## Clinical Research Protocol

# MINERALOCORTICOID RECEPTOR ANTAGONISM CLINICAL EVALUATION IN ATHEROSCLEROSIS ADD ON (MAGMA ADD-ON)

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# 1 SUMMARY

Patiromer add-on to an MRA in patients with Type 2 diabetes mellitus and CKD will reduce blood pressure and LV mass to a greater extent compared to patients with MRA alone and favorably affect key secondary hemodynamic and inflammatory variables including atherosclerosis progression.

Atherosclerosis is the leading cause of morbidity and mortality in Type II diabetes. A cell type called the monocyte/macrophage is critical to development and complications of atherosclerosis.

This project will evaluate the effectiveness of a medication called Spironolactone in addition to Patiromer in preventing atherosclerosis in Type II diabetes through its effects on cells such as the monocyte.

Spironolactone has been demonstrated to be effective for the treatment of patients after a heart attack and stroke. We will evaluate the impact of Spironolactone in combination with Patiromer in reducing atherosclerosis plaque and additionally evaluate its potential in changing inflammation.

We envision that our strategy of simultaneously probing effect of a drug combined with analysis of mechanisms of action and predictive response will likely provide key information with which to design hard event (heart attack, stroke etc.) based trials.

## 2 BACKGROUND

Hyperkalemia is a condition that frequently occurs in patients with Type 2 Diabetes with chronic kidney disease (CKD). Patients at the highest risk for hyperkalemia are those taking renin-angiotensin-aldosterone system (RAAS) inhibitors with stage 3 or higher CKD. Clinicians frequently either avoid using RAAS inhibitors or use them at lower than recommended doses in these patient populations and as a consequence these patients, who are often the highest risk from a cardiovascular (CV) and renal disease perspective are often not on RAAS antagonists and/or blockers of the mineralocorticoid receptor (MR). Patiromer is an orally administered drug approved for the treatment of hyperkalemia. The active moiety, a nonabsorbed polymer that binds potassium in the gastrointestinal tract, increases fecal excretion of potassium and lowers serum potassium levels. Previous Phase 2 and 3 studies in the CKD population and those with concomitant Diabetes and CKD population have demonstrated the safety of this drug and the ability to introduce RAAS antagonists without fear of precipitating hyperkalemia. Additionally, continued lowering of blood pressure along with reduction in aldosterone levels have been demonstrated. There is substantial interest in preventing CV and renal disease progression in the Type 2 diabetic. Activation of the renin angiotensin aldosterone axis (RAS) and the mineralocorticoid receptor (MR) results in pro-inflammatory effects. Further the phenomenon of aldosterone escape provides a rationale for MR antagonism in addition to an ACEI/ARB agent. Agents that target the RAAS cascade have shown benefit in Type 2 Diabetics although combined RAS blockade such as using ACEI+ARB or ACEI/ARB+Renin inhibtion have met with failure primarily owing to adverse effects such as hypotension and renal failure/hyperkalemia requiring dialysis. It has been speculated that dual RAS blockade or use of ACEI/ARB in conjunction with MRA may potentially be beneficial if one controls hyperkalemia and/or avoid excess hypotension. As a foundation for this current proposal, we have demonstrated an important role for RAAS and MR antagonism in reducing atherosclerosis and inflammation in experimental animal models and limited studies in humans. We are currently testing the efficacy of Spironolactone in reducing atherosclerosis on top of ACEI/ARB in high-risk patients with T2DM with concomitant CKD as part of a Randomized Double-blind controlled clinical trial. Given the fact that as much as 20-40% of a diabetic patient population with CKD may have problems of hyperkalemia on spironolactone, particularly those already on ACEI/ARB therapy, that would preclude their participation in this trial, we would like to propose an open label supplemental arm to where in patients who are ineligible for participation owing to baseline hyperkalemia or hyperkalemia on the dose escalation phase will be eligible to participate in the PRIMARY-Add on trial. The addition of Patiromer will enable introduction of MRA therapy at therapeutic doses and avoidance of hyperkalemia. We thus propose a prospective open label trial with blinded assessment of end-points (PROBE) study which test the relative safety and efficacy of Patiromer on top of Spironolactone in T2DM on LV mass regression and occurrence of hypokalemia (Co-Primary End-points) as well as its effect on 24-hour ABP at 6 weeks, central aortic blood pressure at 6 weeks, atherosclerosis progression at 12 months and measures of monocyte inflammatory potential. If successful, the studies outlined in this proposal will extend the utility of Patiromer in high-risk diabetics at risk for future CV events and provide new information.

## 2.1 Preliminary Studies

**RESEARCH STRATEGY**

Pharmacological studies over > 20 years have defined the importance of the RAAS system in hypertension and heart failure. A number of trials have validated the use of MR antagonists in the management of patients with heart failure (RALES, EMPHASIS) and post myocardial infarction (EPHESUS)(1-4). Recent studies suggest that MR may link metabolic dysregulation with susceptibility to type II diabetes (T2DM) and atherosclerosis(5-12). MR is an ancient member of the 51-member, steroid-thyroid-retinoid receptor family. In response to ligand binding, MR undergoes conformational changes and is translocated to the nucleus where it binds to response elements in promoters, increasing transcription of target genes (13, 14). Despite its importance, the utilization of MR antagonists (MRAs) in clinical practice is abysmally low owing the perception that these agents cause excessive hypokalemia. Patiromer is a nonabsorbed anion polymer that exchanges a calcium-sorbitol counter ion for potassium cations in the GI lumen. Binding of free potassium in the GI tract leads to a decrease in serum potassium levels. Patiromer binds to 8.5 to 8.8 mEq of potassium per gram of polymer at a pH similar to that found in the colon and has a much higher potassium-binding capacity compared with other resins, including polystyrene sulfonate. In a series of Phase 2 and 3 clinical trials in patients with CKD, concomitant diabetes and heart failure, often necessitating concomitant therapies with RAAS blockers, Patiromer was shown to be effective in reducing potassium.(15-19) Recently Patiromer was shown to reduce aldosterone levels in patients receiving RAAS blockers suggesting that this strategy may be effective in lowering aldosterone levels in patients at risk and potentially providing a rationale to use this agent in patients Type 2 DM in conjunction with MR antagonists given the benefits of reducing MR activation articulated below. (Weir et al. Kidney International 2016. In press).

**Cardiovascular Effects of MR Activation**: MR is widely expressed in the cardiovascular system (20-23) and is a major determinant of endothelial function, smooth muscle tone, vascular remodeling, fibrosis and blood pressure (BP)(24-37). *In vitro*, animal, and human data support a role for MR activation in promoting vascular oxidative stress, inflammation, proliferation, migration, vasoconstriction, vascular remodeling and fibrosis (FIGURE. 1)(5, 29, 32, 37-45).

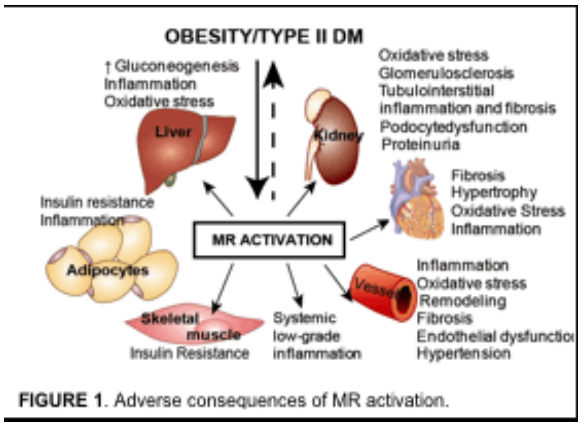



**FIGURE 1**. Adverse consequences of MR activation.

Similarly, MR antagonism is anti-inflammatory and antifibrotic with evidence in humans indicating reversal of endothelial dysfunction, diastolic dysfunction and vascular stiffness (46-50). The visceral adipose renin-angiotensin-aldosterone (RAS) system synthesizes aldo, expresses MR, and predicts IR in both humans and animal models (7, 51, 52). MR expression on macrophages could potentially play a pro-inflammatory role in

tissues such as adipose and vasculature.(53-56) MR blockade/deletion has been shown in both experimental and human studies to ameliorate IR (57-59). MR activation may affect IR through multiple mechanisms that include attenuation of insulin signaling in the heart, vasculature, and skeletal muscle. This may include impairment of expression of insulin receptor and substrate, decreased GLUT4 expression, abnormal phosphorylation of IRS, and activation of multiple stress kinases downstream of insulin receptor/IRS (leading to attenuation of insulin signaling)(60-63). MR activation also promotes hepatic oxidative stress, gluconeogenesis and enhances hyperglycemia (64). Recently, MR activation has been shown to promote lipid storage in brown adipose and inhibit UCP1 expression (65, 66). Consistent with these roles, MR antagonism in humans improves IR (57-59, 67). Relevant to this proposal we have provided evidence for a role for MR in pro-inflammatory macrophage phenotype and reduction in atherosclerosis in animal models. MR activation potentiates classical activation while deletion of MR or antagonism results in AΩ (68).

**CV Trials in Type 2 DM**: T2DM is recognized as a high-risk population for future CV events. However the risk is heterogenous with multiple factors determining risk in the diabetic. These factors include age, duration of diabetes, presence of concomitant risk factors, target organ damage and concomitant therapies including use of statins, RAAS blockers etc. It is widely felt that the presence of concomitant CKD characterizes a patient population at unusually high risk (right hand extreme of FIGURE 2) and this population presents many unique challenges. Importantly, very few therapies have been shown to be beneficial in preventing CV and renal disease progression. Angiotensin receptor blockers and possibly ACEI may reduce progression of renal disease and could potentially prevent occurrence of CV events although recent trials of RAS antagonism have been less conclusive than trials conducted 2 decades ago. There is good mechanistic data implicating continued activation of the RAAS cascade in diabetic CKD.(69) However trials of dual blockade or use of Renin inhibitors on top of ACEI/ARB have not been successful and have noted a higher incidence of mortality, hyperkalemia and hypotension.(69) One pathway that has been suspected to underlie the heightened risk posed by more complete RAAS blockade (defined as treatments that lower activation of the RAAS through the use of 2 or more agents such as an ACEI/ARB-MRA or ACEI/ARB+Renin inhibitor) is hyperkalemia.

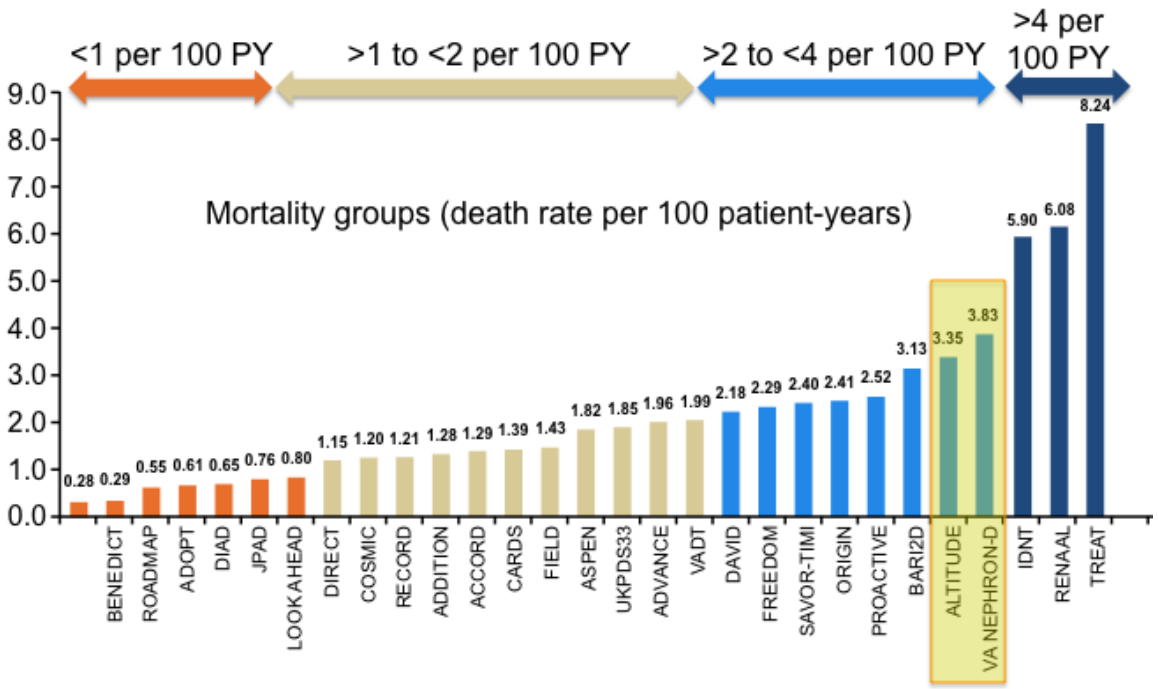



**FIGURE 2.** Mortality rates in Type 2 DM trials. The highlighted trials are for dual RAS blockade that were terminated early owing to excess mortality noted with these studies.

**Hyperkalemia with RAAS Therapy**: High doses of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), are recommended as first line treatment for diabetic nephropathy by various guidelines in light of their consistent cardioprotective role. Similarly there is emerging consensus that MRA on top of ACEI/ARB therapy may be beneficial as aldosterone typically is not completely suppressed. Indeed in HF patients and those with prior MI with LV dysfunction the guidelines do emphasize a Class I indication. However many patients especially diabetics with concomitant CKD are unable to tolerate these drugs particularly when given concomitantly. Effective hyperkalemia management with Patiromer may allow physicians to initiate and/or maintain optimal therapy with RAAS blockers. In the Phase II/III clinical trial experience with Patiromer, its co-administration with RAAS blockade safely and conveniently prevented RAAS-induced hyperkalemia and allowed full dose RAAS blockade to continue. A beneficial effect of the RAAS inhibitor was seen in reducing the level of proteinuria and blood pressure in patients with diabetes and renal disease. In the AMETHYST-DN trial effectively controlled serum potassium levels thereby allowing optimum treatment with RAAS inhibitors for up to one year. Indeed treatment with Patiromer reduced aldosterone levels and together with an MRA may allow complete inhibition of MR activation.

**Patiromer Efficacy in CKD and Dosing Considerations**: In the open-label AMETHYST-DN trial, reductions in serum potassium levels achieved with patiromer, persisted through 52 weeks of treatment.(15) In a continuation phase of the single-blind OPAL-HK trial, 107 patients whose serum potassium levels had fallen below 5.1 mEq/L after 4 weeks of treatment with patiromer were randomized to continue receiving the drug

or switch to placebo. The median increase in serum potassium levels after 8 weeks, the primary endpoint, was significantly greater in patients switched to placebo than in those who continued taking the active drug (0.72 vs 0.00 mEq/L). Patients who continued receiving patiromer were less likely to experience recurrent hyperkalemia than those switched to placebo (15% vs 60%) and more likely to remain on a RAAS inhibitor (94% vs 44%).(17) In another study in 25 patients with hyperkalemia and chronic kidney disease, patiromer 8.4 g twice daily significantly decreased serum potassium levels as early as 7 hours after administration of the first dose (-0.21 mEq/L). After 48 hours, mean levels had dropped by 0.75 mEq/L.(18)The Phase 3 studies confirm that the 16.8 g per day dose is reasonable is patients with mild hyperkalemia (defined as potassium concentration >5.0 to 5.5 mEq/L at baseline or at any time during dose titration] while a starting dose of 16.8 g/d is reasonable in patients with moderate hyperkalemia [potassium concentration >5.5 to <6.0 mEq/L]). The mean reduction in K+ with doses in AMETHYST-DN with this dose was 0.51 (95% CI, 0.38-0.64) mEq/L in the mild hyperkalemia group and 0.87 (95% CI, 0.60-1.14) mEq/L in the moderate hyperkalemia group.

**Risk of Hypokalemia/Hypomagnesemia with Patiromer**: In the PEARL-HF trial, the incidence of hypokalemia was 5% in the 30 g/d fixed dose group compared to 0% of the placebo group (titration of Patiromer was not allowed). The incidence of hypomagnesemia was 24% and 2% in the placebo group. In an open-label of Patiromer (RLY5016-204 trial), the starting dose of RLY5016 was 20 g/d and was titrated at weekly visits according to potassium level. With careful titration and follow-up, only one of 63 patients developed hypokalemia (serum K+<3.5), which was promptly reversed by decreasing the dose of Patiromer. Hypomagnesemia (serum Mg2+< 1.8 mg/dL) occurred in 8/63 (13%) of patients. In AMETHYST-DN, over the 52 week duration of the trial, hypomagnesemia (7.2%) was the most common treatment-related adverse event, with hypokalemia (<3.5 mEq/L) occurring in 5.6% of patients.

## 3 STUDY RATIONALE

There is substantial interest in preventing CV and renal disease progression in the Type 2 diabetic. Activation of the renin angiotensin aldosterone axis (RAS) and the mineralocorticoid receptor (MR) results in pro-inflammatory effects. Further the phenomenon of aldosterone escape provides a rationale for MR antagonism in addition to an ACEI/ARB agent. Agents that target the RAAS cascade have shown benefit in Type 2 Diabetics although combined RAS blockade such as using ACEI+ARB or ACEI/ARB+Renin inhibtion have met with failure primarily owing to adverse effects such as hypotension and renal failure/hyperkalemia requiring dialysis. It has been speculated that dual RAS blockade or use of ACEI/ARB in conjunction with MRA may potentially be beneficial if one controls hyperkalemia and/or avoid excess hypotension. As a foundation for this current proposal, we have demonstrated an important role for RAAS and MR antagonism in reducing atherosclerosis and inflammation in experimental animal models and limited studies in humans. We are currently testing the efficacy of Spironolactone in reducing atherosclerosis on top of ACEI/ARB in high-risk patients with T2DM with concomitant CKD as part of a Randomized Double-blind controlled clinical

trial. Given the fact that as much as 20-40% of a diabetic patient population with CKD may have problems of hyperkalemia on spironolactone, particularly those already on ACEI/ARB therapy, that would preclude their participation in this trial, we would like to propose an open label supplemental arm to where in patients who are ineligible for participation owing to baseline hyperkalemia or hyperkalemia on the dose escalation phase will be eligible to participate in the PRIMARY-Add on trial. The addition of Patiromer will enable introduction of MRA therapy at therapeutic doses and avoidance of hyperkalemia. We thus propose a prospective open label trial with blinded assessment of end-points (PROBE) study which test the relative safety and efficacy of Patiromer on top of Spironolactone in T2DM on LV mass regression and occurrence of hypokalemia (Co-Primary End-points) as well as its effect on 24-hour ABP at 6 weeks, central aortic blood pressure at 6 weeks, atherosclerosis progression at 12 months and measures of monocyte inflammatory potential. If successful, the studies outlined in this proposal will extend the utility of Patiromer in high-risk diabetics at risk for future CV events and provide new information.

## 3.1 Risk / Benefit Assessment

All potential patients will be informed of the potential side effect profile prior to enrollment in the study and full informed consent will be utilized.

### 3.1.1 Risks of an MRI Scan

There are no risks associated with the MRI scan. In our center approximately 10% of patients are genuinely claustrophobic. Side Effects Related to Study Drug

#### 3.1.2 Reproductive Risks

Spironolactone may cause risks to the unborn fetus and or the baby of a nursing mother. Therefore, pregnant women and women who are nursing their babies should not participate in the study. Woman must be either post-menopausal for one year, surgically sterile, or using effective contraception. A pregnancy test will be required at screening for all woman who may become pregnant. A negative test is required for the individual to enroll in the study. Participants who become pregnant will report to the study PI immediately, and stop taking the pills.

Spironolactone can decrease the effectiveness of birth control pills. Women who use oral birth control methods will be excluded from the study. Women of child bearing potential should use another reliable form of contraception. Acceptable methods of birth control include subcutaneous implants, intrauterine devices (IUD), barrier methods, surgical sterility, transdermal birth control path, and abstinence.

#### *3.1.1.1 Common Side Effects*

- Hyperkalemia: We anticipate that approximately 1% of patients may develop serious hyperkalemia that may warrant discontinuation. However this may be considerably higher in patients with GFR of 40-50 ml/minute who will constitute a minority of the patients in the trial.
- Increases in BUN and creatinine

- Hypomagnesemia
- Gynecomastia or breast discomfort. Gynecomastia is a well-described adverse effect of spironolactone and is related to dose and duration of treatment; we anticipate that approximately 10% of patients may develop gynecomastia that may warrant discontinuation. Generally, discontinuation of treatment results in resolution of gynecomastia.

#### *3.1.1.2 Other Side Effects*

- Cardiovascular: Vasculitis
- Central nervous system: Ataxia, confusion, drowsiness, headache, lethargy
- Dermatologic: Erythematous maculopapular rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria
- Endocrine & metabolic: Amenorrhea
- Gastrointestinal: Abdominal cramps, diarrhea, gastritis, gastrointestinal hemorrhage, gastrointestinal ulcer, nausea, constipation, flatulence, vomiting
- Genitourinary: Impotence, irregular menses, postmenopausal bleeding
- Hematologic & oncologic: Agranulocytosis, malignant neoplasm of breast
- Hepatic: Hepatotoxicity
- Hypersensitivity: Anaphylaxis
- Immunologic: DRESS syndrome
- Renal: Increased BUN, renal failure, renal insufficiency
- Miscellaneous: Fever

### 3.1.2 Potential Benefits of the Proposed Research to the Subjects and Others

It is possible that there may be a benefit with Spironolactone in terms of organ protection and patients may see benefits relating to reduction of atherosclerotic plaque including reduction in risk for events such as heart attacks, stroke, renal failure and need for hospitalization. The potential benefits must obviously be contrasted with the risk for renal failure and hyperkalemia. Adding Patiromer to Spironolactone in patients with Type 2 diabetes mellitus and chronic kidney disease may reduce blood pressure and left ventricular mass to a greater extent compared to patients with Spironolactone alone, and favorably affect key secondary hemodynamic and inflammatory variables including atherosclerosis progression.

### 3.1.3 Importance of the Knowledge to be Gained

There is an urgent need for clinical trials aimed at reducing the disproportionate cardiovascular disease burden and mortality in Type II diabetes. The multiple cardiovascular benefits of mineralocorticoid receptor (MR) blockade (using spironolactone or eplerenone) are well recognized in patients *without* Type II diabetes in

the setting of congestive heart failure or myocardial infarction. However, randomized trials of MR Blockade have not been conducted in patients with atherosclerosis. A potential role for MR blockade for slowing atherosclerosis progression as well as influencing cardiovascular outcomes in diabetic patients is only beginning to attract the attention of cardiologists. Patients with atherosclerosis may benefit from MR blockade if, on one end of the spectrum, such intervention is made relatively early in the course of Type II diabetes to slow progression and of atherosclerosis and inflammation or plausibly at the other extreme when patients are already at very high risk patient population for cardiovascular events and mortality. The use of Spironolactone in conjunction with Patiromer in patients with type II diabetes and atherosclerosis has not been well studied. The addition of Patiromer will enable introduction of MRA therapy at therapeutic doses and avoidance of hyperkalemia.

### 3.2 Safety Evaluations

Change in clinical laboratory findings (e.g. BUN, Creatinine, electrolytes).

Incidence of adverse events.

## 4. STUDY OBJECTIVES

### 4.1 Primary Objective

Specific Aim 1: To conduct a prospective open label proof-of-concept clinical trial in 50 patients with Type II diabetes evaluating the effects of MRA + Patiromer on LV mass and plaque regression over 12 months of treatment by MRI. Primary outcome measures will be change in LV mass of patients receiving Patiromer + Spironolactone at the end of 12 months and end-point of safety during this period. An additional co-primary measure will include percent change in atheroma volume (PAV) in the thoracic aorta on Patiromer + Spironolactone at the end of 12 months. Additional secondary measures will include central aortic blooc pressure, 24-hour mean systolic blood pressure and measures of insulin resistance (HOMA-IR) at 12 weeks.

### 4.2 Secondary Objective

Specific Aim 2: To compare monocyte polarization and inflammatory activation (flow cytometry and gene expression) after 6 weeks of Patiromer therapy. Specific Aim 2b: Results from this aim will help provide insights into mechanisms of disease progression and preservation of pathways by Patiromer.

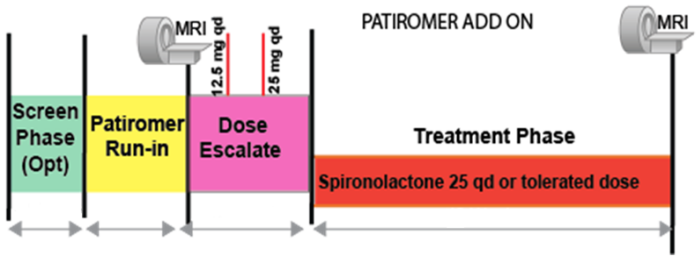
## 5. STUDY DESIGN

**OVERALL STUDY DESIGN AND EXECUTION**

This will be a multicenter trial that will provide a logical extension to a recently funded NIH sponsored trial to assess efficacy of Spironolactone in patients with Type 2 DM and CKD (GFR 20-90ml/m2) compared to placebo (NCT02169089). In this extension study to

NCT02169089, patients with GFR 20-70 ml/m2 who are hyperkalemic at baseline (with or without RAAS therapy) precluding an MRA and/or develop hyperkalemia on an MRA (**FIGURE 3**) will be enrolled and placed on Spironolactone. The primary efficacy variables being LV mass change and in patients treated with Patiromer and MRA. Our hypothesis is that Patiromer use in conjunction with an MRA will result in more effective blood pressure lowering, LV mass regression and plaque regression due to more effective lowering of aldosterone and inflammation. The primary safety variable is development of serious hyperkalemia on treatment in Patiromer+Spironolactone arm. Several secondary variables will be obtained, including monocyte-macrophage inflammatory indices, central aortic blood pressure and 24-hour blood pressure at 6 weeks and arterial compliance.

**Figure 3.**




## 6. CRITERIA FOR EVALUATION

### 6.1 Aim 1A Protocol

Cardiac and aortic MRI images will be obtained at Visit 2 and Visit 8. Patients will be imaged on a 3T 32-channel whole-body MR imaging system (Trio 3.0T, Siemens, Erlangen) with maximum gradient amplitude of 60 mT/m and a slew rate of 400 mT/m/ms. The system's integrated body coil will be used for radiofrequency signal transmission. Signal reception will be accomplished with the use of two flexible 6-element phase array body coil matrix in combination with the spine coil. After acquiring the low resolution, images for localization, each patient will undergo trueFISP cine imaging (8–10 short axis and 3 LV long axis with 20–30 cardiac phases depending on heart rate). Additional details on sequence parameters are provided on the Manual of operations. Following acquisition of cardiac MRI images, fat suppressed 3D turbo-spin echo (TSE) images using, dark blood acquisition protocol, based on SPACE sequence with 1mm3 resolution. MRI parameters are as follows: TR/TE= R-R interval/22ms, field of view FOV=320x272 mm2, slices per slab 56, averages =1.7, bandwidth-BW=781Hz/px, echo spacing=2.9ms, turbo factor= 45, echo train/slice=3.

***Quantitative evaluation:***

**LV mass estimation:** the images from the participating sites will be loaded onto a dedicated workstation (*Leonardo*™, Siemens Medical Solutions, Erlangen, Germany). Using specialized software (A*rgus*™, Siemens Medical Solutions, Erlangen, Germany), the short-axis views of the heart will be automatically sorted into slice positions (rows)

and cardiac phases (columns). End-diastole (ED) and end-systole (ES) will be visually identified as those phases with maximum and minimum area in a midventricular short-axis view of the LV cavity, using the position of the mitral and aortic valve as an aid to identify the phase of the cardiac cycle. The images will be cropped and zoomed to enhance detection of the myocardium-blood pool and myocardium-fat interfaces. Endocardial contours will be traced automatically in each of the short-axis views both in ED and ES. To improve the accuracy of the measurement, subsequent manual correction will be performed. In addition, the epicardial contour will be traced in ED. The papillary muscles will be included within both contours and considered ventricular wall, as this method has proven close agreement with pathologic quantifications of myocardial mass (70-72). The contours will lie on the ventricular "side" of the interface myocardium-blood (72). One of the major sources of variability in the analysis of LV function is the correct determination of the most basal slice of the LV, as this moves during the cardiac cycle with longitudinal shortening of the heart in systole (73). In our experience, the LV base is typically located in one slice position in ED and in the contiguous more apical slice in ES. The determination of the most basal slice of the LV both in ED and ES will be aided by simultaneous display of the slice position overlaying the four-chamber cine image used to prescribe the short-axis slices. An equivalent approach will be used for the most apical segment. The criteria for inclusion of the basal slice will follow standard recommendations (74): a rim of ventricular myocardium has to encircle at least 50% of the blood pool area; if both ventricular and atrial myocardium are clearly seen in the same slice, both ends of the ventricular wall are joined by a straight line and the resulting portion is included in the LV quantification; the LV outflow tract is included up to the level of the aortic valve. The sum of the areas contained inside the endocardial contours in ED and ES in each slice, multiplied by the section thickness (Simpson's method) yields the left ventricular end-diastolic and end-systolic volumes (LVEDV and LVESV respectively) (74, 75). No geometrical assumptions are made and therefore the method can be used in the presence of segmental abnormalities (76). The software automatically adds the interslice gap to the slice thickness. The same approach will be used to calculate LV myocardial volume, defined as the volume between the endocardial and epicardial contours, subsequently multiplied by the specific density of the myocardium (1.05 g/cm3) to obtain LV mass (70). The LV mass will be obtained systematically from ED images (71). Left ventricular stroke volume (LVSV) is calculated as LVEDV-LVESV, and the LVSV times the heart rate will be used to derive the cardiac output (CO). Left ventricular ejection fraction (LVEF) will be quantified using the formula: (LVSV/LVEDV)*100.

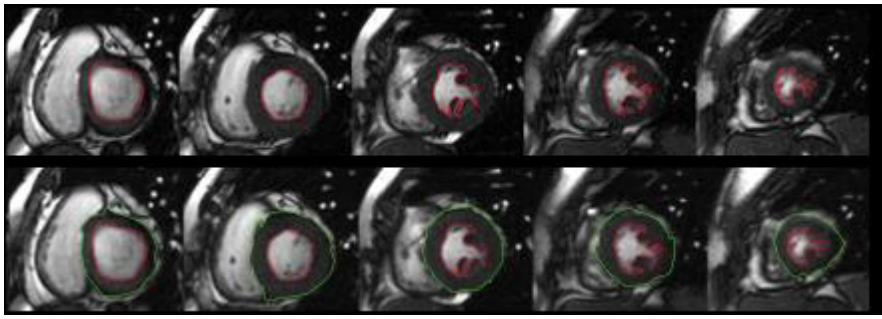


**Figure**. Direct assessment of myocardial mass and volumes with CMRI. This figure shows the ease with which epicardial and endocardial borders can be drawn.

**Plaque Volume Calculation**: For each patient MRI images acquired from baseline and post studies will be co-registered on a workstation (FUSION, Siemens Healthcare, Inc.). Multiplanar images perpendicular to the aorta will be generated from both data sets at the same location and evaluated using a custom designed plaque analysis tool (Terarecon, CA). A dedicated and trained technician will perform manual measurements of lumen cross section area (LCSA) and media-adventia cross section area or MCSA. Vessel wall area measurements will be generated by subtracting the luminal area from outer border of the vessel wall for the images. Total Plaque Area (TPA) at each time point (1-baseline, 2-post-treatment) for each patient will be defined as the sum of the difference between media-adventitia cross section area (MCSA) and the lumen cross section area (LCSA) in each slice. The change in total plaque volume (ΔTPV) and the percentage change (%Δ TPV or PAV) for each of the two groups (Spiro and Placebo) will be calculated as follows:

***Formula 1***: Derivation of total plaque area (*TPA*)
$TPA = \Sigma_{N\ patient}(MCSA - LCSA)$. Using Formula 1 we will obtain $TPA_{base}$(baseline) and $TPA_{post}$(post-treatment) for each patient, where $N_{patient}$ is the number of slices per patient. To account for different number of acquired slices in different patients, the atherosclerotic plaque volume (TPV) for each patient at each time point will be normalized to the median number of slices in that group ($N_{median\text{-}group}$) as shown below in Formula 2.

***Formula 2***: Derivation of total plaque volume (*TPV*)
$TPV = Z \times \frac{N_{median-group}}{N_{patient}} \times TPA$. We will then obtain $TPV_{base}$ (baseline) and $TPV_{post}$(end-of treatment) for each patient; Z=slice thickness. The change in total plaque volume ($\Delta TPV_{group}$) and percentage change in total plaque volume ($\%\Delta TPV_{group}$) in each group (Spiro/placebo) will be calculated as indicated in Formula 3 (A and B).

***Formula 3***: Derivation of absolute change ($\Delta TPV_{group}$) and percent change in atheroma volume (PAV or $\%\Delta TPV_{group}$)

$$\Delta TPV_{group} = \frac{1}{N_{group}} \Sigma_{patients}(TPV_{post} - TPV_{base}) \qquad (A)$$

$$PAV_{group} = \%\Delta TPV_{group} = 100 \times \frac{1}{N_{group}} \Sigma_{patients} \frac{TPV_{post} - TPV_{base}}{TPV_{base}} = 100 \times \frac{\Delta TPV_{group}}{TPV_{base-group}} \qquad (B)$$

where $N_{group}$ is the number of patients in the group**. PAV or % change in total atheroma volume= Primary end-point**

To account for possible different median number of slices $N_{median-group}$ of the two groups, the normalized total plaque volume change in Spiro and placebo will be additionally calculated as: $Normalized\ \Delta TPV_{group} = \Delta TPV_{group} \times \frac{N_{median-group}}{N_{median-oposite-group}}$.

**Secondary End-points**: Patients will undergo 24-hour ABP and Central Aortic Blood pressures using a validated device (Oscar 2™system from SunTech Medical®), measuring BP at 15–minute intervals during the day (07.00 h–22.00 h) and at 30–minute intervals during the night (22.00 h–07.00 h), was used to measure ABPM. Aldosterone and HOMA-IR measurements after overnight fast after resting for 30 minutes after arrival and prior to IV placement and/or MR assessment. Fasting (9 hour) basal insulin sensitivity will be measured by the validated HOMA-IR index. *HOMA-IR* = insulin (μU/mL)x glucose (mmol/L))/22.5] (77). 24-hour ABP will be performed at visit 2 and visit 6.

**6.2 Aim 2 Monocyte and Inflammation Studies**: Peripheral blood mononuclear cells (PBMC) will be isolated via and purified with anti-human CD14 mAb immobilized on magnetic beads using the MACS system (Miltenyi Biotec) and purity confirmed by flow cytometry. Isolated cells will be lysed for RNA purification (see below). A portion of the PBMCs will be frozen at -80°C in RPMI medium with 20% FBS and 10% DMSO (1x107cells/vial) for concurrent future flow analysis. This protocol has been shown to not affect future analysis of surface marker staining (78). We have considerable experience performing flow analysis in batched frozen monocytes to enhance reproducibility. Multicolor flow cytometry analysis will be performed using Anti-human CD14, CD16, CD206, and CD163 antibodies (BD Biosciences). Analysis will initially enumerate the quantity of $CD14^{hi}CD16^{lo}$, $CD14^{hi}CD16^{hi}$ and $CD14^{lo}CD16^{hi}$ monocytes which are similar to what has been described (79). The $CD14^{hi}CD16^{hi}$ and $CD14^{lo}CD16^{hi}$ monocytes are believed to represent inflammatory monocytes in the human. Isolated mRNA will be analyzed for classic inflammatory genes (M1) M2 markers (alternate activation) as well as candidate miRs.

### 6.3 Safety Evaluations

- Change in clinical laboratory findings (e.g. BUN, Creatinine, electrolytes).
- Incidence of adverse events

## 7. SUBJECT SELECTION

### 7.1 Study Population

Subjects with a diagnosis of Type II Diabetes who meet the inclusion and exclusion criteria will be eligible for participation in this study. Labs drawn within 3 months of the screening visit may be used to determine eligibility.

### 7.2 Inclusion Criteria

| |
|---|
| 1. Male or female patients > 45 or > 40 years with known atherosclerotic events (examples include MI, Stroke) and able to provide informed consent (females must be either post-menopausal for one year, surgically sterile, or using effective contraception. Oral contraceptives are disallowed. |
| 2. Patients with type II diabetes with HbA1c ≤ 9.0 on stable anti-glycemic regimen |

| |
|---|
| that may include oral and/or injectable therapy (GLP-1/Insulin etc.). Changes in dose of glycemic regimen is allowed during the course of the trial if felt to be clinically appropriate. |
| 3. GFR <70 and evidence of proteinuria (Urine Albumin/Creatinine Ratio of >30 mg/g or equivalent) in a urine specimen within 12 months OR GFR <60 mg/g regardless of proteinuria |
| 4. Patients must be on ACE and/or ARB therapy with no planned dose adjustments. |
| 5. Serum $K^+ \geq$ 4.6 meq/L at visit 0 (screening). |

### 7.3 Exclusion Criteria

| |
|---|
| 1. Uncontrolled hypertension (SBP>160 and/or DBP>95 mmHg at visit 0 (screening) and SBP >145 mm Hg at visit 2). |
| 2. GFR (MDRD) of <15 at visit 0 (screening) |
| 3. $K^+$ <4.6 meq/L at visit 0 (screening). |
| 4. LDL cholesterol >150 mg/dL |
| 5. Plasma triglycerides > 400 mg/dl |
| 6. Contraindications to MRI (metallic implants, severe claustrophobia). |
| 7. Acute coronary syndrome, Transient ischemic attack, CVA or critical limb ischemia during the last 6 months or coronary/peripheral revascularization within the last 3 months. |
| 8. Evidence of a secondary form of hypertension. |
| 9. Initiation of new therapy with statins, ACEI/ARB, antioxidants, CCBs, diuretics, β blockers. |
| 10. Type I diabetes mellitus |
| 11. Known contraindication, including history of allergy to Spironolactone or Patiromer |
| 12. Any surgical or medical condition which might alter pharmacokinetics of drug (e.g. renal transplant, liver failure, liver transplant) |
| 13. Concurrent potentially life threatening arrhythmia or symptomatic arrhythmia. |
| 14. Significant hyponatremia defined as Na <130 meq/L. |
| 15. History of prior malignancy including leukemia and lymphoma (but not basal cell skin cancer, cured squamous cell cancer and cured prostate cancer). |
| 16. History of any severe, life-threatening disease. |
| 17. Any surgical or medical conditions which place the patient at higher risk derived from his/her participation into the study, or likely to prevent patient from complying with requirements. |
| 18. History of drug abuse within the last 2 years, noncompliance and unwillingness/inability to consent. |
| 19. Pregnant women and nursing mothers |
| 20. Class III or IV Congestive Heart Failure |
| 21. Primary Hyperaldosteronism |

### 7.4 Recruitment Strategy

All patients will be carefully evaluated for study eligibility during screening and will be recruited from clinics at University Hospitals' healthcare systems. The medical records

will be accessed to determine eligibility. PHI will be accessed during the pre-screening portion for medical review. A full waiver is requested. The 2 -week run-in-phase- period will permit assessment of patient compliance as well as determination of baseline sitting blood pressures. Patients must have met all inclusion/exclusion criteria before starting any parts of the study phase. We may call patients who have expressed interest in the study, using an approved phone script. No cold calling will be done. The phone script will be used for patients who would like to be contacted regarding more information about the study after their physician has given them some initial background in person or by letter.

Patients will also be recruited from referrals of the private practice of Tom Tanphaichitr, MD.

### 7.5 Multi-Site Research

MAGMA Add On is a multi-site study that includes NYU Winthrop, University of Maryland, and MetroHealth Systems. NYU Winthrop and the University of Maryland are responsible for their own local IRB while UH will be the IRB of record for MetroHealth System.

In addition to University Hospital CMC recruited patients, UH clinical staff including, DCRU nurses, clinical coordinators, radiology technicians, and PI(s) will also be responsible for assisting Visit 2 & 8 for Metro Health. A research coordinator from Metro Health will be primarily in charge of the coordination of the visit which includes escorting the patient, documentation, and record keeping.

## 8 HEALTH WILL BE PRIMARILY IN CHARGE OF THE COORDINATIOCONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible.

Changes in dose of glycemic regimen is allowed during the course of the trial if felt to be clinically appropriate.

Patients must be on ACE and/or ARB therapy and statin therapy with no planned dose adjustments.

### 8.1 Prohibited Medications and Treatments

The following medications are prohibited during the study:

Oral contraceptives

## 9 STUDY TREATMENTS

### 9.1 Method of Assigning Subjects to Treatment Groups

Up to 50 eligible patients will participate in the study. All study participants will undergo a two week run-in period with Patiromer. Then study medication will be commenced at 12.5 mg Spironolactone and Patiromer 8.4 g/d and escalate to 25 mg Spironolactone over

4 weeks. If needed, to manage $K^+$, Patiromer will increase to 16.8 g/d. Then the treatment phase will commence with tolerated dose of Spironolactone along with Patiromer for 48 weeks.

## 9.2 Blinding

This research protocol is not blinded.

## 9.3 Formulation of Test and Control Products

### 9.3.1 Formulation of Test Product

Spironolactone is an antihypertensive potassium sparing diuretic and Mineralocorticoid (Aldosterone) Receptor Antagonist.

Patiromer (Veltassa) is a potassium binder indicated for the treatment of hyperkalemia.

### 9.3.2 Formulation of Control Product

There is no control product in this research protocol.

### 9.3.3 Dosage

If screening K 4.6-5.2; start Spironolactone "run-in phase" 25 mg qd x 1 week; at 1 week recheck K and creatinine and add Veltassa 8.4 mg qd and continue with the treatment phase
If screening K 5.3-5.5 start Spironolactone 12.5 mg and Veltassa 8.4 mg without a run-in phase and follow the Spironolactone dose escalate phase as in current protocol followed by the treatment phase
If screening K >5.5 start Veltassa "run-in phase" 8.4 mg qd x 2 weeks and Add Spironolactone after 2 weeks 12.5 mg qd with plan to dose escalate to 25 mg qd as per current protocol
The dose may need to be adjusted during the study due to safety lab results (e.g. K+) or if BP <100 mmHg. The study physician will adjust dose as needed.

The active ingredient is patiomer sorbitex calcium, which consists of the active moiety, patiromer, a non-absorbed potassium-binding polymer, and a calcium-sorbitol counterion. Each gram of patiromer is equivalent to a nominal amount of 2 grams of patiromer sorbitex calcium. Therefore, patients will be dosed at 8.4g of patiromer = 16.8g of patiromer sorbitex calcium (one packet) at the start of the study, increasing to 16.8g of patiromer = 33.6g of patiromer sorbitex calcium (two packets) as needed, according to the potassium levels during the study.

## 9.4 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded.

### 9.5 Measures of Treatment Compliance

Subjects will be asked to keep a patient diary noting the day and date they take their study drug and any adverse events. They will be asked to bring their patient diary to each study visit along with all used and unused study drug containers.

## 10 HYPERKALEMIA MANAGEMENT

One of the most significant complications of the study medications is hyperkalemia. This risk is of particular importance in this study population as diabetic patients with chronic kidney disease are at increased risk for selective aldosterone deficiency, predisposing them to the development of hyperkalemia. Mild to moderate hyperkalemia is generally not associated with significant cardiac toxicity, especially when it is chronic (e.g., in dialysis patients) or slowly developing. In contrast, severe (> 6.5 mEq/L) or rapidly developing hyperkalemia is likely to be associated with the development of ECG abnormalities ranging from peaking of the T- wave; to atrial, AV nodal and ventricular conduction delays; and ultimately, with very severe hyperkalemia, to ventricular fibrillation.

Dietary intake of potassium is a major factor in producing hyperkalemia and transient dietary increases in potassium intake can precipitate hyperkalemia in our patients. For example, a single high potassium meal prior to blood draw could result in high potassium at the time of the draw but later on a repeat the potassium may be much lower, as much as 1 mEq/L lower.

Decreased cellular uptake of potassium occurs when insulin is relatively deficient. Even a patient who is not on insulin can have relative insulin deficiency (also known as insulin resistance). Generally decreased cellular uptake of potassium occurs when a patient has ingested a high potassium diet but does not have enough insulin to drive potassium into the cell. This can result in transient hyperkalemia.

Factors that impair renal excretion of potassium and can contribute to hyperkalemia in addition to the study medication include: 1) decreased GFR; 2) drugs including NSAIDS (e.g. ibuprofen), COX-2 inhibitors (e.g. celecoxib) and 3) any process which decreases distal tubular flow rate such as can occur in the setting of volume depletion.

One or all of the above factors can be operative in the same patient. For example, a volume depleted patient can have relative insulin deficiency, a high potassium intake and have taken NSAIDS for pain while ingesting the study medication.

Subjects will be counseled to avoid medications that may increase the risk of hyperkalemia, such as non-prescription non-steroidal anti- inflammatory medications, and potassium-containing salt substitutes. All subjects will be monitored for the development of hyperkalemia at each follow-up visit and an ECG will be obtained for any potassium value > 6.0 mEq/L.

The aggressiveness of treatment of hyperkalemia will depend on the degree of elevation and the presence or absence of ECG findings.

### 10.1 Treatment of hyperkalemia for Potassium > 5.0 meq/L: Dietary potassium

If during follow-up, a subject's potassium level increases to > 5.0 mEq/L, he/she will be prescribed a low potassium diet (0.7-0.8 meq/kg/day to a maximum daily intake of 60

meq/day). An initial step would be to restrict potassium in the diet. Input from a dietician can be helpful.

There is potassium in most foods, but certain foods are especially high in potassium and should be avoided. Some high potassium foods can be eaten after leaching the potassium by soaking. Many salt substitutes are potassium chloride and should be avoided. Fruits and vegetables should be limited to four servings per day. Dairy products should be limited to 1 cup/day.

High Potassium Foods (avoid):

Fruits and juice: apricots, avocado, banana, cantaloupe, honeydew, dried fruit (dates, raisins, prunes, figs), citrus fruits (orange, grapefruit, nectarines)

Vegetables: artichoke, butter beans, dried peas or beans, potatoes (unless leached), sweet potatoes, Swiss chard, winter squash.

Other: chocolate, molasses, nuts, peanuts

Medium potassium foods: Limit to one serving (1/2 cup)/day:

Fruits: blackberries, cherries, peach (1), pear (1), raspberries, strawberries, watermelon (1 cup), plums (2)

Vegetables: broccoli (cooked), carrot, mushroom, peas, corn, cabbage, eggplant, spinach (cooked), pumpkin, tomato, potato (leached), beets

Low potassium foods (note that portion size is 1/2 cup, eating a large amount of a lower potassium food will make it a higher potassium food)

Fruits (including juice): Apple, blueberries, cranberries, grapes, tangerine (1 small)

Vegetables: green beans, wax beans, cucumber, green pepper, lettuce, yellow squash

Leaching vegetables: For potatoes, sweet potatoes, carrots, beets and rutabagas:

Peel and slice vegetables 1/8 inch thick

Rinse

Soak for a minimum of two hours in warm water, using 10 times the amount of water to the amount of vegetables. If soaking longer, change the water every few hours

Rinse under warm water

Cook with five times the amount of water to the amount of vegetable

### 10.2 Treatment of hyperkalemia for Potassium > 5.5 meq/L

In addition to a low potassium diet, if the potassium level increases to >5.5 mEq/L, conservative measures should be instituted.

Possible approaches include:

Increase in diuretics if volume depletion is not a concern. Volume depletion could worsen hyperkalemia

Administration of chronic alkali supplements, such as sodium bicarbonate 1300mg bid if acidosis is present

Liberalization of salt intake (if volume status and uncontrolled blood pressure are not concerns)

Chronic use of low-dose sodium polystyrene sulfonate (15-30 grams 3x/week)

### 10.3 Treatment of hyperkalemia for Potassium > 6.0 meq/L

If the potassium level is > 6.0 mEq/L, the study medication will be held until the level decreases to < 5.5 mEq/L.

Acutely to treat the potassium:

An ECG should be checked. If there are no ECG changes and potassium level is < 6.5, then Kayexalate alone (60 grams) may be sufficient. If there are ECG changes, treatment would include insulin/glucose, beta-agonists and possibly calcium and bicarbonate. If there are ECG changes or if the potassium level is > 6.5 meq/L, the patient should be treated in the emergency room. If there are ECG changes, the patient should be placed on a cardiac monitor.

Reinstitution of Study Medication
If the potassium level was > 6.5, then the study medication will be permanently discontinued and the patient will be removed from the trial. If this is the second episode where potassium > 6.0, then the study medication will be permanently discontinued and the patient will be removed from the trial.
Recheck potassium level 7- 14 days after discontinuation. If K+ is > 5.5 mEq/L, do not restart study medications. Repeat potassium again in 7-14 days. If K+ is ≤ 5.5 mEq/L, the study medication will be reinstituted at 50% of prior dose.

If the study medication was restarted, check potassium level again in two weeks, if K+ is:

- o > 6.0: stop study the study medication permanently
- o 5.5-6.0: treat K+, maintain current dose of the study medication
- o < 5.5: mEq/L and patient is on at least 12.5 mg spironolactone, increase spironolactone to 25mg daily.

## 11 STUDY PROCEDURES AND GUIDELINES

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject. If appropriate, assent must also be obtained prior to conducting any study-related activities. Study visits will be conducted on the scheduled day or within +/- 2 days for weekly study visits and +/- 7 days for monthly visits.

## 11.1 Schedule of Events

### 11.1.1 Main Study Phase

| TABLE 4 | SCREEN | | RUN-IN PHASE | | DOSE ESCALATE | | | | TREATMENT PHASE | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **MONTH*** | **M1** | | **M1** | | **M2** | **M2** | **M 2** | | **M 3** | **M 5** | **M 7** | **M 9** | **M 11** | **M 12** | **M13** |
| **WEEK** | W 1 | W2 | W3 | W 4 | W5 | W6 | W8 | W9 | W11 | W17 | W25 | W33 | W41 | W45 | W53 |
| **VISIT NUMBER** | **0** | | **1** | | **2** | **3** | **4** | **5** | **6** | **TF1** | **7** | **TF2** | **TF3** | **TF4** | **8** |
| Screening Labs (Renal function panel, Lipid panel, HbA1C, Urine sample Alb/Creat) | X | | | | | | | | | | | | | | |
| Safety Labs (Renal function panel) Mag level* | | | | | X* | X | X | Optional | X* | | X | | | | X* |
| History & Targeted Assessment | | | X | | | | | | | | X | | | | X |
| EKG | | | X | | | | | | | | | | | | |
| Vital Signs or 24-hour BP SphygoCor cuff * (includes central aortic BP)) | X | | X | | X* | | X | | X* | | X | | | | X |
| Phone Call | | | | | | | | | | X | | X | X | X | |
| MRI | | | | | X | | | | | | | | | | X |
| Research Labs/Monocyte Studies, (including PIP, PIINP, CITP and chemokines CCL2, CX3, CL1, and CCL5) | | | | | X | | | | X | | | | | | X |
| Insulin/Glucose (HOMA-IR) | | | | | X | | | | | | | | | | X |
| HbA1C | | | | | X | | | | | | X | | | | X |
| Plasma Renin/Aldosterone | | | | | X | | | | | | | | | | X |
| Medication Log | | | X | | | | X | | X | X | X | X | X | X | X |
| Pill counts | | | | | X | | | | X | | X | | | | X |
| Dietary survey/instructions | | | X | | | | | | | | | | | | X |
| Urine sample (Albumin/Creat) | | | X | | X | | | | X | | X | | | | X |
| Spot Urine Na/K/Creat | | | | | X | | | | | | | | | | |
| Interim Event log | | | | | X | | X | | X | X | X | X | X | X | X |
| Questionnaire & Instructions | | | X | | | | | | | | | | | | |

A complete medical history and physical exam will be performed at baseline and will include a 12-lead electrocardiogram (EKG), cardiovascular risk factor assessment, intercurrent CV events, 7-day physical activity recall, active/passive smoking questionnaires and dietary recall questionnaire. Sitting systolic blood pressure, pulse rate, body weight, interim event logs, pill counts, medication logs will be recorded at most clinic visits. Central aortic blood pressure and pulse wave velocity will be obtained during

visit 2 (base), 6 (mid-point) and 8 (exit) while 24-hour BP will be measured at Visit 2 and 6.

Dietary Na+ consumption: Since Na intake is an important determinant of MR responsiveness we will ensure that all patients receive dietary survey/instructions (Visit 0) on maintaining a personalized diabetic diet that is stable and is medium to low in sodium (<4 g). We will obtain Na, K and Creatinine levels (Visit 1) to assess Na intake. The kawasaki formula will be used to estimate 24 hour urine.

### 11.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

### 11.1.3 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study.

## 11.2 Clinical Laboratory Measurements

Urinary Na levels, albumin, and creatinine

Serum levels of carboxyl-terminal peptide of procollagen type I (PIP), carboxyl-terminal telopeptide of collagen type I (CITP), and amino-terminal peptide of procollagen type III (PIIINP) and chemokines

Safety labs (BUN, creatinine, electrolytes), HOMA-IR, Hem A1C and Plasma Renin Aldosterone, magnesium

## 11.3 Urgent Study Alerts

An Investigator should be notified immediately if any of the following are noted at study visits:

Blood Pressure Immediate Alert Values:

- Systolic Blood Pressure < 80
- Systolic Blood Pressure >180
- Diastolic Blood Pressure >110

Acute Distress: (signs or symptoms constituting an emergency):

- Chest Pain
- Severe Respiratory Distress
- Acute Neurological Symptoms

Urgent Lab Values:

- Potassium ≤ 3.0 mEq/L
- Potassium ≥ 6.0 mEq/L
- Glucose < 50 mg/dL

- Glucose >350 mg/dL
- Creatinine doubling from last value

**Coronavirus Outbreak (COVID-19) Management Plan under Public Health Mandates**

The following guidelines were developed under polices set forth by UH Cleveland Medical Center, the University of Maryland, NYU Winthrop, and MetroHealth Systems.

**Recruitment and Enrollment**

The new public health mandates concerning the COVID-19 have led to the decision to permanently close enrollment. At the time COVID-19 policies were implemented, University of Maryland, NYU Winthrop, and MetroHealth Systems had not enrolled any patients. Study procedures for the remaining UH participants will revert to the original procedures described in Section 11 "Procedures and Guidelines" once the mandates are lifted.

**Active Participants and Follow up Visits**

At University Hospitals, all active participants fell into the "treatment phase" of the study procedures timeline of events (See 11.1.2 Main Study Phase).

TREATMENT-PHASE
In order to simultaneously reduce transmission of the virus while maintaining the management of participant's follow up care to the best extent possible, pertinent study activities (i.e. safety labs & vital signs) will be attempted in conjunction with any provider scheduled clinical encounter deemed essential for clinical care. If this is not possible, patients will be given an additional prescription until the essential study activities can be performed safely (length of prescription may vary based on patients' recent bloodwork and BP/HR, policies, and investigator's medical judgment).

**Additional important details**

Remote study visits are not appropriate for this study.

Participants will be compensated for their participation at the same amount specified in the original consent.

All enrolled participants will be notified by phone call of these protocol changes enacted during the period of public health mandates.

# 12 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

## 12.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF.

### AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) in Table 1 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. If the experience is not covered in the CTCAE, the guidelines shown in Table 2 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious. K+ >6.0 will be considered an adverse event. K+<6.0 will be considered an expected side effect of the medication. As previously described, all K+>5.0 will be treated according to the hyperkalemia protocol.

**Table 1. National Cancer Institute's Common Terminology Criteria for Adverse Events**

| Severity (Toxicity Grade) | Description |
|---|---|
| Grade 1, Mild | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| Grade 2, Moderate | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*. |
| Grade 3, Severe | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**. |
| Grade 4, Life-threatening | Life-threatening consequences; urgent intervention indicated. |
| Grade 5, Death | Death related to AE. |

**Table 2. AE Severity Grading**

| Severity (Toxicity Grade) | Description |
|---|---|
| Mild (1) | Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well. |
| Moderate (2) | Mild to moderate limitation in activity, no or minimal medical intervention/therapy required. |
| Severe (3) | Marked limitation in activity, medical intervention/therapy required, hospitalizations possible. |
| Life-threatening (4) | The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe. |

**AE Relationship to Study Drug**

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 3.

**Table 3. AE Relationship to Study Drug**

| Relationship to Drug | Comment |
|---|---|
| Definitely | Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis. |
| Probably | An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions. |
| Possibly | An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors. |
| Unrelated | An event that can be determined with certainty to have no relationship to the study drug. |

### 12.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

#### 12.2.1 Serious Adverse Experience Reporting

Adverse events will be documented per the University Hospitals Cleveland Medical Center, Human Research Protections guidelines, reported to the IRB, DSMB and the sponsor. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

### 12.3 Medical Monitoring

Dr. Matthew Weir and/or Dr. Jeffrey Fink should be contacted directly to report medical concerns or questions regarding safety.

## 13 DISCONTINUATION OF SUBJECTS

### 13.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

Subject withdrawal of consent (or assent)

Subject is not compliant with study procedures

Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment

Protocol violation requiring discontinuation of study treatment

Lost to follow-up

Sponsor request for early termination of study

Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

## 14 DATA SAFETY MONITORING

A Data Safety Monitoring Board (DSMB) will be established to review data relating to safety and efficacy, to conduct and review interim analyses, and to ensure the continued scientific validity and merit of the study. Reviews will be conducted by the DSMB every 3 months for the purpose of monitoring study conduct and assessing patient safety.

## 15 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

General Statistical Considerations: All the tests are two-sided. We use log transformations for most continuous measures, and arc-sin square root transformations for percentages, both of which have excellent variance stabilizing properties for pooling variance.

## 16 DATA COLLECTION, RETENTION AND MONITORING

### 16.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents but will be identified by a subject number.

*For eCRFs:* If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. *For paper CRFs:* If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

### 16.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

### 16.3 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

### 16.4 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

### 16.5 Subject Confidentiality

In order to maintain subject confidentiality, only a subject number will identify all study subjects on CRFs and other documentation submitted to the Sponsor.

## 17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

## 17.1 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Subjects will be given ample opportunity to inquire about details of the study. If a subject is unable to sign the informed consent form and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

## 17.2 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement with the study Sponsor. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

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