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(71) Demandeurs/Applicants:
BOEHRINGER INGELHEIM VETMEDICA GMBH, DE;
UNIVERSITY OF GEORGIA RESEARCH
FOUNDATION, INC., US
(72) Inventeurs/Inventors:
TRAAS, ANNE MICHELLE, US;
COLEMAN, AMANDA ERICKSON, US;
FERREIRA DE MOURA LOURENCO, BIANCA
NATALIA, US;
CREEVY, KATE, ELIZABETH, US;

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The present invention relates to telmisartan or a pharmaceutically acceptable salt thereof as a medicament for the treatment of hypertension in dogs, wherein the therapeutically effective amount of telmisartan is administered in a daily dosage amount that is varied over a treatment period.

(72) Inventeurs(suite)/Inventors(continued): BROWN, SCOTT ALAN, US

(74) Agent: LOOPER, YWE J.

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(71) Applicants: **BOEHRINGER INGELHEIM VETMEDI-****CA GMBH** [DE/DE]; Binger Strasse 173, Ingelheim am Rhein 55216 (DE). **UNIVERSITY OF GEORGIA RESEARCH FOUNDATION, INC.** [US/US]; 310 East Campus Road, Tucker Hall, Athens, GA 30602 (US).(72) Inventors: **TRAAS, Anne, Michelle**; c/o VP, IP, LegalBoehringer Ingelheim USA Corp., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877-0368 (US). **COLEMAN, Amanda, Erickson**; 1091 Planters Trail, Bogart, GA 30622 (US). **LOURENCO, Bianca, Natália Ferreira de Moura**; 245 Willow Run, Athens, GA 30606 (US). **CREEVY, Kate, Elizabeth**; 11903 Hopes Creek Road, College Station, TX 77845 (US). **BROWN, Scott, Alan**; 855 Double Bridges Road, Winterville, GA 30683 (US).(74) Agent: **ALDAG, Andrew, J** et al.; c/o. PV. IP Legal,

Boehringer Ingelheim USA Corporation, 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 6877-0368 (US).

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TELMISARTAN FOR THE TREATMENT OF HYPERTENSION IN DOGS

5 FIELD OF THE INVENTION

The present invention relates to telmisartan or a pharmaceutically acceptable salt thereof for use in a method for the treatment of hypertension in a dog in need of such treatment, wherein the method comprises administration of a therapeutically effective amount of
10 telmisartan to the dog, wherein the therapeutically effective amount of telmisartan is administered in a daily dosage amount that is varied over a treatment period.

BACKGROUND OF THE INVENTION

Systemic hypertension (SHT) is described as sustained systolic arterial blood pressure
15 (SBP) over 140 mmHg, although interbreed differences in blood pressure have been described in dogs [1-4].

SHT recognition has increased in the last years improving the management of different diseases. SHT causes injury to tissues causing kidney damage resulting in proteinuria, retinopathy and hypertensive encephalopathy. These are called the target organ damage
20 (TOD). The prevalence of hypertension is not perfectly established and varies from 1 to 10 per cent in dogs [3].

Primary or idiopathic SHT is considered a rare condition in dogs due to the fact that only few cases have been diagnosed without an identifiable cause [4], but secondary SHT is relatively common and associated with different disorders as primary aldosteronism,
25 hyperadrenocorticism, pheochromocytoma, chronic kidney disease (CKD) and hyperthyroidism as well as with some medications like glucocorticoids, mineralocorticoids, erythropoietin, non-steroidal anti-inflammatory drugs and inhibitors of tyrosine kinase [3, 5–9].

Idiopathic SHT is considered a health risk factor in itself. Severe consequences of SHT, described when SBP is over 180 mmHg, are retinopathy, intra-ocular hemorrhage and
30 hypertensive encephalopathy, while the threshold for tissue injury is assumed to be 160 mmHg in cats and most breeds of dogs [4, 10]. Other conditions, including left ventricular hyper-trophy [11], proteinuria and further loss of functional kidney tissue [12], can be a cause

or consequence of SHT. In addition, secondary SHT is considered an additional progression factor of the underlying disease.

The ACVIM Consensus Statement guidelines for the management of hypertension in dogs and cats propose different strategies including ACEI, calcium channel blockers (CCB), beta-blockers and diuretics. Monotherapy and daily dose administration is the first choice to control SHT, but some patients are refractory and need a combination of different drugs to achieve good control of SBP [3].

ACEIs are widely used as first-line treatment for SHT in dogs due to the role of the renin-angiotensin-aldosterone system (RAAS) in its development, but they provide an incomplete block of angiotensin II production that can result in poor control of SHT. This phenomenon, called 'aldosterone breakthrough', is due to the release of angiotensin II by other sites compared with those regulated by the ACE and independent of the dose of ACEI administered [14].

Amlodipine, a CCB, either by switching or as add-on therapy, is the alternative treatment when dogs are refractory to ACEI [6, 15]; however, aldosterone breakthrough may also occur in combined treatments with amlodipine and ACEI [16].

Although diuretics are frequently administered to hypertensive people, these agents are not first-choice drugs for veterinary patients, mainly in CKD where dehydration and volume depletion may prove problematic, but can be useful in hypertensive animals in which volume overload is apparent (e.g., those with edema) [3].

If an antihypertensive agent of choice is not completely effective, the usual approach is to increase the dosage or add an additional drug [13, 17]. However, certain combinations like ACEI and angiotensin II receptor blocker (ARB) must be used with caution or avoided, as recent publications in humans showed a higher risk of kidney failure in these cases [13, 18, 19].

Telmisartan, an ARB, is a novel drug used in veterinary medicine to reduce proteinuria associated with CKD in cats [20].

In dogs, it has been described that a daily oral dose of telmisartan produces vasodilation, diuresis and natriuresis without influencing potassium or creatinine excretion, and prevents potassium depletion by inhibiting the release of aldosterone in a dose-dependent manner [21, 22]. The standard recommended dose in the management of proteinuria in dogs is 1 mg/kg [13]. It has also been reported to have an effect on blood pressure in dogs at a 1 mg/kg daily dose [23].

In addition, a daily dose of 1.0 mg/kg of body weight of telmisartan has been used in combination with amlodipine in dogs to control systemic hypertension refractory to standard hypertension therapy [24].

5 In another case study, the successful management of refractory proteinuria and systemic hypertension in an 11-year old Yorkshire terrier with renal cell carcinoma with surgery, 0.43 mg/kg of telmisartan and 0.3 mg/kg of amlodipine has been described [25].

The International patent application WO 2019/008077 teaches an administration scheme of sartans for prophylaxis or treatment of hypertension in a cat, where the initial dosage is 1.0 to 5.0 mg/kg of bodyweight and is decreased in a subsequent period.

10 There is, therefore, a critical need for additional anti-hypertensive and sustainable options for canine patients suffering from systemic hypertension.

SUMMARY OF THE INVENTION

Now, it has been found that dogs can be treated against hypertension, in particular systemic hypertension (SHT) by administering therapeutically effective amounts of telmisartan, wherein the therapeutically effective amount of telmisartan is administered in a daily dosage amount that is varied over a treatment period, the daily dosage amount of telmisartan for a first period of time during the treatment period is at least 1.0 mg/kg of body weight, and the daily dosage amount of telmisartan is increased for a second period of time subsequent the first period of time during the treatment period.

Thus, one objective of the present invention consists in providing a new therapeutic approach for the treatment of dogs against systemic hypertension.

Therefore, the invention relates to telmisartan or a pharmaceutically acceptable salt thereof for use in a method for the treatment of hypertension, in a dog in need of such treatment, wherein the method comprises administration of a therapeutically effective amount of telmisartan to the dog, wherein the therapeutically effective amount of telmisartan is administered in a daily dosage amount that is varied over a treatment period, the daily dosage amount of telmisartan for a first period of time during the treatment period is at least 1.0 mg/kg of body weight, and the daily dosage amount of telmisartan is increased for a second period of time subsequent the first period of time during the treatment period.

Furthermore, the invention relates to telmisartan or a pharmaceutically acceptable salt thereof as a medicament for the treatment of hypertension in dogs, which are non-refractory to the treatment with ACE inhibitors.

In a further embodiment of the invention there is provided a method for the treatment of hypertension, in a dog in need of such treatment, wherein the method comprises administration of a therapeutically effective amount of telmisartan or a pharmaceutically acceptable salt thereof to the dog, wherein the therapeutically effective amount of telmisartan is administered in a daily dosage amount that is varied over a treatment period, the daily dosage amount of telmisartan for a first period of time during the treatment period is at least 1.0 mg/kg of body weight, and the daily dosage amount of telmisartan is increased for a second period of time subsequent the first period of time during the treatment period.

In a further embodiment, the invention provides a method for the treatment of hypertension in dogs, which are non-refractory to the treatment with ACE inhibitors, which method comprises administration of a therapeutically effective amount of telmisartan or a pharmaceutically acceptable salt thereof to a dog in need of such a treatment.

Furthermore the invention relates to a pharmaceutical composition for use in a method for the treatment of hypertension, in a dog in need of such treatment, which comprises telmisartan or a pharmaceutically acceptable salt thereof according to the invention and a pharmaceutically acceptable carrier.

20

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plot of the average SBP change from baseline, from day 30 to day 120 in dogs with hypertension at day 0, which did not receive amlodipine; on day 90 the dogs received a dose of either enalapril or telmisartan in addition to the initial drug administered.

FIG. 2 is a plot of the average percent SBP change from baseline, from day 30 to day 120 in dogs with hypertension at day 0, which did not receive amlodipine; on day 90 the dogs received a dose of either enalapril (---•--- E) or telmisartan (—•— T) in addition to the initial drug administered.

FIG. 3 depicts the average SBP change from baseline, from day 30 to day 90 in dogs with hypertension at day 0, which received amlodipine.

FIG. 4 depicts the average SBP in mmHg from day 0 to day 90 in dogs with hypertension at day 0, which did not receive amlodipine.

DETAILED DESCRIPTION OF THE INVENTION

Before the embodiments of the present invention it shall be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless
5 the context clearly dictates otherwise. Thus, for example, reference to "a preparation" includes a plurality of such preparations, reference to the "carrier" is a reference to one or more carriers and equivalents thereof known to those skilled in the art, and so forth. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. All
10 given ranges and values may vary by 1 to 5 % unless indicated otherwise or known otherwise by the person skilled in the art, therefore, the term "about" was omitted from the description. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are now described. All publications mentioned herein are incorporated
15 herein by reference for the purpose of describing and disclosing the substances, excipients, carriers, and methodologies as reported in the publications which might be used in connection with the invention.

Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

20 The solution to the above technical problem is achieved by the description and the embodiments characterized in the claims.

In accordance with the present invention, methods are described herein for the treatment of hypertension in a dog in need of such treatment, where the methods comprise administration of a therapeutically effective amount of telmisartan to the dog, the therapeutically effective
25 amount of telmisartan being administered in a daily dosage amount that is varied over a treatment period starting with an initial dose of at least 1.0 mg/kg of bodyweight. For example, the daily dosage amount of telmisartan for a first period of time during the treatment period can be 1.0 to 1.5 mg/kg of body weight, where the daily dosage amount of telmisartan is increased for a second period of time subsequent the first period of time during
30 the treatment period.

As used herein, the term "pharmaceutically acceptable salts" includes the metal salts or the addition salts which can be used in dosage forms. For example, the pharmaceutically acceptable salts of the compounds provided herein can be acid addition salts, base addition

salts or metal salts, and can be synthesized from parent compounds containing a basic or acid residue by means of conventional chemical processes. Such salts are generally prepared, for example, by reacting the free acid or base forms of these compounds with a stoichiometric amount of the suitable base or acid in water or in an organic solvent or in a mixture of both. Non-aqueous media are generally preferred, such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile. Examples of acid addition salts include mineral acid additions salts such as, for example, hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, organic acid addition salts such as, for example, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulfonate and p-toluenesulfonate. Examples of alkali addition salts include inorganic salts such as, for example, ammonium salts and organic alkaline salts such as, for example, diethylamine, ethylenediamine, ethanolamine, N,N-dialkyl ethanolamine, triethanolamine, glutamine and basic amino acid salts. Examples of metal salts include, for example, sodium, potassium, calcium, magnesium, aluminium and lithium salts.

As used herein, the term "pharmaceutically acceptable" relates to molecular entities and compositions that are physiologically tolerable and do not normally cause an allergic reaction or a similar adverse reaction, such as gastric discomfort, dizziness and the like, when administered to humans. As used herein, the term "pharmaceutically acceptable" preferably means that it is approved by a regulatory agency of the federal or state government or listed in the US pharmacopoeia or another pharmacopoeia, generally recognized for its use in animals, preferably in mammals and more particularly in dogs.

As used herein, the term "hypertension" refers to an elevated pressure of the blood against the walls of arteries during the time the heart contracts and empties itself of blood as well as during the time the heart relaxes and fills with blood and in. The term embraces systemic hypertension and idiopathic hypertension.

The term "systemic hypertension" is applied to sustained increases in systolic blood pressure (SBP > 140 mmHg), and generally can be categorized into 1 of 3 types: (i) it may be caused by environmental or situational stressors, (ii) it may occur in association with other disease processes that increase BP (ie, secondary hypertension), or (iii) it may occur in the absence of other potentially causative disease processes (ie, idiopathic hypertension).

"Systemic hypertension" in dogs is classified based on the risk of target organ damage (TOD) according to the ACVIM consensus statement [26], as follows:

As used herein, the term "non-refractory to the treatment with ACE inhibitors" refers to dogs suffering from hypertension, which can be treated with an ACE inhibitor, but with less efficacy

than telmisartan. To the contrary the high values of sustained systolic arterial blood pressure (SBP) of dogs that are refractory to ACE inhibitors cannot be lowered with the aid of ACE inhibitors.

5 In the non-refractory sub-population of dogs the efficacy of treatment with an ACE inhibitor is 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, more than 50%, more than 60%, or more than 70% less effective than telmisartan for lowering their SBP values.

10 In a preferred embodiment the telmisartan and/or the method according to the invention relates to the treatment of the non-refractory subpopulation of dogs. However, the administration scheme according to the invention may advantageously be administered to both the subpopulations, the non-refractory as well as to refractory dogs.

The dogs to be treated with telmisartan according to the invention are preferably pet dogs of any breed including any kind of mongrel. Depending on the size of the breed or mongrel they may suffer from hypertension at an any age, but more frequently at an age of 5 years or more, preferably from 7 to 18 years, in particular from 10 to 16 years. Small breeds will as a rule suffer at a later age, preferably from 12 to 18, from this disease than big ones, which may be affected at an age of 10 to 16 years.

20 As used herein, the terms "together with" or "in combination with" covers both separate and sequential administration of telmisartan and another drug. For example, when the agents are administered sequentially, either the telmisartan or the other drug may be administered first. When administration is simultaneous, the agents may be administered either in the same or a different pharmaceutical composition. Adjunctive therapy, i.e. where one agent is used as a primary treatment and the other agent is used to assist that primary treatment, is also an embodiment of the present invention.

25 The one or more active ingredients may be used either as separate formulations or as a single combined formulation. When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation.

30 Formulations of the invention include those suitable for oral, parenteral (including subcutaneous e.g. by injection or by depot tablet, intradermal, intrathecal, intramuscular e.g. by depot and intravenous), rectal and topical (including dermal, buccal and sublingual) or in a form suitable for administration by inhalation or insufflation administration. The most suitable route of administration may depend upon the condition and disorder of the patient. Preferably, the compositions of the invention are formulated for oral administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy e.g. as described in "Remington: The Science and Practice of Pharmacy", Lippincott Williams and Wilkins, 21st Edition, (2005). Suitable methods include the step of bringing into association active ingredients with a carrier which constitutes one or more excipients. In general, formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation. It will be appreciated that when the two active ingredients are administered independently, each may be administered by a different means.

- 5
- 10 Formulations suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets, in particular chewable tablets, each containing a predetermined amount of active ingredient; as powder or granules; as a solution or suspension in an aqueous liquid or non-aqueous liquid; or as an oil-in-water liquid emulsion or water-in-oil liquid emulsion. The active ingredients may also be presented a bolus, electuary or paste.
- 15 Alternatively, the active ingredients may be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups or elixirs. Formulations containing the active ingredients may also be presented as a dry product for constitution with water or another suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose, glucose/sugar
- 20 syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel and/or hydrogenated edible fats), emulsifying agents (e.g. lecithin, sorbitan mono-oleate and/or acacia), non-aqueous vehicles (e.g. edible oils, such as almond oil, fractionated coconut oil, oily esters, propylene glycol and/or ethyl alcohol), and preservatives (e.g. methyl or propyl p-hydroxybenzoates and/or sorbic acid).
- 25 In addition, the oral formulation may contain one or more flavoring agents, which enhance the compliance of the dog to be treated to chew and swallow the medication.

Most preferably telmisartan is administered orally in form of a chewable tablet or as an aqueous solution containing benzalkonium chloride as in the product Semintra®, which is commercially available from Boehringer Ingelheim Vetmedica GmbH, Ingelheim Germany.

- 30 In particular, the following items are disclosed herein:
- a) Telmisartan or a pharmaceutically acceptable salt thereof for use in a method for the treatment of hypertension, in a dog in need of such treatment, wherein the method comprises administration of a therapeutically effective amount of telmisartan to the dog,

wherein the therapeutically effective amount of telmisartan is administered in a daily dosage amount that is varied over a treatment period, the daily dosage amount of telmisartan for a first period of time during the treatment period is at least 1.0 mg/kg of body weight, and the daily dosage amount of telmisartan is increased for a second period of time subsequent the first period of time during the treatment period.

- b) Telmisartan according to item a), wherein hypertension is associated with the elevated urinary protein-to creatinine concentration (UPC) levels.
- c) Telmisartan according to item a) or b), which is the sodium or potassium salt thereof.
- d) Telmisartan according to any of the items a) to c) for the treatment of dogs that are non-refractory to the treatment with ACE inhibitors.
- e) Telmisartan according to any of the items a) to c) for the treatment of dogs that are refractory with ACE inhibitors.
- f) Telmisartan according to any of the items a) to e), wherein the daily therapeutically effective amount thereof ranges from 1.0 to 10.0 mg/kg, preferably from 1.0 to 4.0 mg/kg, in particular from 1.0 to 3.5 mg/kg, most preferred from 1.0 to 3.0 mg/kg of body weight.
- g) Telmisartan according to any of the items a) to f), wherein the daily dosage amount of telmisartan is increased for the second period of time by an incremental amount ranging from 0.25 to 2.50 mg/kg of body weight.
- h) Telmisartan according to any of the items a) to g), wherein the daily dosage amount of telmisartan for a first period of time during the treatment period is 1.0 to 1.5 mg/kg of body weight, and the daily dosage amount of telmisartan for the second period of time is 1.75 to 3.50 mg/kg of body weight.
- i) Telmisartan according to any of the items a) to h), wherein the daily dosage amount of telmisartan is decreased after the second period of time by an incremental amount ranging from 0.25 to 2.50 mg/kg of body weight.
- j) Telmisartan according to any of the items a) to i), wherein the daily dosage amount of telmisartan is decreased after the second period of time upon a systolic blood pressure (SBP) value measured for the dog.
- k) Telmisartan according to any of the items a) to j), wherein the daily dosage amount of telmisartan is decreased when a systolic blood pressure (SBP) value measured for the dog decreases after the second period of time by at least 10 mmHg or at least 20 mmHg

or by 10 to 150 mmHg, 10 to 100 mmHg, 10 to 80 mmHg, 10 to 50 mmHg, 10 to 30 mmHg, 10 to 20 mmHg, 20 to 150 mmHg, 20 to 100 mmHg, 20 to 80 mmHg, 20 to 50 mmHg, or 20 to 30 mmHg in relation to a baseline SBP value measured for the dog prior to the first period of time.

5 l) Telmisartan according to any of the items a) to k), which is administered together with at least one other drug to a dog in need of such a treatment.

m) Telmisartan according to item l), wherein the other drug is selected from the group consisting of calcium channel blockers, preferably amlodipine, cardiotonic- calcium sensitizing agents, preferably pimobendan or levosimendan, ACE inhibitors, preferably
10 ramipril, benazepril or enalapril, in particular enalapril.

n) Telmisartan according to any of the items a) to m), wherein the SBP of the dogs treated are lowered by at least at least 50%, or at least 40%, 30%, or 20% over a period of time. Preferably said period of time is period measured in days, such as 10 days, 20 days, 30 days, 60 days, 90 days, 120 days or more than 120 days up to a point in time when the
15 SBP values are constantly well below the threshold of hypertension.

A significantly greater proportion of telmisartan-treated dogs show a reduction of almost 20% in SBP at day 30, whereas the SBP in enalapril-treated dogs increased even by more than 10 % as shown in FIG. 2.

As shown in FIG. 1 the average reduction in SBP is greater from day 30 to day 90 for
20 telmisartan treated dogs compared to enalapril treated dogs. In addition, the combination of telmisartan and enalapril from day 90 to day 120 achieves a reduction of more than 40 mmHg of the average SBP in dogs which were treated with telmisartan from day 0 to day 90.

o) A method for the treatment of hypertension in a dog in need of such treatment, wherein
25 the method comprises administration of a therapeutically effective amount of telmisartan or a pharmaceutically acceptable salt thereof to the dog, wherein the therapeutically effective amount of telmisartan is administered in a daily dosage amount that is varied over a treatment period, the daily dosage amount of telmisartan for a first period of time during the treatment period is at least 1.0 mg/kg of body weight, and the daily dosage
30 amount of telmisartan is increased for a second period of time subsequent the first period of time during the treatment period.

p) The method according to item n), wherein hypertension is associated with elevated urinary protein-to creatinine concentration (UPC) levels.

- q) The method according to item o) or p), which comprises administration of an effective amount of the sodium or potassium salt of telmisartan.
- r) The method according to any of the items o) to q) for the treatment of dogs that are non-refractory or refractory to the treatment with ACE inhibitors.
- 5 s) The method according to one of the items o) to r), wherein the daily therapeutically effective amount of telmisartan ranges from 1.0 to 10.0 mg/kg, preferably from 1.0 to 4.0 mg/kg, in particular from 1.0 to 3.5 mg/kg, most preferred from 1.0 to 3.0 mg/kg of body weight.
- 10 t) The method according to one of the items o) to s), wherein the daily dosage amount of telmisartan is increased for the second period of time by an incremental amount ranging from 0.25 to 2.50 mg/kg of body weight.
- u) The method according to one of the items o) to t), wherein the daily dosage amount of telmisartan is decreased after the second period of time by an incremental amount ranging from 0.25 to 2.50 mg/kg of body weight.
- 15 v) The method according to one of the items o) to u), wherein the daily dosage amount of telmisartan is decreased after the second period of time when the SBP value measured for the dog decreases by at least 20 % in relation to a baseline SBP value measured for the dog prior to the first period of time.
- 20 w) The method according to one of the items o) to v), wherein the method further comprises administration of at least one other drug to such dog in need of such a treatment.
- x) The method according to one of the items o) to w), wherein the other drug is selected from the group consisting of calcium channel blockers, cardiotonic- calcium sensitizing agents and ACE inhibitors.
- 25 y) The method according to one of the items o) to x), wherein the other drug is selected from the group consisting of amlodipine, pimobendan, levosimendan, ramipril, benazepril and enalapril, in particular enalapril.
- 30 z) The method according to one of the items o) to y), wherein the SBP of the dogs treated are lowered by at least at least 50%, or at least 40%, 30%, or 20% over a period of time. Preferably said period of time is period measured in days, such as 10 days, 20 days, 30 days, 60 days, 90 days, 120 days or more than 120 days up to a point in time when the SBP values are constantly well below the threshold of hypertension.

The invention now being generally described, will be more readily understood by reference to the following Examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

5

EXAMPLES

Experimental Methods and Design. A prospective, block-randomized, double-blind clinical trial has been carried out. Fifty-four client-owned dogs with persistent pathologic renal proteinuria have been recruited over a 2-year period.

10 *Example 1*

Animals. Azotemic and non-azotemic dogs (N = 54) with hypertensive and non-hypertensive CKD have been recruited prospectively from patients presented to the hospital. Dogs included as cases will have confirmed persistent pathologic renal proteinuria due to CKD; in order to be classified as such, fulfillment of the criteria described below will be required.

15 **Inclusion criteria.** Included animals had an UPC level of approximately 2.0 (for non-azotemic patients; IRIS stage 1) or approximately 0.5 (for azotemic patients; IRIS stages 2-4), documented in each of two urine samples collected 2 weeks apart. Abdominal ultrasound findings consistent with CKD (bilaterally small, irregular kidneys) and absence of renal neoplasia have also been documented.

20 **Exclusion criteria.** Animals have been excluded if one or more of the following are identified: evidence of hemorrhage, inflammation or bacteria on urine sediment analysis; positive urine culture at the time of identification of proteinuria; positive heartworm antigen test within 3 months of identification of proteinuria and/or not currently receiving regular monthly heartworm preventive; historical, physical examination or clinical pathologic findings
25 suggestive of acute kidney injury, infectious nephropathy or lower urinary tract infection; systolic hypotension (SBP<120 mm Hg); moderate-to-severe hyperkalemia (serum K >6.5 mmol/L); history of having received oral ACEi and/or corticosteroids in the month (ACEi) or 2 weeks (corticosteroids) preceding examination; concurrent illness associated with proteinuria, the treatment of which might result in mitigation of proteinuria (e.g., systemic
30 lupus erythematosus, ehrlichiosis, neoplasia). Dogs with suspected or confirmed hyperadrenocorticism and diabetes mellitus have been included if their disease is considered well controlled with medical therapy.

Patient grouping for block randomization: Once included in the study and based on the presence/degree of azotemia, dogs have been grouped according to the International Renal Interest Society (IRIS) classification scheme for CKD. Those classified as IRIS stages 2-4 (serum creatinine ≥ 1.4 mg/dL with inappropriately dilute urine [USG <1.030]) have been considered azotemic (AZ), and those classified as IRIS stage 1 (creatinine <1.4 mg/dL) have been considered non-azotemic (non-AZ). Within each of these two groups, dogs will then be stratified according to IRIS recommendations for arterial pressure (AP) substaging. According to this scheme, dogs with persistent average indirect arterial systolic BP <150 mm Hg will be classified as AP0 (minimal risk for target organ damage). Those with persistent average indirect arterial systolic BP ≥ 150 mm Hg have been classified as AP1-3 (at risk for target organ damage). Four groups will thus be identified:

1. AZ (IRIS Stages 2-4), IRIS substage AP1-3 3. non-AZ (IRIS Stage 1), IRIS substage AP1-3
2. AZ (IRIS Stages 2-4), IRIS substage AP0 4. non-AZ (IRIS Stage 1), IRIS substage AP0

Once placed into one of these four groups, each patient has then been assigned, based on a randomized blocking scheme, to receive either enalapril (n=27) or telmisartan (n=27), as described below, with the aim of grouping being to ensure that equal numbers of each are included into the two treatment groups.

Baseline. On inclusion (day 0), all owners have been required to read/sign a form consenting to their pets' participation in the study. The following baseline data have been collected for each case: full physical examination (performed by one of the study investigators), fundic examination, blood pressure measurement, serum chemistry panel, urinalysis, abdominal ultrasound, UPC and urine culture. The results of screening tests, if performed within 2 weeks of inclusion in the study, may be used as baseline information. Baseline UPC has been defined as the average of two measurements, taken 2 weeks apart, prior to enrollment.

ARB/ACEi therapy. On day 0, each dog has been randomized to receive telmisartan at 1 mg/kg PO q 24 h (TEL group, n=27) or enalapril at 0.5 mg/kg PO q 12 h (ENAL group, n=27) in a double-blind manner. Randomization and dispensation of telmisartan or enalapril has been carried out at the appropriate doses. Owners have been provided with appropriate contact numbers in the event of an emergency. Enalapril is readily available and telmisartan has been provided by Boehringer Ingelheim Vetmedica Inc., St. Joseph, MO in form of the aqueous solution, which is commercially available as Semintra®.

Antihypertensive/other therapy. For dogs that are classified as AP3 (SBP $\geq$ 180 mmHg; $\geq$ 200 mmHg in sighthounds), a calcium channel blocker (CCB; amlodipine, 0.1 mg/kg PO q 24 hours) has been administered contemporaneously. Co-administration of RAAS-inhibitors and CCB is common in human patients, recommended by a panel of veterinary experts and shown to be efficacious in a laboratory model of proteinuria. All dogs have been started or maintained on a commercially available diet formulated to be low in phosphorus and protein, for at least 1 month prior to enrollment. During the study period, diet remained constant. Treatment with fish oil has been allowed, provided that the dog has been receiving this supplement for >1 month at the time of enrollment.

Monitoring: The monitoring protocol followed the recommendations of the IRIS Canine GN Study Group Standard Therapy Subgroup. All dogs have been rechecked on day 7, at which time physical examination, SBP, serum creatinine (sCr) and serum potassium (K) have been evaluated. An increase in sCr of >30% compared to baseline or identification of moderate/severe hyperkalemia (serum K>6.5 mmol/L) or systolic hypotension (SBP<120) has prompt the investigator unmasking and removal of the patient from the study. For dogs in which average SBP of approximately 180 mm Hg was reliably identified (i.e. dogs classified as AP3), amlodipine will be up-titrated to 0.1 mg/kg PO BID. Thereafter, dogs classified as AP3 have been rechecked at 7-day intervals to ensure efficacy of therapy with adjustment of antihypertensive therapy. At each visit, if average SBP measurements remained at about 180 mm Hg, then the dog's amlodipine dose have been increased in increments of 0.05 mg/kg BID to a maximum dose of 0.3 mg/kg BID. SBP and sCr have been rechecked 7 d following any adjustments.

Final phase I visit. On day 30, all dogs have undergone physical examination, SBP, serum biochemistry, urinalysis and UPC measurement. At this and all subsequent time points, urine for UPC measurement will consist of a pooled sample, created by combining three free-catch specimens collected and refrigerated by the owner on the preceding day.

Objective endpoints. The objective endpoints of phase I was the reduction of the SBP and the percentage change in UPC (Δ UPC).

Conclusions. The average change of SBP in telmisartan-treated dogs was -compared to enalapril-treated dogs – a reduction of at least 30 mmHg at day 30 as shown in FIG. 2.

Example 2

Specific Objectives #2 and #3 (Phases II and III; intermediate-term phases)

Phase II of this study compared the efficacy of enalapril and telmisartan when these drugs were used as part of protocols that allow their up-titration, and phase III will evaluate their combination in dogs whose proteinuria persisted in the face of the highest doses of each drug alone. Each of the 54 dogs will remain in the treatment group to which he/she was assigned in phase I. Within these groups, up-titration of study drugs, followed by combination therapy have been performed if proteinuria persisted with UPC at about 0.5 on monthly rechecks.

ARB/ACEi therapy.

Phase II (days 31-90): For those dogs in which $UPC < 0.5$ was identified on day 30, treatment continued with telmisartan at a dose of 1 mg/kg PO q 24 h or enalapril at a dose of 0.5 mg/kg PO BID until the end of the study (day 120). For those in which $UPC \sim 0.5$ was identified on day 30, the dose of study drug has been up-titrated monthly in increments of 1 mg/kg PO q 24 h (TEL group) or 0.5 mg/kg BID (ENAL group) until a target $UPC < 0.5$ was attained OR a “ceiling dose” (3 mg/kg PO q 24 h for telmisartan or 1.5 mg/kg PO BID for enalapril) of either drug is reached, whichever occurs first.

Phase III (days 91-120): For those dogs in which $UPC < 0.5$ was identified on or before day 90, treatment continued with telmisartan or enalapril at the dose producing proteinuria control until the end of the study. For those in which UPC approximately 0.5 was identified on day 90, enalapril at a dose of 0.5 mg/kg BID or telmisartan at a dose of 1 mg/kg q 24 h has been added for dogs in the TEL and ENAL groups, respectively. Combination therapy continued for 1 month, until the end of the study.

Monitoring. If a change was made to an individual dog's treatment regimen on day 30, he/she has been rechecked one week later (day 37), at which time SBP, sCr and serum K levels have been evaluated. An increase in creatinine of $>30\%$ or identification of moderate/severe hyperkalemia (serum K > 6.5 mmol/L) prompted the investigator unmasking and removal of the patient from the study. If mild hyperkalemia (serum K of 6.1-6.5 mmol/L) was identified, up-titration to the next dose has not been performed, regardless of UPC.

Thereafter, persistently proteinuric dogs have been monitored monthly (i.e., on days 60, 90) by means of SBP, UPC and urinalysis. Urine culture have been performed if active urinary sediment was identified. For dogs in which proteinuria persisted and up-titration of drug was required, SBP, sCr and serum K have been rechecked one week after adjustments (days 67, 97), with criteria for unmasking and further dose up-titration as outlined above. Dogs in which $UPC < 0.5$ was identified at any time point have undergone recheck of monitoring parameters at the conclusion of the study only (d 120).

Final visit: On day 120, all dogs have undergone full physical examination, SBP, serum renal biochemistry, urinalysis (cystocentesis) and UPC measurement.

Objective endpoints. The objective endpoints for phase II included AUPC from baseline and percentage of patients achieving 50% reduction or decrease to < 0.5 of UPC following a total of 3 months of therapy, as well as an average reduction of SBP by about 20 % from baseline. Phase III's objective endpoints included AUPC from baseline, AUPC over the month of therapy (UPCday90 – UPCday120) and an average reduction of SBP by at least 40 % from baseline.

Conclusions. As shown in FIGs. 1 and 2 the average change in SBP was greater from day 30 to day 90 for telmisartan treated dogs compared to enalapril treated dogs with a greater change realized at day 90 for Telmisartan treated dogs.

In addition, the combination of Telmisartan and Enalapril from day 90 to day 120 lowers the average SBP by more than 70 mmHg and achieves in average a > 40 % reduction of the SBP in the group of dogs that were treated with telmisartan as shown in the following tables I and II.

Table I Average of SBP change

Active Ingredient	SBP change [mmHg] day 30	SBP change [mmHg] day 60	SBP change [mmHg] day 90	SBP change [mmHg] day 120
Enalapril	+20.00	+1.00	+3.00	-32.00 ¹
Telmisartan	-31.50	-31.00	-37.00	-76.00 ²

¹ additional telmisartan has been administered after SBP measurement on day 90

² additional enalapril has been administered after SBP measurement on day 90

Table II Average of SBP % change

Active Ingredient	SBP change [%] day 30	SBP change [%] day 60	SBP change [%] day 90	SBP change [%] day 120
Enalapril	+12.90	+0.65	+1.94	-20.65 ¹
Telmisartan	-18.88	-18.42	-22.58	-42.70 ²

1 additional telmisartan has been administered after SBP measurement on day 90

2 additional enalapril has been administered after SBP measurement on day 90

As shown in FIG. 3, the average SBP change from baseline was greater at day 30, day 60,
5 and day 90 in dogs that were hypertensive with SBP of at least 150mmHg at day 0, which
received amlodipine and the extra drug, in telmisartan treated dogs compared to those
treated with enalapril.

Moreover, the absolute average SBP of dogs that received telmisartan was much lower than
of those dogs which were treated with enalapril as shown in FIG. 4. Whereas the SBP of the
10 dogs treated with enalapril was reduced from 163 mmHg to 153 mmHg on day 30, but
increased again on days 60 and 90, the average SBP values of the dogs treated with
telmisartan was constantly lowered during the period of treatment from initially 163 mmHg to
132 mmHg on day 90 as shown in table III

15 Table III Average of SBP

Active Ingredient	SBP [mmHg] day 0	SBP [mmHg] day 30	SBP [mmHg] day 60	SBP [mmHg] day 90
Enalapril	163.17	153.80	153.00	158.00
Telmisartan	163.57	140.86	138.60	132.33

REFERENCES

The following publications are hereby incorporated by reference in their entirety as if each
individual publication is specifically and individually indicated to be incorporated by reference.

20 In case of conflict, the present application, including any definitions herein, will control.

[1] Bodey AR, Michell AR. Epidemiological study of blood pressure in domestic dogs. *J Small Anim Pract* 1996; 37:116–25.

[2] Brown S. Pathophysiology of systemic hypertension. In: Ettinger SJ, Feldman EC,
25 eds. *Textbook of veterinary internal medicine. Diseases of the dog and cat, vol. 1*. 6th
edn. St. Louis (MO): Elsevier Saunders, 2005:472–6.

- [3] Brown S, Atkins C, Bagley R, *et al.* Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. *J Vet Intern Med* 2007; 21:542–58.
- [4] Reusch CE, Schellenberg S, Wenger M. Endocrine hypertension in small animals. *Vet Clin North Am Small Anim Pract* 2010; 40:335–52.
- [5] Cortadellas O, del Palacio MJ, Bayón A, *et al.* Systemic hypertension in dogs with leishmaniasis: prevalence and clinical consequences. *J Vet Intern Med* 2006; 20:941–7.
- [6] Geigy CA, Schweighauser A, Doherr M, *et al.* Occurrence of systemic hypertension in dogs with acute kidney injury and treatment with amlodipine besylate. *J Small Anim Pract* 2011; 52:340–6.
- [7] Herring IP, Panciera DL, Werre SR. Longitudinal prevalence of hypertension, proteinuria, and retinopathy in dogs with spontaneous diabetes mellitus. *J Vet Intern Med* 2014; 28:488–95.
- [8] Hanzlicek AS, Baumwart RD, Payton ME. Systolic arterial blood pressure estimated by mitral regurgitation velocity, high definition oscillometry, and Doppler ultrasonography dogs with naturally occurring degenerative mitral valve disease. *J Vet Cardiol* 2016; 18:22 6–33.
- [9] Tjostheim SS, Stepien RL, Markovic LE, *et al.* Effects of Toceranib Phosphate on Systolic Blood Pressure and Proteinuria in Dogs. *J Vet Intern Med* 2016; 30:951–7.
- [10] Leblanc NL, Stepien RL, Bentley E. Ocular lesions associated with systemic hypertension in dogs: 65 cases (2005-2007). *J Am Vet Med Assoc* 2011; 23 8:915–21.
- [11] Takano H, Kokubu A, Sugimoto K, *et al.* Left ventricular structural and functional abnormalities in dogs with hyperadrenocorticism. *J Vet Cardiol* 2015; 17:173–81.
- [12] Wehner A, Hartmann K, Hirschberger J. Associations between proteinuria, systemic hypertension and glomerular filtration rate in dogs with renal and non-renal diseases. *Vet Rec* 2008; 162:141–7.
- [13] Brown S, Elliot J, Francey T, *et al.* IRIS Canine GN Study Group Standard Therapy Subgroup, Consensus Recommendations for Standard Therapy of Glomerular Disease in Dogs. *J Vet Intern Med* 2013; 27:S27–43.
- [14] Ames MK, Atkins CE, Lee S, *et al.* Effects of high doses of enalapril and benazepril on the pharmacologically activated renin-angiotensin-aldosterone system in clinically normal dogs. *Am J Vet Res* 2015; 76:1041–50.

- [15] Jepson RE, Elliott J, Brodbelt D, *et al.* Effect of control of systolic blood pressure on survival in cats with systemic hypertension. *J Vet Intern Med* 2007; 21:402–9.
- [16] Ames MK, Atkins CE, Lantis AC, *et al.* Evaluation of subacute change in RAAS activity (as indicated by urinary aldosterone:creatinine, after pharmacologic provocation) and the response to ACE inhibition. *J Renin Angiotensin Aldosterone Syst* 2016; 17:1–12.
- [17] Schmieder RE, Volpe M, Waeber B, *et al.* A guide for easy- and difficult-to-treat hypertension. *Int J Cardiol* 2014; 172:17–22.
- [18] St Peter WL, Odum LE, Whaley-Connell AT. To RAS or not to RAS? The evidence for and cautions with renin-angiotensin system inhibition in patients with diabetic kidney disease. *Pharmacotherapy* 2013; 33:496–514.
- [19] European Medicines Agency. *PRAC recommends against combined use of medicines affecting the renin-angiotensin (RAS) system*, 2014. EMA EMA/196502/2014.
- [20] Sent U, Gössl R, Elliott J, *et al.* Comparison of Efficacy of Long-term Oral Treatment with Telmisartan and Benazepril in Cats with Chronic Kidney Disease. *J Vet Intern Med* 2015; 29:1479–87.
- [21] Wienen W, Entzeroth M, Meel JCA, *et al.* A Review on Telmisartan: A Novel, Long-Acting Angiotensin II-Receptor Antagonist. *Cardiovasc Drug Rev* 2000;18: 127–54.
- [22] Schierok H, Pairet M, Huel N, *et al.* Effects of telmisartan on renal excretory function in conscious dogs. *J Int Med Res* 2001;29:131–9.
- [23] Coleman AE, Schmiedt CW, Handsford CG, *et al.* Attenuation Of The Pressor Response To Exogenous Angiotensin By Angiotensin Receptor Blockers In Normal Dogs. *J Vet Intern Med* 2014;28.
- [24] Caro-Vadillo A, Daza-González MA, Gonzalez-Alonso-Alegre E, *et al.* *Effect of a combination of telmisartan and amlodipine in hypertensive dogs.* *Vet Rec Case Rep* 2018; 6:e000471.
- [25] Kwon Y-J, Suh G-H, Kang S-S, Kim H-J, *Can Vet J* 2018;59:759-762.
- [26] Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats, Mark J. Acierno *et al*, *J Vet Intern Med*, 2018

CLAIMS

1. Telmisartan or a pharmaceutically acceptable salt thereof for use in a method for the treatment of hypertension in a dog in need of such treatment, wherein the method
5 comprises administration of a therapeutically effective amount of telmisartan to the dog, wherein the therapeutically effective amount of telmisartan is administered in a daily dosage amount that is varied over a treatment period, the daily dosage amount of telmisartan for a first period of time during the treatment period is at least 1.0 mg/kg of body weight, and the daily dosage amount of telmisartan is increased for a second
10 period of time subsequent the first period of time during the treatment period.
2. Telmisartan according to claim 1, wherein the hypertension is associated with systemic chronic kidney disease (CKD), elevated urinary protein-to-creatinine ratio (UPC) levels and/or hyperthyroidism.
15
3. Telmisartan according to claim 1 or 2, which is the sodium or potassium salt thereof.
4. Telmisartan according to any one of claims 1 to 3, wherein the hypertension is idiopathic hypertension.
20
5. Telmisartan according to any one of claims 1 to 4, wherein the daily therapeutically effective amount thereof ranges from 1.0 to 10.0 mg/kg of body weight.
6. Telmisartan according to any one of claims 1 to 5, wherein the daily dosage amount of
25 telmisartan is increased for the second period of time by an incremental amount ranging from 0.25 to 2.50 mg/kg of body weight.
7. Telmisartan according to any one of claims 1 to 6, wherein the daily dosage amount of telmisartan for a first period of time during the treatment period is 1.0 to 1.5 mg/kg of
30 body weight, and the daily dosage amount of telmisartan for the second period of time is 1.75 to 3.50 mg/kg of body weight.
8. Telmisartan according to any one of claims 1 to 7, wherein the daily dosage amount of
35 telmisartan is decreased after the second period of time by an incremental amount ranging from 0.25 to 2.50 mg/kg of body weight.

9. Telmisartan according to any one of claims 1 to 8, wherein the daily dosage amount of telmisartan is decreased after the second period of time upon a systolic blood pressure (SBP) value measured for the dog.

5

10. Telmisartan according to any one of claims 1 to 10, wherein daily dosage amount of telmisartan is decreased when a systolic blood pressure (SBP) value measured for the dog decreases after the second period of time by at least 10 mmHg or at least 20 mmHg or by 10 to 150 mmHg, 10 to 100 mmHg, 10 to 80 mmHg, 10 to 50 mmHg, 10 to 30 mmHg, 10 to 20 mmHg, 20 to 150 mmHg, 20 to 100 mmHg, 20 to 80 mmHg, 20 to 50 mmHg, or 20 to 30 mmHg in relation to a baseline SBP value measured for the dog prior to the first period of time.

10

11. Telmisartan according to any one of claims 1 to 11, which is administered together with at least one other drug to a dog in need of such a treatment.

15

12. Telmisartan according to claim 11, wherein the other drug is selected from the group consisting of calcium channel blockers, preferably amlodipine, cardiotonic- calcium sensitizing agents, preferably pimobendan or levosimendan, ACE inhibitors, preferably ramipril, benazepril or enalapril.

20

13. Telmisartan or a pharmaceutically acceptable salt thereof as a medicament for the treatment of hypertension, which is non-refractory to the treatment with ACE inhibitors in dogs.

25

14. A method for the treatment of hypertension in a dog in need of such treatment, wherein the method comprises administration of a therapeutically effective amount of telmisartan or a pharmaceutically acceptable salt thereof to the dog, wherein the therapeutically effective amount of telmisartan is administered in a daily dosage amount that is varied over a treatment period, the daily dosage amount of telmisartan for a first period of time during the treatment period is at least 1.0 mg/kg of body weight, and the daily dosage amount of telmisartan is increased for a second period of time subsequent the first period of time during the treatment period.

30

15. The method according to claim 14, wherein the hypertension is associated with systemic chronic kidney disease (CKD), elevated urinary protein-to-creatinine ratio (UPC) levels and/or hyperthyroidism.
- 5 16. The method according to claim 14, which comprises administration of an effective amount of the sodium or potassium salt of telmisartan.
17. Telmisartan according to claim 14, wherein the hypertension is idiopathic hypertension.
- 10 18. The method according to claim 14, wherein the daily therapeutically effective amount of telmisartan ranges from 1.0 to 10.0 mg/kg of body weight.
19. The method according to claim 14, wherein the daily dosage amount of telmisartan is increased for the second period of time by an incremental amount ranging from 0.25 to 2.50 mg/kg of body weight.
- 15 20. The method according to claim 19, wherein the daily dosage amount of telmisartan for a first period of time during the treatment period is 1.0 to 1.5 mg/kg of body weight, and the daily dosage amount of telmisartan for the second period of time is 1.75 to 4.0 mg/kg of body weight.
- 20 21. The method according to claim 14, wherein the daily dosage amount of telmisartan is decreased after the second period of time by an incremental amount ranging from 0.25 to 2.50 mg/kg of body weight.
- 25 22. The method according to claim 14, wherein the daily dosage amount of telmisartan is decreased after the second period of time upon a systolic blood pressure (SBP) value measured for the dog.
- 30 23. The method according to claim 22, wherein daily dosage amount of telmisartan is decreased when a systolic blood pressure (SBP) value measured for the dog decreases after the second period of time by at least 10 mmHg or at least 20 mmHg or by 10 to 150 mmHg, 10 to 100 mmHg, 10 to 80 mmHg, 10 to 50 mmHg, 10 to 30 mmHg, 10 to 20 mmHg, 20 to 150 mmHg, 20 to 100 mmHg, 20 to 80 mmHg, 20 to 50 mmHg, or 20 to 30

mmHg in relation to a baseline SBP value measured for the dog prior to the first period of time.

24. The method according to claim 14, wherein the method further comprises administration
5 of at least one other drug to such dog in need of such a treatment.

25. The method according to claim 24, wherein the other drug is selected from the group
consisting of calcium channel blockers, cardiotonic- calcium sensitizing agents and ACE
inhibitors.

10

26. The method according to claim 25, wherein the other drug is selected from the group
consisting of amlodipine, pimobendan, levosimendan, ramipril, benazepril and enalapril.

15

27. A method for the treatment of hypertension, which is non-refractory to the treatment with
ACE inhibitors in dogs, which method comprises administration of a therapeutically
effective amount of telmisartan or a pharmaceutically acceptable salt thereof to a dog in
need of such a treatment.

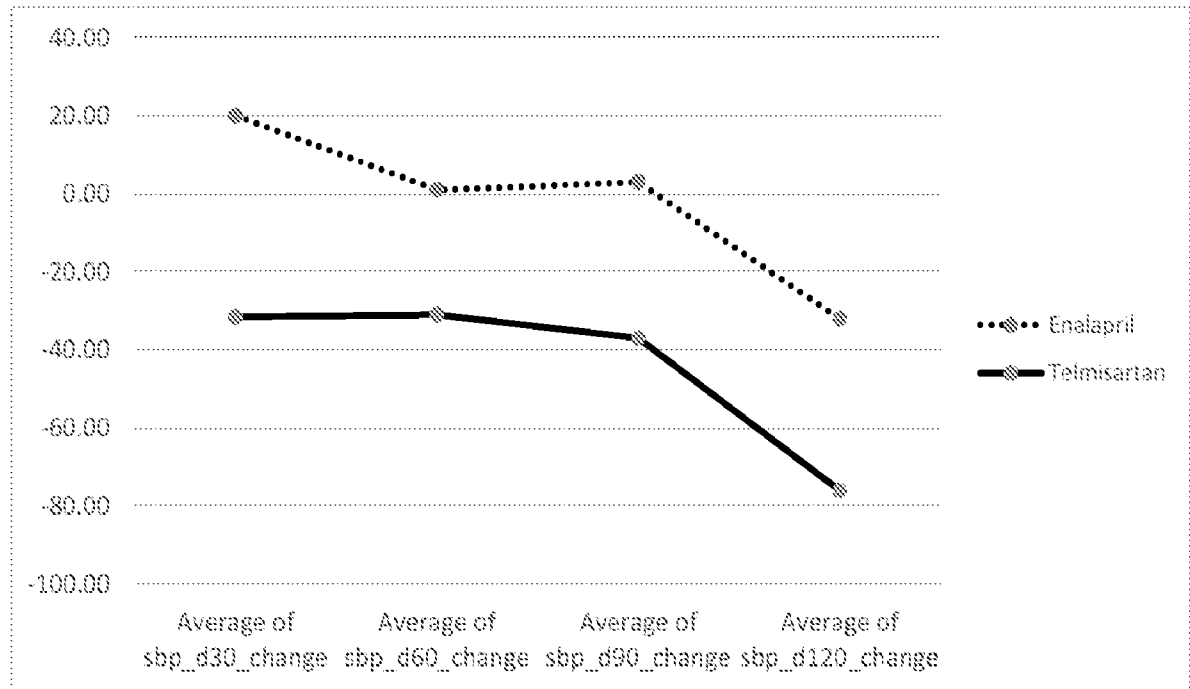


FIG. 1

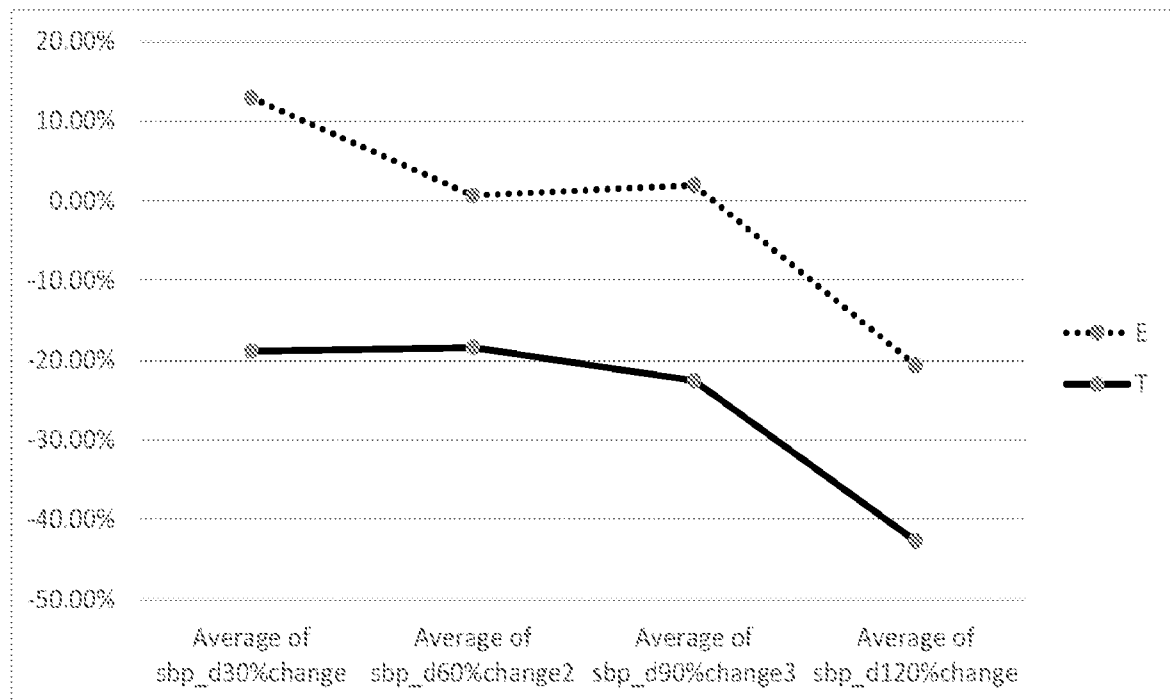
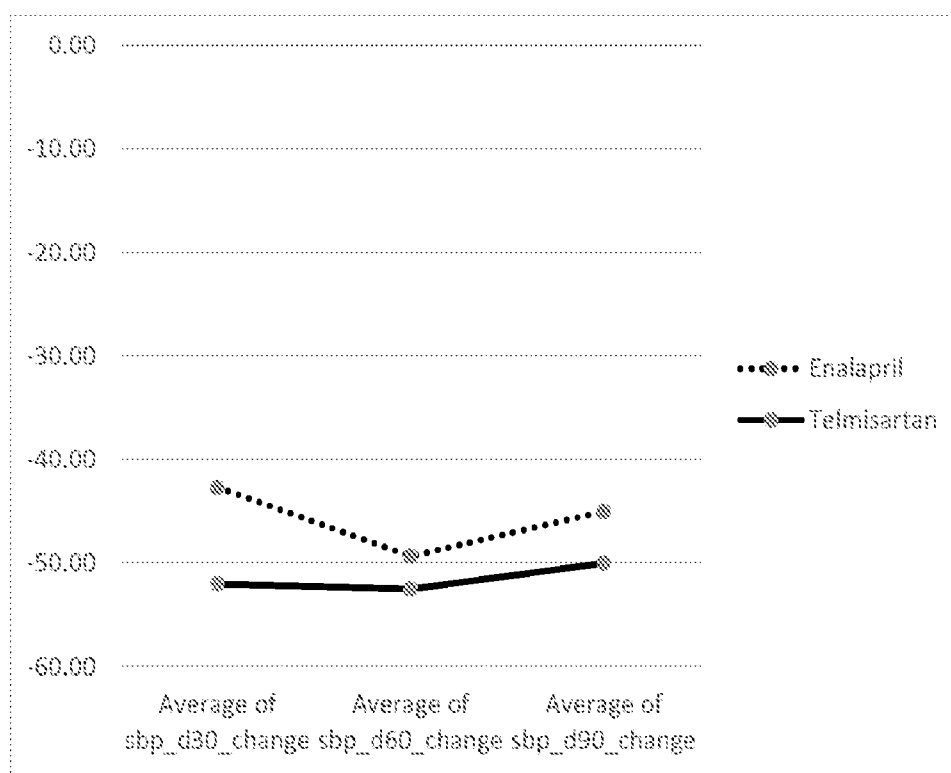
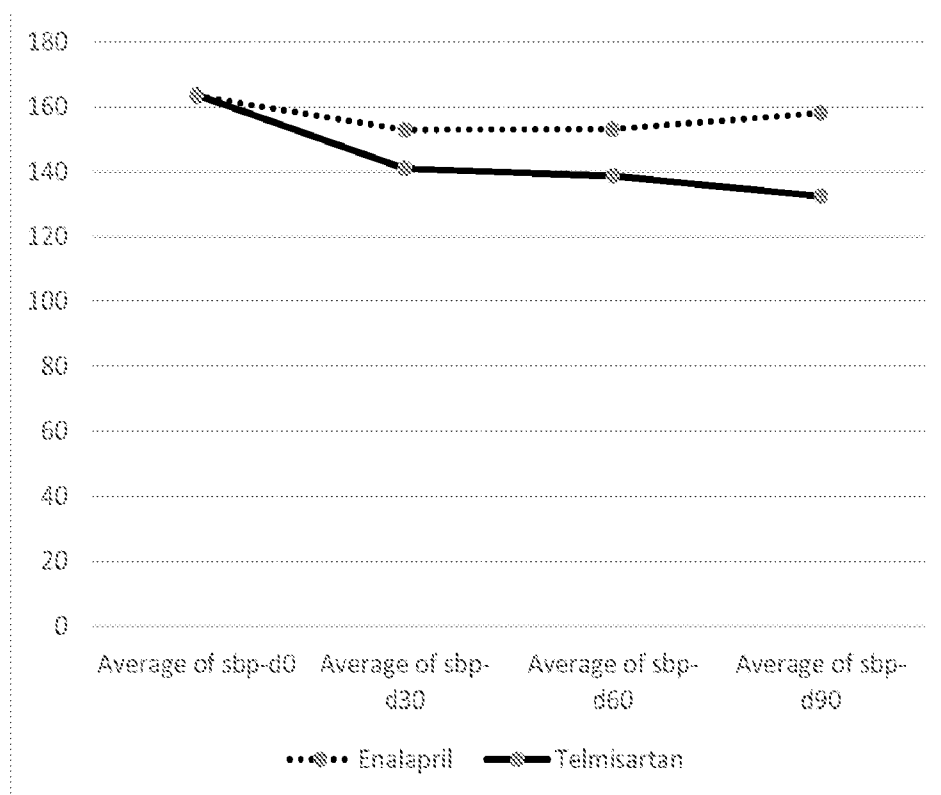


FIG. 2

**FIG. 3****FIG. 4**