albumin (g/dL)	2,413	4.30 (4.10 – 4.50)	262	4.20 (3.90 – 4.40)	2,151	4.30 (4.10 – 4.50)	< 0.0001
LDL-C (mg/dL)	2,395	65 (49 – 85)	262	65.5 (48 – 91)	2,133	65 (49 – 85)	0.62
HDL-C (mg/dL)	2,413	33 (30 – 37)	262	34 (30 – 37)	2,151	33 (30 – 37)	0.29
ApoA-1† (mg/dL)	483	118 (109 – 129)	50	119 (108 – 133)	433	118 (109 – 129)	0.95
hsCRP+ (mg/dL)	493	2.81 (1.20 – 6.15)	53	3.45 (1.12 – 8.43)	440	2.74 (1.12 – 5.93)	0.23
Fibrinogen† (mg/dL)	471	385 (318 – 454)	51	396 (332 – 452)	420	384 (316 – 454)	0.32
HbA1c (%)	2,369	7.30 (6.40 – 8.70)	257	7.20 (6.40 – 8.50)	2,112	7.30 (6.40 – 8.70)	0.27
Platelets (10 ⁹ /L)	2,295	249 (207 – 301)	251	241 (197 – 307)	2,044	250 (208 – 300)	0.34
NLR (ratio)	2,313	2.57 (1.99 – 3.36)	251	2.87 (2.20 – 3.90)	2,062	2.54 (1.95 – 3.31)	< 0.0001

† results from visit 2/wk 0, whereas all other values are from visit 1/screening IQR: Interquartile Range * Mann-Whitney U-Test (Wilcoxon Rank-Sum Test)

BETonMACE Study Design Screening Period Treatment Period Active Arm: apabetalone 100 mg b.i.d **Statin run-in** 40-80 mg atorvastatin 20-40 mg rosuvastati Placebo Arm: matching placebo 1-2 weeks For Duration of Study (Minimum 24 weeks) 3-5 weeks Baseline MoCA Test in Elderly MoCA Test at MoCA Test at Patients (Ages ≥70 yrs) Week 104 Week 52 **Primary Endpoint** Time to first occurrence of • Type II Diabetes Mellitus (HbA1c > 6.5% or history of diabetes adjudication-confirmed narrowly CAD event 7 days - 90 days prior to screening including MI, unstable defined MACE (cardiovascular death, non-fatal MI and stroke) angina or percutaneous coronary intervention HDL < 45 mg/dL for males and < 45 mg/dL for females

The study is an event-based trial and continues until 250 MACE have occurred

Apabetalone Mechanism of Action



BET proteins bind acetylated lysine (Ac) on histones via bromodomains (BD), and recruit transcriptional machinery to drive expression of BET sensitive genes which drives inflammation and other key markers of cognitive decline. Apabetalone is a small molecute that binds preferentially BD2 thereby inhibiting BET proteins, causing release from chromatin and downregulation of BET sensitive gene expression.

Pill size: selectivity of apabetalone for BD2

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Summary and Conclusions

- BETonMACE is a Phase 3 trial testing the cardiovascular efficacy of apabetalone, a first in class BET inhibitor, in reducing MACE in high-risk patients with DM, recent ACS, and low HDL-C when added on top of established, evidence based treatment.
- BETonMACE will also provide insights about the potential for BET inhibition to modulate renal and cognitive function in prespecified subgroups of patients.