STATISTICAL PLAN

Official title: **MR Antagonist – Eplerenone vs Amolidipine and STRIATIN**

Document number: **NCT03683069**

Date: **12/14/2024**

Statistical Plan and Power Calculations

After screening, 105 subjects will be randomized to amlodipine or eplerenone, using random block sizes in this double-blind study, with at least 45 on each arm expected to have complete data for analysis as previously described. For the **first** independent approach, subjects will be on a liberal salt diet and come to the clinic between 8-9 AM after fasting overnight before randomization and at the end of the trial. We will measure their BP using a 24-hour ambulatory BP monitoring system at each point. From previous studies in general hypertensive populations, our initial and final doses of eplerenone vs amlodipine have produced similar 24-hr and daytime ambulatory systolic BP reductions (delta final doses 12-14 mm Hg). However, we anticipate that in hypertensive Striatin single SNP (rs2540923) or diplotype (rs888083/rs6744560**)** risk allele carriers, the mean change in daytime automated systolic BP from baseline to end of study treated with eplerenone will be greater, while with amlodipine it will be less, because of the specific mechanism (increased ALDO) causing the HTN. We assume the relative delta systolic BP will be ~16 in response to eplerenone and ~10 in response to amlodipine. The within-group standard deviation for the change in automated mean daytime systolic BP is expected to be 8-10 mmHg as previously reported. As shown in **Table 1**, with a 0.05 significance level, we will have >80% power with 45 in each group, and sufficient power for more conservative effect sizes as well.

Table 1: Scenarios providing sufficient power and a 5% 2-sided alpha

Baseline BP minus BP end of study (mmHg)		Within-group standard deviation of the changes (mmHg)	Power
Amlodipine (n=45)	eplerenone (n=45)		
9.0	15.0	10.0	0.81.
9.0	16.0	10.0	0.91
9.0	17.0	10.0	0.97
10.0	15.0	9.0	0.75
10.0	16.0	10.0	0.81
11.0	16.0	9.0	0.75
11.0	17.0	9	0.89

For this analysis, we will use the mean daytime ambulatory systolic BP as our dependent variable adjusted for sex, race, body mass index, and age.

For the **second** independent approach, we will compare the groups regarding the maximum dose needed to achieve goal BP (≤140/90 mmHg) determined by the home BP averaged for the last two days of the liberal salt diet at the end of each month as previously described[58,61-68]. For the anticipated effect size, we used the rank of the drug dose to equate eplerenone and amlodipine dosing, with rankings of 1, 2, and 3 for the ordered maximum dose for each drug, and a ranking of four for the failure to reach BP goal by the end of the study. The anticipated percentage of subjects in each group with each ranking is shown in **Table 2.** Power to compare the arms will be >90%. Data will be inspected and plotted to check distributional assumptions, e.g., 24-hour urine Na+ excretion >160 mEq on the liberal salt diet and <30 mEq on the restricted salt diet, and veracity of outliers, if any.

Table 2: Anticipated proportions of subjects reaching goal BP at each successive ranked dose

	Maximum dose rank			
	1	2	3	4
Amlodipine (n=45)	0.10	0.30	0.35	0.25
Eplerenone (n=45)	0.30	0.40	0.20	0.10

The primary analytical approach will be a Kaplan-Meier survival analysis with Cox regression. Thus, this ordinal logistic regression or “survival” curve analyses will be used, predicting the ordered maximum dose category, assuming a proportional odds model. The odds ratio and 95% confidence interval for eplerenone relative to amlodipine will be reported, representing the relative cumulative odds of needing a higher (or lower) maximum dose to achieve goal BP. Body mass index, sex, race, and age will be potential covariates.

Secondary analysis will be the same as used above in our primary analyses except performed for each sex separately and only in response to eplerenone. However, it is unlikely that we will have sufficient power to achieve a 0.025 significance level, but a positive trend may warrant the performance of a larger, focused future clinical trial.

Exploratory analysis will include the difference in systolic home BP calculated at baseline and at the end of the first dose for each subject to provide an indication of BP sensitivity to each drug. Effect sizes will be reported to improve the design of a future confirmatory study. In addition, we will analyze with adjustments (separately in each sex): 24-hr ambulatory mean systolic SSBP; 24-hr ambulatory mean systolic BP on the liberal Na+ diet; 24-hr mean diastolic BP on the liberal Na+ diet; serum and urine ALDO (also adjusted for serum K+ and cortisol); and ALDO/PRA ratio.