SECTION 5. BASELINE

5.0.1 General Principles of Baseline

The Screening and Baseline periods is expected to last about two months. Before entering Baseline, participants will be screened to ensure that they meet the inclusion criteria and that none of the exclusion criteria are present. Some of these will require confirmation by laboratory tests (e.g., SV2 serum glucose must be less than or equal to 200; SV2 WBC must be greater than equal to 2500). During the baseline period, new participants' blood pressures will be documented to be in the qualifying range (DBP $\geq$ 95 mmHg). Those on antihypertensives at baseline must show this once. This may require reducing or discontinuing antihypertensive agents they are currently receiving (back titration). Those not on antihypertensives at baseline must show this twice. Blood pressures will then be controlled toward a MAP $\leq$ 107 mmHg either by using agents that the participant is currently receiving or by prescribing a regimen that excludes the three initial randomized drug classes (BBs, CCBs, or CEIs), if possible. If participants are currently receiving any initial randomized drug class, all efforts will be made to reduce or discontinue these agents, assuming satisfactory control of blood pressure can be achieved and maintained with other agents.

During Baseline, GFRs by iothalamate clearance will be obtained on two occasions separated by at least one week. Participants will qualify for the study based on the first baseline GFR (20-65 ml/min/1.73m^2). Other procedures done in the screening and Baseline period include a medical history, a physical examination, laboratory tests including a 24-hour urine, biochemical profiles (SMA-18), documentation of patient symptoms, and quality of life assessment. Compliance with visit schedules, procedures, and the medication regimen will be carefully documented. Additional visits may be required when hypertension is being documented or blood pressure control is being established. The schedule of visits that follow are the visits at which data will be collected and transmitted to the Data Coordinating Center. Every effort should be made to promote adherence to this schedule. Following are Baseline visits and procedures.

Visit Period	**Visit Designation**
Screening	Screening Visit 1 (SV1)
	Screening Visit 2 (SV2)
Baseline	Back titration 1-99 visits (BT1-BT99)
	GFR Visit 1 (G1)
	GFR Visit 2 (G2)
Consent	Consent Visit*
Randomization	

* = If consent for follow-up is not obtained at G2

Suggested guidelines for Intervals Between Screening and Baseline Visits are indicated below:

Interval	**Target Suggested Range**
SV1-SV2 (if SV1 is done)	1 week 2 to 21 days
SV2-G1	1 week 1 to 3 weeks
G1-G2	1 week 1 to 3 weeks
G2-Randomization	1 week 0 to 10 days

The total length of the Screening and Baseline periods could be as short as 3 weeks. It is desirable for the G1 eligibility GFR to be as close as is feasible to the time of randomization. The interval between SV2 and G2 must be no more than 24 weeks. Also, that time from G2 to Randomization must be no more than 8 weeks.

Follow-up visits during the first six months post randomization will be scheduled one month apart, with a window of ±15 days, starting with FV0-0 held as soon as possible after randomization.

5.0.2 Glomerular Filtration Rate

During Baseline, GFR will be measured on two occasions. The first measurement, G1, will be performed after screening and after the participant has been shown to meet blood pressure inclusion criteria. This measurement will determine GFR eligibility for randomization. Therefore, it must be within the range of 20-65 ml/min/1.73m^2 in order for the participant to continue in Baseline. The second GFR, G2, will be measured one week or more following the first GFR. The purposes of the second study are: 1) to provide information on the variability of GFR in the recruited population; and 2) to average with initial GFR, providing a reference point to compare to post randomization GFR's. The clinical center will be blinded to the absolute GFR values at baseline and during follow-up throughout the study.

The consent for randomization or sincere discussion regarding randomization should be held no sooner than the G2 visits to guarantee that the patient has experienced at least one GFR before consenting to GFR's for the duration of the study.

5.0.3 Laboratory Tests from Screening through Randomization

Laboratory tests will include both blood and urine analyses. Analyses will be done locally for CBC, HCG, and urinalysis; and centrally for SMA-18, lipid profile and 24-hour urine values. The buffy coat sample will be stored centrally but not analyzed. Following is information about when and where the required tests should be done.

5.0.3.1 Baseline Laboratory Test Schedule

Blood Tests (SMA-18, CBC)	Screening Visit 2 and G1 Visit
Lipid Profile (fasting)	G1
24-Hour Urine	Once at Baseline, at Screening Visit 2 or G1 Visit
Creatinine Clearance	G1
Urinalysis	Screening Visit 2
GFR Samples	GFR Visits 1 and 2
Buffy Coat (held)	G1
HCG (females of child bearing potential only)	G1 and G2 Visits

5.0.3.2 Baseline 24-Hour Urine Collections

Participants collect a 24-hour urine either at SV2 or G1 during Baseline. The 24-hour urine collected during Baseline should be labelled as B1-0. Participants will be given urine collection equipment and instructions for collection prior to each collection. Participants will be queried about the completeness and accuracy of each urine collection. Urine should not be collected during a short term illness.

24-Hour Urine (Urine analysis is done centrally)
- Total Volume (measured locally)
- U. Protein
- U. Urea Nitrogen
- U. Creatinine
- U. Sodium
- U. Potassium

5.0.3.3 Baseline Blood Tests

Serum chemistries will be analyzed centrally. Whole blood measurers will be done locally. Certain serum tests may also be done locally for patient care and patient safety reasons. Local analysis can provide a quick turn around, when results are needed rapidly.

SMA-18: Sodium
Potassium
Chloride
Bicarbonate
Urea Nitrogen
Glucose
Creatinine
Total Protein
Albumin
Asparate transaminase (AST)
LDH
Alkaline Phosphatase
Total Bilirubin
Calcium
Phosphorus
Uric Acid
Magnesium
GGT

CBC: WBC
RBC
Hemoglobin
Hematocrit

GFR samples will be processed at the Central GFR Lab.

HCG will be done locally on females of child bearing potential prior to GFR's.

The Central Biochemistry Laboratory will not accept repeat specimens for measurement unless a sample is hemolyzed during Baseline or an error in shipping or procedure has occurred.

5.0.3.4 Electrocardiogram

An electrocardiogram will be done at Screening Visit 2, then every two years thereafter at F24 and F48.

5.0.4 Screening Medication Status

During the screening visits, many of the participants may be taking a variety of medications including antihypertensive agents as well as drugs for other indications. During the screening visits, the Clinical Center study team will:

1) review the indications for all prescribed medication;
2)ensure that the participants are not receiving medication that would result in an exclusion;

3)ensure that there are no contraindications to discontinuing any of the randomized drugs that the participant is currently receiving (e.g., BBs for angina, CEIs for congestive heart failure, etc.)

4)screen for any condition that precludes the participant from being randomized to any of the study drugs.

Any medication that does not result in the exclusion of the participant may be continued as necessary during the study (e.g. for thyroid replacement). However, the participant must be able to withhold NSAIDs (for 5 days) and drugs that interfere with creatinine secretion (for 48 hours) prior to GFR measurement.

5.0.5 History and Physical Examination

A full history and physical examination will be performed during the SV2 using Form 4 and Form 12. The physical examination will include evaluation of MAP, vital signs, height, weight, general appearance, funduscopic examination and grading of hypertensive retinal changes, chest, heart, and extremities (including pulses and bruits).

At all other Screening and Baseline visits, a limited interval history and physical examination will be performed if there is a change in reported symptoms. It will consist of weight, vital signs, including MAP determined by an average of the last 2 of 3 measurements obtained in the sitting position with the random-zero sphygmomanometer; heart and lung examination; and a check for peripheral edema.

5.0.6 Blood Pressure Measurement

Blood pressure will be measured by trained and certified personnel at each visit using the techniques and procedures listed in Section 6. Hawksley random-zero sphygmomanometers (MKII) will be used at each clinical center. Three consecutive seated readings will be recorded with the mean of the last two readings documented as the clinic visit measurement.

5.0.7 Participant Questionnaires

Any symptoms of hypotension and any new symptoms volunteered by participants since the last visit will be recorded at each visit. The check list on Form 11 will be used to record the responses. Reasons for missed visits will also be documented on Form 11.

Answers to questions related to compliance (such as lack of adherence to medication regimen) will be documented on Form 16.

Information regarding participants' quality of life will be elicited using the SF36 (Form 80) at baseline and annually.

5.0.8 Treatment of Hypertension during Baseline Period

The main goal of the treatment of hypertension during the baseline period is to improve arterial pressure MAP toward normal (i.e., < 107 mmHg). In addition, agents belonging to the classes of the randomized drugs should be discontinued during this period if blood pressure control can be adequately maintained without their use. Adjustments in antihypertensive agents during screening will be dependent on two factors, namely 1) the medication status of participants at their first visit, and 2) the level of blood pressure.

5.0.8.1 Participants Not On Antihypertensive Therapy

For participants who are not receiving antihypertensive drug therapy or not taking antihypertensive medication sporadically (none within the week preceding the first visit), blood pressure will be measured off drug therapy at both screening visits (SV-1 and SV-2). Participants will be considered BP eligible if their average diastolic BP is greater than or equal to 95 mmHg on two consecutive visits. Participants with JNC Stage IV hypertension (SBP $\geq$ 210 or DBP $\geq$ 120) at SV-1 will be considered to have met the entry blood pressure criteria after only one visit and will be eligible for the initiation of drug therapy during Baseline. The purpose will be to improve BP toward a normal (i.e., a mean arterial pressure of $\leq$ 107 mmHg).

The AASK Study therapy consists of a regimen that includes the randomized drugs, diuretics, alpha blocker, central agonist and vasodilator therapies, sequentially added as needed. The medications will be provided free-of-charge to eligible and interested participants. (The clonidine patch cannot be provided free-of-charge because of its expense.) Only the blinded randomized medications will be provided centrally by the Drug Distribution Center.

5.0.8.2 Participants Already on Antihypertensive Therapy

At SV-1, participants taking antihypertensive medications will have their BP measured on current therapy.

A) Those with a diastolic BP $\geq$ 95 mmHg on their current medications meet BP eligibility. Antihypertensive agents will then be increased or added in order to improve mean arterial pressure towards normal (i.e., $\leq$ 107 mmHg). During the Baseline, whenever possible, attempts will be made to decrease and discontinue any of the initial randomized drugs that the participants are currently receiving. Agents other than BBs, CCBs, and CEIs should be used to control blood pressure. Thus, the latter agents may be continued to maintain blood pressure control, if deemed necessary by the investigator. To enhance BP control, participants will have the option, when possible, of either receiving antihypertensive therapy free-of-charge or continuing/augmenting their own therapy at their own cost but under the supervision of clinic center staff.

B) Those participants with well-controlled BP on treatment at the first visit will have medications back titrated/stopped in order to confirm hypertension. CEI, CCB or BB will be preferentially stopped. Once hypertension is confirmed, a regimen excluding BB, CCB or CEI will be implemented, if possible, in order to improve mean arterial pressure toward normal (i.e., $\leq$ 107 mmHg).

5.0.9 Randomization

At randomization, the participants will be assigned to a blood pressure control group. Each patient will receive a pair of bottles including either BB, CCB, or CEI in one and placebo in the other. All beta-blockers, calcium channel blockers, and angiotensin converting enzyme inhibitors must be discontinued at least 24-hour prior to the first post randomization visit (FV0-0). Reduction of prior therapy dosages may accompany concomitant increases of the randomized agent. The investigators should also use level 1-4 agents as necessary to reach the blood pressure goal.

5.0.10 Assessment of Compliance to Study Protocol

Participants will be considered compliant to study protocol and eligible for randomization if they:

1. Complete all of the following: Screening Visits 1 and 2 and two GFR visits. (Patients judged likely not to be able to follow the visit schedule are excluded.)
2. Complete required Screening and GFR visits in less than 24 weeks so the patient can be randomized within 24 weeks.
3. Agree to have blood drawn at the screening visits, and results of the blood work show no exclusions.
4. Take recommended antihypertensive medication per protocol, in the judgement of the study team. (Patients judged likely not to be able to adhere to medications are excluded.)
5. Agree to participate in study by signing the follow-up consent form or providing follow-up consent during a sincere discussion held at the G2 or Consent visit.

5.0.11 Additional Assessments and Exclusions during the Baseline Period

Participants will not be considered for randomization if any one of the following conditions exist:

1. Suspected poor or doubtful likelihood of compliance to randomized protocol and/or randomized drug regimen on the basis of baseline experience.
2. If during the baseline period the participant develops any of the exclusion criteria that would have prevented entry to the baseline period.

5.1 Back Titration Visits (BT-1, BT-2, BT-3, etc.)

At this time, antihypertension medications will be withdrawn if necessary until the blood pressure

increases to a qualifying range. At each BT Visit, measurement of blood pressure (Form 10) and a limited physical examination (Protocol Visit Form 11) will be completed.

5.2 GFR Measurements (G1 and G2)

GFRs will be done by both ^{125}I-iothalamate and a creatinine clearance will be determined. The time between GFR 1 and GFR 2 is a minimum of 1 week, and a maximum of 3 weeks (these are recommended timelines). If the participant is a menstruating female, a quantitative serum pregnancy test must be obtained within 72 hours of the scheduled GFR measurement by ^{125}I-iothalamate. **A participant who does not have both Baseline GFR's by ^{125}I-iothalamate and a 24-hour urine for creatinine/protein ratio and creatinine clearance, cannot be randomized** (see Protocol). At each GFR visit the GFR Technician or Study Coordinator should complete the GFR Procedures Form #24.

5.3 Unblinding of a GFR Result

A patient is no longer eligible to be re-enrolled into baseline if their GFR value is provided. A Baseline GFR value will be revealed by DCC staff only if the G-1 GFR is a value that was reported as 'Too Low' in the Report 55 (Should we do a 2nd GFR?). The following steps should be followed:

1. The Clinical Center contacts DCC personnel and asks that a given patients G-1 GFR value be revealed.
2. The DCC runs the Report 55 and confirms that the G-1 GFR falls in the range of 'Too low'.
3. The DCC accesses the AASK database and updates field that indicates a patient is never eligible to be re-enrolled into the AASK Study.

5.4 Limited Physical Examination

A limited physical examination will be performed at each Baseline Visit. This will include an examination of the heart, lungs, extremities, weight and vital signs. The Protocol Visit Form 11 will be completed on each visit during Baseline, as well as the blood pressure Form 10. Hawksley random-zero sphygmomanometers will be used at each clinical center. Three consecutive seated readings will be recorded with the average of the last two readings documented as the clinic visit measurement.

5.5 Laboratory Tests

Laboratory tests will be obtained at SV1 or SV2, G1, G2. Laboratory tests for each follow-up visit are listed in the Protocol on Tables 18.1 and 18.2.

Some laboratory tests will be done locally and some centrally, **and are noted as such in the Protocol on Tables 18.1 and 18.2**. The study coordinator or the GFR technician will complete the appropriate forms for the central laboratory mailing. These forms will include the CBL Serum (Form 22) and Urine Mailing Form 23, and GFR Procedures Form 24. For local laboratory test, Local Laboratory Form 13 will be completed.

5.6 24-hour Urine Collection

A 24-hour urine collection is required during the Baseline period at either SV2 or G1. The Baseline urine is labelled as B1-0. The urine should be refrigerated after it has been mixed, measured and aliquoted and must arrive at the Central Laboratory within one week of collection. The GFR Technician or Study Coordinator will complete the Mailing Form 23.

It is important to ascertain whether the urine collection is accurate and complete (i.e., if the participant remembers to discard the first urine sample and collect all of the urine for the next 24 hours). Otherwise, the urine should not be sent to the Central Laboratory, and the participant should collect another urine. The participant should be given a 4 liter container with 250 ml. of 5% acetic acid at either SV2, and is to be returned with a 24-hour urine collection. Prior to the G2 visit the participant should have collected one 24-hour urine specimen. Results from one urine is required for randomization.

5.7 EKG

An EKG is required at the Screening Visit 2, then every two years thereafter. The EKG readings are to be obtained to document the participant's status and for participant safety. The EKG is not an end point in the study. They are to be read locally. The Local EKG Form #14 will be completed at this visit.

5.8 Restarting Patients in Baseline

A patient can restart the screening process 6 months after they have been identified as ineligible. Since patients can become ineligible at different points in time during the screening/baseline period, and since they become ineligible for different reasons, rules have been implemented in determining the earliest date a patient can restart the screening process. (See Form 47 instructions in the Forms Usage Manual for details.)

A patient can restart the screening process after one month if the Principal Investigator believes that the patient was excluded due to a problem in laboratory measurement, clinical center test procedures or clinical center sample preparation procedures. The Quality Control Subcommittee, after receiving the Principal Investigator's written explanation, will inform

the Data Coordinating Center if the patient is eligible to re-enroll in writing. The date of restart is one month from the date the Quality Control Subcommittee approves the restart. (See Form 47 instructions located in the Forms Usage Manual for details.)

A patient can restart the screening process after one month if the patient was enrolled in baseline and was excluded for a logistic rather than a medical reason. This applies to all who are eligible on the basis of SV2, have no medical exclusions and are not randomized during the allotted time. (See Form 47 instructions located in the Forms Usage Manual for details.)

An excluded patient is also eligible to restart the Screening/Baseline process after one month if the patient was G1 GFR Eligible and met all other biochemical and clinical eligibility criteria but was not randomized during the allotted time. This includes those situations in which the G2 GFR was not done within 24 weeks of the SV2 visit or in which the person was not randomized within 8 weeks of the G2 GFR. (See Form 47 instructions located in the Forms Usage Manual for details.)

All patients who restart Baseline do not have to re-qualify for blood pressure (back titration) as long as they met the blood pressure criteria the first time in Baseline.

Also, Form 53 must be entered prior to restarting the patient. Please review Form 47 instructions which detail the restart procedure.