Supplemental Material

Appendix A: Statistical Analysis Plan

Table A: Minimally adjusted hazard ratios (HR) for composite and component events in apabetalone vs placebo across CKD status for major adverse cardiovascular events (MACE).

Appendix A: Statistical Analysis Plan

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: Renal Version 14
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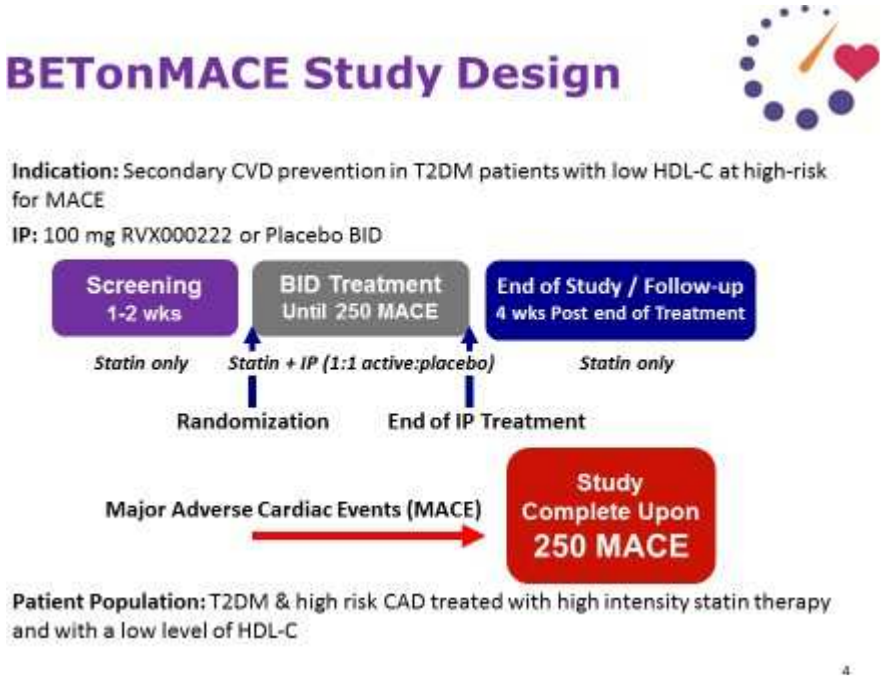
on behalf of BETonMACE Clinical Steering Committee.

Background: BETonMACE is a pivotal phase 3 trial in 2425 post-ACS patients with diabetes and low HDL-C levels. Its primary objective is to evaluate whether treatment with apabetalone 100 mg bid vs. placebo (standard of care treatment with randomization 1:1) increases time to first occurrence of the composite endpoint of 3-point major adverse cardiovascular events (3P-MACE) defined as occurrence of any of cardiovascular (CV) death, non-fatal myocardial infarction (MI), or stroke. It is powered to detect a hazard ratio (HR) for 3P-MACE of 0.7 with a target number of 250 primary events (first occurrence of 3P- MACE). A key secondary endpoint is "broadly defined MACE", defined as the composite of 3P-MACE (CV death, non-fatal MI and stroke) and hospitalization for CVD events (defined as either (i) unstable angina with evidence of new or presumed new progressive obstructive coronary disease; or (ii) emergence revascularization procedures at any time or urgent revascularization procedures at least 30 days after the pre-randomization index event). Additional secondary and exploratory endpoints are also defined.
The overall design is shown in Figure 1 below; for a more detailed discussion of the design and a summary of baseline results, see the American Heart Journal manuscript (accepted July 2019).

Figure 1. BETonMACE principle study design



In BETonMACE approximately 11% (n=250) of the patients have compromised renal function at randomization/baseline as defined by eGFR (estimated glomerular filtration rate) of 30 - <60 mL/min/1.73² , i.e., Chronic Kidney Disease (CKD) stage 3A (eGFR 45 - <60), and stage 3B (eGFR 30 - <45 mL/min/1.73²). Additionally, a number of patients will develop de novo CKD during the trial, i.e. having

eGFR ≥60 at randomization and declining to <60 mL/min/1.73² during the course of the study. Estimated mean treatment duration at termination of patients in BETonMACE is 26 months (range 8-44 months).

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.* It includes as a secondary endpoint the apabetalone vs. placebo effects on renal function, i.e., eGFR change within and between treatment arms over time, in the patients with a baseline eGFR <60 mL/min/1.73² at randomization.

The purpose of this BETonMACE supplemental/"academic" renal SAP is to pre-specify more detailed analyses of the effect of randomization to apabetalone vs. placebo on renal function. The analysis objectives are to evaluate the hypotheses that:

a) Apabetalone delays or reverses progression of CKD (renal tissue effects)
b) Apabetalone lowers a composite of renal and CVD events
c) The effect of apabetalone on CVD events varies by baseline CKD status

The analyses proposed in this renal SAP will be fully pre-specified and finalized prior to unblinding of the trial data. Except where otherwise indicated, analyses conducted under this SAP will use the same general analysis conventions (e.g., statistical approaches, analysis sets, time point definitions, etc.) as documented in the main SAP.

<u>Analysis Objective 1 –Evaluate the hypothesis that apabetalone delays or reverses progression of CKD (renal tissue effects)</u>

For the analyses below, we will define the following seven "baseline renal subgroups" of BETonMACE patients:

- All patients (the full analysis set [FAS], as defined in the main SAP)
- CKD subpopulation (subset of FAS with baseline eGFR <60 mL/min/1.73²)
    - CKD stage 3A subpopulation (subset with eGFR 45 - <60 mL/min/1.73²)
    - CKD stage 3B subpopulation (subset with eGFR 30 - <45 mL/min/1.73²)
- Non-CKD subpopulation (subset with baseline eGFR ≥60 mL/min/1.73²)
- CKD subpopulation (subset of FAS with baseline eGFR <90 mL/min/1.73²)
- Non-CKD subpopulation (subset with baseline eGFR ≥90 mL/min/1.73²)

Baseline Characteristics

To characterize the baseline renal subgroups, we will produce subgroup summaries (see example Table 1 below) of baseline characteristics to include demographics, relevant concomitant medications at baseline, ACS category (MI, UA +/- PTCA), statin (rosuvastatin vs. atorvastatin), etc. overall and by randomized treatment group. We will produce similar subgroup summaries of baseline clinical chemistry (see example Table 2 below).

CKD Prevention Paradigm

To assess the effect of apabetalone on the prevention of *de novo* CKD (prevention paradigm assessment), we will evaluate **in the non-CKD baseline renal subgroup(s):**

a) Descriptives statistics (means, SDs, quantiles) for measured values, and absolute and percent change from baseline by treatment at all time points of eGFR, serum creatinine, serum albumin, serum ALP, and hsCRP.
b) Linear mixed effects models of these analytes by time to estimate change/year.
c) Counts and percentages (see example Table 3 below) by treatment of number of patients reaching different CKD stages based on eGFR <60, <45, <30 <15 and dialysis during study, within the first year, and within the second year.
d) Counts and percentages by treatment of number of patients with:
    i. eGFR decrease by 25%, 33.3 %, and 50% from baseline, respectively
    ii. Serum-creatinine increase by 33.3%, 50% and 100% from baseline, respectively

The above analyses will be conducted overall and by statin subgroup (atorvastatin vs. rosuvastatin).

CKD Treatment Paradigm

To assess the effect of apabetalone on the prevention or slowing of progression of CKD (treatment paradigm assessment), we will evaluate **in the CKD baseline renal subgroup,** the same set of analyses described in the "CKD Prevention Paradigm" section above.

a) Figures Absolute and % Change in eGFR, serum-creatinine, serum albumin over time, serum ALP, hsCRP calculate changes over time, e.g. per year for the variables for each group Table 3 (example below) number of patients from the 6 groups reaching CKD stage with eGFR <60, <45, <30, and <15 mL/min/1.73² and number of patient starting dialysis (during study and estimated per year for all variables).
b) number of patients in the 6 groups, who during the course of the study:
    i. have eGFR decrease 25%, 33.3 %*, and 50%, respectively
    ii. have an increase of serum-creatinine of 33.3%, 50%* and 100%, respectively
    iii. require dialysis

Analysis Objective 2 – Evaluate the hypothesis that apabetalone lowers a composite of renal and CVD events

We will define and analyze a composite of renal and CVD events in accordance with the approach taken in the Credence study (Perkovic et al. NEJM June 13, 2019). Since the post-ACS BETonMACE population at baseline has higher CVD risk and less severe degree of renal disease than in the Credence study, we adopt a composite event definition with a renal component that is slightly relaxed to allow for more renal events. The "renal/CV composite" is defined as the first of either broadly defined MACE (as defined above) or a "renal event" defined by a ≥50% serum creatinine increase from baseline or a ≥33.3% eGFR decrease from baseline.

We will conduct analyses of time to first renal/CV composite event consisting of:

(a) Kaplan-Meier analysis by treatment
(b) Estimation of the hazard ratio (HR) with 95% confidence interval using a Cox proportional hazard model with stratification by country and statin. A log-rank statistic will be used.
(c) Additional subgroup analyses as described in the main SAP (including the rosuvastatin and atorvastatin subgroups), if warranted by the overall results.

We will also conduct analyses of total (first and recurrent) renal/CV composite events consisting of:

(a) Estimation of the mean cumulative incidence functions by treatment
(b) Estimation of the hazard ratio with 95% confidence intervals based on the Andersen-Gill generalization of the Cox model using a random frailty effect (per subject with gamma distribution). A Wald test will be used for testing the significance of the treatment effect. As in the main SAP, an analysis stratified by country and statin will be used.
(c) Additional subgroup analyses as described in the main SAP (including the rosuvastatin and atorvastatin subgroups, as well as age, sex, baseline LDL, HDL, hsCRP, etc.), if warranted by the overall results.

Similar analysis will also be conducted on the renal component (>50% serum creatinine increase from baseline or a ≥33.3% eGFR decrease from baseline) alone.

Analysis Objective 3 – Evaluate the hypothesis that the effect of apabetalone on CVD events varies by baseline CKD status

The main SAP includes analyses of CVD events by subgroup for the CKD (eGFR <60) and Non-CKD (eGFR
≥60) baseline renal subgroups. We will also conduct CVD event analyses for the additional baseline renal subgroups defined above (CKD stage 3A and CKD stage 3B). These analyses will include analyses of total (first and recurrent) broadly defined MACE, time to first 3P-MACE, CV mortality, and all-cause mortality. Given the high prevalence of congestive heart failure in the CKD population we will also calculate CV-death, CHF hospitalizations (first, and total) alone and together (ref. DAPA-HF, McMurray et al. ESC 2020).

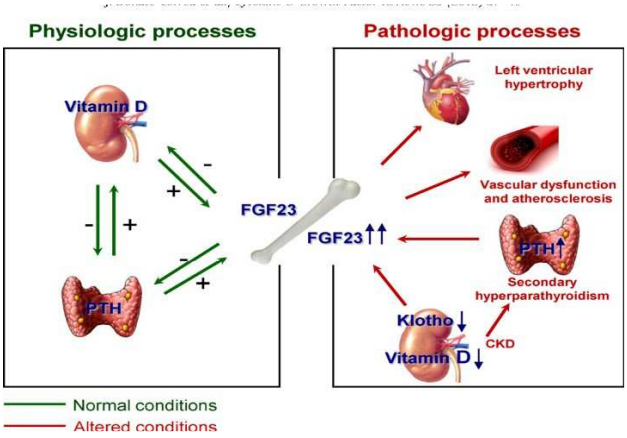
Similar apabetalone vs. placebo analysis for effects on events will also be performed for eGFR <90 vs. eGFR =>90.

*Contingency analyses based on archive sample biomarker analysis.

Following a statistically significant favorable effect on eGFR by apabetalone vs. placebo, additional analysis may be performed and assessed for baseline and change characteristics, including:

- Cystatin C (as creatinine independent GFR assessment),
- Parathyroid Hormone (PTH),
- Vitamin D, Vitamin B6/pyridoxal-5'-phosphate ((PLP),
- Pyrophosphate (PPi), Osteoprotegerin, and,
- Klotho and FGF23 (established risk factor for osteoporosis and CHF).

For general rationale, see Figure below and Lu and Hu 2017 (Lu X, Hu MC. Klotho/FGF23 Axis in Chronic Kidney Disease and Cardiovascular Disease. Kidney Dis (Basel). 2017 Jul;3(1):15-23).



In addition, following significant effects on eGFR, indicating renal function preservation, a non-biased proteomics assessment will be considered. The objective is to better understand the detailed MoA of apabetalone on renal tissue preservation.

Urine analysis for protein/creatinine-ratio is performed in Russia at baseline, 6 months and yearly. We only expect about 4 patients to have CKD and two patients with CKD to be treated with apabetalone out of the 35 Russian participants. As anecdotal cases we will follow over-time-change in urine protein-to-creatinine-ratio and change in serum eGFR, creatinine, albumin, hsCRP and ALP.

Missing values: For addressing missing values Mixed-Effect Model Repeated Measure (MMRM) model will be applied as a rule, and when not appropriate last-value-carried-forward model. Reference: Siddiqui O[1], Hung HM, O'Neill R. J Biopharm Stat. 2009;19(2):227-46. MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets.

Table 1. Baseline demographics, all patients, non-CKD, CKD, CKD stage 3a, CKD stage 3B (5 groups)

Parameter	All patients (n=)	non-CKD (n=)	CKD eGFR 30-59	CKD Stage 3A (n=)	CKD Stage 3B
Age (years)					
Male (%)					
Cucasian (%)					
Randomizatiion inclusion criteria;					
Acute coronary syndrome/myocardial infarction					
Unstable angina					
PTCA/stenting					
Diabetes History (medium years)					
History of taking diabetes medication Yes%					
History of taking diabetes medication No%					
HbA1c ≥6.5% at Visit 1					
BMI (kg/m2)					
Hypertension (%)					
ACS history (%)					
Smoker (%)					
Standard of care medication;					
Insulin (%)					
Oral DM medication (%)					
Metformine					
Sulfonylureas					
glyburide/glibenclamide(DiaBeta, Glynase, or Micronase)					
glimepiridine(Amaryl)					
chlorpropamide(Diabinase)					
glipizide (Glucotrol)					
tolazamide) (Tolinaze)					
Tolbutamide					
GLP-1 agonist (%)					
exenatide (Byetta/Bydureon)					
liraglutide (Victoza, Saxenda)					
lixisenatide (Lyxumia)					
albiglutide (Tanzeum)					
dulaglutide (Trulicity)					
semaglutide (Ozempic)					
SGLT2 inhibitor (%)					
canagliflozin (Invokana) dapagliflozin (Farxiga) empagliflozin (Jardiance) empagliflozin/linagliptin (Glyxambi) empagliflozin/metformin (Synjardy) dapagliflozin/metformin (Xigduo XR)					
Atorvastatin (%)					
Rosuvastatin (%)					
ACE-inhib.					
lisinopril (Zestril), benazepril (Lotensin) and enalapril (Vasotec)					
ARBs					
losartan(Cozaar), valsartan (Diovan) and irbesartan (Avapro)					
B-blockers (%)					
Antiplatelet agents (%)					
Double antiplatelets agents (%)					
*Mann-Whitney U-test, Groups 1-2, 1-3, 2-3, 4-5					

Table 2. Baseline serum chemistry CKD populations

Parameter	All patients (n=)	non-CKD (n=)	CKD/eGFR 30-59	CKD Stage 3A (n=)	CKD Stage 3B
Alkaline Phosphatase†, U/L (n=)					
eGFR, mL/min/1.73 m2 (n=)					
Albumin, g/dL					
LDL-C, mg/dL					
(n=) HDL-C,					
mg/dL (n=)					
Apolipoprotein A-I†, mg/dL (n=)					
hsCRP†, mg/L (n=)					
Fibrinogen‡, mg/L (n=)					
HbA1c, % (n=)					
Platelets, 10^9/ L (n=)					
NLR, ratio (n=)					
LD					
Bilirubin					
GGT					
other values are from visit 1/screening					
Statistical analysis groups 1-2, 1-3,2-3, 4-5					

Table 3. Apabetalone all, apabetalone + Rosuva, apabetalone +Atorva vs. placebo all, placebo +Rosuva, placebo + Atorva (total 6 groups) effects in preventing non-CKD patients (eGFR ≥60 mL/min/ 1.73²) deteriorate to CKD stages

Non-CKD population reaching	ABL All	ABL Rosuva	ABL Atorva	Placebo All	PL Rosuva	PL Atorva
During study eGFR;	All					
<60						
<45						
<30						
<15						
starting dialysis						
First year;						
<60						
<45						
<30						
<15						
starting dialysis						

<u>Supplemental Table A</u>: Minimally adjusted hazard ratios (HR) for composite and component events in apabetalone vs placebo across CKD status for major adverse cardiovascular events (MACE).

		eGFR < 60 ml/min/1.73 m^2	eGFR ≥ 60 ml/min/1.73 m^2	
		HR (95% CI)	**HR (95% CI)**	**Int. P-Value**
Primary Outcome				
	MACE	**0.50** [0.26,0.96]	0.94 [0.73,1.22]	0.032
Composite Events				
	MACE + CHF	**0.48** [0.26,0.89]	0.89 [0.70,1.14]	0.033
Components				
	CV death	0.47 [0.18,1.21]	0.98 [0.63,1.54]	0.12
	Non-fatal MI	0.60 [0.27,1.34]	0.88 [0.63,1.22]	0.26
	Non-fatal stroke	0.55 [0.11,2.79]	1.35 [0.62,2.94]	0.20
	CHF hospitalization	**0.26** [0.07,0.94]	0.74 [0.45,1.24]	0.12

Abbreviations: eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; MACE, major adverse cardiovascular events; HCHF, hospitalization for congestive heart failure; CHF, congestive heart failure

Shown are HRs and 95% CIs for indicated composite and component endpoints. All analyses are stratified for statin and country, in accordance with the primary analyses.[18] Interaction P-value tests for difference by CKD status in the effect of apabetalone on event rates.