

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
27 July 2006 (27.07.2006)

PCT

(10) International Publication Number  
**WO 2006/078606 A2**

(51) International Patent Classification:  
*A61K 31/41* (2006.01) *A61P 9/12* (2006.01)

(21) International Application Number:  
PCT/US2006/001507

(22) International Filing Date: 17 January 2006 (17.01.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/645,328 19 January 2005 (19.01.2005) US

(71) Applicant (for all designated States except US): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant (for AT only): **NOVARTIS PHARMA GmbH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **DALEY, William Lionel** [US/US]; 1415 Gates Court, Morris Plains, New Jersey 07950 (US). **GRAVES, Kurt Chum** [US/CH]; Höhenweg 44, CH-4142 Münchenstein (CH).

(74) Agent: **FERRARO, Gregory, D.**; NOVARTIS, Corporate Intellectual Property Department, One Health Plaza, Bldg 104, East Hanover, NJ 07936-1080 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS OF TREATMENT

(57) Abstract: The invention relates to a method of preventing or treating vascular inflammation and other conditions mediated by CRP comprising administering an ARB, particularly valsartan, alone or in conjunction with other therapeutic agents.



WO 2006/078606 A2

## Methods of Treatment

### BACKGROUND OF THE INVENTION

Hypertension (HTN) is a major cardiovascular risk factor and the most common primary diagnosis in the United States (1). However, despite intense efforts to improve medical care and the availability of multiple antihypertensive medications, hypertension (HTN) control rates remain low and the incidence of associated cardiovascular events continue to increase. The recent guidelines for the treatment of hypertension (HTN) reported by the Joint National Committee (JNC 7) highlighted the need to enhance control rates and offered different strategies for improvement, including putting more emphasis on life-style and dietary modifications and a recommendation to use thiazide diuretics to enhance the antihypertensive efficacy of multidrug regimens. In addition, the committee recognized that most patients with the diagnosis of hypertension, particularly those with stage 2 hypertension (BP $\geq$ 160/100 mmHg), may require 2 or more antihypertensive medications to achieve their blood pressure (BP) goals and recommended the initiation of aggressive drug therapy with more than one agent in patients with stage 2 hypertension, as this may increase the likelihood of achieving blood pressure goals in a more timely fashion.

Multiple studies have documented that blood pressure reduction is associated with a major decrease in the incidence of stroke, myocardial infarction and heart failure (2). This reduction in major cardiovascular events is even greater in patients with established cardiovascular disease or target-organ damage (3). However, the mechanisms by which blood pressure reduction offers cardiovascular protection remain relatively unclear.

Vascular inflammation has been traditionally recognized as an important mechanism for vessel remodeling and dysfunction in the setting of atherosclerotic and coronary artery disease (CAD). However, an increasing number of studies suggest that vascular inflammation also occurs in the setting of essential hypertension. Studies in hypertensive animal models have shown evidence of early inflammatory vascular changes including perivascular leukocyte infiltration, as well as the expression of multiple cytokines in the vasculature of target organs such as kidney and heart (4-6).

At the clinical level, emerging data also suggest that inflammation may be an important mediator of the cardiovascular damage associated with hypertension. Studies by Chae and

coworkers have shown that circulating inflammatory markers such as soluble ICAM-1 and IL-6 correlate significantly with blood pressure in apparently healthy individuals (7). More recently, Ridker and collaborators have reported an important association between hypertension, serum high sensitivity C-reactive protein (hs-CRP), a marker of low-grade inflammation, and cardiovascular risk. These data importantly add to previous studies in which hsCRP was found to be a strong and independent predictor of cardiovascular risk among apparently healthy individuals, patients undergoing elective revascularization procedures, and patients presenting with acute coronary syndrome (ACS). Specifically, the results from this new study demonstrated a direct and strong correlation between blood pressure and hsCRP levels. However, they also documented for the first time that both hsCRP levels and blood pressure were independent predictors of future cardiovascular events, in that patients with both elevated hsCRP levels and elevated blood pressure had a greater relative risk for future cardiovascular events than those with high blood pressure and low hsCRP or low blood pressure and high hsCRP. This association was most pronounced in subjects with stage 2 hypertension (HTN) in which the presence of an elevated hsCRP level increased in almost 70% the risk of developing cardiovascular disease (Ridker presentation, ACC 2003). Moreover, Ridker et al have also recently shown that increasing levels of hsCRP predict the development of incident hypertension, even among those with low blood pressure at study entry.

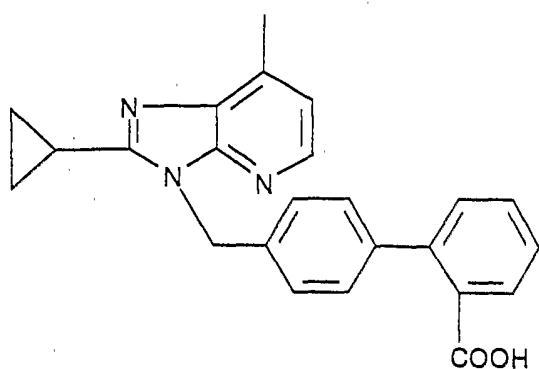
Despite the emerging evidence supporting a role for vascular inflammation in the pathophysiology of cardiovascular damage in hypertension, until the present invention clinical studies evaluating the potential efficacy of blood pressure lowering to reduce hsCRP levels in hypertensive individuals have been missing. In previous studies, inhibitors of 3-Hydroxy-3-Methylglutaryl coenzyme A reductase (statins) were found to reduce hsCRP levels in patients with or without prior history of cardiovascular disease. However, until the present invention antihypertensive therapies have not demonstrated that they also have the ability to reduce hsCRP levels.

(i) DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

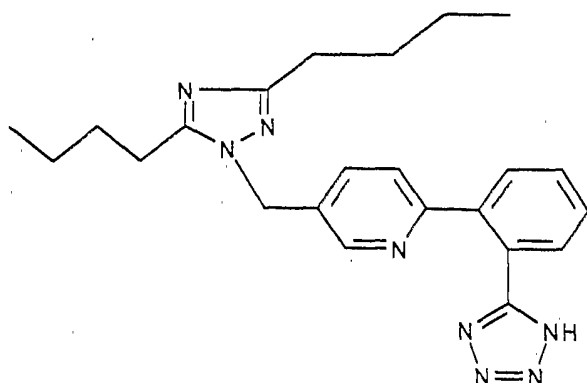
In one aspect the present invention relates to a method for the prevention of, delay of progression of or treatment of inflammation, particularly vascular inflammation or conditions

mediated by C-reactive protein (CRP) comprising administering to a warm-blooded animal, including man, in need thereof a pharmaceutical composition comprising an AT<sub>1</sub>-receptor antagonist or a pharmaceutically acceptable salt thereof.

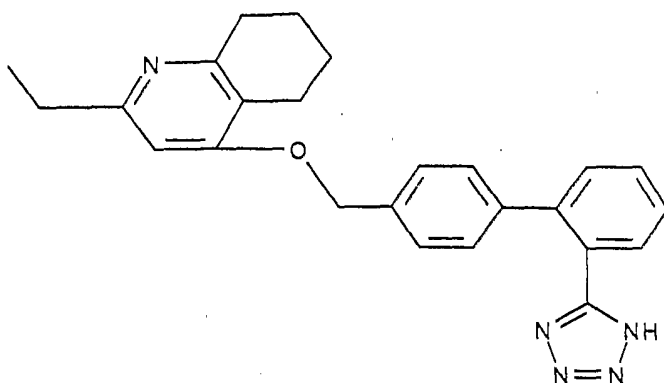
The class of AT<sub>1</sub> receptor antagonists comprises compounds having differing structural features, essentially preferred are the non-peptidic ones. For example, mention may be made of the compounds that are selected from the group consisting of valsartan (cf. EP 443983), losartan (cf. EP253310), candesartan (cf. 459136), eprosartan (cf. EP 403159), irbesartan (cf. EP454511), olmesartan (cf. EP 503785), tasosartan (cf. EP539086), telmisartan (cf. EP 522314), the compound with the designation E-1477 of the following formula



the compound with the designation SC-52458 of the following formula



and the compound with the designation the compound ZD-8731 of the following formula



or, in each case, a pharmaceutically acceptable salt thereof.

Preferred AT<sub>1</sub>-receptor antagonist are those agents that have been marketed, most preferred is valsartan or a pharmaceutically acceptable salt thereof.

In another aspect the present invention relates to a method for the prevention of, delay of progression of or treatment of inflammation, particularly vascular inflammation or conditions mediated by CRP comprising administering to a warm-blooded animal, including man, in need thereof a pharmaceutical composition consisting essentially of a therapeutically effective amount of an AT<sub>1</sub>-receptor antagonist or a pharmaceutically acceptable salt thereof. Preferably the AT<sub>1</sub>-receptor antagonist is Valsartan.

In yet another aspect the present invention relates to a method for the prevention of, delay of progression of, treatment of inflammation, particularly vascular inflammation or conditions mediated by CRP comprising administering to a warm-blooded animal, including man, in need thereof a pharmaceutical composition comprising an AT<sub>1</sub>-receptor antagonist or a pharmaceutically acceptable salt thereof in combination with at least one therapeutic agent selected from the group consisting of

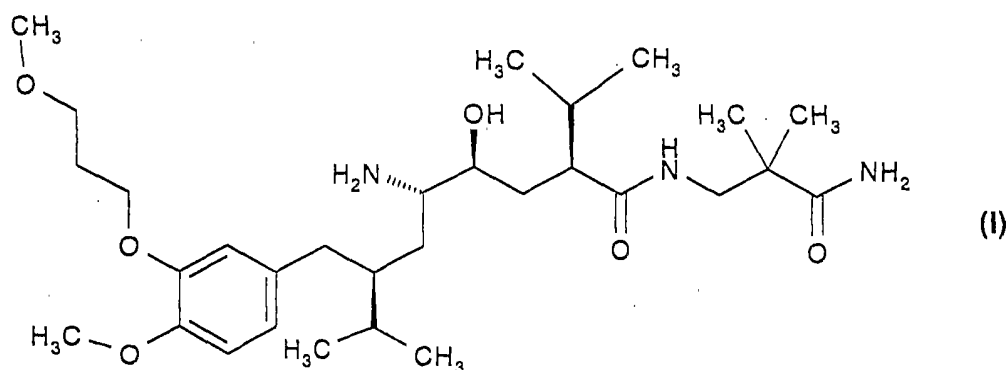
- (i) renin inhibitors or a pharmaceutically acceptable salt thereof,
- (ii) an angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable salt thereof,
- (iii) an Calcium channel blocker or a pharmaceutically acceptable salt thereof,
- (iv) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,
- (v) an aldosterone antagonist or a pharmaceutically acceptable salt thereof,
- (vi) an dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof,

- (vii) an endothelin antagonist or a pharmaceutically acceptable salt thereof, and
- (viii) a diuretic or a pharmaceutically acceptable salt thereof.

Preferably the AT<sub>1</sub>-receptor antagonist is Valsartan.

Renin inhibitors comprise, e.g., peptidic and, preferably, non-peptidic renin inhibitors.

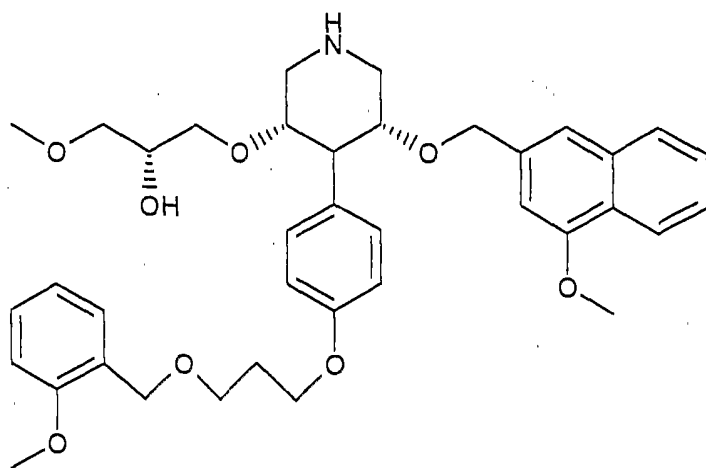
A non-peptidic renin inhibitor is, e.g., ditekiren, terlakiren, zankiren, SPP-100 or a compound of formula (I)



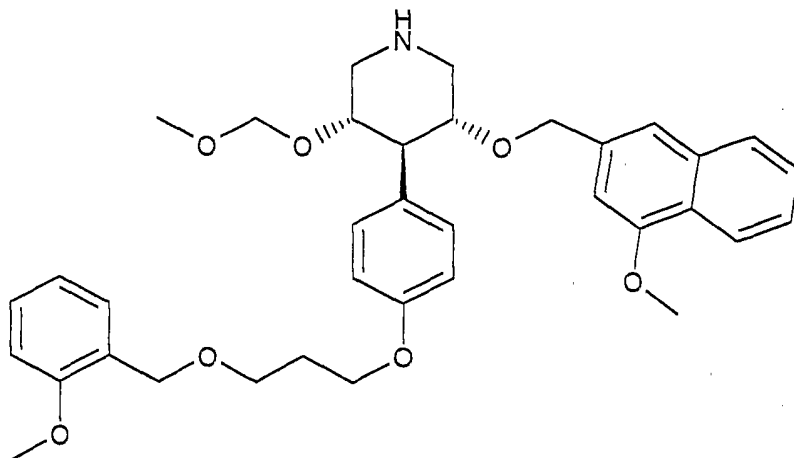
or, in each case, a pharmaceutically acceptable salt thereof.

The renin inhibitor of formula (I), chemically defined as 2(*S*),4(*S*),5(*S*),7(*S*)-*N*-(3-amino-2,2-dimethyl-3-oxopropyl)-2,7-di(1-methylethyl)-4-hydroxy-5-amino-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide, is specifically disclosed in EP 678503 A. Especially preferred is the hemi-fumarate salt thereof.

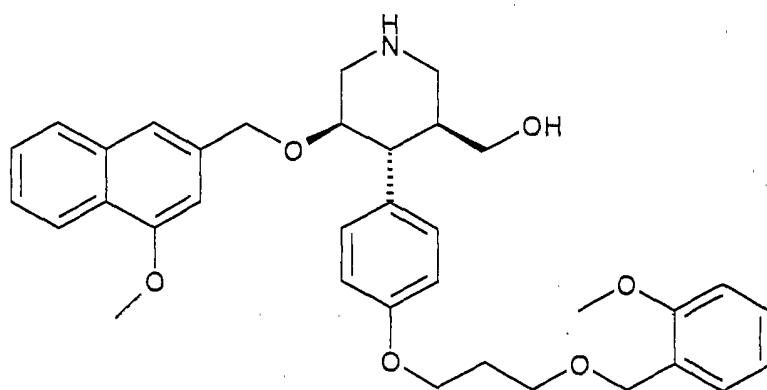
Non-peptidic renin inhibitor comprise those that are disclosed in WO 97/09311, especially corresponding renin inhibitors as disclosed in the claims and working examples, especially SPP100 of the formula



especially and of RO 66-1132 and RO-66-1168 of formula



or



respectively, WO 04/002957, especially those renin inhibitors as disclosed in the working examples and claims. The corresponding subject matter of said WO applications is herein incorporated by reference into the present invention.

The class of ACE inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds which are selected from the group

consisting of alacepril, benazepril, benazeprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, moveltopril, perindopril, quinapril, ramipril, spirapril, temocapril, and trandolapril, or, in each case, a pharmaceutically acceptable salt thereof.

Preferred ACE inhibitors are those agents that have been marketed, most preferred are benazepril and enalapril.

The class of CCBs essentially comprises dihydropyridines (DHPs) and non-DHPs such as diltiazem-type and verapamil-type CCBs.

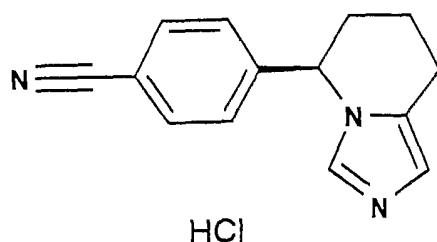
A CCB useful in said combination is preferably a DHP representative selected from the group consisting of amlodipine, felodipine, ryosidine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, and nivaldipine, and is preferably a non-DHP representative selected from the group consisting of flunarizine, prenylamine, diltiazem, fendiline, gallopamil, mibefradil, anipamil, tiapamil and verapamil, and in each case, a pharmaceutically acceptable salt thereof. All these CCBs are therapeutically used, e.g. as anti-hypertensive, anti-angina pectoris or anti-arrhythmic drugs. Preferred CCBs comprise amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, and verapamil, or, e.g. dependent on the specific CCB, a pharmaceutically acceptable salt thereof. Especially preferred as DHP is amlodipine or a pharmaceutically acceptable salt, especially the besylate, thereof. An especially preferred representative of non-DHPs is verapamil or a pharmaceutically acceptable salt, especially the hydrochloride, thereof.

Aldosterone synthase inhibitor is an enzyme that converts corticosterone to aldosterone to by hydroxylating cortocosterone to form 18-OH-corticosterone and 18-OH-corticosterone to aldosterone. The class of aldosterone synthase inhibitors is known to be applied for the treatment of hypertension and primary aldosteronism comprises both steroidal and non-steroidal aldosterone synthase inhibitors, the later being most preferred.

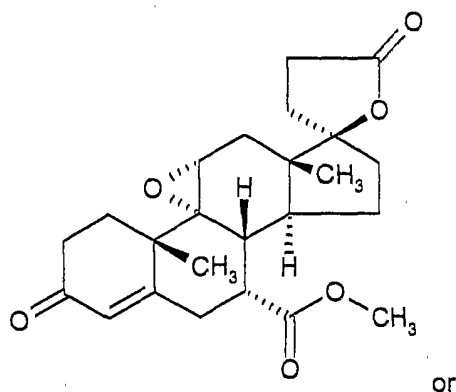
Preference is given to commercially available aldosterone synthase inhibitors or those aldosterone synthase inhibitors that have been approved by the health authorities.

The class of aldosterone synthase inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds which are selected from the group consisting of the non-steroidal aromatase inhibitors anastrozole, fadrozole (including the (+)-enantiomer thereof), as well as the steroidal aromatase inhibitor exemestane, or, in each case where applicable, a pharmaceutically acceptable salt thereof.

The most preferred non-steroidal aldosterone synthase inhibitor is the (+)-enantiomer of the hydrochloride of fadrozole (US patents 4617307 and 4889861) of formula



A preferred steroidal aldosterone antagonist is eplerenone of the formula



spironolactone.

A preferred dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor is, for example, omapatrilate (cf. EP 629627), fasidotril or fasidotrilate, or, if appropriate, a pharmaceutically acceptable salt thereof.

A preferred endothelin antagonist is, for example, bosentan (cf. EP 526708 A), furthermore, tezosentan (cf. WO 96/19459), or in each case, a pharmaceutically acceptable salt thereof.

A diuretic is, for example, a thiazide derivative selected from the group consisting of chlorothiazide, hydrochlorothiazide, methyclothiazide, and chlorothalidon. The most preferred is hydrochlorothiazide.

In another aspect the present invention relates to a method for the prevention of, delay of progression of treatment of inflammation, particularly vascular inflammation or conditions mediated by CRP comprising administering to a warm-blooded animal, including man, in need thereof a pharmaceutical composition consisting essentially of a therapeutically effective amount of an AT<sub>1</sub>-receptor antagonist or a pharmaceutically acceptable salt thereof in combination with at least one therapeutic agent selected from the group consisting of (i) through (viii) above. Preferably the AT<sub>1</sub>-receptor antagonist is Valsartan.

The structure of the active agents identified by generic or tradenames may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference.

The corresponding active ingredients or a pharmaceutically acceptable salts thereof may also be used in form of a solvate, such as a hydrate or including other solvents, used for crystallization.

The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having an acid group (for example COOH) can also form salts with bases.

A further aspect of the present invention is a kit for the prevention of, delay of progression of treatment of inflammation, particularly vascular inflammation, or conditions mediated by CRP comprising

- (a) an amount of an AT<sub>1</sub>-receptor antagonist or a pharmaceutically acceptable salt thereof in a first unit dosage form;

- (b) an amount of at least one therapeutic agent selected from the group consisting of components (i) to (viii), or, in each case, where appropriate, a pharmaceutically acceptable salt thereof in a second etc. unit dosage form; and
  - (c) a container for containing said first, second etc. unit forms.
- Preferably the AT<sub>1</sub>-receptor antagonist is Valsartan.

In another embodiment of this aspect of the present invention there is provided a kit for the prevention of, delay of progression of treatment of inflammation, particularly vascular inflammation or conditions mediated by CRP consisting essentially of

- (a) an amount of an AT<sub>1</sub>-receptor antagonist or a pharmaceutically acceptable salt thereof in a first unit dosage form;
  - (b) one therapeutic agent selected from the group consisting of components (i) to (viii), or, in each case, where appropriate, a pharmaceutically acceptable salt thereof in a second etc. unit dosage form; and
  - (c) a container for containing said first, second etc. unit forms.
- Preferably the AT<sub>1</sub>-receptor antagonist is Valsartan.

In a variation thereof, the present invention likewise relates to a "kit-of-parts", for example, in the sense that the components to be combined according to the present invention can be dosed independently or by use of different fixed combinations with distinguished amounts of the components, i.e. simultaneously or at different time points. The parts of the kit of parts can then e.g. be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Preferably, the time intervals are chosen such that the effect on the treated disease or condition in the combined use of the parts is larger than the effect that would be obtained by use of only any one of the components.

The invention furthermore relates to a commercial package comprising the combinations according to the present invention together with instructions for simultaneous, separate or sequential use.

A therapeutically effective amount of each of the component of the combinations of the present invention may be administered simultaneously or sequentially and in any order.

The corresponding active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of the pharmacologically active compound, alone or in combination with one or more pharmaceutically acceptable carriers, especially suitable for enteral or parenteral application. Typical oral formulations include tablets, capsules, syrups, elixirs and suspensions. Typical injectable formulations include solutions and suspensions. The typical pharmaceutically acceptable carriers for use in the formulations described above are exemplified by: sugars such as lactose, sucrose, mannitol and sorbitol; starches such as cornstarch, tapioca starch and potato starch; cellulose and derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; calcium phosphates such as dicalcium phosphate and tricalcium phosphate; sodium sulfate; calcium sulfate; polyvinylpyrrolidone; polyvinyl alcohol; stearic acid; alkaline earth metal stearates such as magnesium stearate and calcium stearate; stearic acid; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil and corn oil; non-ionic, cationic and anionic surfactants; ethylene glycol polymers; betacyclodextrin; fatty alcohols; and hydrolyzed cereal solids, as well as other non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, antioxidants, lubricants, flavoring agents, and the like commonly used in pharmaceutical formulations.

These pharmaceutical preparations are for enteral, such as oral, and also rectal or parenteral, administration to homeotherms, with the preparations comprising the pharmacological active compound either alone or together with customary pharmaceutical auxiliary substances. For example, the pharmaceutical preparations consist of from about 0.1 % to 90 %, preferably of from about 1 % to about 80 %, of the active compound. Pharmaceutical preparations for enteral or parenteral, and also for ocular, administration are, for example, in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner that is known per se, for example using conventional mixing, granulation, coating, solubilizing or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compound with solid excipients, if desired granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

Preferred dosages for the active ingredients of the pharmaceutical combination according to the present invention are therapeutically effective dosages, especially those which are commercially available.

Normally, in the case of oral administration, an approximate daily dose of from about 1 mg to about 360 mg is to be estimated e.g. for a patient of approximately 75 kg in weight.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

Valsartan, as a representative of the class of AT<sub>1</sub>-receptor antagonists, will be supplied in the form of suitable dosage unit form, for example, a capsule or tablet, and comprising a therapeutically effective amount, e.g. from about 20 to about 320 mg, of valsartan which may be applied to patients. While the precise dosage will vary depending on the individual patient, and some adjustment by the treating physician may be required, suitable dosages are generally as known in the art for the compounds for use in monotherapy. The application of the active ingredient may occur up to three times a day, starting e.g. with a daily dose of 20 mg or 40 mg of valsartan, increasing via 80 mg daily and further to 160 mg daily up to 320 mg daily. Preferably, valsartan is applied twice a day with a dose of 80 mg or 160 mg, respectively, each. Corresponding doses may be taken, for example, in the morning, at mid-day or in the evening. Preferred is b.i.d. administration.

The doses of renin inhibitor of formula (I) to be administered to warm-blooded animals, for example human beings, of, for example, approximately 70kg body weight, especially the doses effective in the inhibition of the enzyme renin, e.g. in lowering blood pressure and/or in improving the symptoms of glaucoma, are from approximately 3mg to approximately 3g, preferably from approximately 10mg to approximately 1 g, for example approximately from 20mg to 200mg, per person per day, divided preferably into 1 to 4 single doses which may, for example, be of the same size. Usually, children receive about half of the adult dose. The

dose necessary for each individual can be monitored, for example by measuring the serum concentration of the active ingredient, and adjusted to an optimum level. Single doses comprise, for example, 10, 40 or 100 mg per adult patient.

In case of ACE inhibitors, preferred dosage unit forms of ACE inhibitors are, for example, tablets or capsules comprising e.g. from about 5 mg to about 20 mg, preferably 5 mg, 10 mg, 20 mg or 40 mg, of benazepril; from about 6.5 mg to 100 mg, preferably 6.25 mg, 12.5 mg, 25 mg, 50 mg, 75 mg or 100 mg, of captopril; from about 2.5 mg to about 20 mg, preferably 2.5 mg, 5 mg, 10 mg or 20 mg, of enalapril; from about 10 mg to about 20 mg, preferably 10 mg or 20 mg, of fosinopril; from about 2.5 mg to about 4 mg, preferably 2 mg or 4 mg, of perindopril; from about 5 mg to about 20 mg, preferably 5 mg, 10 mg or 20 mg, of quinapril; or from about 1.25 mg to about 5 mg, preferably 1.25 mg, 2.5 mg, or 5 mg, of ramipril. Preferred is t.i.d. administration.

The following examples illustrate the above-described invention; however, it is not intended to restrict the scope of this invention in any manner.

#### Example 1

### 1 Introduction

The present study will compare the efficacy of an aggressive versus a moderate initial antihypertensive regimen to reduce blood pressure in patients with stage 2 hypertension with primary focus on systolic blood pressure reduction following the recommendation of the JNC 7 report. In addition, the study will examine the effects of blood pressure reduction on the levels of high sensitivity hsCRP in this patient population. Although the main goal will be to determine the overall effect of blood pressure reduction on hsCRP levels, analyses will also be performed to evaluate whether an aggressive antihypertensive regimen is more effective than a moderate one to reduce hsCRP levels. Thus, stage 2 hypertensive patients will be randomized to receive initial therapy with either Diovan alone (moderate approach) or Diovan in combination with a thiazide diuretic, Diovan HCT (aggressive approach). The results of this study will provide novel information around the potential value of an aggressive initial antihypertensive regimen with two agents versus only one as a strategy to better reduce blood pressure and hsCRP levels, a well-recognized CV risk factor, in patients with stage 2 hypertension.

## **2 Study Objectives**

### **2.1 Primary Objectives**

1. To compare the efficacy to reduce systolic blood pressure starting with a moderate versus an aggressive antihypertensive regimen after 6 weeks of treatment in subjects with stage 2 hypertension.
2. To evaluate the change in plasma hsCRP levels after 12 weeks of antihypertensive therapy in patients with stage 2 hypertension.
3. To evaluate the change in plasma hsCRP levels after 6 weeks with a moderate versus an aggressive initial antihypertensive regimen in subjects with stage 2 hypertension.

### **2.2 Secondary Objectives**

1. To compare the efficacy of a moderate versus an aggressive initial antihypertensive regimen to reduce diastolic blood pressure and pulse pressure.
2. To assess the relationship between the changes in CRP levels and systolic blood pressure, diastolic blood pressure, and pulse pressure.
3. To perform exploratory pharmacogenetic assessments to examine whether individual genetic variation in genes relating to drug metabolism, hypertension, and the drug target pathway confer differential response to Diovan® and Diovan HCT®.

## **3 Investigational plan**

### **3.1 Overall study design**

Baseline Evaluation → 2 weeks Diovan 160 mg or Diovan HCT 160/12.5 mg → 10 weeks Diovan 320 mg or Diovan HCT 320/12.5 mg → End of Study Visit/Evaluation

This will be a multicenter, randomized, open-label study with two parallel groups designed to (a) compare the ability of a moderate versus an aggressive initial antihypertensive regimen to reduce systolic blood pressure, diastolic blood pressure, and pulse pressure in patients with stage 2 hypertension; and (b) evaluate the effects of this blood pressure reduction on hsCRP and (c) compare the ability of a moderate versus an aggressive initial antihypertensive regimen to reduce hsCRP. The diagnosis of stage 2 hypertension (HTN) is defined as either systolic  $\geq 160$  mmHg or diastolic blood pressure  $\geq 100$  mm Hg. This diagnosis will be based on the mean of three (3) consecutive, properly measured seated blood pressure readings at Visit 1 (Day 0). Patients with systolic blood pressure  $> 185$  or diastolic blood pressure  $> 109$  will not be included in the present study. Following a screening evaluation, patients will be randomized to either Diovan 160 mg once daily for 2 weeks or Diovan HCT 160/12.5 mg once daily for 2 weeks.

Baseline blood pressure for this study will be defined as the mean of three seated systolic and diastolic blood pressure measurements performed with the Omron electronic BP

monitoring system prior to study drug initiation. During the screening period (Day -7 to Day -1), eligibility will be determined according to blood pressure, inclusion/exclusion criteria, and concomitant medication criteria. Should the patient not have documentation that the above laboratory measurements were conducted within the appropriate timeframe, new measurements must be obtained during the screening period, and criteria satisfied prior to randomization of the patient in the study.

If eligible, the patient will be scheduled to come to the office for Visit 1 (Day 0) to perform the baseline blood pressure measurements and obtain a blood sample for determination of baseline plasma hsCRP levels. The patient will be given the study medication with instructions to take one Diovan 160 mg tablet once daily for 2 weeks or instructions to take one Diovan HCT 160/12.5 tablet once daily for 2 weeks, according to randomization.

At Visit 2 (Week 2), subjects will complete evaluations for electronic blood pressure measurements and an inquiry regarding the occurrence of adverse events. The patient will be force-titrated to the next level and instructed to take either Diovan 320 mg (one Diovan 320 mg tablet) once daily for 4 weeks or Diovan HCT 320/12.5 mg (one Diovan HCT 160/12.5 mg tablet plus one Diovan 160mg tablet) once daily for 4 weeks. Patients should be asked not to take study medication, for that day, before coming to the office for Visit 2. The first dose of new level should be administered at the site during Visit 2, after all measurements have been taken.

At Visit 3 (Week 6), patients will complete evaluations for electronic blood pressure measurements and an inquiry regarding the occurrence of adverse events. Patients will also provide a blood sample for determination of plasma hsCRP levels. If blood pressure remains uncontrolled (SBP  $\geq 140$  or DBP  $\geq 90$ ), the Principal Investigator will be permitted to adjust the dosing regimen as follows: 1) for patients receiving Diovan 320 mg, the Principal Investigator (PI) may up-titrate and instruct the patient to take Diovan HCT 320/12.5 mg (one Diovan 160 mg tablet plus one Diovan HCT 160/12.5 mg tablet) once daily for 6 weeks; 2) for patients receiving Diovan HCT 320/12.5, the Principal Investigator (PI) may up-titrate and instruct the patient to take Diovan HCT 320/25 mg (one Diovan 160 mg tablet plus one Diovan HCT 160/25 mg tablet) once daily for 6 weeks. Patients must remain on the dosing regimen provided at Visit 3 (Week 6) until the end of study (Visit 4, Week 12). Patients should be asked not to take study medication before coming to the office for Visit 3. The first dose of new level should be administered at the site during Visit 3, after all measurements have been taken.

At Visit 4 (Week 12), patients will return for the final visit. Evaluations will include electronic blood pressure measurements and an inquiry regarding the occurrence of adverse events. Patients will also provide a blood sample for determination of plasma hsCRP levels.

Approximately 2528 subjects with stage 2 hypertension (HTN) will be randomized in approximately 500-700 centers in the United States.

A diagram of the study is shown below with times indicated relative to treatment start:

### 3.2 Discussion of design

Twelve (12) weeks of open label, randomized treatment, two arm, parallel group, was selected for this study to evaluate the effect of moderate versus aggressive antihypertensive therapy to reduce systolic and diastolic blood pressure and plasma CRP levels in subjects

with stage 2 hypertension (BP  $\geq 160/100$ ). Blood pressure will be measured by the mean of three (3) seated blood pressure measurements using an Omron electronic blood pressure measuring system at all visits (Visit 1, 2, 3 and 4).

Subjects will be randomized to either Diovan or Diovan HCT at Visit 1 (Day 0). Subjects randomized to Diovan will take Diovan 160 mg for 2 weeks and be force titrated to Diovan 320 mg at Visit 2 (Week 2) for an additional 4 weeks period. Subjects randomized to Diovan HCT will take Diovan HCT 160/12.5 mg for 2 weeks and be force titrated to Diovan HCT 320/12.5mg at Visit 2 (Week 2) for an additional 4 weeks period.

At Visit 3 (Week 6), subjects randomized to Diovan 320 mg at Visit 2 (Week 2), who have achieved blood pressure control of  $< 140/90$  mm Hg will receive instructions to take Diovan 320mg once daily for an additional 6 weeks, until the end of the study. Subjects randomized to Diovan 320 mg at Visit 2, who have not achieved blood pressure control of  $< 140/90$  mmHg may be up-titrated, at the Principal Investigator's discretion, and given instructions to take Diovan HCT 320/12.5 mg (one Diovan 160 mg tablet plus one Diovan HCT 160/12.5 mg tablet) once daily until the end of the study. Subjects randomized to Diovan HCT 320/12.5 mg at Visit 2, who have achieved blood pressure control of  $< 140/90$  mmHg will receive instructions to take Diovan HCT 320/12.5 mg once daily for an additional 6 weeks, until the end of the study. Subjects randomized to Diovan HCT 320/12.5 mg at Visit 2, who have not achieved blood pressure control of  $< 140/90$  mmHg may be up-titrated, at the Principal Investigator's (PIs) discretion, and given instructions to take Diovan HCT 320/25 mg (one Diovan 160 mg tablet plus one Diovan HCT 160/25 mg tablet) once daily until the end of the study.

Plasma hsCRP levels will be measured at Visit 1 (Day 0) to establish a baseline measurement. The plasma hsCRP level will be repeated at Visit 3 (Week 6) and at Visit 4 (Week 12).

#### **Treatment Phase:**

The purpose of Visit 1 (Day 0) will be to confirm screening the patient and determine if the patient meets entry criteria. If the patient meets entry criteria, a plasma hsCRP level will be measured to capture a baseline value.

Eligible subjects who are determined to have stage 2 hypertension (HTN) will be enrolled into the study at Visit 1 (Day 0) and be treated with a once daily dose of Diovan 160 mg or Diovan HCT 160/12.5 mg for a period of two (2) weeks. At Visit 2 (Week 2), subjects will return to the office and receive a force titrated dose of either Diovan 320 mg or Diovan HCT 320/12.5 mg, according to their randomization. The subject will remain on this dose for four (4) weeks until Visit 3 (Week 6). (See diagram in Section 3.1).

If blood pressure is still uncontrolled at Visit 3 (Week 6), the Principal Investigator (PI) is allowed to up-titrate the dose to either Diovan HCT 320/12.5 mg (for subjects randomized to Diovan 320 mg at Visit 2) or Diovan HCT 320/25 mg (for subjects receiving Diovan HCT 320/12.5 mg at Visit 2). The subject will remain on this dose for 6 weeks until the final visit (Visit 4, Week 12). Plasma Serum hsCRP levels will also be measured at Visit 3.

At Visit 4 (Week 12), the subject will return to the office for the End of Study visit and a plasma serum hsCRP level will be measured.

Approximately 2528 subjects will be enrolled at approximately 500-700 centers. The total treatment duration for each subject will be thirteen (13) weeks.

### 3.3 Study population

#### 1. 3.3.1 Patient population

Eligible patients will include both male and female patients with stage 2 hypertension (HTN) between 18 and 75 years of age, inclusive. The patients will be required to have hypertension (HTN) with a systolic blood pressure (SBP) of 160 to 185 mmHg, inclusive and/or a diastolic blood pressure (DBP) of 100 to 109 mmHg, inclusive. Patients must not have received ACE inhibitors, aldosterone receptor antagonists, other angiotensin receptor blockers, during the 3 months prior to Visit 1 (Day 0), or thiazide diuretics during the month prior to Visit 1 (Day 0).

A total of 2528 randomized patients will be required for this study. Approximately 500-700 study centers will participate in this trial in which 1264 patients will be assigned to each treatment group. The intent-to-treat (ITT) population, consisting of all randomized patients from whom at least one post-baseline hsCRP measurement is obtained, will be used as a primary efficacy population. (Refer to Section 6, Statistical methods, for justification of sample size.)

#### 2. 3.3.2 Inclusion and exclusion criteria

The decision to enroll a patient in the present study will be made by the Principal Investigator (PI) according to the inclusion and exclusion criteria listed below together with a careful evaluation of the medical history, laboratory analyses and physical examination and concomitant medication criteria (refer to Section 3.4.4) for each individual patient.

##### Beispiel 1: Inclusion criteria

Patients enrolled in this study must meet all of the following inclusion criteria.

1. Be able to provide written informed consent to participate in the study prior to any screening or study procedures and be able to come to the office visits in the morning (between 7 am and 10:00 am), Monday through Thursday
2. Male or female, 18-75 years of age, inclusive
3. Stage 2 hypertension as defined by the mean of three (3) repeated seated blood pressure measurements (taken consecutively) using an Omron electronic blood pressure measuring system at visit 1 (Day 0) of:
  - SBP of 160 to 185 mmHg, inclusive and/or
  - DBP of 100 to 109 mmHg, inclusive
4. Patients must have documentation of serum creatinine  $\leq 2.0$  mg/dL, serum potassium  $\geq 3.5$  and  $\leq 5.5$  mmol/L, and serum AST or ALT ( $< 2 \times$  ULN) obtained within 3 months prior to visit 1
5. Patients must have documentation of HbA1C  $\leq 11.0\%$  obtained within 1 month prior to visit 1

Should the patient not have documentation that the above laboratory measurements were conducted within the indicated time frame, new measurements must be obtained during the screening period, and criteria satisfied prior to randomization of the patient in the study.

6. Ability to communicate and comply with all study requirements
7. All females of childbearing potential must be practicing an effective non-hormonal method of birth control

Women of Child Bearing Potential (WOCBP) include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea  $\geq 12$  consecutive months). Even women who are using mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g. vasectomy), should be considered of child bearing potential.

WOCBP must have a negative urine pregnancy test at Visit 1 (week 0).

Beispiel 2: Exclusion criteria

A patient with any of the following exclusion criteria cannot be enrolled in the study:

1. History of secondary hypertension (including primary aldosteronism, renovascular hypertension, pheochromocytoma, etc.)
2. Mean SBP  $> 185$  mmHg and/or mean DBP  $> 109$  mmHg
3. Pharmacologic antihypertensive therapy with ACE inhibitors, angiotensin receptor blockers, or aldosterone blockers, within 3 months prior to Visit 1 or with thiazide diuretics within 1 month prior to Visit 1. Use of other classes of agents which lower blood pressure but are being used for the treatment of myocardial infarction or angina (such as calcium channel blockers and beta-blockers) or for the treatment of hypertension are allowed as long as these agents are started at least 3 months prior to randomization and are not initiated after enrollment (refer to Section 3.4.4) and doses remain unchanged during the study
4. Initiation of lipid-lowering pharmacologic therapy or any change in lipid-lowering dose less than 6 weeks prior to Visit 1. The dose cannot be modified at any time during the course of the study
5. Myocardial infarction, stroke, or cardiovascular revascularization/angioplasty, unstable angina pectoris, or onset of congestive heart failure within the last 6 months
6. History of hospitalization within the last month prior to Visit 1
7. Pregnant or lactating females
8. A positive urine pregnancy test at Visit 1 (week 0)
9. Uncontrolled treated diabetes mellitus (DM) defined as:
  - HbA<sub>1c</sub>  $> 11.0$  % within the month prior to Visit 1
10. Diagnosis of cancer, excluding basal cell carcinoma, within 5 years prior to enrollment in the study, or any life threatening illness with expected death within 5 years
11. Documentation of serum creatinine  $> 2.0$  mg/dl within 3 months prior to Visit 1
12. Documentation of serum potassium  $< 3.5$  or  $> 5.5$  mEq/L within 3 months prior to Visit 1

13. Documentation of any serum AST or ALT elevation 2 x the upper limit of normal within 3 months prior to Visit 1
14. Hypersensitivity to Diovan or other angiotensin II receptor blockers (ARBs) or hydrochlorothiazide (HCT)
15. Any chronic inflammatory condition such as rheumatoid arthritis, osteoarthritis, lupus, chronic inflammatory bowel disease or need for chronic anti-inflammatory therapy such as prednisone, or other steroid agents. The use of inhaled, topical or nasal steroids or the use of occasional aspirin or ibuprofen-type drugs at any dose is allowed during the study
16. Any medical condition in the investigator's opinion, which renders the patient unable to complete the study or which would produce significant risk to the patient
17. Administration of any other investigational drug within 30 days of planned enrollment into the study

### 3. 3.3.3 Interruption or discontinuation of treatment

In case of interruption of study drug, as defined above, for > 72 hours the subject must be discontinued in the study and the Study Completion CRF must be completed.

Any subject who discontinues study medication for ≤ 72 hours should restart the study medication at the next scheduled dosing time as per the prescribed dosing regimen.

It will be documented whether or not each subject completed twelve weeks of therapy. In the event of early discontinuation from the study, the reason for discontinuation must be documented in the CRF. Reasons that a subject may discontinue participation in a clinical study include the following:

1. adverse event(s)
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. unsatisfactory therapeutic effect
5. subject's condition no longer requires study treatment
6. protocol violation
7. subject withdrew consent
8. lost to follow-up
9. administrative problems
10. death

If a subject is discontinued or decides to withdraw from the study, all Visit 4 (Week 12) evaluations should be performed within the week of discontinuation.

If a subject discontinues early due to a serious adverse event (SAE), the SAE case report form must be completed regardless of causality.

All dispensed medication supplies should be reconciled, and the Adverse Events and Concomitant Medications CRFs should be updated. It will be documented whether or not each subject completed the clinical study on the Study Completion CRF and the reason discontinuation of either study treatment or observations will be recorded.

Every subject has the right to discontinue study participation at any time, and every subject may be discontinued from the study for any reason the subject or the investigator may find important to his/her well being. All data generated up to the time of discontinuation from the study will be evaluated. If a subject is lost to follow-up, every possible effort should be made to contact the subject to obtain visit information and unused study drug.

Beispiel 1: Discontinuation due to uncontrolled hypertension

In the event that following randomization at Visit 1 (Day 0), and not including Visit 3, the patient demonstrates a mean blood pressure: SBP measurement  $\geq 186$  mmHg or a DBP measurement  $\geq 110$  mmHg, the patient should be brought back to the office for an unscheduled visit within 48 hours. The Unscheduled Visit CRF page must be completed. If during the follow-up visit, the mean SBP measurement remains  $\geq 186$  mmHg or the mean DBP measurement remains  $\geq 110$  mmHg, the patient must be discontinued from the study and appropriate treatment for HTN instituted. The patient should complete the End of Study Procedures (Visit 4, Week 12).

Similarly, if BP is found to be  $\geq 180/105$  mmHg at Visit 3 (Week 6), the patient must be discontinued from the study and complete the End of Study Procedures (Visit 4, Week 12). Appropriate treatment for hypertension (HTN) should then be instituted.

Note: The addition of concomitant antihypertensive medication (refer to Section 3.4.4) is not permitted during the study.

Beispiel 2: Discontinuation due to hypotension

If the subject demonstrates clinical symptoms of hypotension or a SBP measurement  $<105$  mmHg, the subject should be told to stop taking study drug and return to the office within 2 days (48 hours). The subject should complete the End of Study procedures (Visit 4, Week 12) and be discontinued from the study.

Down titration of the study medication is not permitted.

Beispiel 3: Pregnancy

A urine pregnancy test will be performed at every visit for women of child bearing potential (WOCBP). If a female subject becomes pregnant during the course of the study, the study drug must be discontinued immediately and the subject must be terminated from the study. The subject should complete the End of Study procedures (Visit 4, Week 12). Appropriate treatment for hypertension (HTN) should be instituted. The Novartis Pregnancy SAE Form must be completed, as per Section 9.1.2 Instructions for rapid notification of pregnancies.

### 3.4 Treatments

#### 1. 3.4.1 Investigational therapy and reference therapy

The sponsor will supply Diovan 160 mg, Diovan 320 mg, Diovan HCT 160/12.5 mg and Diovan HCT 160/25 mg tablets. Study drug will be supplied in bottles. The study drug is to be taken once daily orally between 7:00 am and 10:00 am.

The study drugs must be stored in a locked storage facility until returned as per the sponsor's instructions at the end of the study.

Medication labels will comply with legal requirements. The storage conditions for study drug will be described on the medication label.

### General Dosing Instructions

Beispiel 1: Starting at Visit 1 (Day 0), each patient will take one (1) Diovan 160 mg tablet or one (1) Diovan HCT 160/12.5mg tablet per day for a two (2) week duration. Patients will be reminded not to take study medication in the morning of the day they are scheduled to come for Visit 2. At Visit 2 (Week 2), each patient will be given a force titrated dose of Diovan 320mg or Diovan HCT 320/12.5 mg with instructions to take the dose once daily for an additional four (4) weeks. Patients receiving Diovan 320mg will be given one (1) new bottle with Diovan 320 mg tablets with instructions to take one (1) tablet per day. Patients receiving Diovan HCT 320/12.5 mg will receive one (1) new bottle of Diovan HCT 160/12.5 mg tablets plus one (1) bottle of Diovan 160mg tablets with instructions to take one (1) tablet from each bottle per day, at the same time. Should the patient forget and take the study medication in the morning of the day of Visit 2, the patient should begin their new dose the morning after their Visit 2. At Visit 3 (Week 6), each patient will either receive the same dose of medication that was given to them at Visit 2 (Week 4) or be up-titrated to Diovan HCT 320/12.5 mg (one Diovan 160 mg tablet plus one Diovan HCT 160/12.5 mg tablet per day, taken at the same time) or Diovan HCT 320/25 mg (one Diovan 160 mg tablet plus one Diovan HCT 160/25 mg tablet per day, taken at the same time), with instructions to take this dose for an additional six (6) weeks.

Patients must be instructed on the following points related to study medication dosing:

- On the day of a scheduled visit, study medication will be taken at the site in the morning after all assessments are completed
- Study medication must be taken between 7:00 am and 10:00 am
- If a dose is missed, the patient is to skip that dose and not take a next dose until the following day
- Medication bottles must be brought back to the study center at the next visit
- Attempt to maintain the same dosing schedule each day

### 2. 3.4.2 Treatment assignment

Each investigational center is given a unique four-digit center (or site) number (i.e. 0001, 0121, 2467). The center, or site, number is not part of the patient number. The patient identification number will consist of five digits. At the Screening Visit, each patient will be assigned a unique patient identification number. Patient numbering is sequential and consecutive at each site. For example, at site 0121, the first patient who signs the informed

consent form will be patient 00001/initials. The second patient who signs the informed consent form at center 0121 will be patient 00002/initials. Patient numbers are recorded in the headers of case report forms (CRFs).

The patient number assigned at the Screening visit will be used by the patient subject for the remainder of the study and cannot be reused by any other patient subject.

Patients who meet the criteria for randomization will be assigned a unique four-digit randomization number in sequential order of the drug supply at the clinical site. The randomization number must be recorded on page 2 of the CRF. Once a patient is assigned to a randomization arm and allocation, this allocation and randomization assignment will remain consistent with the patient for the duration of the study.

The randomization code will be listed on the patient kit (medication pack) and on the bottles located inside the patient's medication pack. The Principal Investigator will label the patient's medication pack and the bottles with the patient initials and patient number. The Principal Investigator will supply the patient with the medication and instructions for the first two (2) weeks of the study. When the patient returns for visit 2 (Week 2), the Principal Investigator (PI) will supply the force-titrated dose with instructions for the next four weeks, after which patients will return for Visit 3 (Week 6). The same dose or an optional up-titrated dose will be given to the patient at Visit 3 (Week 6).

Randomization will be performed by Novartis Drug Supply Management using a validated system that automates the random assignment of treatment groups to randomization numbers. The randomization scheme will be reviewed by the Quality Management Biostatistics Group and locked by them after approval.

### 3. 3.4.3 Blinding

There is no blinding of study medication in this study. Investigators and Patients will be blinded from CRP measurements. The central laboratory will have no knowledge of the study group for any sample and will be blinded from the treatment randomization.

### 4. 3.4.4 Concomitant therapy

The investigators should be familiar with the indications, contraindications, warnings, and precautions listed in the Diovan and Diovan HCT package insert located in the Investigator Brochure located in the investigator binder.

The patient must be instructed not to take any additional medication (including over-the-counter medications) without informing the investigator. The classification of concomitant medications and treatments will be recorded in the CRF at each visit. Classifications used will be: Cardiovascular; Anti-hypercholesterolemics; CNS agents; GI agents; Anti-diabetic agents; Anti-inflammatory agents; Anti-infectives; Other.

Initiation of other concomitant pharmacological treatment for the indication of hypertension (HTN) will not be allowed during the course of the study. If a patient has been receiving antihypertensive medications other than ACE inhibitors, angiotensin receptor blockers or aldosterone blockers, either for the treatment of hypertension or for indications other than hypertension (HTN) (e.g., calcium channel blockers and beta-blockers for angina), these medications must have been started at least 3 months prior to Visit 1 (Day 0) and the doses should not be altered during the course of the study. Patients with a previous history of

treatment with a thiazide diuretic must have been off this type of agent for at least one month prior to Visit 1.

The initiation of lipid-lowering pharmacologic therapy is not allowed at any time during the study. If a patient is receiving lipid lowering therapy prior to enrollment in the study, therapy must have been started at least 6 weeks prior to Visit 1 (Day 0) and the dose of the lipid lowering medication cannot be modified at any time during the study.

The use of the following medications may interfere with the evaluation of efficacy, safety and tolerability and are therefore excluded throughout the study, from the beginning of the Visit 1 (Day 0) to the end of the treatment period. Patients who are required to use such medication(s) after Visit 1 (Day 0) should be excluded:

- ACE inhibitors
- Aldosterone receptor antagonists (i.e. **spironolactone, eplerenone**)
- Other angiotensin receptor blockers
- Steroidal anti-inflammatory medications (with the exception of inhaled/nasally applied /topical steroidal medications) or chronic non-steroidal anti-inflammatory medications
- Diuretics (other than assigned study medication, if applicable)
- Chronic aspirin > 325 mg per day

All other prior non-study medication(s) will be allowed, provided the need for such medication(s) is a continuation of a need that existed prior to entry into the study and the manner in which the medication(s) will be used remains unchanged. All current and newly administered or prescribed concomitant medication(s), including over-the-counter medication, must be recorded on the Concomitant Medications/Significant Non-Drug Therapies CRF.

Acute and intermittent use of acetaminophen or aspirin (> 325 mg per day) is permitted during the trial, as is occasional use of non-steroidal anti-inflammatory medications.

Medications deemed necessary for the general health and well-being of the patient, including potassium supplements, except those listed above will be allowed before and during the course of the study.

If any of the above excluded medications are taken after Visit 1 (Day 0), it is considered a protocol violation that must be reported to the Val-MARC Study Team at Novartis.

Restrictions referenced in the Diovan Package Insert and Diovan HCT Package Insert, located in the Investigator Binder, should be adhered to during the study.

#### 5. 3.4.5 Treatment compliance

Records of study medication used, dosages administered, and intervals between visits will be kept during the study by the study coordinator. These records will be retained at the site as part of the source documents. Drug accountability will be noted by the field monitor during required site visits and at the completion of the trial, during the close out visit. Subjects will be asked to return all unused medication at the end of the study.

### 3.5 Visit schedule and assessments

#### Beispiel 1: 3.5.1 Evaluation and Visit Schedule

##### **Screening Period (Day -7 to -1)**

During this period, Principal Investigators will review and evaluate the eligibility of patients to participate in the study based on the inclusion and exclusion criteria. Also, the protocol should be discussed with the patient during this period. The patient should read and sign the informed consent. Written informed consent must be obtained prior to conducting any study procedures, including blood draws for screening lab. If the patient lacks any of the laboratory measurements required to determine eligibility to participate in the study, new measurements must be obtained during this period.

##### **Visit 1 (Day 0)**

Patients who meet eligibility criteria (see 3.3 Study Population) will be scheduled for this visit.

The following will be performed or reported:

- Confirm that the patient has read and signed the informed consent. Written informed consent must be obtained prior to conducting any study procedures.
- Take a medical history and document any pre-existing conditions/concomitant illnesses. Any new or worsening event occurring between Screening and Baseline should be considered part of the patient's medical history.
- Inquire about any concomitant medications or significant non-prescription therapies with which the patient is currently being treated. The patient must be instructed not to take any concomitant medication including over the counter medications without informing the investigator.
- Perform urine pregnancy test for WOCBP.
- Using the Omron blood pressure monitor, measure the sitting pulse rate and mean of 3 consecutive seated blood pressures using the electronic blood pressure monitoring system as described in Section 3.5.3. Using the print out from the electronic blood pressure monitoring system, record the mean sitting pulse rate and each of the 3 consecutive seated blood pressure measurements.
- Perform a Physical Examination.
- Verify that the patient meets the protocol inclusion/exclusion criteria and completed the Inclusion/Exclusion Criteria Form. The Principal Investigator must sign this form at this time.
- Inquire about any Serious Adverse Events
- Collect blood sample for plasma hsCRP analysis and pharmacogenetics assessments.
- Dispense and administer first dose of medication to the patient as outlined in Section 3.3. The patient will receive either Diovan 160 mg or Diovan HCT 160/12.5 mg according to randomization. Instruct the patient to take the dose daily in the morning (between 7 am and 10 am) for the duration of the study except for the morning of Visits 2, 3, and 4.

- Schedule Visit 2 (Week 2) with the patient. Patients will be scheduled in the morning, between 7 AM and 10 AM. Remind the patient not to take their study medication the morning of Visit 2.
- Complete the Visit 1 case report form (CRF).

### **Visit 2 (Week 2)**

Visit 2 will be scheduled 2 weeks  $\pm$  3 days after Visit 1.

The following will be performed or reported:

- Collect medication bottle from prior visit. Ask patient if he/she took study medication that morning
- Inquire about any concomitant medications or significant non-drug therapies with which the patient is currently being treated.
- Inquire about any newly occurring or worsening adverse experiences since the previous visit or about any change in current medical condition.
- Perform urine pregnancy test for WOCBP.
- Measure the sitting pulse rate and mean of 3 consecutive seated blood pressures using the electronic blood pressure monitoring system as described in Section 3.5.3. Using the print out from the electronic blood pressure monitoring system, record the mean sitting pulse rate and each of the 3 seated blood pressure measurements
- Dispense and administer a new dose from next bottles if morning dose of study medication not taken. If patient took dose on the day of the visit, instruct the patient to take a new dose of study medication in the morning of the next day
- Schedule Visit 3 (Week 6) with the patient. Patients will be scheduled in the morning, between 7 am and 10 am. Remind the subject not to take the dose of study medication in the morning of their Visit 3
- Complete Visit 2 case report form (CRF).

### **Visit 3 (Week 6)**

Visit 3 will be scheduled 6 weeks  $\pm$  7 days after Visit 1.

The following will be performed or reported:

- Collect medication bottles from prior visit. Ask patient if he/she took study medication that morning
- Inquire about any concomitant medications or significant non-drug therapies with which the patient is currently being treated.
- Inquire about any adverse experiences since the previous visit or about any change in current medical condition.
- Perform urine pregnancy test for WOCBP.
- Measure the sitting pulse rate and mean of 3 consecutive seated blood pressures using the electronic blood pressure monitoring system as described in Section 3.5.3. Using the

print out from the electronic blood pressure monitoring system, record the mean sitting pulse rate and each of the 3 seated blood pressure measurements

- Collect blood sample for determination of plasma hsCRP levels.
- Determine if patient has achieved normal BP of < 140/90 mmHg.
- Dispense and administer an assigned dose or optional dose of study medication according to patient's mean BP. Instruct the patient to take a new dose of study medication in the morning of the next day
- Schedule Visit 4 (Week 12) with the patient. Patients will be scheduled in the morning, between 7 AM and 10 AM. Remind the patient not to take the dose of study medication in the morning of their Visit 4
- Complete Visit 3 case report form (CRF).

#### **Visit 4 (Week 12, end of study)**

Visit 4 will be scheduled 12 weeks  $\pm$  7 days after Visit 1.

At Visit 4, the following will be performed or reported:

- Collect any remaining medication bottles from the patient.
- Inquire about any concomitant medications or significant non-drug therapies with which the patient is currently being treated.
- Inquire about any newly occurring or worsening adverse experiences since the previous visit or about any change in current medical condition
- Perform urine pregnancy test for WOCBP.
- Measure the sitting pulse rate and mean of 3 seated blood pressures using the electronic blood pressure monitoring system as described in Section 3.3.2. Using the print out from the electronic blood pressure monitoring system, record the mean sitting pulse rate and each of the 3 seated blood pressure measurements
- Administer the last dose of study medication, if patient did not take study medication that morning, prior to their visit.
- Collect blood sample from patient for determination of plasma hsCRP levels
- Complete Visit 4 case report form (CRF).

## **2. 3.5.2 Efficacy assessments**

### **Primary Efficacy Variables:**

The primary efficacy variables are:

1. Change in mean sitting systolic blood pressure from baseline to Week 6.
2. Percent change in plasma hsCRP level from baseline to Week 6.

**Secondary Efficacy Variables:**

The secondary variables are:

1. Proportion of responders with respect to change in systolic blood pressure from baseline to Week 6. Responders are those subjects who achieve  $\geq 15$  mm Hg mean reduction in systolic blood pressure.
2. Time to achieving first systolic blood pressure reduction of  $\geq 15$  mm Hg.
3. Proportion of patients achieving first systolic blood pressure control by Week 6. Control rate is defined by systolic blood pressure  $< 140$  mmHg.
4. Change in mean sitting diastolic blood pressure from baseline to Week 6.
5. Change in mean pulse pressure from baseline to Week 6. Proportion of patients achieving first diastolic blood pressure control ( $< 90$  mm Hg) by Week 6.
6. Proportion of patients achieving a systolic blood pressure of  $< 130$  mm Hg by Week 6.
7. Percentage change in plasma hsCRP level from baseline to week 6 for patients with baseline hsCRP  $\geq 3.0$  mg/L.
- 98 Proportion of patients demonstrating a reduction in plasma hsCRP level by week 6.

**3. 3.5.3 Safety assessments**

Beispiel 1: Throughout the study, safety assessment will be assessed based on the incidence of adverse events, serious adverse events, and measurement of vital signs and a physical examinations (PE) at Visit 1.

**Beispiel 2: Adverse events**

Adverse events, whether volunteered by the subject, discovered during general questioning by the investigator, or other means will be recorded on the Adverse Event Case Report Form and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug, whether considered drug-related or not.

Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Clinical events occurring before starting study drug but after signing the informed consent form are recorded on the Medical History section of the case report form. The adverse event should be recorded in block print on the space provided in the case report form.

As far as possible, each adverse event will be described by:

1. its duration (start date)
2. the severity grade (mild, moderate, severe)
3. its relationship to study drug (suspected/not suspected)
4. action taken (with regard to study drug or concomitant therapy)
5. whether or not the AE is resolved (yes/no)

Examples of the relationship to study drug as presented in the case report form are provided in the Investigator Manual Instructions for completing the adverse event case report forms.

### Beispiel 3: Serious adverse events

Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report Form. To ensure subject safety each serious adverse event must also be reported to Novartis within 24 hours of learning of its occurrence. A serious adverse event is an undesirable sign, symptom or medical condition which:

1. is fatal or life-threatening
2. required or prolonged hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. is medically significant, in that it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen
- admission to a hospital or other institution for general care, not associated with any deterioration in condition
- treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious given above and **not** resulting in hospital admission.

Any serious adverse event occurring after the subject has provided informed consent and until 4 weeks after the subject has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a subject (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected. Instructions about completing initial and follow-up Serious Adverse Event Report Forms and sending them to Novartis are given in Section 9.1.1, instructions for rapid notification of serious adverse events

### Beispiel 4: Laboratory evaluations

Study subjects will be asked to provide blood samples at baseline Visit 1 (Week 0), Visit 3 (Week 6) and at Visit 4 (Week 12). All blood samples will be collected in EDTA using a standardized collection kit and will be shipped by overnight courier in cooled packing to the core laboratory repository and samples will be stored in liquid nitrogen at the Center for Cardiovascular Disease Prevention at the Brigham and Women's Hospital, Boston, MA and then be aliquotted into plasma and buffy coat fractions and is laboratory until analyses are performed. Levels of hsCRP will be determined in plasma using a clinically validated high sensitivity assay. With the exception of hsCRP analysis and pharmacogenetics assessments, no other laboratory studies will be performed during the course of the study. However, after study completion, stored samples may be used for future biochemical

analyses, but only after study samples are fully de-identified such that no patient specific information can be linked to any given blood sample.

**Beispiel 5: Pregnancy Test**

A urine pregnancy test is to be performed at all visits for WOCBP. If pregnancy is confirmed or suspected during the study, the subject must discontinue drug as soon as pregnancy is detected and be withdrawn from the study. Refer to Section 9.1.2., Instructions for rapid notification of pregnancies.

**Beispiel 6: Vital signs/Pulse/Blood pressure measurements**

The seated pulse rate and seated blood pressure will be measured at all visits. Blood pressure measurements will be obtained with an electronic blood pressure monitoring system to reduce the possibility of human error on the determination of the systolic and diastolic blood pressure values. All sites will be trained in the use of a standardized electronic blood pressure device as described in the manual of operations.

**Physical Examination**

A physical examination (PE) will be completed at Visit 1 (Day 0). Information about the physical examination must be present in the source documentation at the study site.

Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions Case Report Form. Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded on the Adverse Event Case Report Form.

This assessment will include examination of the skin, neck, including thyroid, eyes, ears, nose, throat, breasts (optional), lungs, heart, abdomen, lymph nodes, extremities and neurological examination.

**4. 3.5.4 Drug levels and pharmacokinetic assessments**

**Beispiel 1: Special tests**

There are no special tests in the study.

**3.5.5 Pharmacogenetic assessments**

The Study includes an optional pharmacogenetic component which requires a separate signature if the patient agrees to participate. It is required as part of this protocol that the Investigator presents these options to the patient.

Exploratory pharmacogenetics research studies are planned as a part of this study with the objectives of identifying inherited genetic factors which may (1) be related to hypertension, (2) predict response to treatment with Diovan® and Diovan HCT®, (3) predict relative susceptibility to drug-drug interactions, or (4) predict genetic predisposition to side effects.

The genetic markers that may be studied are those which relate to the etiology of hypertension may include polymorphisms in the angiotensin I converting enzyme 1 (ACE), angiotensinogen (AGT), angiotensin II receptor, type 1 (AGTR1) and nitric oxide synthase 3 (NOS3, endothelial cell) genes. Polymorphisms in genes that relate to the mechanism of

action may include those in angiotensin II receptor, type 1 (AGTR1), interleukin- 6 (IL6) and C-reactive protein (hsCRP).

Despite continuing advances in genetics research, not all of the polymorphisms relevant to drug metabolism, drug action and hypertension have been identified. Therefore, additional polymorphisms will be added within the restricted scope of these studies as described above.

We hope to develop a better understanding of hypertension and how subjects respond to Diovan® or Diovan HCT®. Information from these studies will only be used for research purposes, to help develop safer and more effective treatments for hypertension. The information will not be used to change the diagnosis or alter the therapy of the subject.

Sample collection: In order to perform these assessments, DNA will be isolated from the buffy coat fractions of the blood samples that were collected in EDTA tubes at Visit 1 (Week 0). These buffy coat fractions were labeled with the subject number. Upon extraction of the DNA from these samples, a second code will be assigned. The label on the DNA sample will only contain the second code.

The DNA will be analyzed and stored under the control of Novartis Pharmaceuticals Corporation in East Hanover, NJ.

#### **4 Protocol amendments, other changes in study conduct**

##### **4.1 Protocol amendments**

Any change or addition to this protocol requires a written protocol amendment that must be approved by Novartis and the Investigator before implementation. Amendments significantly affecting the safety of Subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC of all centers. A copy of the written approval of the IRB/IEC, which becomes part of the protocol, must be given to the Novartis monitor or CRO designee.

##### **4.2 Other changes in study conduct**

Changes in study conduct are not permitted. Any unforeseen changes in study conduct will be recorded in the clinical trial report.

#### **5 Data management**

##### **5.1 Data collection**

Designated investigator staff must enter the information required by the protocol onto the Novartis Case Report Forms (CRFs) that are printed on 3-part, non carbon required (NCR) paper. Contract Research Organization CRO field monitors will review the CRFs for completeness and accuracy, and instruct site personnel to make any required corrections or additions. The CRFs are forwarded to the CRO, by field monitors, one copy being retained at the investigational site. Once the CRFs are received by the CRO, their receipt is recorded, the original copy is placed in Central Files and the NCR copy is forwarded to the responsible medical data management staff for processing. All CRFs sent to the CRO are reviewed upon receipt for any serious adverse events. At the end of the study, the CRO will forward all

CRFs to Novartis. The details of this process will be determined at the conclusion of the study.

## 5.2 Database management and quality control

Data items from the CRFs are entered into the study database using double data entry with verification upon second entry. Alternatively, text items (e.g., comments) may be entered once and checked manually against the CRFs.

Subsequently, the information entered into the database is systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Obvious errors will be corrected by the CRO as per Novartis guidelines. Other errors or omissions will be entered on Data Query Forms (DQFs), which will be returned to the investigational site for resolution. A copy of the signed DQF is to be kept with CRF at the investigator site. Once the signed original DQF is received at the CRO, the database will be updated as necessary and as per the DQF resolution. Quality control audits of all key safety and efficacy data in the database will be performed.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List Dictionary, which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally through a central laboratory (Center for Cardiovascular Disease Prevention Laboratory, Brigham and Women's Hospital, Boston, MA) and the results will be sent electronically to the CRO.

When the database has been declared to be complete and accurate, the database will be locked and unblinded. Any changes to the database after that time can only be made by joint written agreement between the Novartis Clinical Trial Leader, the Trial Statistician and the Trial Data Manager.

### Pharmacogenetic samples:

To maximize confidentiality, all pharmacogenetic samples and the information associated with the samples will be double-coded to prevent the exposure of the patient's information and identity. This double-coding process allows Novartis to go back and destroy the sample at the patient's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database.

Any DNA derived from the sample that remains after analysis may be stored for up to 20 years to research scientific questions related to Diovan® and Diovan HCT®, hypertension or cardiovascular disorders.

The use of pharmacogenetics to search for biomarkers of disease and drug action is exploratory. Any results from these exploratory pharmacogenetic studies will not be placed in the patient's medical records.

## 6 Statistical methods

The study design is changed from a non-inferiority study to a superiority study. The Statistical Methods section has been rewritten to incorporate appropriate hypotheses and

tests corresponding to the revised primary objectives of the study and to include an option for an interim analysis for sample size recalculation. This version of Section 6 replaces the Statistical Methods section of the original protocol.

## 6.1 Statistical methods

A designated Contract Research Organization will perform the statistical analysis. The full data set will also be made available to the Head of the Steering Committee, Dr. Paul Ridker, in order to allow additional statistical analyses of the primary and secondary efficacy variables.

Unless otherwise specified, all statistical tests will be conducted against a two-sided alternative hypotheses, employing a significance level of 0.05.

It is planned that the data from all centers that participate in this protocol will be combined, so that an adequate number of patients will also be available for each sub-group analysis. Unless otherwise mentioned all analyses will be presented by group as defined in Section 6.1.1 below.

### 1. 6.1.1 Populations

All patients who are randomized and take at least one dose of study medication will be used for safety analysis. The intent-to-treat (ITT) population, consisting of all randomized patients from whom at least one valid post-baseline efficacy measurement is obtained, will be used for efficacy analyses. Completers population, consisting of those randomized patients from whom baseline, week 6, and Week 12 post-baseline measurement of valid hsCRP are obtained, will be used for analyses of hsCRP data.

In addition, sub-populations within each treatment group will be defined based on age (<65 years, ≥65 years), race (Caucasian, Black, Oriental and others), gender, and treatment dose. As appropriate, other subpopulations will be based on baseline hsCRP and blood pressure levels and their changes. (See the subsection 'Subgroup Analyses' in Section 6.1.5)

### 2. 6.1.2 Background and demographic characteristics

Background and relevant baseline information will be presented and summarized with appropriate descriptive statistics (mean, standard deviation, median and range for continuous variables; number and percentage for categorical variables). Chi-squared test for categorical variables and two-sample t-test for continuous variables will be used to test for homogeneity between the two treatment groups.

It should be noted that the p-values obtained from these comparisons will be provided for descriptive purposes, and are not to be considered to define any formal basis for determining factors, which should be included in statistical analysis models.

### 3. 6.1.3 Study medication

Summary statistics will be used to describe the number of days of exposure to study medication.

#### 4. 6.1.4 Concomitant therapy

All specified concomitant medications will be listed for each patient. The number and percentage of patients taking such medications will be summarized.

#### 5. 6.1.5 Efficacy evaluation

Three primary efficacy hypotheses will be evaluated for this study. A stepwise multiple test procedure (Bauer 1991) controlling for the overall type I error rate of 0.05 will be used. Under this method, in general, the null hypotheses of the primary analyses are a-priori ordered as follows: 1)  $H_{01}$ ; 2)  $H_{02}$ ; 3)  $H_{03}, \dots, n) H_{0n}$ . In order to control the overall type I error rate of 0.05, a hypothesis  $H_{0i}$  is rejected in a confirmatory way only if  $H_{0i}$  and all preceding hypotheses  $H_{01}, \dots, H_{0(i-1)}$  are rejected each at level 0.05.

The order of the primary hypotheses to be tested are as follows:

1. Superiority of Diovan HCT arm versus Diovan arm using systolic blood pressure
2. Non-zero percent change in hsCRP from baseline to Week 12 (end of study) for the combined and treatment groups
3. Superiority of Diovan HCT arm versus Diovan arm using hsCRP

For these above three primary hypotheses, the relevant efficacy variables are:

1. Change in mean sitting systolic blood pressure from baseline to Week 6
2. Percent change in serum hsCRP level from baseline to Week 12
3. Percent change in serum hsCRP level from baseline to Week 6

Change and percent change are defined as:

Change = Post-baseline assessment – baseline assessment;

Percent change = (Change/baseline assessment)X100.

Primary efficacy hypothesis 1

Hypothesis for superiority:

The test for the superiority of the Diovan HCT arm versus the Diovan arm in terms of systolic blood pressure reduction will be based on the following hypotheses:

$$1 \quad H_{01}: \mu_{SDH} = \mu_{SD} \quad \text{versus} \quad H_{a1}: \mu_{SDH} \neq \mu_{SD}.$$

where  $\mu_{SDH}$  and  $\mu_{SD}$  are the population mean change in systolic blood pressure (primary efficacy variable 1) for the Diovan HCT arm and the Diovan arm, respectively.

A two-sided test will be performed at 5% level of significance. The Diovan HCT arm will be considered statistically significantly better than the Diovan arm for change in systolic blood pressure if this test rejects the null hypothesis  $H_{01}$  and a greater mean reduction in systolic blood pressure is observed in Diovan HCT arm compared to Diovan arm.

Primary efficacy hypothesis 2

Hypothesis for non-zero percent change in hsCRP from baseline in the combined treatment groups:

The test for the non-zero percent change in hsCRP from baseline to Week 12 of the combined treatment groups will be based on the following hypothesis:

2  $H_{02}: \Delta\mu_c = 0$  versus  $H_{a2}: \Delta\mu_c \neq 0$ .

where  $\Delta\mu_c$  is the population mean percent change in hsCRP from baseline to Week 12 (primary efficacy variable 2) for the combined treatment groups.

A two-sided test will be performed at 5% level of significance. The overall mean percent change in hsCRP from baseline for the combined treatment group will be considered statistically significant if this test rejects the null hypothesis  $H_{02}$ .

Primary efficacy hypothesis 3

Hypothesis for superiority:

The test for the superiority of the Diovan HCT arm versus the Diovan arm in terms of hsCRP reduction will be based on the following hypotheses:

(3)  $H_{03}: \mu_{cDH} = \mu_{cD}$  versus  $H_{a3}: \mu_{cDH} \neq \mu_{cD}$ .

Where  $\mu_{cDH}$  and  $\mu_{cD}$  are the population mean percent change in serum hsCRP (primary efficacy variable 3) for the Diovan HCT arm and the Diovan arm, respectively.

A two-sided test will be performed at 5% level of significance using percent change in hsCRP at Week 6 (primary efficacy variable 3). The Diovan HCT arm will be considered significantly better than the Diovan arm if this test rejects the null hypothesis  $H_{03}$  and a greater mean reduction in hsCRP is observed in Diovan HCT arm compared to Diovan arm.

Primary efficacy analyses

The primary time point for testing primary efficacy hypotheses 1 and 3 is Week 6. Analysis of Covariance (ANCOVA) models with baseline measurement and treatment as covariate/factors will be used to analyze and estimate treatment effects for testing primary efficacy hypotheses 1 and 3. Also, a two-sided 95% confidence intervals for the difference between the two treatment groups will be reported. These analyses will be performed at Week 12 also.

A nonparametric test (i.e., the Wilcoxon Rank-Sum test) will be used to compare the two treatment groups as sensitivity analyses.

The primary time point for testing primary efficacy hypothesis 2 is Week 12.

For testing primary efficacy hypothesis 2, data from the two treatment groups will be combined. Paired t-test will be used to test the hypothesis. In addition, a two-sided 95% confidence interval for the mean percent change from baseline will be provided. These analyses will be performed at Week 6 and Week 12. If the assumptions of the parametric test are not satisfied, then a nonparametric test (i.e., the Wilcoxon Signed Rank test) will be considered.

The primary analyses for testing the primary efficacy hypothesis 1 will be based on ITT population. The last observation carried forward (LOCF) method will be used for replacing the missing values with post baseline assessments, if available. Baseline value will not be carried forward for replacing missing values. In addition, Observed Case (OC) analysis will also be performed.

But using the completers population, only the Observed Case (OC) analysis will be performed for testing primary efficacy hypotheses 2 and 3. If missing values are observed at Week 12, then additional analysis will be performed by replacing the missing value at Week 12 by the non-missing value from Week 6

Secondary efficacy variables

1. Proportion of responders with respect to change in systolic blood pressure from baseline to Week 6. Responders are those subjects who achieve  $\geq 15$  mm Hg mean reduction in systolic blood pressure
2. Time to achieving first systolic blood pressure reduction of  $\geq 15$  mm Hg
3. Proportion of patients achieving a systolic blood pressure control by Week 6
4. Control rate is defined by systolic blood pressure  $< 140$  mmHg
5. Proportion of patients achieving a systolic blood pressure of  $< 130$  mm Hg by Week 6
6. Change in mean sitting diastolic blood pressure from baseline to Week 6
7. Change in mean pulse pressure from baseline to Week 6
8. Proportion of patients achieving first diastolic blood pressure control (  $< 90$  mm Hg) by Week 6
9. Percentage change in plasma hsCRP level from baseline to week 6 for patients with baseline hsCRP  $\geq 3.0$  mg/L
10. Proportion of patients demonstrating a reduction in plasma hsCRP level by week 6

Treatment comparison for secondary efficacy variables 1, 3, 4, 7, and 9 between the Diovan HCT and Diovan arm will be examined using the chi-square test with continuity correction. A sensitivity analysis will be performed using a logistic regression model with treatment as a factor in the model.

For the time-to-event variable (secondary efficacy variable 2), Kaplan-Meier estimates will be presented in terms of the median and its 95% confidence interval, the 25th and 75th percentiles. The log-rank test will be used to test the survival curve difference between treatment groups.

For secondary efficacy variables 5, 6, and 8 analysis similar to that of the primary efficacy variables will be performed.

The Intent-to-treat (ITT) population will be used for the analyses of the secondary efficacy variables 1, 2, 3, 4, 5, 6, and 7. For the secondary efficacy variables 1, 3, 4, 5, 6, and 7, the last observation carried forward (LOCF) will be employed for replacing the missing values with post baseline assessments, if available. But only the Observed Case (OC) analysis will be performed for the secondary efficacy variables 8 and 9.

Summary statistics (percent, mean, median, inter quartile range, standard deviation, minimum, and maximum) of all efficacy variables by treatment group, visit and dose will be displayed for the baseline and post-baseline evaluations, as well as change from baseline. If the assumptions of the parametric test are not satisfied, then an appropriate nonparametric test will be considered.

The primary time point for the analysis of all the secondary efficacy variables is Week 6. But the same analyses will also be repeated at Week 12.

#### Sub-group Analysis

To further evaluate the treatment differences between the Diovan HCT and Diovan treatment regimens and to assess the relationship between hsCRP and blood pressure, the above analyses of all the above primary and secondary efficacy variables will be performed for the patients sub-groups defined based on the following:

- Baseline hsCRP level by quartiles (25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>)
- Baseline systolic blood pressure by quartiles (25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>)
- Baseline pulse pressure by quartiles (25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>)

As appropriate, analyses for between treatment groups and 'combined' may be performed on other sub-populations based on relevant demographic variables.

#### Exploratory Analysis

In order to assess for any evidence of association of the following and their respective changes, Spearman correlation coefficients will be computed.

- between the baseline hsCRP, baseline blood pressure and pulse pressure;
- between Week-6 hsCRP, blood pressure and pulse pressure;
- between end-of-study hsCRP, blood pressure and pulse pressure

The relation of other demographic and baseline characteristics with hsCRP will also be assessed. If appropriate, linear and/or logistic regression models will be used to evaluate relationship between hsCRP, blood pressure and pulse pressure reduction for both Diovan HCT and Diovan arms.

Additional exploratory analyses will be performed for the following:

- Regression analyses of the percent change in hsCRP level (on a log scale) from baseline to Week 6 with baseline hsCRP and other factors in the model will be explored

#### 6. 6.1.6 Safety evaluation

The safety and tolerability of Diovan HCT and Diovan treatment groups will be evaluated using the following safety analyses.

The assessment of safety will be based mainly on the frequency of adverse events. Other safety data (e.g., vital signs) will be considered as appropriate.

Adverse events will be summarized by presenting the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event. Any other information collected (e.g., severity or relatedness to study medication) will be listed as appropriate.

Laboratory data will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (means, means, standard deviations, ranges) and by the flagging of notable values in data listings.

Data from other tests (e.g., vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

Summary of the numbers and percentage of patients discontinued from the study will also be presented by reason of discontinuation.

#### 7. 6.1.7 Interim analyses

The primary purpose of the interim analysis is to recalculate the sample size for this study by estimating:

1. variability of the percent change in hsCRP at Week 6 and Week 12
2. dropout rate at Week 6 and Week 12
3. percent of patients with valid hsCRP at Week 6 and Week 12

The protocol was designed to randomize 2528 patients in the study allowing for 40% dropout rate and standard deviation (SD) of percent change in hsCRP equals to 30%. Thus it was

expected that approximately 1516 patients will complete Week 6 of the study. These estimates of dropout rate and standard deviation could not be substantiated based on prior data from the patient population under this study.

The dropout rate and variability (SD) of percent change in hsCRP by Week 6 and Week 12 will be estimated using treatment code blinded hsCRP data after 500 patients have completed 6 weeks of treatment period.

Also, it is planned for this study to collect additional safety data on Diovan HCT. If the recalculated sample size is larger than the originally planned number of patients to be randomized (N=2528), then Novartis management may consider increasing the sample size subject to budgetary constraints. But, if the recalculated sample size is smaller than 2528, then the study will continue to randomize 2528 patients to allow for more precise estimation of adverse event rates for Diovan HCT treatment. Approximately, 1264 patients in the Diovan HCT group will allow estimation of actual adverse event rates (<10%) with a margin of error up to 1.7%.

#### 8. 6.1.8 Other topics

There are no other topics in the study.

#### Beispiel 1: 6.1.9 Pharmacogenetic data analysis

The exploratory pharmacogenetic studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of strong association, the population in the clinical study cannot be controlled for any particular genotype. Thus, all statistical analysis to be performed will be considered exploratory. If the numbers of subjects enrolled in the study are too small to complete proper statistical analyses, these data will be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

### 6.2 Sample size and power considerations

The sample size was based on assessing the superiority of treatment effects between the Diovan HCT treatment regimen (Diovan HCT 160/12.5 mg, 320/12.5 mg) over the Diovan treatment regimen (Diovan 160 mg, Diovan 320 mg) with respect to the third primary efficacy variable, the percent change in serum hsCRP from baseline to Week 6. The sample size was determined based on 90% power assuming the expected difference in percent change in hsCRP between the Diovan HCT and Diovan treatment regimens as 5%, and a standard deviation of 30% with a two-sided significance level of 0.05, and allowing for a dropout rate of 40% after randomization. Thus a sample size of 2528 randomized patients (1264 per group) is necessary for this study.

For the primary efficacy variable 1, this sample size provides more than 99% power for the test of superiority at the two-sided significance level of 0.05 for detecting at least a 3 mmHg between-treatment difference in reduction in systolic blood pressure with a standard deviation of 12 mmHg.

Illustrative of the invention, Valsartan caused a slight but significant in CRP vs. placebo over a 24 month period in patients with heart failure.

**Reference List**

1. Chobanian AV, Bakris GL, Black HR, et al (2003); The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA; May 2003; 289(19): 2560-2572.
2. Neal B, MacMahon S, Chapman N (2000); Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs. Lancet; 1955-1964; 356.
3. Ogden LG, He J, Lydick E, et al (2000). Long-term absolute benefit of lowering blood pressure in hypertensive patients according to the JNC VI risk stratification. Hypertension; 35:539-543.
4. Nicoletti A, Heudes D, Mandet C, et al (1996). Inflammatory cells and myocardial fibrosis: spatial and temporal distribution in renovascular hypertensive rats. Cardiovasc Res.; Dec 1996; 32(6):1096-107.
5. Pueyo ME, Gonzalez W, Nicoletti A, et al (2000) Angiotensin II stimulates endothelial vascular cell adhesion molecule-1 via nuclear factor-kappaB activation induced by intracellular oxidative stress. Arterioscler Thromb Vasc Biol. Mar 2000; 20(3):645-51.
6. Muller DN, Mervaala EM, Dechend R, et al (2000) Angiotensin II (AT(1)) receptor blockade reduces vascular tissue factor in angiotensin II-induced cardiac vasculopathy. Am J Pathol. Jul 2000; 157(1):111-22.
7. Chae CU, Lee RT, Rifai N, et al (2001) Blood pressure and inflammation in apparently healthy men. Hypertension; Sep 2001; 38(3):399-403.
8. EMEA (2000) CPMP/EWP/482/99. Points to consider on switching between superiority and non-inferiority. London, July 2000.
9. Bauer P. (1991) Multiple testing in clinical trials. Statistics in Medicine; 10:871-890

What is claimed is:

1. A method for the prevention of, delay of progression of or treatment of vascular inflammation, comprising administering to a warm-blooded animal, including man, in need thereof a pharmaceutical composition comprising an AT<sub>1</sub>-receptor antagonist or a pharmaceutically acceptable salt thereof.
2. The method of claim 1 wherein the AT<sub>1</sub>-receptor antagonist is Valsartan.
3. A method for the prevention of, delay of progression of or treatment of conditions mediated by CRP comprising administering to a warm-blooded animal, including man, in need thereof a pharmaceutical composition comprising an AT<sub>1</sub>-receptor antagonist or a pharmaceutically acceptable salt thereof.
4. The method of claim 3 wherein the AT<sub>1</sub>-receptor antagonist is Valsartan.
5. A method for the prevention of, delay of progression of treatment of vascular inflammation comprising administering to a warm-blooded animal in need thereof a pharmaceutical composition comprising an AT<sub>1</sub>-receptor antagonist or a pharmaceutically acceptable salt thereof in combination with at least one therapeutic agent selected from the group consisting of
  - (i) renin inhibitors or a pharmaceutically acceptable salt thereof,
  - (ii) an angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable salt thereof,
  - (iii) an Calcium channel blocker or a pharmaceutically acceptable salt thereof,
  - (iv) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,
  - (v) an aldosterone antagonist or a pharmaceutically acceptable salt thereof,
  - (vi) an dual angiotensin converting enzyme/neutral endopetidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof,
  - (vii) an endothelin antagonist or a pharmaceutically acceptable salt thereof, and
  - (viii) a diuretic or a pharmaceutically acceptable salt thereof.
6. The method of claim 6 wherein the AT<sub>1</sub>-receptor antagonist is Valsartan.
7. A method for the prevention of, delay of progression of treatment of vascular inflammation comprising administering to a warm-blooded animal, including man, in need thereof a pharmaceutical composition consisting essentially of a therapeutically effective amount of an AT<sub>1</sub>-receptor antagonist or a pharmaceutically acceptable salt thereof.

8. The method of claim 7 wherein the AT<sub>1</sub>-receptor antagonist is Valsartan.
9. A method for the prevention of, delay of progression of treatment of vascular inflammation comprising administering to a warm-blooded animal in need thereof a pharmaceutical composition consisting essentially of a therapeutically effective amount of an AT<sub>1</sub>-receptor antagonist or a pharmaceutically acceptable salt thereof in combination with at least one therapeutic agent selected from the group consisting of (i) renin inhibitors or a pharmaceutically acceptable salt thereof,  
(ii) an angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable salt thereof,  
(iii) an Calcium channel blocker or a pharmaceutically acceptable salt thereof,  
(iv) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,  
(v) an aldosterone antagonist or a pharmaceutically acceptable salt thereof,  
(vi) an dual angiotensin converting enzyme/neutral endopetidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof,  
(vii) an endothelin antagonist or a pharmaceutically acceptable salt thereof,  
and  
(viii) a diuretic or a pharmaceutically acceptable salt thereof.
10. The method of claim 9 wherein the AT<sub>1</sub>-receptor antagonist is Valsartan.