

Chapter 11. Hypertensive Vascular Disease

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I. INTRODUCTORY REMARKS

Over the last 3 decades, the treatment of essential hypertension has evolved with new objectives and new classes of drugs. The objectives of the treatment have changed from the reduction in blood pressure to the prevention of cardiovascular disease by the reduction and normalization of blood pressure. Treatment is also evolving towards a more individual approach of the treatment taking into considerations such variables such as age, gender, race and the associated diseases such as among others diabetes, renal function, and cardiac function. There have been new classes of drugs which have been evaluated such as the calcium channel blockers, the ACE inhibitors, the renin- angiotensin blockers and others which are currently being tested such as the aldosterone receptor blockers.

The inhibition of the renin-angiotensin system was successfully used in the treatment of hypertension and heart failure. The first approach used was the inhibition of the angiotensin-converting enzyme (ACE). However, ACE-inhibitors induce the accumulation of other peptides such as substance P or bradykinin, and consequently untoward drug effects like cough and angioedema can become apparent. A more recent approach to counteract increased blood pressure and sympathetic tone, as well as harmful cardiovascular hypertrophy and renal lesions, was to decrease the activity of angiotensin II receptors. Pharmacological blockade of AT₁-subtype angiotensin II receptors appears to be clinically equally effective but the generation of angiotensin II remains unopposed during AT₁-blockade and leaves the potential for stimulation of other angiotensin II receptor subtypes. These two classes of drugs have been proven to be effective and very well tolerated. These drugs have not been shown to be superior to conventional treatment such as diuretics in a general population but have been shown to be superior to beta blockers in some groups of patients with hypertension such as the patients with LVH (left ventricular hypertrophy). Despite the addition of these two classes of drugs, there is still definitely a need for more effective, as safe and possibly more specific drugs to treat hypertension. Moreover, the effect of antihypertensive therapy on cardiovascular events, on cerebrovascular events, on diabetic complications progression needs to be part of the evaluation process. Further studies are needed to document the long-term benefit of antihypertensive therapy alone or in association with other cardiovascular medications.

II. PHASE II STUDIES TO EVALUATE THE EFFECTIVENESS AND SAFETY OF NEW ANTIHYPERTENSIVE DRUGS

Studies will have to assess the effect of a drug directly on blood pressure, e.g. looking primarily for an antihypertensive action and they will have also to assess the effect of the drug in special situations such as renal dysfunction or others and in special populations.

Long term studies may have eventually as an objective to assess the effect of an antihypertensive agent on cardiovascular events such as coronary events, including myocardial infarction, sudden or rapid death from cardiac causes, heart failure, acute occlusion of a major feeding artery in any vascular bed other than cerebral or coronary, death from non-coronary cardiac causes, dissecting or ruptured aortic aneurysm, or death from vascular causes, cerebrovascular events, including stroke and transient ischemic attacks, and on progression of hypertensive kidney disease, diabetic nephropathy, diabetic retinopathy, and arterial wall thickness. These studies usually are conducted over the period of 5 years and are considered long-term studies.

II.1. Outline of a potential development plan

Multicenter, randomized, double-blind, placebo-controlled, parallel group study in patients with mild-to-moderate essential hypertension (WHO classification grades 1 and 2) who have been completely withdrawn from their previous antihypertensive medication or in patients who have been newly diagnosed with mild-to-moderate essential hypertension and who are not currently taking any antihypertensive

medication(s). The objective of these phase II studies is to find the effective dose of the compound compared to a placebo. These are normally dose finding placebo controlled studies. A reference drug can be included in some studies. These studies are of primary importance to determine the dose which will be used in the phase III studies to demonstrate better efficacy and tolerability than the marketed compounds.

In these phase II protocols or in phase III protocols, the evaluation of the antihypertensive drugs in special situations can be assessed. These studies need to give the information of the effect of the drug in the elderly whether defined as over 65 or 75 years. Information needs to be obtained in both groups. More and more information will be asked in the individuals over the age of 85 years. There is limited data on the benefit of treatment in this age category but we need also at least to obtain information on the effectiveness of the drug in terms of BP lowering and dose efficacy.

Protocols need to be done in patients with isolated systolic hypertension or primarily systolic hypertension. These patients are generally elderly individuals with a specific form of hypertension which is becoming more prevalent as our population ages.

Information is required on the use of the drug according to gender and race. Black population may have a different response than other races as has been shown now in various studies.

Specific information needs also to be obtained in subgroups of hypertensive patients. Those subgroups are those with renal dysfunction that is, with a creatinine clearance of <60 ml/min, <30 ml/min and lower, as well as the patients with hepatic dysfunction

Special populations which need to be studied are also those with associated disease such as diabetes and left ventricular hypertrophy. Although not a requirement, this information will become necessary to the proper utilization of the drug

II.2. Short term studies

II.2.A. Study Objectives

Primary objectives

- a. To determine the efficacy of the investigational drug X at given doses compared to placebo or the reference drug Y in patients with WHO classification grades 1 and 2 uncomplicated diastolic essential hypertension (mean sitting diastolic blood pressure [MSDBP] ≥ 95 mmHg and < 110 mmHg).
- b. To determine the safety of the investigational drug X compared to the placebo in patients with WHO classification grades 1 and 2 uncomplicated diastolic essential hypertension (MSDBP ≥ 95 mmHg and < 110 mmHg).

Secondary objectives

- a. To determine the efficacy and safety of different doses of the investigational drug X compared to placebo in the treatment of patients with WHO classification grades 1 and 2 uncomplicated systolic essential hypertension (systolic blood pressure [MSSBP] ≥ 145 mmHg and < 180 mmHg).
- b. To assess the effects of the investigational drug X and the reference drug on standing blood pressure, sitting pulse and standing pulse.

II.2.B. Primary endpoints

- a. Change from baseline in MSDBP at trough.

- Response rate: patients were defined as "normalized" responders if their blood pressure values were < 140/90 mm Hg, or as "non-normalized" responders if the reduction in blood pressure was 10 mm Hg or more, compared with baseline.
- b. Changes in sitting blood pressure at the end of the study.

II.2.C. Secondary endpoints

- a. Change from baseline in MSSBP at trough.
- b. Other variables to be analyzed include the change in standing diastolic and systolic blood pressures, sitting and standing pulse.

A variable such as the ambulatory blood pressure measurement (ABPM) is a requirement now to more precisely measure the course of action of the medication over the period of 24 hours including the peak effect and the trough effect. It will help determine the duration of action, the peak to trough ratio. Specific protocols will be planned to evaluate the effects of the drug on ABPM and some of its variables (day pressure, night pressure, smoothness of curve etc)

II.2.D. Study Design

Eligible patients enter a washout period during which antihypertensive medication is withdrawn and no other is allowed. The washout period is followed by a 2 to 4 -week single-blind placebo run-in period. Patients who meet the study inclusion/exclusion criteria at the end of the single-blind placebo run-in period are then randomized in double-blind fashion to either the investigational drug X or placebo once daily for an 8-week treatment period in a parallel designed trial. The effect of the investigated medication can also be evaluated at the end of the trial by a period of drug withdrawal by recording blood pressure and adverse events from one to seven days or more after the last dose of study medication.

Blood pressure measurement

Blood pressure will be measured using a calibrated standard mercury sphygmomanometer or a calibrated electronic automatic sphygmomanometer with digital reading. Personnel recording the blood pressure should receive training on the measurement of blood pressure and follow guidelines such as the one reported in the annex 1. The standard measurement is done in the sitting position, but standing pressure is also recorded in most protocols, as well as pulse rate. Sitting and standing blood pressure will be measured and recorded at each visit. Every effort will be made to have the same staff member obtain blood pressure measurements for the same patient, at the same time of day, using the same equipment, at each visit.

Pulse rate

At each visit, the pulse rate will be measured for 30 seconds just prior to the blood pressure measurements; once in the sitting position and once in the standing position.

Concomitant therapy

Use of the following medications may interfere with the evaluation of efficacy, safety and/or tolerability. Therefore, these medications are excluded throughout the trial, from the beginning of the washout period until the end of the double-blind treatment period. Patients who are receiving such medications should be excluded, or if ethically justified, the medications may be withdrawn according to the manufacturer's instructions.

- a. Drugs approved for the treatment of hypertension even if prescribed for another indication.
- b. Any antidepressant drugs in the class of MAO inhibitors and tricyclics. Other psychotropic drugs such as benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) will be allowed if well tolerated when previously taken, and if the dosage is expected to remain stable throughout the study.

- c. Any systemic use of corticosteroids. Topical and nasal steroid preparations may be used as needed, but not on a daily basis.
- d. Use of hormonal contraceptives, including subdermal contraceptive implants, within one month prior to Visit 1 (Week -4).
- e. Thyroid medication and/or oestrogen replacement therapy, unless these have been stable maintenance replacement doses for 6 months preceding Visit 1 (Week -4).
- f. Insulin.
- g. Chronic administration of sympathomimetic drugs such as those found in nasal decongestants (pseudoephedrine and phenylpropanolamine) and bronchodilators (e.g., metaproterenol).
- h. Antacids in amounts greater than package labelling.
- i. Ergot preparations.
- j. Antiarrhythmic drugs; digoxin will be permitted provided serum levels have been stable and no dose adjustments have been made during the 6 months preceding Visit 1 (Week -4).
- k. Diuretics of any kind.
- l. Psychotropic drugs, except for hypnotics and mild anxiolytic agents such as benzodiazepines, if these were used occasionally (pm) before the start of the study.
- m. Aspirin above 325 mg daily. Aspirin will be allowed at a maximum daily dose of 325 mg for cardiac protection. Patients must have been on a stable dose prior to entry and maintain the same dose throughout the study.
- n. The use of drug(s) in the 6 months prior to Visit 1 (Week -4) which are potentially hepatotoxic (e.g., methotrexate) or nephrotoxic (e.g., gentamicin).
- o. Antianginal medication of any kind including calcium channel blockers or beta blockers (including beta blocker eye drops).
- p. Drugs which interfere with the metabolism of the other compound such as through the inhibition or stimulation of isozymes of the cytochrome P450 known to influence the compound under study should be excluded.

II.2.E. Planned sample

The sample size is calculated on the basis of the objective to be obtained. Sample size to obtain a clinically significant reduction or difference in blood pressure can be calculated with sufficient power for example. Statistical help is required for the best accurate determination of these calculations and different tools are available on the internet to calculate sample size:

- a. To conclude non-inferiority of the investigational drug within a margin of 2 mm Hg when there is no true treatment difference between the investigational drug X mg and the reference drug Y mg OD.
- b. To detect a true 3 mm Hg difference between the reference drug Y mg (or the investigational drug X mg) OD and placebo under the null hypothesis that the mean difference is 0.
- c. To have sufficient power to examine dose-response relationship of the investigational drug at different dose levels.

II.2.F. Study population

Patients with mild-to-moderate essential hypertension (WHO classification grades 1 and 2) who have been completely withdrawn from their previous antihypertensive medication or in patients who have been newly diagnosed with mild-to-moderate essential hypertension and who are not currently taking any antihypertensive medication(s).

II.2.G. Inclusion criteria

- a. Outpatients 21 and older. The age limit will be determined by the protocol or the planned development program which should include at one point studies in elderly and very elderly patients
- b. Male or female patients are eligible. Female patients must be either post-menopausal for one year or surgically sterile, or using effective contraceptive methods such as barrier method with

spermicide or an intra-uterine device. Oral or implant contraceptives are not be allowed because of their interactions and effect on blood pressure.

- c. Patients with mild to moderate essential diastolic hypertension (WHO classification grades 1 or 2) measured by calibrated standard sphygmomanometer or calibrated standardized automatic sphygmomanometer. Patients must have a MSDBP ≥ 95 mmHg and < 110 mm Hg. Blood pressure criteria will be different in studies such as those in diabetic patients.
- d. Patients must have a variability of ≤ 10 mmHg in their MSDBP between pre-randomization.
- e. Patients who are eligible and able to participate in the study, and who consent to do so after the purpose and nature of the investigation have been clearly explained to them (written informed consent).

II.2.H. Exclusion criteria

Patients with any of the following physiological states or concomitant medical conditions will be excluded from further participation in the study.

- a. Severe hypertension (defined as MSDBP ≥ 110 mmHg and/or MSSBP ≥ 180 mmHg or 200 mm Hg).
- b. Inability to discontinue all prior anti-hypertensive medications safely for a period of 12 weeks.
- c. Known Keith-Wagener grade III or IV hypertensive retinopathy.
- d. History of hypertensive encephalopathy or cerebrovascular accident within the preceding 6 months.
- e. Transient ischemic cerebral attack during the 12 months prior to Visit 1 (Week -4).
- f. Evidence of a secondary form of hypertension, such as coarctation of the aorta, hyperaldosteronism, unilateral renal disease, or pheochromocytoma, etc.
- g. Type 1 diabetes mellitus.
- h. Type 2 diabetes mellitus with poor glucose control as defined by fasting glycosylated hemoglobin (Hb_{A1c}) $> 8\%$ or requiring insulin treatment.
- i. Known or suspected contraindications, including history of hypersensitivity to the class of antihypertensive agent.
- j. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of any drug including but not limited to any of the following:
 - History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection.
 - Currently active or previously active inflammatory bowel syndrome during the 12 months prior to Visit 1 (Week -4).
 - Currently active gastritis, duodenal or gastric ulcers, or gastrointestinal/rectal bleeding during the 3 months prior to Visit 1 (Week-4).
 - Any history of pancreatic injury, pancreatitis or evidence of impaired pancreatic function/injury as indicated by abnormal lipase or amylase.
 - Evidence of hepatic disease as determined by any one of the following: SGOT or SGPT values exceeding 2 x ULN at Visit 1 (Week -4), a history of hepatic encephalopathy, a history of oesophageal varices, or a history of portocaval shunt.
 - Evidence of renal impairment as determined by any one of the following: serum creatinine > 1.5 ULN or a level higher than normal depending on the population under study, a history of dialysis, or a history of nephrotic syndrome.
 - Current obstruction of the urinary tract or difficulty in voiding due to mechanical or inflammatory conditions which is likely to require intervention during the course of the study or is regarded as clinically meaningful by the investigator.
- k. History or diagnosis of heart failure during the 6 months prior to Visit 1 (Week -4).
- l. History of myocardial infarction during the 6 months prior to Visit 1 (Week -4).
- m. Second or third degree heart block without a pacemaker.
- n. Unstable angina pectoris.
- o. Concurrent potentially life threatening arrhythmia or symptomatic arrhythmia.

- p. Clinically significant valvular heart disease.
- q. Volume depletion or dehydration.
- r. History of malignancy including leukemia and lymphoma (but not basal cell skin cancer) within the past five years.
- s. History of any severe or life-threatening disease(s).
- t. Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the trial period.
- u. History of drug or alcohol abuse within the last 12 months.
- v. History of non-compliance to medical regimens or unwillingness to comply with a study protocol.
- w. Participation in any investigational drug trial within one month of Visit 1 (Week -4).
- x. Unwillingness or inability to give informed consent.
- y. Persons directly involved in the execution of this protocol.
- z. Pregnant or nursing women or women of childbearing potential not practicing effective contraceptive methods.
- aa. History of clinically significant allergies, including asthma, or multiple drug allergies.
- bb. History of autoimmune disorders, such as, but not limited to rheumatoid arthritis, systemic lupus erythematosus or glomerulonephritis.

II.2.I. Tools for assessing endpoints

Efficacy assessment

Using a calibrated standard sphygmomanometer and appropriate size cuff, arterial blood pressure determinations will be made in accordance with the Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure or that of other societies (1). With the arm supported at the level of the heart, systolic pressure will be recorded when the initial sound is heard (Phase I of the Korotkoff sound); diastolic pressure will be recorded at the disappearance of the sound (Phase V of the Korotkoff sound). The cuff should be deflated at a rate not greater than 2 mm Hg/sec.

The ambulatory blood pressure measurement (ABPM) will be measured using standard procedures (Appendix 2).

Safety assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), the regular monitoring of haematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations. An ECG evaluation will be obtained at Visit 2 (Week -2).

II.2.J. Specific criteria for early withdrawal and discontinuation

- a. Reasons why a patient may discontinue participation in a study include the following:
 - b. Adverse event(s)
 - c. Abnormal laboratory value(s)
 - d. Abnormal test procedure result(s)
 - e. Unsatisfactory therapeutic effect
 - f. Patient's condition no longer requires study treatment
 - g. Protocol violation
 - h. Subject withdrew consent
 - i. Lost to follow-up
 - j. Administrative reasons
 - k. Death

Patients with MSDBP ≥ 110 mmHg or MSSBP ≥ 180 mmHg at any time during the single-blind or double-blind treatment phases must be permanently discontinued from the trial.

II.2.K. Data analysis method

The proportion of patients in each treatment achieving a successful reduction in MSDBP during the double-blind period will be compared at the endpoint using a one-way logistic model with treatment as the factor at Visit 7 (Week 8) for all randomized patients. Success is defined as a mean sitting diastolic blood pressure < 90 mmHg or a decrease ≥ 10 mmHg sitting diastolic blood pressure from the randomization visit.

The changes from baseline will be analyzed using a two-way analysis of covariance model with treatment and center as factors, and the baseline as a covariate as well as treatment-by-baseline interaction. All pairwise treatment comparisons will be made based on this analysis model. Due to a large number of study centers and treatment groups planned in this study, treatment-by-center interaction effect may be difficult to interpret in a statistical model. However, a summary of means by treatment and center will be provided for the primary analysis.

III. PHASE III STUDIES TO EVALUATE THE EFFECTIVENESS AND SAFETY OF NEW ANTIHYPERTENSIVE DRUGS

III.1. Outline of a typical development plan

The phase III studies have the objective to demonstrate and compare the efficacy of the antihypertensive agent against the usual antihypertensive compounds. The new compound will be tested for efficacy and compared to conventional treatments such as diuretics (hydrochlorothiazide), beta blockers (metoprolol or atenolol), long acting dihydropyridine calcium channel blockers (amlodipine or long acting nifedipine), ACE inhibitors (enalapril or lisinopril) and AT₁ receptor blockers such as losartan.

Since the treatment of hypertension requires more than one antihypertensive agent, it will also be a requirement to test the new agent in combination to the most commonly used other antihypertensive agent either as a specific trial such as a combination with a thiazide diuretic or as an add-on protocol where non responsive patients will receive add on treatments to normalize blood pressure. Combination will also be required where the new medication will be added as a second line agent to conventional treatment to evaluate potential synergistic effect on BP reduction but also potential adverse effects.

Phase III long-term studies are done to follow up on the long term effectiveness on blood pressure and adverse effects of the medication over a period which could be up to two years of follow up in small number of patients who generally have participated in phase II or III studies and are asked to continue on the medication in an open study of efficacy and safety

III.2. Short-term studies

III.2.A. Objectives

The objective is to demonstrate the relative efficacy and safety of the new compound.

III.2.B. Primary endpoints

- a. The decrease in blood pressure whether systolic or diastolic blood pressure measured in standard conditions at through compared to other antihypertensive treatments.
- b. Responders rate are also measured in terms of % of patients obtaining a predetermined endpoint of BP such as diastolic BP less than 90 mm Hg and systolic pressure less than 160 mm Hg or 140 mm Hg.

III.2.C. Secondary end-points

As described for phase II studies in II.2.C.

III.2.D. Study design

Eligible patients will enter a 2 to 4 weeks washout period followed by a 2 to 4 weeks single blind placebo period to determine if patients can meet the inclusion criteria for blood pressure or if they have to be excluded for other exclusion criteria. They will then be randomized to either treatments conventional or experimental to evaluate efficacy and safety. The duration of the short term active treatment phase is of the order of 8 weeks

III.2.E. Planned sample

As described for phase II studies in II.2.E.

III.2.F. Study population

As described for phase II studies in II.2.F.

III.2.G. Specific inclusion criteria

As described for phase II studies in II.2.G.

III.2.H. Specific exclusion criteria

As described for phase II studies in II.2.H.

III.2.I. Tools for assessing endpoints

As described for phase II studies in II.2.I.

III.2.J. Specific criteria for early withdrawal and discontinuation

As described for phase II studies in II.2.J.

III.2.K. Data analysis method

The proportion of patients in each treatment achieving a successful reduction in MSDBP during the double-blind period will be compared at the endpoint using a one-way logistic model with treatment as the factor at Visit 7 (Week 8) for all randomized patients. Success is defined as a mean sitting diastolic blood pressure < 90 mmHg or a decrease ≥ 10 mmHg sitting diastolic blood pressure from the randomization visit.

The changes from baseline will be analyzed using a two-way analysis of covariance model with treatment and center as factors, and the baseline as a covariate as well as treatment-by-baseline interaction. All pairwise treatment comparisons will be made based on this analysis model. Due to a large number of study centers and treatment groups planned in this study, treatment-by-center interaction effect may be difficult to interpret in a statistical model. However, a summary of means by treatment and center will be provided for the primary analysis.

The following pairwise comparisons shall be performed:

- a. Investigational vs. reference drug
 - Primary comparison: non-inferiority and/or superiority of the investigational drug X mg OD vs. reference drug Y mg OD.
 - i. Step 1: non-inferiority Test (one-sided 97.5% CI) to show the investigational drug is as good as or not worse than the reference drug by a predefined margin (2,3).
 - ii. Step 2: superiority Test (one-sided $\alpha = 0.025$) to show the investigational drug is superior to the reference drug. This test is performed only if non-inferiority in Step 1 is shown.

- Secondary comparison: superiority of the investigational drug 2X and 4X mg OD vs. reference drug Y mg.
- b. Investigational drug vs. placebo

Primary analysis: dose-response via a regression analysis. A second-order regression analysis with the dose as predictor variable will be performed for the change from baseline in MSDBP at Visit 7 (Week 8) and endpoint to examine the relationship between the efficacy response and the dose. A test for lack-of-fit will be performed at significance level of 0.1.

Secondary analysis: pairwise comparison of investigational drug X, 2X and 4X mg OD vs. placebo.

The statistical test for each of the pairwise comparisons will be made at a two-sided 0.05 statistical significance level. Summary statistics for the changes from baseline of efficacy variables will be presented by treatment group and time point, as well as by treatment group, trial center, and visit; treatment group, age and visit; treatment group, sex and visit; and treatment group, race, and visit. Within-treatment analysis for all the efficacy variables will be performed by a paired t-test at the endpoint.

IV. OTHER STUDIES

PHASE IV MORTALITY AND MORBIDITY STUDIES

IV.1. Outline of a typical development plan

To evaluate the effect of antihypertensive therapy on cardiovascular events in hypertensive patients; the outcomes in subjects with hypertension who were treated with the new medication will be compared with the outcomes in those treated with conventional treatments. The study will be a double-blind, multicenter, randomized, parallel-group trial in subjects with essential hypertension (sitting blood pressure 160–200/95–115 mm Hg) or has been in some occasions a PROBE study (Prospective Open Blinded Endpoints).

IV.2. Long-term studies

IV.2.A. Objectives

Primary objectives

To compare the effect of either regimens in preventing cardiovascular complications either cardiac, cerebrovascular or a combination of endpoints which generally include cardiovascular death, acute MI, stroke and heart failure requiring hospitalization.

Secondary objectives

To compare the two regimens on some individual endpoints:

- a. hospitalization for angina, cardiac revascularization , heart failure, transient ischemic attack , accelerated or malignant hypertension, or renal failure in addition to the primary outcome;
- b. all-cause mortality;
- c. cancer.

IV.2.B. Primary endpoints

IV.2.C. Secondary endpoints

IV.2.D. Study design

Patients are randomized to once daily treatments under study-based antihypertensive treatment in a parallel-group for at least 4 years and until the calculated number of patients has a primary cardiovascular

event which has been validated (death, myocardial infarction, or stroke). The patients will be followed for the duration of period calculated to be necessary to see the predicted number of events. Patients are generally followed for a period of 4 to 6 years depending on the number of events required. They are followed at regular visits to obtain target blood pressures of less than 140/90 mm Hg. Central laboratory are required to standardize measurements such as ECG, echocardiogram or other specific measurements being used as endpoints.

As for other large morbidity and mortality trials, there are independent committees to adjudicate events and Data Monitoring safety Boards to guarantee the security and safety of the participants. The trial is generally run by a steering committee which determines a steering committee to organize the protocol

Other medications

Usually, other drugs are permitted if clinically indicated. The choice of the drug will depend upon the drugs on study, in the sense that drugs of different class may be added. Any additional antihypertensive agent may be added as a step 3 medication (non-blinded).

IV.2.E. Planned sample

If the trial aims to document the effect of antihypertensive therapy on cardiovascular morbidity and mortality, patients with secondary hypertension, myocardial infarction or stroke within the previous 6 months, angina pectoris requiring treatment with β -blockers or calcium-antagonists, heart failure or left ventricular ejection fraction of 40% or less, or with a disorder that, in the treating physician's opinion, requires treatment with drugs of the same class of the tested drugs will be excluded.

The design of a phase IV study of morbidity and mortality requires the use of statisticians in the calculation of sample sizes based on the requirements determined by the investigators. These calculations take into account the primary endpoints, the potential duration of the study and the population under study to obtain predetermined objectives. It also assumes a percentage of non-compliance to the study, drop-outs to the trial and loss to follow-up during the trial. The population when comparing two active based treatments can be in the order of 15,000 patients up to 40,000 as was seen in the ALLHAT trail recently with a follow-up of 4 years (4).

IV.2.F. Study population

IV.2.G. Specific inclusion criteria

IV.2.H. Specific exclusion criteria

IV.2.I. Tools to assess endpoints

Efficacy assessment

The method of assessment will differ greatly depending upon the primary and secondary objectives of the trial. Trials have assessed the effect of test drugs on cardiovascular morbidity and mortality documenting left ventricular hypertrophy by means of electrocardiograms (5). In other trial, deaths were documented through the National Death Index; acute MI required two out of three of the following conditions:

- a. symptoms compatible with acute MI (e.g., chest pain) lasting longer than 15 minutes;
- b. electrocardiographic changes (new persistent ST-segment elevation or pathological Q waves in 2 contiguous leads); and
- c. increased cardiac enzymes (more than twice the upper limit of normal).

A diagnosis of stroke required the presence of focal neurological deficit lasting longer than 24 hours. Imaging studies were not required to document a stroke. Any death thought to be compatible with

coronary heart disease (e.g., heart failure, sudden death) or cardiovascular disease was counted as a cardiovascular disease-related death (6).

An additional trial assessed the study outcomes at follow-up visits and reported to the clinical trials center. Hospitalized outcomes were primarily based on clinic investigator reports, and copies of death certificates and hospital discharge summaries were requested. In addition, searches for outcomes were accomplished through the Center for Medicare and Medicaid Services, the Department of Veterans Affairs, the National Death Index, and the Social Security Administration databases. A death was ascertained by clinic report or by match with the aforementioned databases plus a confirmatory death certificate. Medical reviewers from the clinical trials center verified the physician-assigned diagnoses of outcomes using death certificates and hospital discharge summaries. More detailed information was collected on a random subset of CHD and stroke events to validate the procedure of using physician diagnoses (4).

The frequency of the measure of endpoints depends on the objective of the trial. For instance, to assess cardiovascular endpoints, in one trial, participants were seen at least semi-annually for blood pressure measurements, treatment dispensing, and endpoint surveillance. On-site data verification was performed at least annually. An independent data and safety monitoring board met semi-annually to review accumulating data. Confidence intervals based on the Lan-DeMets version of the O'Brien-Fleming group sequential boundaries were used as guidelines for early termination. All analyses were performed independently of the sponsor. All study investigators and the study sponsors were blinded to all between-treatment comparisons until completion of end point data collection and review (6).

In another trial, patients were followed for at least 4 years with regular visits and increases in drug doses to reach a target blood pressure of less than 140/90 mm Hg. All screening, baseline, serial, yearly, and endpoint electrocardiograms were centrally assessed for signs of LVH and Minnesota coded at one reading center. Since combined ECG assessment of QRS voltage and duration enhances sensitivity for detection of LVH at acceptable levels of specificity, the product of QRS duration and Cornell voltage (with adjustment of 8 mm in women and a partition value of >2440 mm \times ms) was used to recognize LVH. These composite ECG criteria have about 95% specificity in healthy people and 50% sensitivity in patients with LVH ascertained at necropsy or by echocardiography LVH (5).

IV.2.J. Specific criteria for early withdrawal and discontinuation

As described for phase II studies in II.2.J.

IV.2.K. Data analysis method

In one trial, time to event methods (Cox proportional hazards model and Kaplan Meier curves) were used to compare outcomes for participants randomly assigned to the investigational drug and the comparators. Analyses were by modified intent to treat (modified by the exclusion of 2 sites with data integrity concerns), unless otherwise specified, and were stratified by the choice of standard of care and geographic region in which the participant's clinical site was located. Analyses of primary and secondary events considered censoring due to losses to follow-up (e.g., participants for whom the primary event status was unknown on the closing date), non-cardiovascular disease-related deaths (as appropriate), and the closing date of the study. Losses were censored at the date the primary event status was last known (either the date provided by the site during the closeout process; or the date of the last follow-up visit). The proportional hazards assumption was tested by including an interaction term between the randomized treatment indicator and log-transformed follow-up time. Blood pressure changes from baseline were compared between the 2 treatment groups using the t test. All analyses were performed using SAS statistical software (Version 8.0, SAS Institute Inc, Cary, NC) (6).

In the second trial, analysis of all cardiovascular endpoints was by intention to treat; all randomized patients were included in their treatment group, and all available follow-up data were included from

randomization to the end of the study. The difference between treatment groups with respect to clinical events was assessed by a Cox regression model with degree of LVH (measured as a continuous variable) and the Framingham risk score defined by baseline characteristics as covariates. Treatment effects were measured by hazard ratios (relative risks) and 95% CIs by Cox regression models. The risk reduction for drug XXX against drug YYY was calculated as $100 \times (1 - \text{relative risk})$. Event rates over time are presented as Kaplan-Meier curves. Adjustment for blood pressure was derived from Cox regression models with blood pressures throughout the trial as time-varying covariates. Differences between groups in changes in ECG measures of LVH were analysed with the Wilcoxon rank-sum test, and the frequency of adverse experiences with Fisher's exact test (5).

V. REFERENCES

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APPENDIX 1 – Canadian Hypertension Recommendations

Recommended techniques for measuring blood pressure

1. Measurements should be taken with a sphygmomanometer that is known to be accurate. Although a mercury manometer may be preferable, a recently calibrated aneroid, or a validated and recently calibrated electronic device, can be used. Aneroid devices and mercury columns need to be clearly visible at eye level.
2. Choose a cuff with an appropriate bladder width matched to the size of the arm. The optimal bladder width equals the arm circumference/2.5, with an acceptable range of 80% to 100% of the arm circumference.
3. Place the cuff so that the lower edge is 3 cm above the elbow crease and the bladder is centred over the brachial artery. The patient should be resting comfortably for 5 min. in the seated position with back support. The arm should be bare and supported with the antecubital fossa at heart level because a lower position will result in an erroneously higher systolic blood pressure and diastolic blood pressure. There should be no talking, and the patient's legs should not be crossed. At least two measurements should be taken in the same arm with the patient in the same position. Blood pressure also should be assessed after 2 min. of standing and at times when patients report symptoms suggestive of postural hypotension. Supine blood pressure measurements may also be helpful in assessing elderly and diabetic patients.
4. Increase the pressure rapidly to 30 mmHg above the level at which the radial pulse is extinguished (to exclude the possibility of a systolic auscultatory gap). Continue to auscultate at least 10 mmHg below phase V to exclude a diastolic auscultatory gap.
5. Place the bell or diaphragm of the stethoscope gently and steadily over the brachial artery.
6. Open the control valve so that the rate of deflation of the cuff is approximately 2 mmHg/heart beat. A cuff deflation rate of 2 mmHg/heart beat is necessary for accurate systolic and diastolic estimation.
7. Read the systolic level – the first appearance of a clear tapping sound (phase I Korotkoff) – and the diastolic level B the point at which the sounds disappear (phase V Korotkoff). Record the blood pressure to the closest 2 mmHg on the manometer (or 1 mmHg on electronic devices), as well as on the arm used, and note whether the patient was supine, sitting or standing. Record the patient's heart rate. The seated blood pressure is used to determine and monitor treatment decisions. The standing blood pressure is used to examine for postural hypotension, if present, which may modify the treatment.
8. If Korotkoff sounds persist as the level approaches 0 mmHg, then the point of muffling of the sound is used (phase IV) to indicate the diastolic pressure.
9. In the case of arrhythmia, additional readings may be required to estimate the average systolic and diastolic pressure. Isolated extra beats should be ignored. Note the rhythm and pulse rate.
10. Leaving the cuff partially inflated for too long will fill the venous system and make the sounds difficult to hear. To avoid venous congestion, it is recommended that at least 1 min. should elapse between readings.
11. Blood pressure should be taken at least once in both arms, and if an arm has a consistently higher pressure, then that arm should be clearly noted and subsequently used for blood pressure measurement and interpretation.

APPENDIX 2 - Guidelines for the Measurement of Blood Pressure by ambulatory blood pressure monitor

Ambulatory blood pressure measurements will be made using the Spacelabs Model 90207 monitor.

On the days that the ABPM equipment will be applied, patients should arrive at approximately 8h00 AM to allow additional time for ABPM procedures such that dosing of medication occurs as close to 9:00 AM as possible.

The ABPM monitors will be programmed to measure blood pressure every 30 minutes throughout the day (0500 – 2300) and every 60 minutes at night (2300 – 0500). Patients will be advised not to move the arm during each blood pressure measurement and will also be given instructions concerning interruption of measurement in case of malfunction of the device or repositioning of the cuff if it slips.

For each of the two 24-hour ABPM monitoring sessions, the following procedures will be performed:

1. **Do not reuse batteries.** Always install four (4) fresh AA batteries prior to initializing the monitor.
2. Connect the cable from the modem to the monitor.
3. When attaching the monitor to the patient, first palpate the patient's brachial artery (you can mark location with felt-tip pen) then apply an appropriate sized ambulatory BP cuff to patient's non-dominant arm (e.g. if patient is right-handed, apply cuff to left arm).
4. Take up to five correlation readings. Attach T-tube to office sphygmomanometer, monitor and cuff. Allow cuff to inflate and listen to pressure. The monitor must be within 10 mm Hg of the pressure obtained by the column of mercury. If not, adjust cuff and try again.
5. Remove T-tube and attach cuff to monitor.
6. Manually trigger one or two ABPM readings to make sure the monitor is working properly. Give the patient a dose of study medication and then manually trigger another ABPM reading. The official "**dose time**" for the 24-hour recording will be the time shown on the ABPM clock as you pressed the blue start/stop button for the manual reading. Do not use your watch or a wall clock. Record the noted ABPM clock time on the CRF as the dose time. Dosing must occur at 8:00 AM plus or minus one hour.
7. Just prior to removal of the monitor, take a final manual reading using the start/stop button. The final manual reading should occur as close to 24 hours since prior dosing as recorded on the CRF. (The patient might need to repeat the ABPM if the monitoring is < 24 hours in duration, reference Appendix 11.3.3.) If you see "Ecxx" (i.e. error code) on the ABPM display, take another reading to ensure you have a captured BP reading. Remove the monitor from the patient's arm.
8. After downloading of your patient's data is complete, you may initialize the monitor for future use, making certain to first install fresh batteries. Make sure the monitor is turned off for storage.

The data collected will be evaluated to determine if it meets the criteria for a successful monitoring session.

Operating instructions for ambulatory blood pressure monitoring

Refer to the operating manual for a detailed explanation of ABPM operation.

HANDLING OF ABPM DATA FOR ANALYSIS

All data editing will be performed on blinded data with no further editing performed once patient treatment assignments are known.

Screening Rules for Individual Readings

The following screening rules will be used by the ABPM vendor to evaluate the validity of the individual readings from a patient's monitor.

Screening Rules For Individual 20-Minute Interval Readings:

1. If the observed systolic blood pressure reading is either <50 mm Hg or >250 mm Hg, then the entire monitoring record will be considered invalid.
2. If the observed diastolic blood pressure reading is either <20 mm Hg or >130 mm Hg, then the entire monitoring record will be considered invalid.
3. If the calculated pulse pressure (i.e. SBP minus DBP) is either <15 mm Hg or >150 mm Hg, then the entire monitoring record will be considered invalid.
4. If the observed pulse rate reading is either <20 bpm or >200 bpm, then the entire monitoring record will be considered invalid.

An entire monitoring record refers to all readings and/or calculations, e.g. SBP, DBP, mean arterial pressure (MAP), pulse pressure (PP), and pulse rate (PR), for a particular 20-minute interval.

In addition, prior to statistical analysis of the ABPM results, the following screening rule will be used to further determine the validity of the individual SBP, DBP, and PR readings from a patient’s monitor.

5. For each observed reading, the six readings surrounding the observed reading (i.e. three before and three after) will be averaged together (the average will exclude the observed reading). If the observed reading differs by more than three standard deviations of the mean of the six surrounding readings and is outside of the range of values considered plausible for that particular measurement (see below) then the observed reading will be considered invalid. For observed readings that are numbered 1, 2, 3, 3rd to last, 2nd to last, or last, a wrap-around technique will be used to apply this screening rule.

Plausible Range of Observed Readings:

SBP	mean ± 40 mm Hg
DBP	mean ± 20 mm Hg
PR	mean ± 20 bpm

Calculation of hourly means

Hourly means relative to both the dosing time and clock time will involve only valid 20-minute interval ABPM records. No imputation of missing or invalid readings/records will be performed. Additionally, one valid 20-minute interval reading per hour will be adequate for a hourly mean for each of the variables (e.g. SBP, DBP, MAP, PP, and PR).

Hourly means relative to dose time

Hour relative to dose time will be defined starting at dose time and incremented every 60 minutes. Valid readings collected at dosing and up to (but not including) one hour after dosing will be averaged to yield a 1-hour post-dose mean, valid readings collected at one hour post-dose and up to (but not including) two hours post-dose will be averaged to yield a 2-hour mean, etc. Hourly means will then be calculated for each of the hours post-dose that the monitor recorded measurements.

For example, if dosing was at 08:14 then records taken at 08:14 to 09:13 will be considered as within dose time hour 1, records taken at 09:14 to 10:13 will be considered as within dose time hour 2, etc., with hourly means relative to dose time calculated accordingly.

Hourly means relative to clock time

Clock time hour will be defined as given below with hourly means calculated for each clock time hour.

<u>Time Interval</u>	<u>Clock Time Hour</u>	<u>Time Interval</u>	<u>Clock Time Hour</u>
24:00 – 00:59	0	12:00 – 12:59	12
01:00 – 01:59	1	13:00 – 13:59	13
02:00 – 02:59	2	14:00 – 14:59	14
03:00 – 03:59	3	15:00 – 15:59	15

04:00 – 04:59	4	16:00 – 16:59	16
05:00 – 05:59	5	17:00 – 17:59	17
06:00 – 06:59	6	18:00 – 18:59	18
07:00 – 07:59	7	19:00 – 19:59	19
08:00 – 08:59	8	20:00 – 20:59	20
09:00 – 09:59	9	21:00 – 21:59	21
10:00 – 10:59	10	22:00 – 22:59	22
11:00 – 11:59	11	23:00 – 23:59	23

Readings of valid records taken at the end of a monitoring that are less than 24 hours since dosing and which would have the same clock time hour as the first clock time hour defined at the beginning of the dosing period will be used. All readings taken at or beyond 24-hours after dosing will not be used in the calculation of hourly means relative to clock time. For example, if dosing was at 08:14 then records taken the following morning from 08:00 to 08:13 will be used in the calculation of the hourly mean for clock time hour 8 while all records taken after 08:13 will not be used.

Criteria for a successful monitoring

The following rules will be used to evaluate whether the entire 24-hour interval of readings is unsuccessful and may need to be repeated.

Criteria for Successful Monitors:

The following types of monitors will **not** be considered successful:

1. those with more than a total of six non-consecutive hourly means missing during the 24-hour dosing period, or
2. those with more than three consecutive hourly means missing during the entire 24-hour dosing period.

Although there are potentially inherent differences in the hourly means relative to dose time and relative to clock time, as well as inherent differences due to the method of defining clock time hour, determination of whether or not a monitoring is “successful” and potentially needs to be repeated will be based on the ABPM vendor’s calculations.

ABPM Derived Endpoints

For all successful monitorings at baseline the ABPM vendor will calculate the 24-hour mean relative to clock time for diastolic blood pressure (DBP) to determine whether the patient qualifies for randomization into the active treatment phase.

Additionally, for all successful ABPMs the following endpoints as defined below will be derived:

1. Last 6-hour mean for systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and pulse rate (PR), based on the hourly means relative to dose time,
2. 24-hour mean for SBP, DBP, MAP and PR, based on the hourly means relative to dose time,
3. Morning (06:00-11:59) mean for SBP, DBP, MAP and PR, based on the hourly means relative to clock time,
4. Daytime (06:00-21:59) mean for SBP, DBP, MAP and PR, based on the hourly means relative to clock time,
5. Night time (22:00-05:59) mean for SBP, DBP, MAP and PR, based on the hourly means relative to clock time,
6. Systolic and diastolic load (i.e. the overall percentage of valid measurements for SBP above 140 mm Hg during the daytime and above 130 mm Hg during the night time, and the overall percentage of valid measurements for DBP above 90 mm Hg during the daytime and above 85 mm Hg during the night time, respectively).

ABPM response rate definitions are:

- 1) ABPM DBP "control" rate: 24-hour mean DBP < 80 mm Hg
- 2) ABPM DBP "response" rate: 24-hour mean DBP < 80 mm Hg or a reduction from baseline of ≥ 10 mm Hg
- 3) ABPM SBP "response" rate: 24-hour mean SBP < 130 mm Hg or a reduction from baseline of ≥ 10 mm Hg.

Graphical Presentation of Hourly Means

The hourly ABPM means (relative to dosing time) at baseline and at the end of the study will be averaged over all patients to get overall mean blood pressure profiles over the 24 hour post-dose period. These mean profiles will be graphically displayed for all treatment groups.

The mean profiles of the change from baseline in hourly means (relative to dose time) will also be graphically displayed for all treatment groups.

It is only intended to perform these analyses for the primary ABPM analysis dataset as specified in the STATISTICS section of the protocol.