MB001-067 A PROSPECTIVE, DOUBLE BLIND, PLACEBO CONTROLLED, PARALLEL GROUP, RANDOMIZED TRIAL OF EXTENDED RELEASE EXENATIDE VERSUS PLACEBO (COHORT A) AND A PROSPECTIVE, SINGLE GROUP, OPEN-LABEL, BLINDED OUTCOME TRIAL OF EXTENDED RELEASE EXENATIDE (COHORT B) IN DIABETIC PATIENTS WITH TYPE 4 CARDIORENAL SYNDROME (EXTEND-CRS TRIAL) AMENDMENT 3

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Background/Rationale

There has been considerable attention given to the cardiovascular safety of antidiabetic therapeutic agents in recent years.[1] Some agents, in post-approval studies were linked to higher rates of myocardial infarction, heart failure, and cardiovascular death. In addition, modern

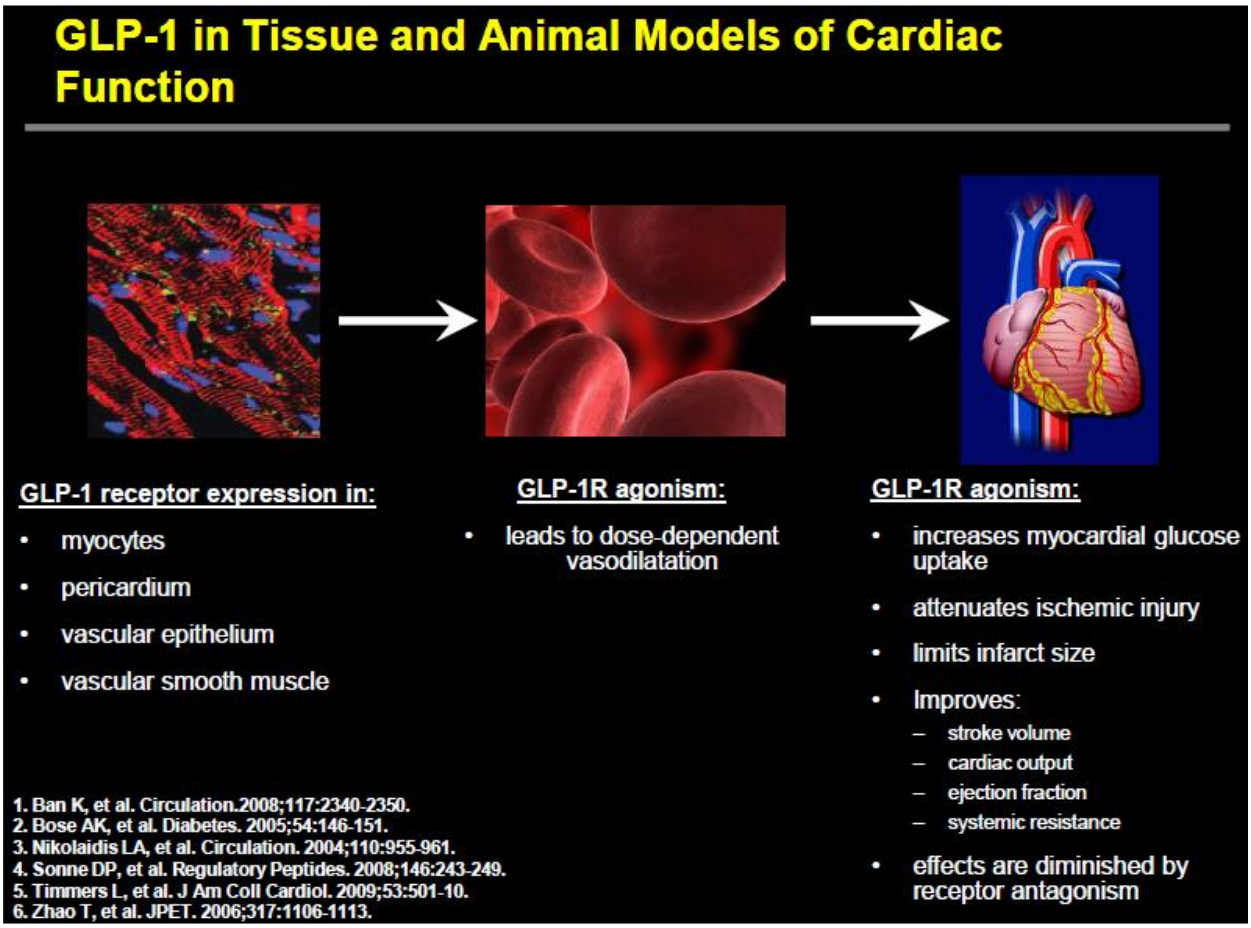
strategy trials linked tight glycemic control to risk of hypoglycemic events and cardiovascular death.[2] Many of the issues that came out of the debate dealt with a lack of biologic plausibility for specific agents and atherosclerotic or myocardial disease progression as well as statistical uncertainty of the post-marketing studies where events were not adjudicated at occurred at very low frequencies over short durations of followup.[3] In response, the U.S. Food and Drug administration issued guidance for sponsors of pharmaceutical trials in terms of acceptable rates of myocardial infarction, stroke, and cardiovascular death in randomized controlled trials.[4] Importantly, heart failure was not addressed in this guidance, and as a result, two recent trials have raised concerns regarding increased risks of heart failure with new drugs recently approved (alogliptin, saxagliptin).[5] [6] Hence, there is a need for high-quality trials in patients with diabetes evaluating treatment effects on the myocardium with the most sophisticated imaging and molecular measurements.

We are in the midst of chronic disease epidemics of type 2 diabetes mellitus (T2DM) and heart failure (HF). It is recognized that approximately half of all patients diagnosed with HF have preserved left ventricular ejection fraction (HFpEF), otherwise known as diastolic HF (DHF). For the sake of this proposal, which will evaluate diastolic function in detail, the abbreviation DHF will be used. The determinants, pathophysiology, contribution of ischemia, and relationship to arrhythmias with DHF are all incompletely understood.[7] It is believed that a core pathophysiologic process involved in DHF is cardiac fibrosis and the crosslinking of procollagen to collagen which is regulated in part, by the renin-angiotensin aldosterone system.[8] Once this structural event has occurred in the interstitium of the myocardium, it is unlikely that any form of neurohumoral modification will reverse, degrade, or influence the cross-linked collagen matrix. Thus, there is considerable interest in upstream use of neurohumoral antagonism to prevent or retard the progression of cardiac fibrosis in patients who ultimately develop DHF. There are currently no approved therapies for DHF and trials of conventional agents used in systolic HF have not led to reductions in heart failure hospitalizations or HF death. These data all support the notion that therapies may be applied too late in the course of DHF.

There is now widespread recognition that chronic kidney disease (CKD) contributes to the initiation and progression of HF. Cardiorenal syndrome type 4 is the clinical circumstance in which the progression of CKD directly leads to derangements in cardiac function and ultimately sodium and water retention, volume overload, neurohumoral changes, micronutrient abnormalities, all of which result in DHF.

Recent data suggest glucagonlike peptide-1 (GLP-1) agonists may have anti-apoptotic effects on cardiomyocytes in the setting of HF.[9] Vyas and colleagues recently conducted a study in a murine model where the GLP-1 agonist exenatide was administered twice daily to a mice with dilated cardiomyopathy (TG9) starting at 56 days of life.[10] TG9 mice develop congestive heart failure and secondary insulin resistance in a highly predictable manner with death by 12 weeks

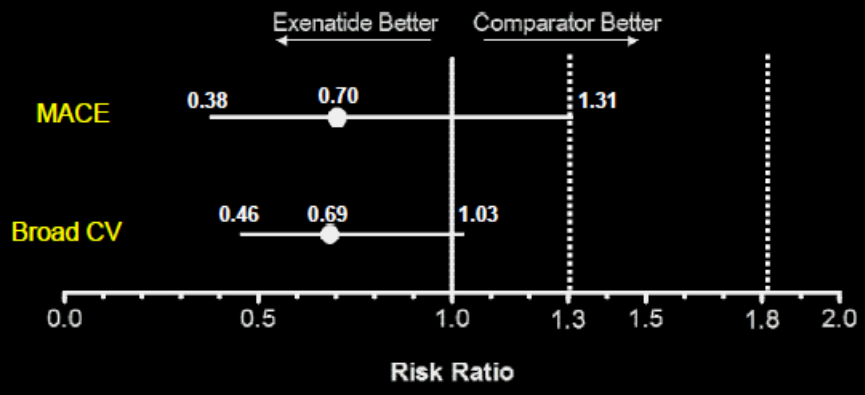
of age. Glucose homeostasis was assessed by measuring glucose tolerance at 8 and 10 weeks and tissue 2-deoxyglucose uptake at 75 days. Exenatide treatment improved glucose tolerance, myocardial GLUT4 expression and 2-deoxyglucose uptake, cardiac contractility, and survival over control vehicle-treated TG9 mice. Phosphorylation of AMP kinase and AKT was also increased in exenatide-treated animals. Total myocardial GLUT1 levels were not different between groups. Lui and coworkers recently studied the potential of GLP-1 cardioprotective effects in an animal model of myocardial infarction (MI).[11] The hypothesis was that chronic treatment with GLP-1 or the exenatide analog AC3174 would improve cardiac function, cardiac remodeling, insulin sensitivity, and exercise capacity (EC) in rats with MI-induced chronic heart failure (HF) caused by coronary artery ligation. Two weeks post-MI, male Sprague-Dawley rats were treated with GLP-1 (2.5 or 25 pmol/kg/min), AC3174 (1.7 or 5 pmol/kg/min) or vehicle via subcutaneous infusion for 11 weeks. Cardiac function and morphology were assessed by echocardiography during treatment. Metabolic, hemodynamic, exercise-capacity, and body composition measurements were made at study end. Compared with vehicle-treated rats with HF, GLP-1 or AC3174 significantly improved cardiac function, including left ventricular (LV) ejection fraction, and end diastolic pressure. Cardiac dimensions also improved as evidenced by reduced LV end diastolic and systolic volumes and reduced left atrial volume. Vehicle-treated HF rats exhibited fasting hyperglycemia and hyperinsulinemia. In contrast, GLP-1 or AC3174 normalized fasting plasma insulin and glucose levels. GLP-1 or AC3174 also significantly reduced body fat and fluid mass and improved exercise capacity and respiratory efficiency. Four of 16 vehicle control HF rats died during the study compared with 1 of 44 rats treated with GLP-1 or AC3174. The cellular mechanism by which GLP-1 or AC3174 exert cardioprotective effects appears unrelated to changes in GLUT1 or GLUT4 translocation or expression. Lui concluded that chronic treatment with either GLP-1 or AC3174 showed promising cardioprotective effects in a rat model of HF. There are a variety of additional proposed mechanisms for the myocardial effects of exenatide as GLP-1 receptor agonist as shown in the figure ranging from cardioprotection after an acute ischemic event to fundamental changes in substrate utilization by myocardial cells. Of note, because transport of glucose and potassium can affect the QT interval, investigators have evaluated the impact of exenatide on the QTcorrected and have demonstrated no significant change.[12] Hence, GLP-1 receptor agonists may represent a novel approach for the treatment of patients with HF or cardiovascular disease associated with type 2 diabetes.



Best and colleagues have recently demonstrated in the LifeLink database that use of exenatide twice daily in 21,754 patients compared to non-use in 361,771 using propensity matching was associated with a 19% reduction in cardiovascular events, p=0.01.[13] These observations have been extended by Best and coworkers using the General Electric database where exenatide use was associated with an adjusted risk hear failure, OR=0.46, 95% CI 0.38-0.56, for all patients who received twice daily exenatide (n = 103,776).[14] Of note, this protective effect was greater for those who were receiving concomitant insulin therapy compared to those without. There have been consistent cardiovascular benefits seen in the integrated database assembled for safety for exenatide over the course of many clinical trials as shown in the Figure.[15]

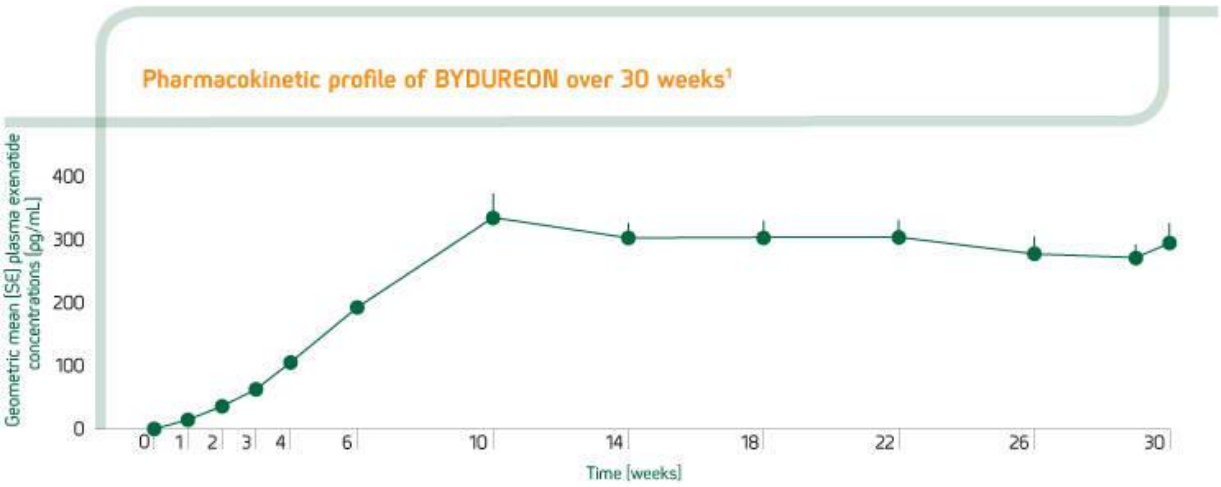
Relative Risk of Cardiovascular Endpoints

- Forest plot showing risk ratio point estimate and 95% CI



	CV Death	Myocardial Infarction	Stroke	Acute Coronary Syndrome	Revascularization Procedures	Arrhythmia/ Conduction	Heart Failure/ Mechanical
MACE	X	X	X	X	X		
Broad CV	X	X	X	X	X	X	X

The clinical development of exenatide has progressed to a once-weekly subcutaneous formulation, BYDUREON™, (Exenatide extended release for injectable suspension) approved by the US FDA for clinical use in January, 2012, which produces elevated and steady state levels of the drug over time as shown in the Figure. This provides theoretical rationale that constant agonism at the GLP-1 receptors on myocardial cells may provide the best overall opportunity to evaluate changes in structure, function, and satellite cell activation over time as a result of exenatide.



There are new laboratory and imaging technologies that reveal the presence of cardiac and possibly renal fibrosis. The 2013 guidelines for HF from the American College of Cardiology recommend several biomarkers for the assessment and management including natriuretic peptides (B-type natriuretic peptide [BNP], N-terminal pro B-type natriuretic peptide [NT-proBNP]), ultrasensitive troponin I or T, galectin-3 and ST2.[16] Numerous studies have demonstrated the usefulness of chronic serial measurements of BNP or NT-proBNP in the monitoring of myocardial disease.[17] [18] In addition, either peptide has proven to be useful as entry criteria for clinical trials HF patients, primary to exclude HF mimics. With the advent of more sensitive assays for troponin, it has been shown that the majority of patients with HF have chronic elevations which are related in a graded fashion to heart failure hospitalization and death.[19] [20] Galectin-3, a novel biomarker produced by cardiac macrophages and pericytes, is a member of the family of animal lectins, which selectively binds β-galactoside residue on the cell surface of fibroblasts, and via the transforming growth factor-beta pathway, signals the production and secretion of procollagen in the extracellular space.[21] Galectin-3 has been demonstrated to be elevated in blood in the presence of HF and is prognostically related to death independently and complementary to the natriuretic peptides.[22] Soluble ST2 is a decoy ligand for the interleukin-33 receptor present in the myocardium and its levels are quantitatively related to the severity of HF and are predictive of future HF hospitalizations and death.[23] [24] Interestingly, among young individuals in the Framingham Heart Study, ST2 levels anticipate the future development of HTN during adulthood.[25] In simplistic terms, ST2 can be thought of as a link between the immune system and left ventricular dysfunction. All four markers, ultrasensitive troponin I or T, BNP or NT-proBNP, galectin-3 and ST2 can be integrated into a chronic Myocardial Injury Summary Score (MISS) as shown below.

Cardiac magnetic resonance imaging MRI using gadolinium has demonstrated that the presence of late gadolinium enhancement is indicative of myocardial tissue fibrosis and is prognostic for cardiac arrhythmias and death in a variety of cardiomyopathies.[26] There is a new technology that complements MRI using ultrasonography with strain rate imaging for assessment of cardiac

fibrosis. In order to determine the health of the heart during treatment, ultrasound imaging will be used to measure the function of the myocardium and those changes will be monitored over time. Given that the muscle fibers of the left ventricle are laid out in a cross hatch formation from the apex to the base (near the mitral valve) and that the chambers are synchronized in their pumping, the overall expansion and contraction of the muscle follows a very complex sequence of events. Any damage to the myocardium due to lack of blood, infection or other events will change this expansion and contraction significantly. Ultrasound strain imaging provides a non-invasive, non-radiation method to assess the heart's ability to expand and contract properly and can detect subtle changes in these events. Strain rate imaging is emerging as the most sensitive technique to evaluate the subtle effects of DM on myocardial function with the ability to detect physiologic changes that cannot be seen on conventional echocardiography or cardiac MRI.[27]

Finally, there are a host of renal biomarkers in development that will complement the urine albumin:creatinine ratio in the detection of chronic renal injury including those outlined below which can be organized into a chronic Kidney Injury Summary Score (KISS):

- Tissue Inhibitor of MetalloProteinases-2 (TIMP-2) x Insulin-like Growth Factor Binding Protein-7 (IGFBP-7), also known as the commercially available NephroCheck® Test
- Neutrophil gelatinase associated lipocalin (NGAL):creatinine (Cr) ratio
- Kidney injury molecule-1 (KIM-1):Cr ratio
- L-Fatty acid binding protein:Cr ratio
- Interleukin-18:Cr ratio
- Alpha glutathione S-transferase (αGST):Cr ratio
- Pi glutathione S-transferase (piGST):Cr ratio
- N-acetyl-β-D-glucosaminidase (NAG):Cr ratio
- Cystatin-C:Cr ratio (uCysC:Cr)
- Albumin:Cr ratio (ACR)

One of the difficulties faced by small trials measuring multiple biomarkers is the integration of multiple markers in order to interpret a therapeutic signal of benefit or harm. This protocol will use an integrative approach for both the myocardial and renal markers as indicated below. Since most of these markers have a skewed distribution to the right, they are amenable to logarithmic transformation, and hence, can be put on a summative scale in order to detect harm (movement to the right or positive) or benefit, movement to the left or negative from zero. The four cardiac

markers will be integrated into a MISS score and the renal markers, similarly will be integrated into a KISS score as follows:

The method involves calculation of a biomarker index, representing from one or more biomarkers. The basic metric is the ratio of the peak value for a biomarker seen after a treatment to the baseline value before treatment. Both the baseline and post-treatment values may represent single assay measurements, or a single value determined from multiple measurements with rules used to ensure robust assay estimates.

The basic component for the score is defined as: $\text{Biomarker(i)}_{\text{Peak}} / \text{Biomarker(i)}_{\text{Baseline}}$

The composite score across multiple biomarkers (i) for a given patient (j) would be defined as:

$$\text{MISS or KISS(j)} = \sum \log_{10} [\ \text{Biomarker(i)}_{\text{Peak}} / \text{Biomarker(i)}_{\text{Baseline}}\ ]/n, \quad i = 1,$$

n=number of individual biomarker terms

The composite score has these features:

1. Individual biomarker values, which may be measured on different scales, are normalized to a ratio value, without units, which can be combined. Use of ratios addresses, in part, the fact that the variability associated with individual biomarkers may be dependent on the magnitude of the values themselves, which make some statistics based on original values (especially, mean values) less suitable for comparing differences between treatment groups.
2. The MISS and KISS values will be estimated at a patient level, so that a lack of change in some biomarkers can be compensated for by increases by others in the panel of biomarkers, reflecting different patient-to-patient expressions of biomarker changes.
3. The logarithmic transformation addresses the observed right-skewing in the distribution of underlying biomarker values, which are bounded by zero but may have relatively large values compared to mean or expected values. Log_{10} values between -1 and +1 cover the range from original ratios of 0.1 to 10 for individual biomarkers. No change in a biomarker value from baseline to post-treatment use would result in a ratio of 1 and a log score of zero (which is appealing). Thus the overall MISS and KISS values will have a range from -1 to +1 and the null hypothesis will be represented by a zero in each score.
4. The MISS and KISS values can be treated as ordinary statistics for purposes of summary, analysis, or sample size estimation for future trials.

Thus, we propose a phase II translational study evaluating Exenatide extended-release, with assessment of its impact, if any, on human measures of cardiac and renal fibrosis in Type 4 cardiorenal syndrome.

Primary Aim

Among adult individuals with T2DM and at risk for early DHF with mildly reduced renal filtration function (Type 4 cardiorenal syndrome), to evaluate the quantitative impact on the MISS cardiac biomarker score, cardiac fibrosis by MRI, cardiac strain by ultrasonography and strain rate imaging, and KISS kidney biomarker score after A) 38 weeks of treatment with exenatide extended-release or placebo or B) 38 weeks of treatment with BYDUREON™ (exenatide extended-release).

Secondary Aim

To evaluate the inter-relationships between demographic, clinical, and biochemical variables (MISS score, KISS score) and of progressive cardiac fibrosis as assessed by MRI, strain-rate imaging, and in adult individuals with T2DM and at risk for early DHF (Type 4 cardiorenal syndrome).

Inclusion Criteria

- Age ≥ 18
- Type 2 diabetes mellitus with hemoglobin A1C 6.6-12.0% with or without the use of insulin
- Estimated glomerular filtration rate (eGFR) between 50 and 130 ml/min/1.73 m^2

Exclusion Criteria

- Allergy or intolerance to gadolinium
- Implanted cardiac pacemaker, defibrillator, loop recorder, or other implanted metallic device
- Any other metallic implanted device that is a contra-indication to MRI scanning
- eGFR < 50 ml/min/1.73 m^2
- eGFR > 130 ml/min/1.73 m^2
- Patient has ever been treated with an approved or investigational GLP-1 receptor agonist e.g. BYETTA™ (exenatide), BYDUREON™ (Exenatide extended-release), VICTOZA™ (liraglutide), or taspoglutide
- Patient is enrolled in another experimental protocol which involves the use of an investigational drug or device, or an intervention that would interfere with the conduct of the trial.
- Disorders of iron metabolism
- Collagen vascular diseases
- Myocardial infarction

- New York Heart Association Class III or IV Heart Failure
- Current use of DPP4 inhibitors and PPAR gamma agonists
- Pregnancy or planned pregnancy during the trial period
- Hemoglobin A1C of ≥ 12.0% or <6.6%
- Fasting glucose ≥ 250mg/dl
- Clinically significant abnormal baseline laboratories
- Morbid obesity or body girth that prohibits the ability to undergo echocardiography or MRI scanning with high-quality image results
- Renal transplantation
- Severe gastrointestinal, liver, or neurodegenerative disease
- Decompensated liver cirrhosis (Child-Pugh score >7)
- Patients have alanine aminotransaminase (ALT) greater than 5 times the upper limit of the reference range.
- Prior pancreatitis
- Personal or family history of medullary thyroid adenoma or carcinoma (MTC)
- Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- History of severe hypoglycemia
- Prior bariatric surgery

Study Restricted Drugs: DPP4 inhibitors (Januvia, Onglyza, Galvus, Tradjenta, Nesina) and PPAR gamma agonists (Actos, Avandia). Subjects may be reconsidered for enrollment upon successful withdrawal and washout of these drugs.

Study Design/Methods

Prospective, 2 cohort trial:
Cohort A: double blind, randomized, parallel group, placebo controlled
Intervention: Drug: Exenatide-extended release (BYDUREON™) 2 mg subcutaneously once per week x 38 weeks
Matching placebo subcutaneously once per week x 38 weeks
Subject Enrollment: approximately 56 subjects will be enrolled

Cohort B: open-label
Intervention: Drug: Exenatide-extended release (BYDUREON™) 2 mg subcutaneously once per week x 38 weeks (single group, open-label, blinded outcome)
Subject Enrollment: approximately 48 subjects will be enrolled

Prescreening: presence of type 2 diabetes mellitus, eGFR 50-130 ml/min/1.73 m^2 within the last year will be the principal prescreening data used by study coordinators to identify potential candidates for the trial. There will be a two week washout of study restricted medications listed

above. Subjects that agree to withdrawal of study restricted medications will be monitored by the investigator. Monitoring will be based on blood sugar values with medication changes as needed as determined by the investigator. An extended pre-screening period of 2-4 weeks will be granted to subjects with high HbA1cs > 12.0% and fasting glucoses > 250 to improve glycemic control by improving anti-diabetic medication compliance. Subjects will then be rescreened at the end of this period to verify improved compliance. Formal screening will occur as indicated in the chart of events. Blood and urine biomarkers and cardiac MRI with gadolinium will be measured at baseline and nine months. All urine and blood specimens will be processed and aliquoted and stored. In general, patient samples will be collected and stored in a -20 or -80 freezer for later use. Samples for some biomarkers may be shipped on dry ice to be processed by a commercial lab or core facility. Other samples will be processed in-house using commercially available sandwich ELISA (enzyme-linked immunosorbent assay) kits. Briefly, a sandwich ELISA is an analytic biochemistry assay that detects the presence of an analyte in a sample. The antibody (Ab) specific for the analyte is bound to the wells of a 96-well plate. Samples containing the analyte of interest are added to the wells. A second Ab, specific for that analyte and conjugated to an enzyme is then added. Finally, a chromogen (colorless enzymatic substrate) is added. The Ab coupled enzyme converts the substrate into a colored product, indicating the proportion of analyte present in the sample. The amount of product is then quantified by measuring the optical density at a specific wavelength utilizing a microplate reader. Detailed laboratory methods and description of the cardiac echocardiography and MRI protocols will be produced for a full trial protocol and manual of operations, and the protocols are briefly outlined below.

Cardiac MRI protocol:

Cardiac MRI will be performed at baseline and at 38 weeks following therapy. The same protocol will be used for baseline MRI scan and at 38 weeks.

Cardiac MRI images will be acquired on a 1.5-T scanner (Philips Achieva 1.5 Tesla for Cohort A and Siemens Aera 1.5 Tesla for Cohort B).

Global and Regional LV function: Steady-state free precession cine images will be acquired in the two, three and four chamber long axis views, and stacked short axis views covering the entire left ventricle.

Late enhancement scan will be acquired per routine protocol following IV administration of gadolinium in the two, three and four chamber views, and stacked short axis views. Standard late gadolinium enhancement imaging will be performed after at least 10 minutes after the dose of contrast agent is administered using spoiled gradient echo segmented inversion recovery and phase-sensitive inversion recovery segmented gradient echo sequences. In patients with renal insufficiency with eGFR<50, contrast will not be administered.

Cardiovascular magnetic resonance Functional Analysis: Post processing of the MRI images will be performed on a separate workstation. Left ventricular mass index (LVMI) g/m2, left ventricular volumes, ejection fraction, and percentage of scar tissue and fibrosis will be calculated using Circle CMR software and/or Precession software.

Echocardiography Protocol:

Standard TTE echocardiogram will be performed at baseline and at 38 weeks following treatment. The same protocol will be used at baseline and at 38 weeks following therapy.

Echocardiography will be performed using standard 2D, color and spectral Doppler acquisitions in the parasternal, apical and subcostal views. Recordings will be made on a GE Vivid 7 machine for Cohort A and a Philips Epiq 7 machine for Cohort B. All data will be stored on a workstation (EchoPAC for offline analysis). Analysis will be performed by an experienced echocardiographer. For each patient conventional analysis of the echocardiography precedes LV strain analysis.

LV systolic and diastolic function, LV ejection fraction (biplane Simpsons), LV volumes, LV mass index LVMI, E/A ratio, Tissue Doppler e- prime, E/e-prime, and pulmonary venous Doppler will be determined.

Mitral inflow E and A wave velocities were measured by the pulse wave Doppler method. Doppler tissue imaging was recorded at level of the septal and lateral mitral annulus.

Strain measurement is based on speckle tracking approach. Global longitudinal, circumferential and radial myocardial deformation will be evaluated from standard 2 D images using 2D strain software. Two dimensional data sets for speckle tracking analysis include three short axis views (basal, midventricular and apical) and three apical longitudinal views (four, three and two chamber). Adjustments to be made in sector depth and angle to yield a temporal resolution of about 80 to 100 frames/sec. By tracing endocardial borders on the end systolic frame, the software automatically tracks the contour on the subsequent frames. Tracking will be confirmed in real time and manually corrected if necessary. Global longitudinal strain (GLS) is the average of the segment strains from the apical four-chamber view. Global radial strain and Global circumferential strain are the averages of the segment strains in the mid parasternal short axis view at an image frame rate between 60-90 Hz. Images will be analyzed offline on a separate EchoPac analysis package.

12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at screening to rule out baseline atrial fibrillation and confirm the subject in sinus rhythm. An additional ECG be performed at 38 weeks again to confirm sinus rhythm as well as to evaluate changes in chamber dimension,

ventricular axis, intervals, and the development of conduction delays if any. If atrial fibrillation develops during the course of treatment, then usual care will be provided and at week 38 efforts will be made at rate control to ensure the highest fidelity echocardiography with strain and cardiac MRI studies.

Body Weight

Body weight in kilograms will be recorded at every clinical visit and the body mass index will be calculated. Studies of exenatide have shown that subjects lost an average of six pounds over 24 weeks, and thus, a change in weight is an anticipated confounder in the analyses evaluating cardiac imaging measures and potentially the cardiac and renal biomarkers.

Concomitant Medications

Concomitant medications will be assessed at every study visit. If a contra-indicated medication has been started by a treating physician (e.g. BYETTA™ (exenatide), BYDUREON™ (Exenatide extended-release), VICTOZA™ (liraglutide), or taspoglutide), then the treating physician will be contacted by the principal investigator and the contra-indicated medication will be suggested for discontinuation. If there is either hyper- or hypo-glycemia that has signaled a change in anti-diabetic agents, then a drug from an allowed class will be selected or deselected in the management (e.g. metformin, secretogogues, insulin).

Liver Function Testing

Exenatide is primarily cleared by the kidney and does not carry high risks of hepatotoxicity. Liver function testing will be measured at screening, and then 4, 16, and 38 weeks. If either the AST or ALT elevate > 3 X the ULN or the bilirubin exceeds 2 X the ULN, then testing will be repeated in two weeks and if elevations remain, the study drug will be discontinued and the tests will again be repeated in two weeks. If they remain elevated, then study subjects will be referred to their primary care physician or hepatologist for evaluation.

Patient Follow-Up:
A retrospective chart review of medical records and the national death registry to capture, medical history, demographic information, outcomes, laboratory and procedure results, medications usage, hospitalizations, new diagnoses, and long-term survival data.

A follow-up phone call will be completed between week 16 and week 38 visits to assess AE's, ConMeds, and study drug compliance.

Patients who wish to withdraw from the study will complete all early term procedures listed in the schedule of events. Additional MRI/Echo scans and/or urine and blood biomarkers may be collected per PI discretion.

Areas of Special Concern

Risk off Thyroid C-cell Tumors

In both genders of rats, exenatide extended-release caused a dose-related and treatment-duration–dependent increase in the incidence of thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures compared to controls. A statistically significant increase in malignant thyroid C-cell carcinomas was observed in female rats receiving exenatide extended-release at 25-times clinical exposure compared to controls and higher incidences were noted in males above controls in all treated groups at ≥ 2-times clinical exposure. The potential of exenatide extended-release to induce C-cell tumors in mice has not been evaluated. Other GLP-1 receptor agonists have also induced thyroid C-cell adenomas and carcinomas in male and female mice and rats at clinically relevant exposures. It is unknown whether BYDUREON will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of exenatide extended-release–induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies. Serum calcitonin was not assessed in the clinical trials supporting the approval of BYDUREON.

Serum calcitonin is a biological marker of MTC. Patients with MTC usually have calcitonin values > 50 ng/L. Patients with thyroid nodules noted on physical examination (to be performed at screening weeks 4, 16, and 38) or on neck imaging done as a part of concurrent clinical care will be referred to an endocrinologist for further evaluation. Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with BYDUREON and will not be performed in the study. Such monitoring may increase the risk of unnecessary procedures, due to the low specificity of serum calcitonin testing for MTC and a high background incidence of thyroid disease. If serum calcitonin is measured as a part of concurrent clinical care and found to be elevated, the patient should be referred to an endocrinologist for further evaluation.

Acute Pancreatitis

Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYDUREON, patients should be carefully observed for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, BYDUREON should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, the study drug will not be restarted.

Hypoglycemia

The risk of hypoglycemia is increased when exenatide is used in combination with a sulfonylurea. Therefore, patients receiving BYDUREON and a sulfonylurea may require a lower dose of the sulfonylurea to minimize the risk of hypoglycemia. It is also possible that the use of BYDUREON with other glucose-independent insulin secretagogues (e.g., meglitinides) could increase the risk of hypoglycemia.

Renal Impairment

Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies. BYDUREON should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease and should be used with caution in patients with renal transplantation because of the risks of increased nausea, vomiting, and hypoglycemia. Estimated glomerular filtration rate will be assessed at every clinical visit and if the eGFR falls below 30 ml/min/1.73 m^2, then the study drug will be discontinued

Primary Endpoints

1) Serum cardiac biomarker MISS score (derived from changes in ultrasensitive troponin, BNP, galectin-3, and ST2)
2) Urine renal biomarker KISS score (derived from 10 renal biomarkers)
3) Mean paired percent change in left ventricular myocardial fibrosis (% of left ventricular mass)
4) Mean paired change in left ventricular strain (%) by strain-rate imaging

Secondary Endpoints

1) Individual components of cardiac biomarker MISS score, mean paired change from baseline
   - Ultrasensitive troponin
   - BNP
   - Galectin-3
   - ST2

2) Individual components of the urine renal biomarker KISS score (derived from 10 renal biomarkers), mean paired change from baseline

- Tissue Inhibitor of MetalloProteinases-2 (TIMP-2) x Insulin-like Growth Factor Binding Protein-7 (IGFBP-7), also known as the commercially available NephroCheck® Test
- Neutrophil gelatinase associated lipocalin (NGAL):creatinine (Cr) ratio
- Kidney injury molecule-1 (KIM-1):Cr ratio

- L-Fatty acid binding protein:Cr ratio
- Interleukin-18:Cr ratio
- Alpha glutathione S-transferase (αGST):Cr ratio
- Pi glutathione S-transferase (piGST):Cr ratio
- N-acetyl-β-D-glucosaminidase (NAG):Cr ratio
- Cystatin-C:Cr ratio (uCysC:Cr)
- Albumin:Cr ratio (ACR)

3) Mean paired change in secondary MRI measurements including left ventricular mass index (LVMI) (g/m^2)
4) Mean paired change in Doppler echocardiographic measurements: EF, E/A ratio, tissue Doppler e-prime, and LVMI
5) Left ventricular strain and strain rate curve analysis
6) Mean paired change in eGFR
7) Mean paired change in hemoglobin A1C from baseline to 16 weeks
8) Mean paired change in fasting glucose from baseline to 16 weeks

Future Biomarker and Genetic Testing

The Baylor Scott & White Institute of Metabolic Disease is actively involved in many types of research in both common and rare diseases. Subjects will be asked to give consent to use any leftover blood and urine in this research for future studies of diabetes, heart, and kidney disease.

At each time point that blood and urine samples are taken in this study, there is an opportunity to save some of the fluid for up to 50 years in order to run future tests related to diabetes, heart, and kidney disease. Subjects will be asked to consent to long-term sample storage. The subjects will be asked to give consent to use stored samples to test for genomic biomarkers (mutations) depending on future advancements in laboratory technology. The urine and blood samples collected from subjects in this study may be used to establish a cell line that could be patented and licensed. After 50 years or sooner if the samples are depleted, the remainder of the fluid will be destroyed. Samples will be stored at the Baylor Scott & White Institute of Metabolic Disease.

How Many People Will Take Part In The Study?

This is a single site study that will enroll up to 104 subjects from 2 consecutive cohorts.

Safety Endpoints Harmonized to the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) Trial[28]

1) Death
2) Hospitalization for acute coronary syndrome
3) Hospitalization for heart failure

ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

Serious Adverse Events

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not

result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See below for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See below for reporting pregnancies.)

The following hospitalizations are not considered SAEs in AstraZeneca (AZ) clinical studies:
- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy). The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to the study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a

complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to AZ (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:
AZ Patient Safety and other reports Email
Address:AEMailboxClinicalTrialTCS@astrazeneca.com
SAE Facsimile Number: +01 302 886 8987

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to AZ (or designee) using the same procedure used for transmitting the initial SAE report.
All SAEs should be followed to resolution or stabilization.

Nonserious Adverse Events

A nonserious adverse event is an AE not classified as serious.

Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see within). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).
Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

Laboratory Test Abnormalities

The following laboratory abnormalities should be captured on the nonserious AE CRF Page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have the study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

Pregnancy

A serum pregnancy test will be done in appropriate subjects to exclude pregnancy with the initial study laboratory tests. If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the AZ (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to AZ (or designee) within 24 hours and in accordance with SAE reporting procedures described within.
Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by

pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the AZ (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to AZ (or designee) within 24 hours and in accordance with SAE reporting procedures described within this document. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Overdose

All occurrences of overdose must be reported as SAEs (see within for reporting details). An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see within for reporting details.).

Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see within. for reporting details).

Potential drug induced liver injury is defined as
1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

SAE's will be reported using MedWatch forms and graded using the severity scale published by the National Cancer Institute. The terms are provided as Attachment A and can be reviewed at the following link.
https://wiki.nci.nih.gov/display/VKC/Common+Terminology+Criteria+for+Adverse+Events+FAQ#CommonTerminologyCriteriaforAdverseEventsFAQ-AdverseEventTerms

Data Monitoring Committee

After funding and contract execution, but before the first subject is screening, a data monitoring committee will be formed consisting of five voting members including one statistician. A charter will be drafted governing the committee's activities which will cover the conventional domains of study execution and subject safety.

Proposed Schedule of Events

Study Assessments	Screening		Follow-Up				
	Day -365 to 1[a]	Day 1[a]	4 weeks	16 Weeks[b]	30 Weeks FU Phone Call (+1 week)[g]	38 weeks (±1 week)	4 weeks after final dose ±5 days[g]/ or early withdrawal
Informed consent	X						
Inclusion/exclusion criteria	X						
Demographics	X						
Medical and disease history	X						
Estimated GFR	X	X	X	X		X	
HbA1C(%)	X	X	X	X		X	
Height	X						
12-lead ECG	X					X	
Echocardiogram with Strain Rate		X				X	
Cardiac MRI with gadolinium		X				X	
Serum pregnancy test	X						
Physical exam		X	X	X		X	
Weight		X	X	X		X	X
Vital signs		X	X	X		X	X
Hematology[c]		X		X		X	
Blood chemistry[d]		X	X	X		X	
Liver function[e]		X	X	X		X	
BNP		X		X		X	
Biomarker panel[f]		X[f]		X[f]		X[f]	
Adverse & clinical endpoint events	X	X	X	X	x	X	X[g]
Concomitant medication	X	X	X	X	x	X	X[g]
Randomization[h]		X					
Study drug administration instructions		X	X	X		X	
Study drug compliance[i]			X	X	x	X	

Day 1 is first day of study drug. Therefore all required elements listed for the Screening visit will be required for patients not seen and consented prior to Day 1. All elements of this evaluation must be obtained prior to study drug administration.

[a] May be obtained from medical record and if not present then drawn for study purposes
[b] May be scheduled ± 1 week
[c] Hematology panel: complete blood count (CBC) with differential and platelets
[d] Blood chemistry panel: sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), serum creatinine, glycohemoglobin, cystatin C and glucose
[e] Liver function: serum albumin, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin
[f] Blood and urine biomarker panels used to calculate cardiac MISS and renal KISS scores
[g] May be assessed by telephone. Coordinator to document on progress note
[h] Not applicable to open-label cohort (Cohort B)
[i] To be collected any time after last dose

Statistical Description

Before the last subject has completed the trial, a full statistical analysis plan will be written and agreed to by the investigators. Intent-to-treat principles will be used. The anticipated dropout-rate with incomplete biomarker and or MRI data is 15%. Last observation carried forward will be used to use as many subjects as possible in the evaluable dataset. In addition, both the MISS and KISS scores are robust to missing individual biomarker data and can collapse down to a scale of -1 to +1 for one marker and its change, up to our proposed -10 to +10 for the ten component KISS score. Univariate statistics will be reported in means with standard deviations or counts with proportions as appropriate with comparisons by one-way analysis of variance or Chi-square (Exact) for dichotomous variables. Bivariate statistics will include Pearson's correlation for continuous variables. Those subjects on insulin at baseline will be considered an a priori subgroup for analysis. Multivariate analysis for the secondary aims will include the general linear model for continuous outcomes with forward selection of significant predictor variables as determined from the univariate analysis.

3:1 allocation: The randomization goal from the original, 1:1 randomized trial is approximately 50% complete. As it was a blocked randomization scheme, the number of patients who have received placebo is equal to the number of patients who have received drug. For the remaining 50% of the trial, the design will change from a 1:1 randomization (drug: placebo) to a drug-only assignment with continued blinded assessment of the outcomes. Doing so will yield a drug: placebo ratio of 3:1. We acknowledge that confounding factors may be present in trials, and particularly so for non-randomized designs. Accordingly, we will test for the presence of systematic bias induced via non-randomization prior to analyzing the data under a pooled 3:1 assignment.

To do so, we will examine baseline data of the patients who received drug according to the phase of the trial, randomized vs. nonrandomized. Continuous variables will be presented as mean ± standard deviation, or median [quartile 1, quartile 3], if skewed. Categorical data will be presented as frequency and percentage. Differences between the groups will be assessed via two-sample t tests and Chi-Square tests, or Wilcoxon Rank Sum tests and Fisher's Exact tests, as appropriate. Tests will be assessed assuming a Type I error rate of 5% and a two-sided hypothesis. If statistically significant differences are observed between the randomized and nonrandomized cohorts, further exploration of the significance level under a preserved family wise error rate construct, with a Bonferroni adjustment, will be conducted.

If it is determined that the patients who received drug during the randomized and nonrandomized phases of the trial are sufficiently different, we will perform 2 identical, but separate analyses: randomized drug vs. randomized placebo and nonrandomized drug vs. randomized placebo. The results of these 2 analyses will then be evaluated in a meta-analytic

framework, with a secondary consideration of pooling based on a heterogeneity term. Results will be visualized with a Forest Plot.

If it is determined that the patients who received drug during the randomized and nonrandomized phases of the trial do not differ significantly, we will perform the analysis as described in the original protocol, but will do so under a 3:1 drug: placebo assignment instead of a 1:1.

Sample Size

Using i = 1,…, n recorded biomarkers for a given patient (j), we calculate the Myocardial Injury Summary Score (MISS) and the Kidney Injury Summary Score (KISS) as follows:

$$\text{MISS}_j \text{ or } \text{KISS}_j = \left[\sum_{i=1}^{n} \log_{10}\left(Biomarker_{i,peak}/Biomarker_{i,baseline}\right)\right]/n.$$

Using the $\log_{10}$ transformation on ratios bounded by (0.1, 10) yields a range of possible values of (-1, 1). If no change is observed between the biomarker value from baseline to post-treatment use (i.e. $Biomarker_{i,peak}/Biomarker_{i,baseline} = 1$), then the log of that ratio is 0. Defining the MISS and KISS scores as averages of $\log_{10}$ ratios enables them to be robust to missing biomarker values. For example, suppose 2 of the 10 individual biomarker components of the KISS score are unavailable. Then in the calculation, we adjust $n = 10$ to $n = 8$ and the range of possible KISS scores is still (-1, 1), meaning it is essentially unaffected by the missing biomarkers.

Because the MISS and KISS scores are novel metrics, we have no prior knowledge with which to estimate their standard deviations. Thus, we use the range rule of thumb to yield plausible estimates for the standard deviations. In so doing, we find a conservative estimated standard deviation of 2/6 = 0.33.

1:1 allocation: We will need a sample size of 104 subjects to yield an evaluable dataset of 90 (45 in each arm) in order to have 99% power to detect 20% difference from zero in the MISS score in any one of the treatment arms at p=0.05. With this sample size, there will be >99% power for the KISS score outcome and all continuous MRI and strain rate imaging variables

Originally, the trial was powered under a 1:1 randomization assumption. The trial has now shifted to a 3:1 allocation of drug: placebo (assuming the pooling assumption is met, as discussed previously). Table 1 below provides a range of empirical power to detect a significant treatment*time interaction in a linear mixed model, treating subjects as a random variable, with varied effect size and within-subject correlations, assuming a Type I error of 5%, two-sided alternative hypothesis, 69 participants on drug, and 23 participants on placebo. These results were generated in R via simulation with 100 replications each.

Table 1. Empirical power from linear mixed model simulation under varying effect size and within-subject correlations

Effect Size = Difference of means/standard deviation	Within-subject correlation	Empirical Power
0.61 = .2/.33	0.4	57%
	0.6	77%
	0.8	98%
0.91 = .3/.33	0.4	93%
	0.6	99%
	0.8	100%

Preliminary Publication Plan

This will be the first trial of a specific therapy in Type 4 Cardiorenal Syndrome at risk for DHF, and thus, will be required to file an Investigational New Drug Application (IND) or IND Exemption with the US Food and Drug Administration. Abstracts with primary results will be presented at the Late Breaking Clinical Trials Sessions of the American College of Cardiology, American Heart Association, American Diabetes Association, American Society of Nephrology, or other relevant meetings depending on which outcomes are highlighted. Because of the novel nature of this translational project, publication is expected in a series of manuscripts that will be targeted for widely read journals including the New England Journal of Medicine, Journal of the American Medical Association, Lancet, Annals of Internal Medicine, Circulation, and the Journal of the American College of Cardiology.

Investigator Comments

This trial will be conducted by hospitals that are owned and operated by Baylor Scott & White Health System, the largest health system in Texas. Dr. McCullough will have a clinical presence at the Baylor University Medical Center in Dallas and will be available for oversight of the all aspects of the trial.

Several methods to identify and recruit potential subjects will be used; these methods may include evaluation of patients from physicians' existing clinical practice, or referrals from other

physicians, medical record search, and/or review of available databases, phone screening, and inpatient screening for patients with this condition for example:

Approach 1:

The physician's office visit schedule, which includes patient names, date of birth, and problem list, is reviewed daily for potential candidates based on matching entry criteria. The potential subjects are then screened in greater detail, via the electronic medical record (EMR), based upon complete inclusion/exclusion criteria.

Approach 2:

The OR schedule, nursing charge reports which includes patient names, date of birth, and problem list, is reviewed daily for potential candidates based on matching entry criteria. The potential subjects are then screened in greater detail, via the EMR, based upon complete inclusion/exclusion criteria.

Approach 3:

A physician and/or a member of the clinic treatment team identify a potential patient and refers them to be evaluated by research staff for inclusion/exclusion criteria. The potential subjects are then screened in greater detail, via the EMR, based upon complete inclusion/exclusion criteria.

Contacting a patient identified in Approach 1, 2, or 3

When a patient is identified that might qualify, unless the patient is scheduled to see the physician within the next two weeks in clinic, the Baylor Scott & White Research Institute (BSWRI) staff supervised by the investigators will obtain approval from the physician prior to study start-up to approach any patient who appears to qualify. BSWRI staff will indicate they are calling/approaching for trial consent on behalf of the physician and explain to them that they may qualify for this study.

For patients that are scheduled to see the physician within the next two weeks in clinic the BSWRI staff will alert the physician and request that they talk to the patient at the next visit. Please see Approach 4.

Approach 4

If during any of the above approaches, the BSWRI staff identifies a patient who will be seen in the next two weeks for a regularly scheduled visit, the physician will have the option to discuss the study with his/her patient during that visit.

During a clinic visit with patient still present, the physician will obtain verbal consent from the patient that the research staff may speak to them about the study. If patient is interested, research

staff will begin thorough informed consent process during a scheduled face-to-face meeting with the potential candidate. Only the designated research personnel listed on this application will be exposed to any subject protected health information (PHI) for recruitment purposes.

The imaging visits for echocardiography and MRI will occur at the Center for Advanced Cardiac Care (CACC) at the Baylor Scott & White Heart Hospital in Plano for cohort A and Baylor Scott & White Heart and Vascular Hospital – Dallas for cohort B. The Data Coordinating Center (DCC) will be housed by the Baylor Scott & White Heart and Vascular Institute, which will be under the supervision of Dr. McCullough. This center will be responsible for the electronic case report form development, database construction, analysis, and results reporting. This center will also develop a site monitoring program. A centralized Research Pharmacy will be employed at the Baylor University Medical Center in Dallas. This center will be responsible for the randomization, blinding, drug distribution and pharmacovigilance. A Data Safety Monitoring plan will be developed with adverse and serious adverse events reported to the DCC, sponsor, and FDA when indicated.

There will be two treatment cohorts. The first cohort was a prospective, double-blind, placebo controlled, parallel group, randomized group of BYDUREON™ (Exenatide extended-release) versus placebo. There are approximately 56 patients randomized in this cohort. Randomization to treatment groups of active study drug or matching placebo was performed with a permuted block design with block sizes of 4.
The second cohort will be a prospective, single-arm, open-label trial of BYDUREON™ (Exenatide extended-release) that will comprise the remaining patients. This second cohort is necessitated by a change in availability of the matching placebo.

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