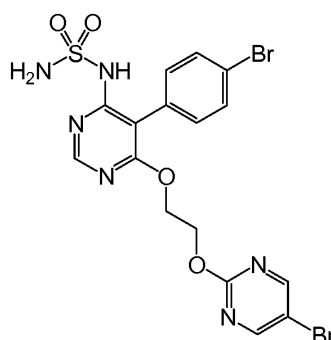


**COMBINATION OF A 4-PYRIMIDINESULFAMIDE DERIVATIVE WITH AN SGLT-2 INHIBITOR FOR THE
TREATMENT OF ENDOTHELIN RELATED DISEASES**

The present invention concerns the compound aprocitentan and its use as endothelin receptor antagonist, in
5 combination with other active ingredients or therapeutic agents comprising a sodium glucose cotransporter 2
(SGLT-2) inhibitor the prophylaxis or treatment of certain endothelin related diseases. The invention further
relates to pharmaceutical compositions comprising aprocitentan in combination with said other active
ingredient(s) or therapeutic agent(s). The invention further relates to such pharmaceutical compositions
10 comprising novel crystalline forms of aprocitentan; pharmaceutical compositions prepared from such crystalline
forms, and to the use of such crystalline forms in combination with said other active ingredients or therapeutic
agents in the prophylaxis or treatment of said endothelin related diseases.

Aprocitentan, {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide
(hereinafter also referred to as "COMPOUND"), has the formula I



15

Formula I

The compound of formula I, also known under the name, and referred to as ACT-132577, is an endothelin
receptor antagonist. The compound of formula I is a member of a structural family that was previously
generically disclosed in WO 02/053557. In particular, the compound of formula I, while showing endothelin
receptor antagonist activity, exhibits *in vivo* a much longer half-life and a much shorter clearance in comparison
20 to corresponding alkylated derivatives. This makes the compound of formula I particularly suitable for long-
acting pharmaceutical compositions, as disclosed in WO 2009/024906.

Because of its ability to inhibit the endothelin binding, the compound of formula I can be used for treatment of
endothelin related diseases which are associated with an increase in vasoconstriction, proliferation or
inflammation due to endothelin occurring in many cardio-renal-metabolic diseases. Examples of such endothelin
25 related diseases are hypertension including especially difficult to treat / resistant hypertension; pulmonary
hypertension; coronary diseases; cardiac insufficiency; renal and myocardial ischemia; chronic kidney disease

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(CKD) [especially CKD of stages 1 to 4 as defined by the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines (and notably CKD of stage 3), and in particular CKD (notably of these stages) caused by / associated with hypertension or diabetes (diabetic kidney disease (DKD), including DKD that is associated, in addition, with hypertension); diabetes, and diabetes related diseases such as diabetic arteriopathy, diabetic nephropathy, diabetic retinopathy, or diabetic vasculopathy; reducing the risk of developing a major cardiovascular event (such as heart failure (HF), myocardial infarction, stroke, or death from cardiovascular causes) in patients who have diabetes, especially in patients who have diabetes that is accompanied by at least one other cardiovascular risk factor (such as hypertension, dyslipidemia, thrombotic phenomenon); therapy and prophylaxis of diabetic complications; (acute and chronic) renal failure; glomerulonephritis; connective tissue diseases; atherosclerosis; peripheral arterial disease including chronic peripheral (obliterant) arteriopathy; digital ulcers; diabetic foot ulcers and/or reducing the risk of lower limb / extremity amputations in patients who have diabetes, or who are smokers, or who have atherosclerosis; heart failure (HF) defined as including especially chronic HF, including in particular systolic HF / HF with reduced ejection fraction (HFrEF) (i.e. ejection fraction < about 40%), and diastolic HF / HF with preserved ejection fraction (HFpEF) (i.e. ejection fraction > about 50%); reducing the risk of developing a major cardiovascular event (such as heart failure (HF), myocardial infarction, stroke, or death from cardiovascular causes) in patients who are at cardiovascular risk (such as patients who have coronary artery disease and/or patients who have demonstrated clinical signs of congestive heart failure); angina pectoris; and diastolic dysfunction. The compound of formula I can also be used in the treatment or prevention of cerebral ischemia; dementia; migraine; subarachnoid hemorrhage; Raynaud's syndrome; portal hypertension; restenosis after balloon or stent angioplasty; inflammation; stomach and duodenal ulcer; cancer; melanoma; prostate cancer; prostatic hypertrophy; erectile dysfunction; eclampsia; hearing loss; amaurosis; chronic bronchitis; asthma; pulmonary fibrosis; gram negative septicemia; shock, sickle cell anemia; renal colic; glaucoma; complications of vascular or cardiac surgery or after organ transplantation; complications of cyclosporin treatment or equivalent therapies showing nephrotoxic profile; pain; dyslipidemia; as well as other diseases presently known to be related to endothelin.

Clinical studies have shown that endothelin receptor antagonists (ERAs) may have significant treatment effect in patients suffering from hypertension and / or renal disease, whether associated or not with diabetes. Endothelin 1 (ET-1) is likely to play a role in the pathogenic mechanisms of chronic diabetic arteriopathy, because of its effects on mediating plaque formation, thrombosis, vasoconstriction, and vascular hypertrophy and because it potentiates the action of other systems, in particular the renin angiotensin and sympathetic systems and/or insulin signalings. Thus, an ERA might be beneficial in the treatment of peripheral arterial obliterant disease including diabetic arteriopathy by having acute (peripheral vasodilation) and chronic (vasodilation, improvement in vascular structure and modulation of sympathetic activity, antithrombotic, antiinflammatory) effects. In a clinical network meta-analysis of studies performed in adults with diabetes and CKD (157 studies comprising 43,256 patients), ERAs were ranked as the most effective agents for the prevention of end-stage kidney disease (S.C. Palmer et al., Lancet (2015), 385 (9982): 2047-2056). However,

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therapeutic benefit needs to be weighted against potential side effects, such as the potential risk of teratogenic activity generally associated with ERAs. In addition and more importantly, both, selective ET_A-antagonists and dual antagonists of both the ET_A and ET_B receptor, may cause fluid retention, a common side effect associated with many previously studied ERAs and sometimes (e.g. if not manageable with diuretics) leading to exaggerated major adverse cardiac events such as heart failure or death. Whereas the risk-benefit balance is in most cases in favor of treatment with an ERA for indications such as pulmonary hypertension (as reflected in the past by successive market approvals e.g. for the ERAs the dual antagonists bosentan and macitentan, and the ET_A-selective antagonist ambrisentan), ERAs have no role in the management of primary hypertension (Laffin et al. *Seminars in Nephrology* 2015, 35, 168-175), and side effects such as fluid retention may remain an issue when a potential treatment of difficult to treat / resistant hypertension (rHT), chronic kidney disease (CKD), whether associated or not with diabetes and / or hypertension, or other hypertension related diseases with an ERA is considered.

The ET_A-selective endothelin receptor antagonist darusentan has been in development for the treatment of resistant hypertension (rHT) (Bakris et al., *Hypertension* 2010, 56,824-830, see also WO2007/098390). In a 14 week phase 3 trial in patients with rHT, it demonstrated efficacy on the reduction of ambulatory blood pressure, but failed to show significant treatment effect on the primary endpoint systolic blood pressure. Patients were eligible to participate if they had treatment resistant hypertension (systolic blood pressure of higher than 140 mm Hg) despite treatment with three or more antihypertensive drugs from different drug classes, including a diuretic, at optimized doses. A minimum dose of 25 mg per day of hydrochlorothiazide (or its equivalent for other thiazide diuretic drugs) was required. Even though during the trial diuretic therapy could be intensified at the discretion of the investigators to manage fluid retention, the most frequent adverse event associated with darusentan was fluid retention/edema at 28% versus 12% in each of the other groups. More patients withdrew because of adverse events on darusentan as compared with placebo.

The ET_A-selective ERA avosentan, in a trial that investigated the effects of avosentan on progression of overt diabetic nephropathy in patients with type 2 diabetes, showed significant treatment effect, associated with a significantly increased discontinuation of trial medications due to adverse events, predominantly related to fluid overload and congestive heart failure (Mann et al., "Avosentan for Overt Diabetic Nephropathy", *J Am Soc Nephrol.* 2010, 21(3): 527-535.). The composite primary outcome was the time to doubling of serum creatinine, ESRD, or death. Secondary outcomes included changes in albumin-to-creatinine ratio (ACR) and cardiovascular outcomes. The study did not detect a difference in the frequency of the primary outcome between groups. Avosentan significantly reduced ACR. The trial was terminated prematurely after a median follow-up of 4 months (maximum 16 months) because of an excess of cardiovascular events with avosentan, and the authors conclude that "it may be that at dosages of 25 to 50 mg avosentan is less selective for the ET_A receptor and thus caused sodium and water retention and peripheral vasodilation with a potential fluid shift from the intravascular to extravascular space". The effect on albuminuria was considered likely due to inhibition of the

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renal ET_A receptor, because it was previously found that the mixed type ET_{A/B} receptor antagonists have a weaker or no effect on proteinuria. According to the authors, the assumption of ET_B receptor blockade with higher dosages of avosentan is further supported by data that showed a natriuretic effect of selective ET_A receptor blockade in people who were treated with ACE inhibitors. Thus, the natriuretic effect / fluid retention
5 that possibly in final consequence lead to the discontinuation of the trial was attributed to a dual blockade of the ET_A and the ET_B receptor, discouraging from using a dual acting ERA in such clinical setting.

Further pre-clinical data showed that the synergistic effect on blood pressure of an ET_A-selective ERA in combination with the ACE inhibitor enalapril was abolished by simultaneous blockade of the ET_B-receptor (Goddard et al., J.Am.Soc.Nephrol. 2004, 15, 2601-2610), thus, discouraging from using a dual acting ERA in
10 a clinical setting where ACE inhibitors may be required as background therapy.

In a review on "Endothelin antagonists for diabetic and non-diabetic chronic kidney disease" (Br J Clin Pharmacol (2012), 76:4, 573-579), D. E. Kohan et al. state that "in general, the prevailing opinion is that ET_A, as opposed to combined ET_{A/B}, receptor antagonists are preferred for treating CKD". Three years later Kohan et al. conclude with regard to a study published in Clin J Am Soc Nephrol (2015), 10: 1568-1574 that "the fluid-
15 retaining effect of ERAs is most likely related to direct effects on renal tubular sodium transport, whereas the antiproteinuric effect of ERAs is likely associated with actions on the vasculature and/or glomerulus. Finally, it could be anticipated that ERA mitigation of proteinuria per se would favor renal fluid excretion; however, ERAs could still promote fluid retention through a separate effect on tubule sodium and water reabsorption".

WO2016/073846 provides a comprehensive summary of ERAs tested for various indications including diabetic
20 and non-diabetic CKD and rHT. WO2016/073846 provides further examples where fluid retention may have led to increased side effects for the ERAs bosentan, tezosentan, ambrisentan, and atrasentan. WO2016/073846 concludes in proposing a method of treating CKD with an ERA, especially with the ET_A-selective ERA atrasentan, using predictors of fluid retention; said method comprising the determination of a risk of fluid retention if an ERA were administered to the subject; and administering the ERA to the subject if the risk is at
25 an acceptable level. The detailed study protocol of a clinical phase 3 study (SONAR) evaluating the effects of the investigational compound atrasentan - when added to standard of care - on progression of kidney disease in patients with stage 2 to 4 chronic kidney disease and type 2 diabetes was published in Heerspink et al, Diabetes Obes. Metab. 2018, 1-8. The protocol reflects the importance given to dose optimization and simultaneous control of sodium retention / fluid retention in the study design, leading to a study design that
30 requires "the selection of individuals at high risk of disease (prognostic enrichment) who also demonstrate a good response to study treatment (predictive enrichment)". However, on December 01, 2017, AbbVie announced its strategic decision to close the SONAR study. The press release states that "the ongoing monitoring of renal events observed in the study has revealed considerably fewer end-points than expected by this time, which will likely affect the ability to test the SONAR study hypothesis. Therefore, AbbVie has

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determined that it cannot justify continuing the participation of patients in the study. The decision to close the SONAR study early was not related to any safety concerns."

Contrary to the conclusions drawn from the avosentan trial, preclinical and clinical data suggest that the ET_A-selective antagonists sitaxentan and ambrisentan pose a greater risk of fluid retention than the dual ERAs bosentan and macitentan (Vercauteren et al., JPET 2017, 361, 322-333). The authors state that their findings "indicate that in rats, stimulation of the unblocked ET_B receptors in presence of ET_A receptor antagonist, but not functional antagonism of the ET_A receptor per se, can be detrimental, and that blockade of both receptors is less likely to cause water retention than single receptor blockade" and continue to speculate that "plasma volume expansion combined with increased vascular permeability could explain the observations obtained with ET_A-selective antagonists". The authors conclude that "several clinical studies with ET_A-selective antagonists have resulted in mortality increases in relation to fluid retention issues, whereas this has not been observed with dual ERAs. Dual ERAs, however, in conditions of preexisting fluid retention or arginine vasopressin (AVP) increase, such as chronic heart failure or chronic renal failure, have caused significant fluid retention".

It has been shown in a phase 2 clinical trial that aprocitentan, an ERA resulting in effective dual blockade of the endothelin receptors, may result in efficacious control of blood pressure in subjects having essential hypertension (aprocitentan was administered as monotherapy, i.e. without background anti-hypertensive therapy) (Actelion Pharmaceuticals Ltd, press release May 22, 2017). Even though some indications of potential fluid retention were observed (e.g. increased body weight at higher doses, dose related decrease in the hemoglobin concentration, four cases of peripheral edema at higher doses), the overall frequency of adverse events was similar to those observed in the placebo group. Thus, different from the methods of WO2016/073846 no risk assessment and/or dose reduction to mitigate side effects related to fluid retention may be required for aprocitentan when used in the treatment of hypertension related diseases, especially resistant hypertension. Thus, aprocitentan may have a different pharmacological profile than the predominantly ET_A-selective antagonists so far tested in resistant hypertension or chronic kidney disease in diabetic and non-diabetic patients.

Moreover, it has been found in rat models of hypertension that aprocitentan may have synergistic pharmacological effect in combination with the angiotensin receptor blocker (ARB) valsartan, synergistic pharmacological effect in combination with the angiotensin converting enzyme (ACE) inhibitor enalapril, and synergistic pharmacological effect in combination with the calcium channel blocker (CCB) amlodipine, compared to the effect of the respective active ingredients alone. ARBs, ACE inhibitors and CCBs are standard treatments per guideline requirements, generally prescribed, alone or in combination, to hypertensive patients, often in combination with a diuretic, especially a diuretic of the thiazide class such as hydrochlorothiazide.

SGLT-2 inhibitors block glucose reabsorption in the kidney, increase glucose excretion, and lower blood glucose concentration. In addition to this well characterized mode of action, SGLT-2 inhibitors reduce blood pressure, decrease vascular stiffness, improve endothelial function, and have anti-inflammatory and anti-fibrotic

properties resembling those of ERAs (H.J. Heerspink et al., *Circulation* (2016), 134(10): 752-772). This unique mechanism of action lead to the development and market approval of several SGLT-2 inhibitors comprising canagliflozin, dapagliflozin and empagliflozin, all indicated to improve glycemic control in adults with type 2 diabetes mellitus, empagliflozin in addition being indicated to reduce the risk of cardiovascular death in such patients having established cardiovascular disease. Sotagliflozin, a dual SGLT-1 and SGLT-2 inhibitor has been reported to be in clinical trials for type 1 diabetes.

WO2010/138535 claims a method for treating type 2 diabetes in a mammalian patient who has previously been treated with one or more oral anti-diabetic agents and/or one or more injectable anti-diabetic agents, which previous treatment has failed, which comprises administering to said patient in need of treatment a therapeutically effective amount of an SGLT2 inhibitor, especially dapagliflozin. WO2010/138535, among numerous other speculative combinations, further discloses such method using an SGLT2 inhibitor such as dapagliflozin in combination with one or more anti-hypertensive agent, which are for example beta adrenergic blockers, calcium channel blockers (L-type and/or T-type; e.g., diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid, tricyclic, chlorthalidone, furosemide, bumetanide, triamterene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazapril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-I receptor antagonists (e.g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g. sitaxsentan, atrasentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), dual ET/All antagonist, neutral endopeptidase (NEP) inhibitors, vasopectidase inhibitors (dual NEP-ACE inhibitors) or nitrates. No data supporting a combination with an anti-hypertensive agent compared to other proposed combinations, nor data supporting any particular combination therapy among the various anti-hypertensive agents are provided. Similarly, Kissei Pharmaceuticals Ltd disclosed in several patent applications SGLT-1 and/or SGLT-2 inhibitors useful for the treatment of hyperglycemia such as diabetes, diabetic complications or obesity (see e.g US 7,732,596, US 7,989,424) which, among numerous other speculative combinations, are disclosed to be useful in combination with endothelin receptor antagonists such as L-749805, TBC-3214, BMS-182874, BQ-610, TA-0201, SB-215355, PD-180988, sodium sitaxsentan, BMS-193884, darusentan, TBC-3711, bosentan, sodium tezosentan, J-104132, YM-598, S-0139, SB-234551, RPR-118031A, ATZ-1993, RO-61-1790, ABT-546, enlasentan, BMS-207940 or the like.

Diabetes often concurs with heart failure (HF) and may contribute to its development. SGLT-2 inhibitors such as empagliflozin may be suitable for the treatment of chronic HF, including especially also HFpEF where treatment options are very limited. The EMPA-REG OUTCOME Trial (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) randomized type II diabetic patients with high cardiovascular risk to empagliflozin or standard of care. The results suggested improvement in cardiovascular death, non-fatal myocardial infarction, nonfatal stroke, hospitalization for HF, and death from any cause. A post hoc study looking at patients with a

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diagnosis of HF at baseline suggested significantly lowered cardiovascular death, HF hospitalization, and all cause hospitalization (D. H. Kim et al., "Pharmacologic Management for Heart Failure and Emerging Therapies" Curr Cardiol. Rep (2017) 19:94). The mode of action of SGLT-2 leads to simultaneous inhibition of glucose and sodium uptake in the proximal tubules of the nephron, believed to result in a reset of the tubulo-glomerular feedback putatively causing the phenomenon of glomerular hyperfiltration. Efficacy of SGLT-2 inhibitors is believed to decrease with lower plasma glucose levels or a drop in glomerular filtration rate (GFR), thus, SGLT-2 inhibitors have an inherent low risk for developing hypoglycemia. In consequence, the properties of SGLT-2 inhibitors may open a pathway to treat HF including HFpEF even in non-diabetic patients (P. Martens et al., "Promise of SGLT2 Inhibitors in Heart Failure: Diabetes and Beyond", Curr Treat Options Cardio Med (2017) 19: 23).

A side effect associated with the pharmacological effects of SGLT-2 inhibitors is volume depletion / intravascular volume contraction, potentially leading to dehydration, hypovolemia, orthostatic hypotension, or hypotension. Thus, SGLT-2 inhibitors generally induce an increase in hematocrit (Hct) a marker of haemoconcentration and increased blood viscosity, a putative cause of vascular injury in a context of peripheral vascular disease. In two large trials evaluating the SGLT-2 inhibitor canagliflozin in patients with diabetes type 2 (CANVAS and CANVAS-R), an increased risk of lower limb amputations was observed. The European Medicines Agency assessed these findings (EMA/PRAC/637349/2016) in view of a potential class effect linked to volume reduction and impaired tissue perfusion in the lower limb so that patients with already impaired perfusion would likely develop conditions that lead to amputations. The EMA concluded that a class effect could be neither proven nor disproven.

Furthermore, data from large clinical trials suggest that SGLT2 inhibitors may induce acute kidney injury and impairment in renal function, especially in patients predisposed to acute kidney injury where hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs and NSAIDs) are to be considered. The pharmacological action of SGLT-2 inhibitors on the kidney includes an increase of serum creatinine and a decrease eGFR.

Thus, aprocitentan, an ERA resulting in effective dual blockade of the endothelin receptors, may be particularly suited for the treatment of endothelin related diseases when prescribed in combination with SGLT-2 inhibitors such as atigliflozin, bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, henagliflozin, ipragliflozin, luseogliflozin, remogliflozin, sotagliflozin, tianagliflozin, or tofogliflozin (especially canagliflozin, dapagliflozin, or empagliflozin; in particular canagliflozin). The use of the dual ERA aprocitentan in combination with an SGLT-2 inhibitor may result in a particularly beneficial complementary pharmacological action of the two modes of action, both in view of complementary, additive or even synergistic treatment effect, as well as complementary mitigation of the respective side effects of each active ingredient of such combination therapy.

When combining an ERA with an SGLT-2 inhibitor, the diuretic effect of such SGLT-2 inhibitor and its potential pharmacological action in reducing the risk of heart failure may be suitable to mitigate the most prominent side

effects generally associated with ERAs such as fluid retention and potentially associated increased risk of congestive heart failure. In particular aprocitentan having shown a particularly benign safety profile in a phase II study in (essential) hypertension patients may be suitable for such combination. Such combination treatment may result in pharmacological action on the disclosed endothelin related diseases, while maintaining a benign side effect profile even at optimal efficacious dosages of aprocitentan, potentially even at increased dosages of aprocitentan when compared to maximum tolerated doses of aprocitentan alone, or aprocitentan in combination for example with standard diuretics such as thiazide-like diuretics including hydrochlorothiazide, and/or aldosterone antagonists. Increased doses of aprocitentan that may become accessible, e.g. due to mitigated side effects, when aprocitentan is used in combination with an SGLT-2 inhibitor may allow to amplify the impact on diseases that are caused by deleterious effects of the endothelin paracrine system widely distributed in the organism. Such combination treatment may improve the benefit/risk ratio and e.g. not require the risk assessment methods of WO2016/073846 and/or dose reductions to mitigate side effects, e.g. related to fluid retention.

In addition to the above-mentioned potential effects of an SGLT-2 inhibitor on the pharmacological effect and / or the side effect profile of the ERA aprocitentan, the ERA aprocitentan in turn may have complementary effect on the pharmacological effect and / or the side effect profile of the respective SGLT-2 inhibitor. ERAs have been described to decrease hematocrit (Hct) via hemodilution. Thus, aprocitentan when used in combination with SGLT-2 inhibitors may antagonize the most prominent side effects generally associated with SGLT-2 inhibitors such as hemoconcentration due to volume depleting effect, possibly contributing to an increased risk of lower extremity / limb amputations. Furthermore, ERAs have been described to provide renal protection and improve renal hemodynamics. Thus, aprocitentan when used in combination with SGLT-2 inhibitors may mitigate the risk of acute renal failure, one of the reported risks of currently approved SGLT-2 inhibitors. Furthermore, ERAs are expected to decrease blood pressure by preventing the vasoconstrictive effect of ET-1 resulting from its binding to ET receptors, thus, aprocitentan when used in combination with SGLT-2 inhibitors may contribute its pronounced pharmacological effect on blood pressure reduction and the consequences of thereof (vascular remodelling, end organ damage, decreased cardiovascular risk caused by / associated with diabetes and/or hypertension). Furthermore, ERAs have been described to improve blood sugar levels by various mechanisms (increased blood flow, improvement of insulin signalling). Thus, aprocitentan when used in combination with SGLT-2 inhibitors may have additive, or even synergistic effects on blood sugar reduction. In addition, volume depletion may be associated with increased blood viscosity. Sloop et al. (Ther Adv Cardiovasc Dis (2015), 9(1) 19–25) state that "The reason why the pathogenesis of chronic vascular diseases, including atherosclerosis, hypertension, and the metabolic syndrome, is not fully understood by the mainstream is because the role of blood viscosity has been ignored.", and that "Theoretically, because flow is inversely proportional to viscosity, reducing blood viscosity should improve perfusion of muscle and increase glucose utilization, decreasing blood glucose levels". Thus, the combination of aprocitentan and a SGLT-2 inhibitor may lead, by a complementary normalization of both the volume depleting effect generally associated with SGLT-2 inhibitors, and the fluid

retention effect generally associated with ERAs, to the beneficial pharmacological effects mentioned above, and potentially to additional beneficial pharmacological effects associated with blood viscosity. Finally, aprocitentan which has the pharmacological effect of a dual ERA may be particularly suited for such combination therapy when compared to a selective ET_A receptor antagonist, as it may have low counteracting activity on the beneficial effect of SGLT-2 inhibitors on sodium re-uptake that is associated to the principal pharmacological effect of SGLT-2 on glucose re-uptake.

It has further been found that certain crystalline forms of aprocitentan that are suitable for the production of pharmaceutical compositions may under certain conditions be found. Said crystalline forms of aprocitentan may have advantageous properties in view of the potential use of aprocitentan as active pharmaceutical ingredient. Such advantages may include better flow properties; less hygroscopicity; better reproducibility in manufacturing (for example better filtration parameters, better reproducibility of formation, and/or better sedimentation); and/or defined morphology. Such crystalline forms of aprocitentan may be particularly suitable in a process of manufacturing certain pharmaceutical compositions. It has also been found that aprocitentan or a pharmaceutically acceptable salt thereof is particularly useful to treat certain disorders, in particular when used in combination with other active ingredients or therapeutic agents.

Description of the Figures

Figure 1 shows the X-ray powder diffraction diagram of COMPOUND in a crystalline form A as obtained from Example 1. The X-ray diffraction diagram shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2theta (selected peaks from the range 3-33° 2theta with relative intensity larger than 10% are reported): 9.8° (18%), 9.9° (18%), 11.7° (14%), 14.5° (10%), 15.4° (14%), 15.6° (29%), 16.9° (19%), 17.2° (16%), 17.8° (100%), 18.6° (50%), 19.9° (54%), 20.0° (67%), 21.5° (24%), 21.9° (10%), 22.8° (18%), 23.2° (49%), 23.5° (83%), 24.9° (32%), 25.1° (20%), 25.3° (24%), 25.6° (33%), 25.9° (16%), 27.1° (23%), 27.3° (39%), 28.5° (13%), 29.0° (23%), 29.4° (15%), 30.1° (12%) and 30.6° (10%).

Figure 2 shows the X-ray powder diffraction diagram of COMPOUND in a crystalline form C as obtained from Example 2. The X-ray diffraction diagram shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2theta (selected peaks from the range 3-33° 2theta with relative intensity larger than 10% are reported): 7.8° (23%), 9.7° (42%), 15.7° (37%), 17.2° (16%), 17.8° (15%), 18.8° (26%), 19.8° (71%), 20.1° (51%), 20.6° (15%), 21.6° (15%), 22.0° (100%), 23.4° (27%), 23.6° (40%), 24.1° (23%), 24.5° (16%), 25.1° (13%), 25.3° (39%), 25.7° (28%), 26.8° (19%), 27.1° (16%), 28.5° (31%), 30.8° (13%) and 30.8° (13%).

It is understood, that the crystalline forms disclosed herein comprise the COMPOUND in a crystalline form of the free base (i.e. not in form of a salt). Furthermore, said crystalline forms may comprise non-coordinated and

/ or coordinated solvent. Coordinated solvent is used herein as term for a crystalline solvate. Likewise, non-coordinated solvent is used herein as term for physisorbed or physically entrapped solvent (definitions according to Polymorphism in the Pharmaceutical Industry (Ed. R. Hilfiker, VCH, 2006), Chapter 8: U.J. Griesser: The Importance of Solvates). Crystalline forms A and C are anhydrate / anhydrate forms.

- 5 **Figure 3** shows the acute effects of ACT-132577 on mean arterial blood pressure ("MAP") in conscious, male hypertensive Dahl salt sensitive rats.

Figure 4 shows the acute effects of ACT-132577 on MAP in conscious, male hypertensive deoxycorticosterone acetate salt rats.

Figure 5 shows the acute effects of ACT-132577 on MAP in conscious, male spontaneously hypertensive rats.

- 10 **Figure 6** shows the acute effects of ACT-132577, used alone or in combination with valsartan, on MAP in conscious, male spontaneously hypertensive rats.

Figure 7 shows the acute effects of ACT-132577, used alone or in combination with valsartan, on MAP in conscious, male hypertensive deoxycorticosterone acetate salt rats.

- 15 **Figure 8** shows the acute effects of ACT-132577, used alone or in combination with enalapril, on MAP in conscious, male spontaneously hypertensive rats.

Figure 9 shows the acute effects of ACT-132577, used alone or in combination with amlodipine, on MAP in conscious, male hypertensive deoxycorticosterone acetate salt rats.

Figure 10 shows the effects of chronic oral administration of ACT-132577 on MAP in conscious, male hypertensive deoxycorticosterone acetate salt rats.

- 20 **Figure 11** shows the effects of chronic oral administration of ACT-132577 on renal vascular resistance in conscious, male hypertensive deoxycorticosterone acetate salt rats.

Figure 12 shows the acute dose-response effect of apocitin 1 mg/kg, 3 mg/kg, 10 mg/kg, 30 mg/kg on haematocrit (Hct) 24 hours after a single oral administration to Wistar rats.

- 25 **Figure 13** shows the acute effects of ACT-132577, used alone or in combination with canagliflozin, on maximal effects on MAP in conscious, male spontaneously hypertensive rats.

Figure 14 shows the acute effects of ACT-132577, used alone or in combination with empagliflozin, on maximal effects on MAP in conscious, male spontaneously hypertensive rats.

Figure 15 shows acute effects of EXFORGE HCT® alone, and EXFORGE HCT® in combination with ACT-132577, in male spontaneously hypertensive rats.

- 30 **Figure 16** shows acute effects of EXFORGE HCT® alone, and EXFORGE HCT® in combination with spironolactone, in male spontaneously hypertensive rats.

Figure 17 shows acute effects of EXFORGE HCT® alone, and EXFORGE HCT® in combination with ACT-132577, in male hypertensive deoxycorticosterone acetate salt rats.

Figure 18 shows acute effects of EXFORGE HCT® alone, and EXFORGE HCT® in combination with spironolactone, in male hypertensive deoxycorticosterone acetate salt rats.

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Detailed Description of the Invention

1) A first embodiment relates to a pharmaceutical composition containing, as active principles, aprocitentan, or a pharmaceutically acceptable salt thereof, in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, as well as at least one pharmaceutically acceptable excipient.

10 2) A further embodiment relates to a pharmaceutical composition according to embodiment 1), wherein the SGLT-2 inhibitor is atigliflozin, bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, henagliflozin, ipragliflozin, luseogliflozin, remogliflozin, sotagliflozin, or tofogliflozin; or a pharmaceutically acceptable salt thereof.

2(i) In a sub-embodiment, the SGLT-2 inhibitor is notably bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, henagliflozin, ipragliflozin, luseogliflozin, sotagliflozin, or tofogliflozin (especially canagliflozin, dapagliflozin, or empagliflozin; in particular canagliflozin); or a pharmaceutically acceptable salt thereof.

3) A further embodiment relates to a pharmaceutical composition according to embodiment 1), wherein the SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, is canagliflozin, dapagliflozin, or empagliflozin (in particular canagliflozin), or a pharmaceutically acceptable salt thereof.

4) A further embodiment relates to a pharmaceutical composition according to embodiment 1), wherein the SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, is canagliflozin, or a pharmaceutically acceptable salt thereof.

5) A further embodiment relates to a pharmaceutical composition according to any one of embodiments 1) to 4), wherein aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 1 to 100 mg, preferably 2.5 to 100 mg (notably 10 to 50 mg); especially 10 mg, 12.5 mg, 20 mg, 25 mg, 30 mg, 40 mg, or 50 mg; in particular 12.5 mg, 25 mg or 50 mg; per day of aprocitentan;

5(i) wherein in a sub-embodiment said dose of aprocitentan is a dose which may be expected to be a tolerated efficacious dose of aprocitentan when given as a single therapy (for example with regard to the treatment of hypertension) (in particular such dose would be 10 to 25 mg, especially 10 mg, 12.5 mg, or 25 mg),

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- 5(ii) wherein in another sub-embodiment said dose of aprocitentan is a dose which may be expected to be a tolerated efficacious dose or higher than a tolerated efficacious dose of aprocitentan when given as a single therapy (for example with regard to the treatment of hypertension) (in particular such dose would be 40 to 100 mg, especially 50 mg per day of aprocitentan);
- 5 5(iii) wherein in another sub-embodiment said dose of aprocitentan is a dose which may be expected to be a tolerated efficacious dose or lower than a tolerated efficacious dose of aprocitentan when given as a single therapy (for example with regard to the treatment of hypertension) (in particular such dose would be 1 mg, 2.5 mg or 5 mg per day of aprocitentan).
- 6) A further embodiment relates to a pharmaceutical composition according to any one of embodiments 1) to 10 4), wherein aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 1 mg, 2.5 mg, 5 mg, 10 mg, 12.5 mg, 20 mg, 25 mg, 30 mg, 40 mg, or 50 mg; (especially 10 mg, 12.5 mg, 20 mg, 25 mg, 30 mg, 40 mg, or 50 mg; notably 12.5 mg, 25 mg or 50 mg) per day of aprocitentan;
- 15 6(i) wherein in a sub-embodiment aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 12.5 mg per day of aprocitentan (i.e. a dose which may be expected to be a tolerated efficacious dose of aprocitentan when given as a single therapy (for example with regard to the treatment of hypertension));
- 20 6(ii) wherein in another sub-embodiment aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 25 mg per day of aprocitentan (i.e. a dose which may be expected to be a tolerated efficacious dose of aprocitentan when given as a single therapy (for example with regard to the treatment of hypertension));
- 25 6(iii) wherein in another sub-embodiment aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 50 mg per day of aprocitentan (i.e. a dose which may be expected to be a tolerated efficacious dose or higher than a tolerated efficacious dose of aprocitentan when given as a single therapy (for example with regard to the treatment of hypertension));
- 30 6(iv) wherein in another sub-embodiment aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 10 mg per day of aprocitentan (i.e. a dose which may be expected to be a tolerated efficacious dose of aprocitentan when given as a single therapy (for example with regard to the treatment of hypertension));
- 6(v) wherein in another sub-embodiment aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 5 mg per day of aprocitentan (i.e. a dose which may be expected to be a tolerated efficacious dose or lower than a

tolerated efficacious dose of aprocitentan when given as a single therapy (for example with regard to the treatment of hypertension));

6(vi) wherein in another sub-embodiment aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 2.5 mg per day of aprocitentan (i.e. a dose which may be expected to be lower than a tolerated efficacious dose of aprocitentan when given as a single therapy (for example with regard to the treatment of hypertension));

6(vii) wherein in another sub-embodiment aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 1 mg per day of aprocitentan (i.e. a dose which may be expected to be lower than a tolerated efficacious dose of aprocitentan when given as a single therapy (for example with regard to the treatment of hypertension)).

7) A further embodiment relates to a pharmaceutical composition according to any one of embodiments 1) to 6), wherein said SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of said SGLT-2 inhibitor, wherein

- bexagliflozin, or a pharmaceutically acceptable salt thereof, if present, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 5 to 50 mg (in particular 20 mg) per day of bexagliflozin;
- canagliflozin, or a pharmaceutically acceptable salt thereof, if present, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 50 to 400 mg (in particular 50 mg, 100 mg, 150 mg, or 300 mg; notably 100 mg, or 300 mg; especially 100 mg) per day of canagliflozin;
- dapagliflozin, or a pharmaceutically acceptable salt thereof, if present, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 1 to 20 mg (in particular 5 mg or 10 mg) per day of dapagliflozin;
- empagliflozin, or a pharmaceutically acceptable salt thereof, if present, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 5 to 50 mg (in particular 10 mg or 25 mg) per day of empagliflozin;
- ertugliflozin, or a pharmaceutically acceptable salt thereof, if present, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 2.5 to 50 mg (in particular 5 mg or 15 mg) per day of ertugliflozin;
- henagliflozin, or a pharmaceutically acceptable salt thereof, if present, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 5 to 100 mg (in particular 25 mg) per day of henagliflozin;

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- ipragliflozin, or a pharmaceutically acceptable salt thereof, if present, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 10 to 100 mg (in particular 25 mg or 50 mg) per day of ipragliflozin;
 - 5 • luseogliflozin, or a pharmaceutically acceptable salt thereof, if present, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 1 to 10 mg (in particular 2.5 mg or 5 mg) per day of luseogliflozin;
 - sotagliflozin, or a pharmaceutically acceptable salt thereof, if present, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 50 to 500 mg (in particular 75 mg, 200 mg or 400 mg) per day of sotagliflozin,
 - 10 • tofogliflozin, or a pharmaceutically acceptable salt thereof, if present, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 10 to 50 mg (in particular 20 mg) per day of tofogliflozin.
- 8) A further embodiment relates to a pharmaceutical composition according to embodiment 4), wherein
- 15 • aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 1 to 100 mg, preferably 2.5 to 100 mg (notably 10 to 50 mg); especially 10 mg, 12.5 mg, 20 mg, 25 mg, 30 mg, 40 mg, or 50 mg; in particular 12.5 mg, 25 mg or 50 mg; per day of aprocitentan; and
 - canagliflozin, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 50 to 400 mg (in particular 50 mg, 100 mg, 150 mg, 20 or 300 mg; notably 100 mg, or 300 mg; especially 100 mg) per day of canagliflozin;
- 8(i) wherein in a sub-embodiment aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 12.5 mg per day of aprocitentan; and canagliflozin, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 50 mg, 100 mg, 150 mg, or 300 mg (notably 100 mg, or 300 mg, especially 100 mg) per day of canagliflozin;
- 25 8(ii) wherein in another sub-embodiment aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 25 mg per day of aprocitentan; and canagliflozin, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 50 mg, 100 mg, 150 mg, or 300 mg (notably 100 mg, or 300 mg, especially 100 mg) per day of canagliflozin;
- 30 8(iii) wherein in another sub-embodiment aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 10 mg per day of aprocitentan; and canagliflozin, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 50 mg, 100 mg, 150 mg, or 300 mg (notably 100 mg, or 300 mg, especially 100 mg) per day of canagliflozin;
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- 8(iv) wherein in another sub-embodiment aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 5 mg per day of aprocitentan; and canagliflozin, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 50 mg, 100 mg, 150 mg, or 300 mg (notably 100 mg, or 300 mg, especially 100 mg) per day of canagliflozin;
- 5
- 8(v) wherein in another sub-embodiment aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 2.5 mg per day of aprocitentan; and canagliflozin, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 50 mg, 100 mg, 150 mg, or 300 mg (notably 100 mg, or 300 mg, especially 100 mg) per day of canagliflozin;
- 10
- 8(vi) wherein in another sub-embodiment aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 1 mg per day of aprocitentan; and canagliflozin, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 50 mg, 100 mg, 150 mg, or 300 mg (notably 100 mg, or 300 mg, especially 100 mg) per day of canagliflozin;
- 15
- 8(vii) wherein in another sub-embodiment aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 50 mg per day of aprocitentan; and canagliflozin, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 50 mg, 100 mg, 150 mg, or 300 mg (notably 100 mg, or 300 mg, especially 100 mg) per day of canagliflozin.
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Likewise, when combined with dapagliflozin or empagliflozin, aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised as set out in embodiment 8) and its sub-embodiments 8(i) to 8(vii) above; and

- dapagliflozin, or a pharmaceutically acceptable salt thereof, if present, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 1 to 20 mg (in particular 5 mg or 10 mg) per day of dapagliflozin; and
 - empagliflozin, or a pharmaceutically acceptable salt thereof, if present, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 5 to 50 mg (in particular 10 mg or 25 mg) per day of empagliflozin.
- 25

- 9) A second aspect of the present invention relates to a pharmaceutical composition according to any one of embodiments 1) to 8); wherein said pharmaceutical composition is (intended) to be administered in combination / co-therapy to conventional background therapy (or first line therapy) suitable for the prevention or treatment of hypertension including especially difficult to treat / resistant hypertension; chronic kidney disease (CKD) [notably CKD of stages 1 to 4 as defined by the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines (and especially CKD of stage 3)], and in particular CKD (notably of these stages) caused by /
- 30

associated with hypertension and/or caused by / associated with diabetes (diabetic kidney disease (DKD)); or diabetes.

- 9(i) In a first sub-embodiment, such conventional background therapy may notably comprise:
- an ACE inhibitor (especially enalapril, as well as ramipril, quinapril, perindopril, lisinopril, benazepril, imidapril, trandolapril, cilazapril), or a pharmaceutically acceptable salt thereof; and/or
 - an angiotensin receptor blocker (especially valsartan, as well as losartan, candesartan, irbesartan, telmisartan, eprosartan, olmesartan, azilsartan, fimasartan), or a pharmaceutically acceptable salt thereof; and/or
 - a calcium channel blocker (especially amlodipine, as well as aranidipine, azelnidipine, barnidipine, benidipine, cilnidipine, clevidipine, efonidipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, pranidipine), or a pharmaceutically acceptable salt thereof; and/or
 - metformin; and/or
 - insulin; and/or
 - a sulfonylurea (especially glibenclamide), or a pharmaceutically acceptable salt thereof; and/or
 - a DPP-4 inhibitor (especially sitagliptin, vildagliptin, saxagliptin, or linagliptin), or a pharmaceutically acceptable salt thereof; and/or
 - a GLP-1 receptor agonist (especially exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, taspoglutide, semaglutide); and/or
 - a thiazolidinedione, or a pharmaceutically acceptable salt thereof.
- 9(ii) In second sub-embodiment, preferred are conventional background therapies which are first line therapies suitable for the prevention or treatment of hypertension and/or diabetes, such as especially an ACE inhibitor or an angiotensin receptor blocker as hypertension treatments; and/or metformin, and/or a DPP-4 inhibitor as diabetes treatment.
- 9(iii) In third sub-embodiment, said background therapy according to any one of embodiments 9), 9(i), or 9(ii) is to be administered in a dosage corresponding to a tolerated efficacious dose of the respective active ingredient, e.g. when given as a single therapy, or in diabetes patients, when given in combination with the respective SGLT-2 inhibitor. In particular, valsartan, or a pharmaceutically acceptable salt thereof, if present, is to be administered in a dosage form suitable for the oral administration of 160 mg or 320 mg per day of valsartan; losartan, or a pharmaceutically acceptable salt thereof, if present, is to be administered in a dosage form suitable for the oral administration of 50 mg or 100 mg per day of losartan; irbesartan, or a pharmaceutically acceptable salt thereof, if present, is to be administered in a dosage form suitable for the oral administration of 75 mg, 150 mg, or 300 mg per day of irbesartan; amlodipine, or a pharmaceutically acceptable salt thereof, if present, is to be administered in a dosage form suitable for the oral administration of 5 mg or 10 mg per day of

- amlodipine; enalapril, or a pharmaceutically acceptable salt thereof, if present, is to be administered in a dosage form suitable for the oral administration of 2.5 mg to 40 mg per day of enalapril; lisinopril, or a pharmaceutically acceptable salt thereof, if present, is to be administered in a dosage form suitable for the oral administration of 2.5 mg to 40 mg per day of lisinopril; ramipril, or a pharmaceutically acceptable salt thereof, if present, is to be administered in a dosage form suitable for the oral administration of 2.5 mg to 20 mg per day of ramipril; metformin, if present, is to be administered in a dosage form suitable for the oral administration of 500 mg to 2000 mg per day of metformin; glibenclamide if present, is to be administered in a dosage form suitable for the oral administration of 1.25 mg to 5 mg per day of glibenclamide; sitagliptin if present, is to be administered in a dosage form suitable for the oral administration of 25 mg to 100 mg per day of sitagliptin; vildagliptin if present, is to be administered in a dosage form suitable for the oral administration of two times 50 mg per day of vildagliptin; saxagliptin if present, is to be administered in a dosage form suitable for the oral administration of 2.5 mg or 5 mg per day of saxagliptin; linagliptin if present, is to be administered in a dosage form suitable for the oral administration of two times 5 mg per day of linagliptin.
- 15 "Angiotensin Receptor Blocker" or "ARB" in particular means in the present application valsartan, losartan, telmisartan, irbesartan, candesartan, olmesartan, azilsartan, or a pharmaceutically acceptable salt of one of these. A preferred ARB is valsartan or a pharmaceutically acceptable salt thereof.
- "Calcium Channel Blocker" or "CCB" in particular means in the present application amlodipine, aranidipine, azelnidipine, bamidipine, benidipine, cilnidipine, clevidipine, isradipine, efonidipine, felodipine, lacidipine, 20 lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, pranidipine, verapamil or diltiazem or a pharmaceutically acceptable salt of one of these. A preferred CCB is amlodipine or a pharmaceutically acceptable salt thereof.
- "Angiotensin Converting Enzyme inhibitor" or "ACE inhibitor" in particular means in the present application captopril, enalapril, ramipril, quinapril, perindopril, lisinopril, imidapril or cilazapril, or a pharmaceutically acceptable salt of one of these. A preferred ACE inhibitor is enalapril, or a pharmaceutically acceptable salt thereof.
- 25 The term "DPP-4 inhibitor" or "DPP-IV inhibitor" refers to inhibitors of dipeptidyl peptidase 4 such as especially sitagliptin, vildagliptin, saxagliptin, and linagliptin, as well as gemigliptin, anagliptin, teneligliptin, alogliptin, trelagliptin, omarigliptin, evogliptin, and dutogliptin.
- 30 The term "GLP-1 receptor agonist" refers to agonists of the glucagon-like peptide-1 receptor such as especially exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, taspoglutide, semaglutide.
- The term "sulfonylurea" refers especially to glibenclamide (glyburide), glibornuride, gliclazide, glipizide, gliquidone, glisoxepide, glycopyramide, or glimepiride.

The term "thiazolidinediones" abbreviated as TZD, also known as glitazones, refers to agonists of the PPAR γ (peroxisome proliferator-activated receptor gamma), and refers especially to pioglitazone, rosiglitazone, or lobeglitazone.

5 A further conventional background therapy, in particular for the treatment of a patient having a history of hypertension, may be a diuretic. Such diuretic may especially be prescribed in addition to the above-mentioned conventional background therapies of hypertension. The term "diuretic" in the present application refers to loop diuretics including furosemide, bumetanide, ethacrynic acid, torsemide; potassium-sparing diuretics including aldosterone antagonists such as spironolactone, eplerenone, or finerenone, or aldosterone synthase inhibitors; carbonic anhydrase inhibitors including acetazolamide and methazolamide; and in particular to diuretics of the thiazide class (thiazide-like diuretics) such as especially chlorthalidone, hydrochlorothiazide, chlorothiazide, indapamide, or metolazone. Preferred thiazide-like diuretic are chlorthalidone or hydrochlorothiazide. For avoidance of doubt, even though having a diuretic pharmacological effect, SGLT-2 inhibitors are not encompassed in the term "diuretic" as used herein.

10 10) A third aspect of the invention relates to a pharmaceutical composition according to any one of embodiments 1) to 9), said composition comprising apocitentan in crystalline Form A characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 17.8°, 20.0°, and 23.5°; wherein said X-ray powder diffraction diagram is obtained by using combined Cu K α 1 and K α 2 radiation, without K α 2 stripping; and the accuracy of the 2θ values is in the range of $2\theta \pm 0.2^\circ$.

15 11) A further embodiment relates to a pharmaceutical composition according to any one of embodiments 1) to 9), said composition comprising apocitentan in crystalline Form A characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 17.8°, 18.6°, 20.0°, 23.2° and 23.5°; wherein said X-ray powder diffraction diagram is obtained by using combined Cu K α 1 and K α 2 radiation, without K α 2 stripping; and the accuracy of the 2θ values is in the range of $2\theta \pm 0.2^\circ$.

20 12) A further embodiment relates to a pharmaceutical composition according to any one of embodiments 1) to 9), said composition comprising apocitentan in crystalline Form A characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.8°, 9.9°, 11.7°, 17.8°, 18.6°, 20.0°, 21.5°, 22.8°, 23.2° and 23.5°; wherein said X-ray powder diffraction diagram is obtained by using combined Cu K α 1 and K α 2 radiation, without K α 2 stripping; and the accuracy of the 2θ values is in the range of $2\theta \pm 0.2^\circ$.

25 30 13) A further embodiment relates to a pharmaceutical composition according to any one of embodiments 1) to 9), said composition comprising apocitentan in crystalline Form A characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.8°, 9.9°, 11.7°, 14.5°, 15.4°, 15.6°, 16.9°, 17.2°, 17.8°, 18.6°, 19.9°, 20.0°, 21.5°, 21.9°, 22.8°, 23.2°, 23.5°, 24.9°, 25.1°, 25.3°, 25.6°, 25.9°, 27.1°, 27.3°, 28.5°, 29.0°, 29.4°, 30.1° and 30.6°; wherein said X-ray powder diffraction diagram is

obtained by using combined Cu K α 1 and K α 2 radiation, without K α 2 stripping; and the accuracy of the 2 θ values is in the range of 2 θ +/- 0.2°.

- 14) A further embodiment relates to a pharmaceutical composition according to any one of embodiments 1) to 9), said composition comprising aprocitentan in crystalline Form A characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2 θ : 9.8° (18%), 9.9° (18%), 11.7° (14%), 14.5° (10%), 15.4° (14%), 15.6° (29%), 16.9° (19%), 17.2° (16%), 17.8° (100%), 18.6° (50%), 19.9° (54%), 20.0° (67%), 21.5° (24%), 21.9° (10%), 22.8° (18%), 23.2° (49%), 23.5° (83%), 24.9° (32%), 25.1° (20%), 25.3° (24%), 25.6° (33%), 25.9° (16%), 27.1° (23%), 27.3° (39%), 28.5° (13%), 29.0° (23%), 29.4° (15%), 30.1° (12%) and 30.6° (10%); wherein said X-ray powder diffraction diagram is obtained by using combined Cu K α 1 and K α 2 radiation, without K α 2 stripping; and the accuracy of the 2 θ values is in the range of 2 θ +/- 0.2°.

The present data show peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parentheses) at the indicated angles of refraction 2 θ (selected peaks from the range 3-33° 2 θ with relative intensity larger than 10% are reported).

- 15) A further embodiment relates to a pharmaceutical composition according to any one of embodiments 1) to 9), said composition comprising aprocitentan in crystalline Form A which essentially shows the X-ray powder diffraction pattern as depicted in Figure 1, wherein said X-ray powder diffraction diagram is obtained by using combined Cu K α 1 and K α 2 radiation, without K α 2 stripping; and the accuracy of the 2 θ values is in the range of 2 θ +/- 0.2°.
- In this context the term "essentially" means that at least the major peaks of the diagram depicted in said figures, i.e. those having a relative intensity of more than 10%, especially more than 20%, as compared to the most intense peak in the diagram, have to be present. However, the person skilled in the art of X-ray powder diffraction will recognize that relative intensities in X-ray powder diffraction diagrams may be subject to strong intensity variations due to preferred orientation effects.
- 16) A further embodiment relates to a pharmaceutical composition according to any one of embodiments 1) to 9), said composition comprising aprocitentan in crystalline Form A obtainable by crystallisation of the COMPOUND in an aqueous solution at pH 6.2 to 6.8.

For avoidance of any doubt, whenever one of the above embodiments refers to "peaks in the X-ray powder diffraction diagram at the following angles of refraction 2 θ ", said X-ray powder diffraction diagram is obtained by using combined Cu K α 1 and K α 2 radiation, without K α 2 stripping; and it should be understood that the accuracy of the 2 θ values as provided herein is in the range of +/- 0.1-0.2°. Notably, when specifying an angle of refraction 2 θ for a peak in the invention embodiments and the claims, the 2 θ value given is to be

understood as an interval from said value minus 0.2° to said value plus 0.2° ($2\theta \pm 0.2^\circ$); and preferably from said value minus 0.1° to said value plus 0.1° ($2\theta \pm 0.1^\circ$).

When defining the presence of peak in e.g. an X-ray powder diffraction diagram, a common approach is to do this in terms of the S/N ratio (S = signal, N = noise). According to this definition, when stating that a peak has
5 to be present in an X-ray powder diffraction diagram, it is understood that the peak in the X-ray powder diffraction diagram is defined by having an S/N ratio (S = signal, N = noise) of greater than x (x being a numerical value greater than 1), usually greater than 2, especially greater than 3.

Unless used regarding temperatures, the term "about" placed before a numerical value "X" refers in the current application to an interval extending from X minus 10% of X to X plus 10% of X, and preferably to an interval
10 extending from X minus 5% of X to X plus 5% of X. In the particular case of temperatures, the term "about" placed before a temperature "Y" refers in the current application to an interval extending from the temperature Y minus 10°C to Y plus 10°C , preferably to an interval extending from Y minus 5°C to Y plus 5°C , notably to an interval extending from Y minus 3°C to Y plus 3°C . Room temperature means a temperature of about 25°C .
When in the current application the term n equivalent(s) is used wherein n is a number, it is meant and within
15 the scope of the current application that n is referring to about the number n, preferably n is referring to the exact number n.

Whenever the word "between" or "to" is used to describe a numerical range, it is to be understood that the end points of the indicated range are explicitly included in the range. For example: if a temperature range is described to be between 40°C and 80°C (or 40°C to 80°C), this means that the end points 40°C and 80°C are
20 included in the range; or if a variable is defined as being an integer between 1 and 4 (or 1 to 4), this means that the variable is the integer 1, 2, 3, or 4.

17) A fourth aspect of the invention relates to a pharmaceutical composition according to any one of embodiments 1) to 9), said composition comprising apocitentan in crystalline Form C characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.7° , 15.7° ,
25 and 22.0° ; wherein said X-ray powder diffraction diagram is obtained by using combined Cu $K\alpha_1$ and $K\alpha_2$ radiation, without $K\alpha_2$ stripping; and the accuracy of the 2θ values is in the range of $2\theta \pm 0.2^\circ$.

18) A further embodiment relates to a pharmaceutical composition according to any one of embodiments 1) to 9), said composition comprising apocitentan in crystalline Form C characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 7.8° , 9.7° , 15.7° , 19.8° and 22.0° ;
30 wherein said X-ray powder diffraction diagram is obtained by using combined Cu $K\alpha_1$ and $K\alpha_2$ radiation, without $K\alpha_2$ stripping; and the accuracy of the 2θ values is in the range of $2\theta \pm 0.2^\circ$.

19) A further embodiment relates to a pharmaceutical composition according to any one of embodiments 1) to 9), said composition comprising apocitentan in crystalline Form C characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 7.8° , 9.7° , 15.7° , 17.2° , 17.8° ,

18.8°, 19.8°, 22.0°, 23.6°, and 25.3°; wherein said X-ray powder diffraction diagram is obtained by using combined Cu K α 1 and K α 2 radiation, without K α 2 stripping; and the accuracy of the 2 θ values is in the range of 2 θ +/- 0.2°.

20) A further embodiment relates to a pharmaceutical composition according to any one of embodiments 1) to 9), said composition comprising apocritentan in crystalline Form C characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2 θ : 7.8°, 9.7°, 15.7°, 17.2°, 17.8°, 18.8°, 19.8°, 20.1°, 20.6°, 21.6°, 22.0°, 23.4°, 23.6°, 24.1°, 24.5°, 25.1°, 25.3°, 25.7°, 26.8°, 27.1°, 28.5°, 30.8° and 30.8°; wherein said X-ray powder diffraction diagram is obtained by using combined Cu K α 1 and K α 2 radiation, without K α 2 stripping; and the accuracy of the 2 θ values is in the range of 2 θ +/- 0.2°.

21) A further embodiment relates to a pharmaceutical composition according to any one of embodiments 1) to 9), said composition comprising apocritentan in crystalline Form C characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2 θ : 7.8° (23%), 9.7° (42%), 15.7° (37%), 17.2° (16%), 17.8° (15%), 18.8° (26%), 19.8° (71%), 20.1° (51%), 20.6° (15%), 21.6° (15%), 22.0° (100%), 23.4° (27%), 23.6° (40%), 24.1° (23%), 24.5° (16%), 25.1° (13%), 25.3° (39%), 25.7° (28%), 26.8° (19%), 27.1° (16%), 28.5° (31%), 30.8° (13%) and 30.8° (13%); wherein said X-ray powder diffraction diagram is obtained by using combined Cu K α 1 and K α 2 radiation, without K α 2 stripping; and the accuracy of the 2 θ values is in the range of 2 θ +/- 0.2°.

The present data show peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parentheses) at the indicated angles of refraction 2 θ (selected peaks from the range 3-33° 2 θ with relative intensity larger than 10% are reported).

22) A further embodiment relates to a pharmaceutical composition according to any one of embodiments 1) to 9), said composition comprising apocritentan in crystalline Form C which essentially shows the X-ray powder diffraction pattern as depicted in Figure 3, wherein said X-ray powder diffraction diagram is obtained by using combined Cu K α 1 and K α 2 radiation, without K α 2 stripping; and the accuracy of the 2 θ values is in the range of 2 θ +/- 0.2°.

In this context the term "essentially" means that at least the major peaks of the diagram depicted in said figures, i.e. those having a relative intensity of more than 10%, especially more than 20%, as compared to the most intense peak in the diagram, have to be present. However, the person skilled in the art of X-ray powder diffraction will recognize that relative intensities in X-ray powder diffraction diagrams may be subject to strong intensity variations due to preferred orientation effects.

23) A further embodiment relates to a pharmaceutical composition according to any one of embodiments 1) to 9), said composition comprising apocritentan in crystalline Form C obtainable by crystallisation of the COMPOUND from MeOH, EtOH or propan-2-ol.

24) A further embodiment relates to a pharmaceutical composition according to any one of embodiments 1) to 9), said composition comprising aprocitentan in amorphous form. Such amorphous form may be obtained by milling form A. For Example, the amorphous form is obtainable by milling in a ball mill (MM200 Retsch Ball Mill, 2 agate beads), 30 min at 30 Hz at ambient temperature.

- 5 The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art (see for example Remington, The Science and Practice of Pharmacy, 21st Edition (2005), Part 5, "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the crystalline forms of the present invention, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, pharmaceutically acceptable solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

25) A further embodiment relates to a solid pharmaceutical composition (in particular in the form of a tablet) according to any one of embodiments 1) to 24), especially according to any one of embodiments 10) to 16), or according to any one of embodiments 17) to 22), comprising as pharmaceutically acceptable excipient inert microcrystalline cellulose, lactose, hydroxypropylcellulose, croscarmellose sodium and magnesium stearate.

- 15 26) Especially, the solid pharmaceutical composition of embodiment 25) will comprise aprocitentan in a total amount from 5 to 25% in weight based on the total weight of the pharmaceutical composition, microcrystalline cellulose in a total amount from 20 to 30% in weight based on the total weight of the pharmaceutical composition, lactose in a total amount from 40 to 65% in weight based on the total weight of the pharmaceutical composition, hydroxypropylcellulose in a total amount from 1 to 3% in weight based on the total weight of the pharmaceutical composition, croscarmellose sodium in a total amount from 2 to 8% in weight based on the total weight of the pharmaceutical composition and magnesium stearate in a total amount from 0.2 to 2% in weight based on the total weight of the pharmaceutical composition, whereby the total percent in weight of the solid pharmaceutical composition will always be 100; the aforementioned solid pharmaceutical composition will particularly be in the form of a tablet.

- 25 27) A further embodiment of the invention relates to a pharmaceutical composition according to embodiments 25) or 26), wherein said pharmaceutical composition is in form of a tablet. In a sub-embodiment, the pharmaceutically active ingredients are comprised in granules prior to compression to said tablet.

- A tablet according to embodiment 27) can optionally be coated with a suitable protective pellicle. Said protective pellicle will notably prevent direct contact of the pharmaceutical composition with moisture; it may also ease imprints that may be desired to be used in order to distinguish the pharmaceutical composition from others.

The coating material for making such protective pellicle may include a low water vapour permeability polymer (such as a polyvinyl alcohol (e.g. Aquapolish® white PVA from manufacturer Bioground) or dimethylaminoethyl methacrylate (e.g. EUDRAGIT® E PO)). The coating material can further include a plasticizing agent (e.g. propylene glycol, triacetone, dibutyl phthalate or dibutyl sebacate), a surfactant (e.g. sodium lauryl sulphate or

a polysorbate such as Tween®) and/or a lubricant/glidant (e.g. stearic acid, magnesium or calcium stearate or talc). Moreover, the coating material can also include a pigment (e.g. iron(II) oxide, iron(III) oxide or titanium oxide) to give the tablet a coloured aspect.

- 28) A further embodiment of the invention relates to a pharmaceutical composition according to any one of
5 embodiments 25) to 26), wherein said pharmaceutical composition is in form of a capsule. In a sub-embodiment, the pharmaceutically active ingredients are comprised in granules prior to filling into said capsules.

For avoidance of any doubt, the invention further relates to the crystalline forms of aprocitentan, especially to crystalline form A, disclosed herein wherein such crystalline form is suitable / is used as final isolation step of aprocitentan (e.g. in order to meet the purity requirements of pharmaceutical production), whereas the final
10 pharmaceutical composition according to embodiments 1 to 28) may or may not contain said crystalline form (e.g. because the originally crystalline form of aprocitentan is further transformed during the manufacturing process and / or is dissolved in the pharmaceutically acceptable carrier material(s); thus, in the final pharmaceutical composition, aprocitentan may be present in non-crystalline form, in another crystalline form, or in dissolved form, or the like).

- 15 Such combination pharmaceutical compositions according to embodiments 1) to 28) are especially useful for the treatment of endothelin related diseases and in a method for the treatment of endothelin related diseases in a subject in need for an ERA.

Such endothelin related diseases may in particular be defined as including hypertension including especially difficult to treat / resistant hypertension; ischemic heart diseases including angina pectoris, coronary diseases,
20 and myocardial ischemia; cardiac insufficiency; chronic kidney disease (CKD) [especially CKD of stages 1 to 4 as defined by the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines (and notably CKD of stage 3)], and in particular CKD (notably of these stages) caused by / associated with hypertension, or caused by / associated with diabetes (also referred to as diabetic kidney disease (DKD), wherein especially such diabetes is type 2 diabetes); diabetes, and diabetes related diseases such as diabetic arteriopathy, diabetic nephropathy,
25 diabetic retinopathy, or diabetic vasculopathy; reducing the risk of developing a major cardiovascular event (such as HF, myocardial infarction, stroke, or death from cardiovascular causes) in patients who have diabetes, especially in patients who have diabetes that is accompanied by at least one other cardiovascular risk factor (such as especially hypertension); therapy and prophylaxis of diabetic complications; (acute and chronic) renal failure; glomerulonephritis; connective tissue diseases; atherosclerosis; peripheral arterial obliterant disease
30 including chronic peripheral arteriopathy; digital ulcers; diabetic foot ulcers and/or reducing the risk of lower extremity / limb amputations in patients who have diabetes; heart failure (HF) defined as including especially chronic HF, including in particular systolic HF / HF with reduced ejection fraction (HFrEF) (i.e. ejection fraction < about 40%), and diastolic HF / HF with preserved ejection fraction (HFpEF) (i.e. ejection fraction > about 50%); reducing the risk of developing a major cardiovascular event (such as HF, myocardial infarction, stroke,
35 or death from cardiovascular causes) in patients who are at cardiovascular risk (such as patients who have

coronary artery disease and/or patients who have demonstrated clinical signs of congestive HF); and diastolic dysfunction.

For avoidance of doubt, the term CKD caused by / associated with diabetes (diabetic kidney disease, DKD) may also include such DKD associated, in addition, with hypertension; wherein especially the diabetes is type 2 diabetes.

Especially, in the context of the present invention, endothelin related diseases include

- chronic kidney disease (CKD) [especially CKD of stages 1 to 4 as defined by the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines (and notably CKD of stage 3)], and in particular CKD (notably of these stages) caused by / associated with hypertension, and/or caused by / associated with diabetes (diabetic kidney disease (DKD)); as well as (acute and chronic) renal failure; diabetic nephropathy; and glomerulonephritis;

in a sub-embodiment, DKD as defined before especially refers to DKD in a patient diagnosed with type 2 diabetes mellitus; in particular to the reduction of the rate of progression of DKD e.g. in a patient diagnosed with type 2 diabetes mellitus, wherein such reduced rate of progression may especially be expressed by a reduction in eGFR, a reduction of events of end-stage kidney disease (ESKD), or a reduction of events of renal death; wherein especially said patient presents in addition a history of hypertension;

in a further sub-embodiment, DKD as defined before especially refers to diabetic nephropathy associated with an elevated serum creatinine and/or proteinuria [especially corresponding to CKD of stages 1 to 4 as defined by the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines (and notably to CKD of stage 3)] in patients with type 2 diabetes, especially in such patients presenting in addition a history of hypertension;

in a further sub-embodiment, DKD as defined before especially refers to such DKD associated, in addition, with hypertension; wherein especially the diabetes is type 2 diabetes;

- diabetes, and diabetes related diseases such as diabetic arteriopathy, diabetic retinopathy, or diabetic vasculopathy; as well as therapy and prophylaxis of diabetic complications; and reducing the risk of developing a major cardiovascular event (such as HF, myocardial infarction, stroke, or death from cardiovascular causes) in patients who have diabetes, especially in patients who have diabetes that is accompanied by at least one other cardiovascular risk factor (such as especially hypertension); as well as diabetic foot ulcers and/or reducing the risk of lower extremity amputations in patients who have diabetes; and

- heart failure (HF) defined as including especially chronic HF, including in particular systolic HF / HF with reduced ejection fraction (HFrEF) (i.e. ejection fraction < about 40%), and diastolic HF / HF with preserved ejection fraction (HFpEF) (i.e. ejection fraction > about 50%); as well as reducing the risk of

developing a major cardiovascular event (such as HF, myocardial infarction, stroke, or death from cardiovascular causes) in patients who are at cardiovascular risk (such as patients who have coronary artery disease and/or patients who have demonstrated clinical signs of congestive HF); angina pectoris; coronary diseases; cardiac insufficiency; and diastolic dysfunction.

- 5 Essential hypertension (also called primary hypertension or idiopathic hypertension) is the form of hypertension that by definition has no identifiable cause. It represents a significant global public health concern, contributing to vascular and renal morbidity and to cardiovascular mortality. The diagnosis of essential hypertension is made when the average of multiple systolic blood pressure measurements on 2 or more subsequent visits is consistently equal to or above a certain threshold value T_{SBP} . Individuals with high normal blood pressure tend to maintain pressures that are above average for the general population and are at greater risk for development of definite hypertension and cardiovascular events than the general population. The threshold value T_{SBP} above which treatment is recommended is regularly discussed among clinicians (see e.g. Mancia et al, *J. Hypertens.* (2013), **31**, 1281-1357); accordingly, depending on the patient's general condition and age, T_{SBP} could be 140 or 130 mm Hg, or another suitable value.
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- 15 The term "resistant hypertension" [equivalent to the term "difficult to treat hypertension"] in the present invention is defined as blood pressure that remains above goal in spite of the concurrent use of three antihypertensive agents of different classes. One of the three therapeutic agents should be a diuretic and all agents should be prescribed at optimal/maximal dose amounts. As defined, resistant hypertension patients include patients whose blood pressure is controlled with use of more than three medications. That is, patients whose blood pressure is controlled but require four or more medications to do so should be considered resistant to treatment (see e.g. Mancia et al, *J. Hypertens.* (2013), **31**, 1281-1357).
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The term "diabetes" as used herein refers to all types of diabetes, especially to type 2 diabetes; as well as type 1 diabetes and latent autoimmune diabetes of adulthood, a form of diabetes mellitus type 1 that occurs in adulthood, often with a slower course of onset than type 1 diabetes diagnosed in juveniles.

- 25 29) A fifth aspect of the invention, thus, relates to aprocitentan, or a pharmaceutically acceptable salt thereof,
- for use in the prophylaxis/prevention or treatment of CKD [especially CKD of stages 1 to 4, notably CKD of stage 3]; and in particular CKD (notably of these stages) caused by / associated with hypertension, and/or caused by / associated with diabetes (DKD); as well as in the prophylaxis/prevention or treatment of acute or chronic renal failure; diabetic nephropathy; or
- 30 glomerulonephritis;

wherein, in a first sub-embodiment, such use is especially for the treatment of such DKD in a patient diagnosed with type 2 diabetes mellitus, wherein in particular aprocitentan reduces the rate of progression of DKD, wherein such reduced rate of progression may especially be expressed by a

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reduction in eGFR, a reduction of events of end-stage kidney disease (ESKD), or a reduction of events of renal death; wherein notably said patient presents in addition a history of hypertension;

wherein, in a second sub-embodiment, such use is especially for the treatment of such DKD, including treatment of diabetic nephropathy associated with an elevated serum creatinine and/or proteinuria [especially corresponding to CKD of stages 1 to 4 as defined by the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines (and notably to such CKD of stage 3)], in patients with type 2 diabetes, especially in such patients presenting in addition a history of hypertension;

- for use in the prophylaxis/prevention or treatment of diabetes, and diabetes related diseases such as diabetic arteriopathy, diabetic retinopathy, or diabetic vasculopathy; as well as diabetic complications;
- for reducing the risk of developing a major cardiovascular event (such as HF, myocardial infarction, stroke, or death from cardiovascular causes) in patients who have diabetes, especially in patients who have diabetes that is accompanied by at least one other cardiovascular risk factor (such as especially hypertension); as well as for use in the prophylaxis/prevention or treatment of diabetic foot ulcers and/or for reducing the risk of lower extremity amputations in patients who have diabetes;
- for use in the prophylaxis/prevention or treatment of heart failure (HF) including especially chronic HF, including in particular systolic HF and diastolic HF; for reducing the risk of developing a major cardiovascular event (such as HF, myocardial infarction, stroke, or death from cardiovascular causes) in patients who are at cardiovascular risk (such as patients who have coronary artery disease and/or patients who have demonstrated clinical signs of congestive HF); as well as for use in the prophylaxis/prevention or treatment of ischemic heart diseases including angina pectoris, coronary diseases, and myocardial ischemia; cardiac insufficiency; or diastolic dysfunction;
- for use in the treatment of hypertension including especially difficult to treat / resistant hypertension;
- for use in the prophylaxis/prevention or treatment of atherosclerosis; as well as of peripheral arterial obliterant disease including chronic peripheral arteriopathy;
- for use in the prophylaxis/prevention or treatment of digital ulcers; or
- for use in the prophylaxis/prevention or treatment of connective tissue diseases;

wherein aprocitentan is (intended) to be administered in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof.

30) A further embodiment relates to aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to embodiment 29); wherein aprocitentan is

- for use in the prophylaxis/prevention or treatment of CKD [especially CKD of stages 1 to 4, notably CKD of stage 3], including CKD [especially CKD of stages 1 to 4, notably CKD of stage 3] caused by / associated with hypertension, and CKD [especially CKD of stages 1 to 4, notably CKD of stage 3] caused by / associated with diabetes (diabetic kidney disease, DKD);

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wherein such use is especially for the treatment of such DKD in a patient diagnosed with type 2 diabetes mellitus, wherein in particular aprocintan reduces the rate of progression of DKD, wherein such reduced rate of progression may especially be expressed by a reduction in eGFR, a reduction of events of end-stage kidney disease (ESKD), or a reduction of events of renal death; wherein notably

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- for use prophylaxis/prevention or treatment of acute renal failure;
- for use prophylaxis/prevention or treatment of chronic renal failure;
- for use prophylaxis/prevention or treatment of diabetic nephropathy;
- for use prophylaxis/prevention or treatment of glomerulonephritis;

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- for reducing the risk of developing a major cardiovascular event (such as HF, myocardial infarction, stroke, or death from cardiovascular causes) in patients who have diabetes, especially in patients who have diabetes that is accompanied by at least one other cardiovascular risk factor (such as especially hypertension);

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- for use in the prophylaxis/prevention or treatment of diabetic foot ulcers and/or for reducing the risk of lower extremity amputations in patients who have diabetes;
- for use in the prophylaxis/prevention or treatment of heart failure (HF) including especially chronic HF; in particular systolic HF or diastolic HF;

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- for reducing the risk of developing a major cardiovascular event such as HF, myocardial infarction, stroke, or death from cardiovascular causes in patients who are at cardiovascular risk (such as patients who have coronary artery disease and/or patients who have demonstrated clinical signs of congestive HF);

- for use in the prophylaxis/prevention or treatment of diastolic dysfunction;
- for use in the treatment of hypertension including especially difficult to treat / resistant hypertension; or

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- for use in the prophylaxis/prevention or treatment of atherosclerosis; as well as of peripheral arterial obliterant disease including chronic peripheral arteriopathy;

wherein aprocintan is (intended) to be administered in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof.

31) A further embodiment relates to aprocintan, or a pharmaceutically acceptable salt thereof, for use according to embodiment 29); wherein aprocintan is

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- for use in the prophylaxis/prevention or treatment of CKD [especially CKD of stages 1 to 4, notably CKD of stage 3] caused by / associated with hypertension;
- for use in the prophylaxis/prevention or treatment of CKD [especially CKD of stages 1 to 4, notably CKD of stage 3] caused by / associated with diabetes (DKD);

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5 wherein such use is especially for the treatment of such DKD in a patient diagnosed with type 2 diabetes mellitus, wherein in particular aprocitentan reduces the rate of progression of DKD, wherein such reduced rate of progression may especially be expressed by a reduction in eGFR, a reduction of events of end-stage kidney disease (ESKD), or a reduction of events of renal death; wherein notably said patient presents in addition a history of hypertension;

- for use prophylaxis/prevention or treatment of chronic renal failure caused by / associated with hypertension or caused by / associated with diabetes; diabetic nephropathy; or glomerulonephritis caused by / associated with hypertension;
- 10 • for reducing the risk of developing a major cardiovascular event (such as HF, myocardial infarction, stroke, or death from cardiovascular causes) in patients who have diabetes, especially in patients who have diabetes that is accompanied by at least one other cardiovascular risk factor (such as especially hypertension);
- for use in the prophylaxis/prevention or treatment of diabetic foot ulcers and/or for reducing the risk of lower extremity amputations in patients who have diabetes; or
- 15 • for use in the prophylaxis/prevention or treatment of heart failure (HF) including especially chronic HF; in particular systolic HF or diastolic HF;

wherein aprocitentan is (intended) to be administered in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof.

20 32) A further embodiment relates to aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to embodiment 29); wherein aprocitentan is

- for use in the prophylaxis/prevention or treatment of CKD [especially CKD of stages 1 to 4, notably CKD of stage 3] caused by / associated with hypertension; and/or
- for use in the prophylaxis/prevention or treatment of CKD [especially CKD of stages 1 to 4, notably CKD of stage 3] caused by / associated with diabetes (DKD);

25 wherein such use is especially for the treatment of such DKD in a patient diagnosed with type 2 diabetes mellitus, wherein in particular aprocitentan reduces the rate of progression of DKD, wherein such reduced rate of progression may especially be expressed by a reduction in eGFR, a reduction of events of end-stage kidney disease (ESKD), or a reduction of events of renal death; wherein notably said patient presents in addition a history of hypertension; and/or

- 30 • for reducing the risk of developing a major cardiovascular event (such as HF, myocardial infarction, stroke, or death from cardiovascular causes) in patients who have diabetes, especially in patients who have diabetes that is accompanied by at least one other cardiovascular risk factor (such as especially hypertension);

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wherein aprocitentan is (intended) to be administered in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof.

33) A further embodiment relates to aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to embodiment 29); wherein aprocitentan is

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- for use in the prophylaxis/prevention or treatment of CKD [especially CKD of stages 1 to 4, notably CKD of stage 3] caused by / associated with hypertension; and/or
 - for use in the prophylaxis/prevention or treatment of CKD [especially CKD of stages 1 to 4, notably CKD of stage 3] caused by / associated with diabetes (DKD);

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wherein such use is especially for the treatment of such DKD in a patient diagnosed with type 2 diabetes mellitus, wherein in particular aprocitentan reduces the rate of progression of DKD, wherein such reduced rate of progression may especially be expressed by a reduction in eGFR, a reduction of events of end-stage kidney disease (ESKD), or a reduction of events of renal death; wherein notably said patient presents in addition a history of hypertension;

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wherein aprocitentan is (intended) to be administered in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof.

34) A further embodiment relates to aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to embodiment 29); wherein aprocitentan is

- for use in the prophylaxis/prevention or treatment of CKD [especially CKD of stages 1 to 4, notably CKD of stage 3] caused by / associated with diabetes (DKD);
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- wherein, in a first sub-embodiment, such use is especially for the treatment of such DKD in a patient diagnosed with type 2 diabetes mellitus, wherein in particular aprocitentan reduces the rate of progression of DKD, wherein such reduced rate of progression may especially be expressed by a reduction in eGFR, a reduction of events of end-stage kidney disease (ESKD), or a reduction of events of renal death; wherein notably said patient presents in addition a history of hypertension;
- 25
- wherein, in a second sub-embodiment, such use is especially for the treatment of such DKD, including treatment of diabetic nephropathy associated with an elevated serum creatinine and/or proteinuria [especially corresponding to CKD of stages 1 to 4 as defined by the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines (and notably to such CKD of stage 3)], in patients with type 2 diabetes, especially in such patients presenting in addition a history of hypertension;

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wherein aprocitentan is (intended) to be administered in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof.

35) A further embodiment relates to aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to embodiment 29); wherein aprocitentan is

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- for reducing the risk of developing a major cardiovascular event (such as HF, myocardial infarction, stroke, or death from cardiovascular causes) in patients who have diabetes, especially in patients who have diabetes that is accompanied by at least one other cardiovascular risk factor (such as especially hypertension);
- 5 wherein aprocitentan is (intended) to be administered in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof.
- 36) A further embodiment relates to aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 29) to 35); wherein the SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, is atigliflozin, bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, henagliflozin, 10 ipragliflozin, luseogliflozin, remogliflozin, sotagliflozin, or tofogliflozin, or a pharmaceutically acceptable salt thereof.
- 36(i) In a sub-embodiment, the SGLT-2 inhibitor is notably bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, henagliflozin, ipragliflozin, luseogliflozin, sotagliflozin, or tofogliflozin (especially canagliflozin, dapagliflozin, or empagliflozin; in particular canagliflozin), or a 15 pharmaceutically acceptable salt thereof.
- 37) A further embodiment relates to aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 29) to 35); wherein the SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, is canagliflozin, dapagliflozin, or empagliflozin (in particular canagliflozin), or a pharmaceutically acceptable salt thereof.
- 20 38) A further embodiment relates to aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 29) to 35); wherein the SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, is canagliflozin, or a pharmaceutically acceptable salt thereof.
- 39) A further embodiment relates to aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 29) to 35); wherein the SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, is dapagliflozin, or a pharmaceutically acceptable salt thereof. 25
- 40) A further embodiment relates to aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 29) to 35); wherein the SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, is empagliflozin, or a pharmaceutically acceptable salt thereof.
- 41) A further embodiment relates to aprocitentan, or a pharmaceutically acceptable salt thereof, for use 30 according to any one of embodiments 29) to 40), wherein, *mutatis mutandis*, the pharmaceutically active ingredients are to be administered in a pharmaceutical unit dosage form as disclosed in any one of embodiments 5), 6), 7), or 8), or any one of their respective sub-embodiments 5(i), 5(ii), 5(iii), 6(i), 6(ii), 6(iii), 6(iv), 6(v), 6(vi), 6(vii), 8(i), 8(ii), 8(iii), 8(iv), 8(v), 8(vi), or 8(vii).

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- 42) A further embodiment relates to aprocitentan, or a pharmaceutically acceptable salt thereof, for use in combination with an SGLT-2 inhibitor according to any one of embodiments 29) to 41), wherein aprocitentan is used in a crystalline form as defined in any one of embodiments 10) to 16), or 17) to 23) [especially as defined in embodiment 10), 11) or 12); or 17), 18), or 19), respectively].
- 5 43) A further embodiment relates to aprocitentan, or a pharmaceutically acceptable salt thereof, for use in combination with an SGLT-2 inhibitor according to any one of embodiments 29) to 41), wherein aprocitentan is used in a crystalline form as defined in any one of embodiments 10) to 16) [especially as defined in embodiment 10), 11) or 12)].
- 44) A further embodiment relates to aprocitentan, or a pharmaceutically acceptable salt thereof, for use in
10 combination with an SGLT-2 inhibitor according to any one of embodiments 29) to 41), wherein, *mutatis mutandis*, aprocitentan is to be administered in combination to a suitable conventional background therapy, wherein said background therapy is especially as defined in embodiment 9) or its sub-embodiments 9(i), 9(ii) or 9(iii).
- 45) One important aspect of the invention, thus, relates to aprocitentan, or a pharmaceutically acceptable salt
15 thereof, for use in combination / co-therapy with an SGLT-2 inhibitor according to any one of embodiments 29) to 44). In particular, based on the dependencies of the different embodiments (or their respective sub-embodiments) as disclosed hereinabove, the following embodiments are, *mutatis mutandis*, possible and intended and herewith specifically disclosed in individualized form:
- 20 29+5, 29+6, 29+7, 29+8, 29+9+5, 29+9+6, 29+9+7, 29+9+8, 29+12+5, 29+12+6, 29+12+7, 29+12+8, 29+12+9+5, 29+12+9+6, 29+12+9+7, 29+12+9+8, 31+5, 31+6, 31+7, 31+8, 31+9+5, 31+9+6, 31+9+7, 31+9+8, 31+12+5, 31+12+6, 31+12+7, 31+12+8, 31+12+9+5, 31+12+9+6, 31+12+9+7, 31+12+9+8, 32+5, 32+6, 32+7, 32+8, 32+9+5, 32+9+6, 32+9+7, 32+9+8, 32+12+5, 32+12+6, 32+12+7, 32+12+8, 32+12+9+5, 32+12+9+6, 32+12+9+7, 32+12+9+8, 33+5, 33+6, 33+7, 33+8, 33+9+5, 33+9+6, 33+9+7, 33+9+8, 33+12+5, 33+12+6, 33+12+7, 33+12+8, 33+12+9+5, 33+12+9+6, 33+12+9+7, 33+12+9+8, 34+5, 34+6, 34+7, 34+8, 34+9+5, 34+9+6, 34+9+7, 34+9+8, 34+12+5, 34+12+6, 34+12+7, 34+12+8, 34+12+9+5, 34+12+9+6, 34+12+9+7, 34+12+9+8, 36+5, 36+6, 36+7, 36+9+5, 36+9+6, 36+9+7, 36+9+8, 36+12+5, 36+12+6, 36+12+7, 36+12+8, 36+12+9+5, 36+12+9+6, 36+12+9+7, 36+12+9+8, 36+29+5, 36+29+6, 36+29+7, 36+29+8, 36+29+9+5, 36+29+9+6, 36+29+9+7, 36+29+9+8, 36+29+12+5, 36+29+12+6, 36+29+12+7, 36+29+12+8, 36+29+12+9+5, 36+29+12+9+6, 36+29+12+9+7, 36+29+12+9+8, 36+31+5, 36+31+6, 36+31+7, 36+31+8, 36+31+9+5, 36+31+9+6, 36+31+9+7, 36+31+9+8, 36+31+12+5, 36+31+12+6, 36+31+12+7, 36+31+12+8, 36+31+12+9+5, 36+31+12+9+6, 36+31+12+9+7, 36+31+12+9+8, 36+32+5, 36+32+6, 36+32+7, 36+32+8, 36+32+9+5, 36+32+9+6, 36+32+9+7, 36+32+9+8, 36+32+12+5, 36+32+12+6, 36+32+12+7, 36+32+12+8, 36+32+12+9+5, 36+32+12+9+6, 36+32+12+9+7, 36+32+12+9+8, 36+33+5, 36+33+6, 36+33+7, 36+33+8, 36+33+9+5, 36+33+9+6, 36+33+9+7, 36+33+9+8, 36+33+12+5, 36+33+12+6, 36+33+12+7, 36+33+12+8, 36+33+12+9+5,
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36+33+12+9+6, 36+33+12+9+7, 36+33+12+9+8, 36+34+5, 36+34+6, 36+34+7, 36+34+8,
 36+34+9+5, 36+34+9+6, 36+34+9+7, 36+34+9+8, 36+34+12+5, 36+34+12+6, 36+34+12+7,
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 38+29+9+6, 38+29+9+7, 38+29+9+8, 38+29+12+5, 38+29+12+6, 38+29+12+7, 38+29+12+8,
 20 38+29+12+9+5, 38+29+12+9+6, 38+29+12+9+7, 38+29+12+9+8, 38+31+5, 38+31+6, 38+31+7,
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 25 38+32+12+9+7, 38+32+12+9+8, 38+33+5, 38+33+6, 38+33+7, 38+33+8, 38+33+9+5, 38+33+9+6,
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 38+34+9+5, 38+34+9+6, 38+34+9+7, 38+34+9+8, 38+34+12+5, 38+34+12+6, 38+34+12+7,
 38+34+12+8, 38+34+12+9+5, 38+34+12+9+6, 38+34+12+9+7, 38+34+12+9+8.

30 In the list above, the numbers refer to the embodiments according to their numbering provided hereinabove
 whereas "+" indicates the dependency from another embodiment. The different individualised embodiments are
 separated by commas. In other words, "34+9+8" for example refers to embodiment 34) depending, *mutatis*
mutandis, on embodiment 9), depending on embodiment 8), i.e. embodiment "34+9+8" corresponds to
 embodiment 34) further limited by the features as defined in embodiments 9) and 8) (or their respective sub-
 35 embodiments).

Accordingly, aprocitan or a pharmaceutically acceptable salt thereof according to this invention is for use in
 combination (or co-therapy) with said further pharmaceutically active ingredients.

A combined treatment (or co-therapy) may be effected simultaneously, separately, or over a period of time (especially simultaneously).

“Simultaneously”, when referring to an administration type, means in the present application that the administration type concerned consists in the administration of two or more active ingredients and/or treatments at approximately the same time; wherein it is understood that a simultaneous administration will lead to exposure of the subject to the two or more active ingredients and/or treatments at the same time. When administered simultaneously, said two or more active ingredients may be administered in a fixed dose combination, or in an equivalent non-fixed dose combination (e.g. by using two or more different pharmaceutical compositions to be administered by the same route of administration at approximately the same time), or by a non-fixed dose combination using two or more different routes of administration; wherein said administration leads to essentially simultaneous exposure of the subject to the two or more active ingredients and/or treatments. When used in combination with an SGLT-2 inhibitor the apicitentan would possibly be used “simultaneously”.

“Fixed dose combination”, when referring to an administration type, means in the present application that the administration type concerned consists in the administration of one single pharmaceutical composition comprising the two or more active ingredients, such as especially the pharmaceutical compositions of any one of embodiments 1) to 28).

“Separately”, when referring to an administration type, means in the present application that the administration type concerned consists in the administration of two or more active ingredients and/or treatments at different points in time; wherein it is understood that a separate administration will lead to a treatment phase (e.g. at least 1 hour, notably at least 6 hours, especially at least 12 hours) where the subject is exposed to the two or more active ingredients and/or treatments at the same time; but a separate administration may also lead to a treatment phase where for a certain period of time (e.g. at least 12 hours, especially at least one day) the subject is exposed to only one of the two or more active ingredients and/or treatments. Separate administration especially refers to situations wherein at least one of the active ingredients and/or treatments is given with a periodicity substantially different from daily (such as once or twice daily) administration (e.g. wherein one active ingredient and/or treatment is given e.g. once or twice a day, and another is given e.g. every other day, or once a week or at even longer distances).

By administration “over a period of time” is meant in the present application the subsequent administration of two or more active ingredients and/or treatments at different times. The term in particular refers to an administration method according to which the entire administration of one of the active ingredients and/or treatments is completed before the administration of the other / the others begins. In this way it is possible to administer one of the active ingredients and/or treatments for several months before administering the other active ingredient(s) and/or treatment(s).

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It is understood that any embodiment relating to aprocitentan, or a pharmaceutically acceptable salt thereof, for use in the treatment of certain endothelin related diseases as specifically defined herein, wherein aprocitentan is (intended) to be administered in combination with an SGLT-2 inhibitor (especially an SGLT-2 inhibitor as specifically defined in such embodiment) also relates

- 5 • to such SGLT-2 inhibitor as disclosed herein (intended) to be administered in combination with aprocitentan, or a pharmaceutically acceptable salt thereof, for use in the treatment of said endothelin related diseases;
- to the use of aprocitentan for the manufacture of a medicament / a pharmaceutical composition comprising aprocitentan, or a pharmaceutically acceptable salt thereof, and said SGLT-2 inhibitor as
10 disclosed herein, for use in the treatment of said endothelin related diseases;
- to the use of aprocitentan for the manufacture of a medicament/pharmaceutical composition comprising, as active ingredient, aprocitentan, or a pharmaceutically acceptable salt thereof, for use in the treatment of said endothelin related diseases; wherein said medicament/pharmaceutical composition is (intended) to be used in combination with an SGLT-2 inhibitor as disclosed herein;
- 15 • to the use of an SGLT-2 inhibitor as disclosed herein for the manufacture of a medicament/pharmaceutical composition comprising, as active ingredient, such SGLT-2 inhibitor as disclosed herein, for use in the treatment of said endothelin related diseases; wherein said medicament/pharmaceutical composition is (intended) to be used in combination with aprocitentan;
- to the use of a pharmaceutical composition comprising aprocitentan, or a pharmaceutically acceptable
20 salt thereof, and such SGLT-2 inhibitor as disclosed herein for the treatment of said endothelin related diseases;
- to a medicament for the prevention or treatment said endothelin related diseases, said medicament comprising aprocitentan, or a pharmaceutically acceptable salt thereof, wherein said medicament is (intended) to be administered in combination with said SGLT-2 inhibitor;
- 25 • to a method of treating said endothelin related diseases comprising administering to a subject (preferably a human) in need thereof an effective amount of aprocitentan, or a pharmaceutically acceptable salt thereof, to be administered in combination with an effective amount of said SGLT-2 inhibitor;
- to a method of treating said endothelin related diseases comprising administering to a subject in need
30 thereof an effective amount of a pharmaceutical composition comprising aprocitentan, or a pharmaceutically acceptable salt thereof, and said SGLT-2 inhibitor as disclosed herein; and
- to a method of treating said endothelin related diseases comprising administering to a subject (preferably a human) in need thereof an effective amount of said SGLT-2 inhibitor as disclosed herein to be administered in combination with an effective amount of aprocitentan, or a pharmaceutically acceptable salt thereof.
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- 35 -

46) A further embodiment relates to aprocitentan, or a pharmaceutically acceptable salt thereof, for use in a method

- 5 • for reducing fluid retention and/or reducing the risk of congestive heart failure in a subject (preferably a human) in need of an ERA, comprising administering to said subject an effective amount of aprocitentan, wherein aprocitentan is to be administered in combination with an SGLT-2 inhibitor as disclosed herein, wherein the characteristics of any one of embodiments 1) to 45) apply *mutatis mutandis*;
- 10 • for reducing volume depletion, and/or normalizing blood viscosity, and/or reducing the risk of lower extremity amputations in a subject (preferably a human) in need of an SGLT-2 inhibitor (such as especially a subject diagnosed with type 2 diabetes and/or DKD), comprising administering to said subject an effective amount of said SGLT-2 inhibitor as disclosed herein, wherein said SGLT-2 inhibitor is to be administered in combination with an effective amount of aprocitentan wherein the characteristics of any one of embodiments 1) to 45) apply *mutatis mutandis*;
- 15 • for protecting the kidney and/or to improve renal hemodynamics, and/or reducing the risk of acute renal failure in a subject (preferably a human) in need of an SGLT-2 inhibitor (such as especially a subject diagnosed with type 2 diabetes and/or DKD), comprising administering to said subject an effective amount of said SGLT-2 inhibitor as disclosed herein, wherein said SGLT-2 inhibitor is to be administered in combination with an effective amount of aprocitentan wherein the characteristics of any one of embodiments 1) to 45) apply *mutatis mutandis*;
- 20 • for reducing blood pressure in a subject (preferably a human), comprising administering to said subject an effective amount of aprocitentan, wherein aprocitentan is to be administered in combination with an SGLT-2 inhibitor as disclosed herein, wherein the characteristics of any one of embodiments 1) to 45) apply *mutatis mutandis*;
- 25 • for reducing blood sugar levels in a subject (preferably a human), comprising administering to said subject an effective amount of aprocitentan, wherein aprocitentan is to be administered in combination with an SGLT-2 inhibitor as disclosed herein, wherein the characteristics of any one of embodiments 1) to 45) apply *mutatis mutandis*; and/or
- 30 • for the prevention or treatment of an endothelin related disease as defined herein, comprising administering to said subject an effective amount of said SGLT-2 inhibitor as disclosed herein, wherein said SGLT-2 inhibitor is to be administered in combination with an effective amount of aprocitentan wherein the characteristics of any one of embodiments 1) to 45) apply *mutatis mutandis*; wherein the beneficial effect said SGLT-2 inhibitor on sodium re-uptake remains unaffected by aprocitentan.

47) A further aspect of the invention relates to aprocitentan, or a pharmaceutically acceptable salt thereof, for use in the treatment of CKD [especially CKD of stages 1 to 4, notably CKD of stage 3] caused by / associated with diabetes (DKD) [including diabetic nephropathy associated with an elevated serum creatinine and/or proteinuria [especially corresponding to CKD of such stages]; wherein, in a sub-embodiment, such use is

- 36 -

especially for the treatment of such DKD in a patient diagnosed with type 2 diabetes mellitus [notably in such patients presenting in addition a history of hypertension], wherein in particular aprocitentan reduces the rate of progression of DKD, wherein such reduced rate of progression may especially be expressed by a reduction in eGFR, a reduction of events of end-stage kidney disease (ESKD), or a reduction of events of renal death;

5 wherein aprocitentan is used as single therapy; or (preferably) in combination / co-therapy [effected simultaneously, separately, or over a period of time (especially simultaneously)] with an SGLT-2 inhibitor, and/or conventional background therapy (or first line therapy) as defined before;

10 • wherein said aprocitentan is to be administered in a suitable pharmaceutically efficacious unit dosage form as defined in embodiments 5) or 6) and their respective sub-embodiments 5(i), 5(ii), 5(iii), 6(i), 6(ii), 6(iii), 6(iv), 6(v), 6(vi), or 6(vii); [in particular in a unit dosage form suitable for the oral administration of 1 mg, 2.5 mg, 5 mg, 10 mg, 12.5 mg, 20 mg, 25 mg, 30 mg, 40 mg, or 50 mg; (especially 10 mg, 12.5 mg, 20 mg, 25 mg, 30 mg, 40 mg, or 50 mg; notably 12.5 mg, 25 mg or 50 mg) per day of aprocitentan];

15 • wherein said SGLT-2 inhibitor, if present, is especially as defined in embodiments 7) or 8); wherein said SGLT-2 inhibitor is especially to be administered in a suitable pharmaceutically efficacious unit dosage form as defined in embodiments 7) or 8) and its sub-embodiments 8(i), 8(ii), 8(iii), 8(iv), 8(v), 8(vi), or 8(vii);

20 • wherein said conventional background therapy, if present, is especially as defined in embodiment 9) and its sub-embodiments; wherein said conventional background therapy is especially to be administered in a suitable pharmaceutically efficacious unit dosage form as defined in embodiment 9) and its sub-embodiments 9(i), 9(ii) or 9(iii);

and wherein said conventional background therapy is suitable, preferably said conventional background therapy is indicated (i.e. approved by a national health authority such as the FDA or the EMA) for the treatment of such DKD according to this embodiment.

25 Particular embodiments of the invention are described in the following Examples, which serve to illustrate the invention in more detail without limiting its scope in any way.

Experimental Procedures

Abbreviations:

The following abbreviations are used throughout the specification and the examples:

30 Ac acetyl
AcOH acetic acid
aq. aqueous
DCM dichloromethane
DMSO dimethylsulfoxide

- 37 -

- EtOAc ethyl acetate
eq. equivalent(s)
FTIR Fourier Transform Infrared Spectroscopy or Spectrum
HPLC High Performance Liquid Chromatography
- 5 iPrOAc isopropyl acetate
MeOH methanol
MIBK methyl iso-butyl ketone
org. organic
rt room temperature
- 10 THF tetrahydrofuran
vol. volume(s)
w/w weight-per-weight ratio
wt. weight unit
XRPD X-ray powder diffraction

15 EXAMPLES

Method for obtaining XRPD patterns

- All XRPD patterns for the solid forms described herein have been obtained as described hereafter. X-ray powder diffraction patterns were collected on a Bruker D8 Advance X-ray diffractometer equipped with a Lynxeye detector operated with CuK α -radiation in reflection mode (coupled two Theta/Theta). Typically, the X-ray tube was run at of 40kV/40mA. A step size of 0.02° (2 θ) and a step time of 76.8 sec over a scanning range of 3 - 50° in 2 θ were applied. The divergence slit was set to fixed 0.3. Powders were slightly pressed into a silicon single crystal sample holder with depth of 0.5 mm and samples were rotated in their own plane during the measurement. Diffraction data are reported using combined Cu K α 1 and K α 2 radiation, without K α 2 stripping. The accuracy of the 2 θ values as provided herein is in the range of +/- 0.1-0.2° as it is generally the case for
- 20 conventionally recorded X-ray powder diffraction patterns.
- 25

Example 1: Form A:

- 1.1. A 3 L double jacketed reactor was charged with 5-(4-bromophenyl)-4-(2-((5-bromopyrimidin-2-yl)oxy)ethoxy)-6 fluoropyrimidine (100 g, 0.213 mol, 1 eq.), sulfamide (40.9 g, 0.425 mol, 2.0 eq.), K₂CO₃ (147 g, 1.06 mol, 5 eq.) and DMSO (500 mL, 5 vol.) doped with water (2 mL, 0.111 mol, 0.5 eq.). The heterogeneous mixture was heated to 70°C during ca. 3 h, after which time complete conversion was observed. After cooling to 20°C, most of the inorganic salt freight was removed by filtration. The filter cake was washed with EtOAc/iPrOAc 1:1 (300 mL, 3 vol.). Celite (100 g, 1 wt.) topped with a layer of charcoal (20 g, 0.2 wt.) was preconditioned with EtOAc/iPrOAc 1:1 (500 mL, 5 vol.) (filtrate discarded). The reaction mixture was filtered over this cake and rinsed with EtOAc/iPrOAc 1:1 (300 mL, 3 vol.). Then 1M aq. NaOAc solution (500 mL,
- 30

0.5 mol, 2.3 eq, 5 vol.) was added while keeping the temperature at 25–35°C. The aq. phase was washed a second time with EtOAc/iPrOAc 1:1 (500 mL, 5 vol.). To the aq. phase, 1M H₂SO₄ (200 mL, 0.2 mol, 1 eq., 2 vol.) was added during 1 h at 25–30°C. Crystallization started at pH 8.5–8.0. The crude product was filtered off as XRPD pattern form K (DMSO solvate) or a mixture of form A and form K. It was washed twice with water (2 x 1000 mL, 2 x 10 vol.). The solid was slurried in water (1000 mL, 10 vol.) at rt for 3 h. The solid was filtered off and slurried a second time in water (1000 mL, 10 vol.) at rt for 3 h. After washing with water (1000 mL, 10 vol.), the pure product was dried in vacuum at 40°C to afford {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide as a white to off-white solid (75 g, 65% yield, XRPD pattern form A).

1.2. A reactor (200 L Hastelloy) was charged with 5-(4-bromophenyl)-4-((5-bromopyrimidin-2-yl)oxy)ethoxy)-6 fluoropyrimidine (24.2 kg, 51.5 mol), sulfamide (9.7 kg, 100.9 mol, 1.96 eq.), potassium carbonate (35.5 kg, 256.9 mol, 5.0 eq.), DMSO (133 kg, 5 vol.) and water (490 g, 27.2 mol, 0.53 eq.). The contents of the reactor were heated to 70–75°C. Monitoring by HPLC showed complete conversion in 4 hours. The contents were cooled to 20–25°C and the solids were centrifuged off. Each load was washed with EtOAc/iPrOAc 1:1 (65 kg, 3vol.). The filtrate was re-charged in the reactor and charcoal (2.4kg, 10%w/w) and Celite® (4.8 kg, 20% w/w) were added. The contents were agitated for 1 h at 15–20°C and filtered through a cartridge filter back into the reactor. The filters were rinsed with EtOAc/iPrOAc 1:1 (43 kg, 2 vol.). NaOAc (8% in water) (124 kg, 5 vol.) was added over 2 h, keeping the temperature below 25°C. After phase separation, the aq. layer was washed with EtOAc/iPrOAc 1: 1 (109 kg, 5 vol.) at 20–25°C. Sulfuric acid (5% in water; 64 L, 32.6 mol, 0.63 eq.) was added to the aq. layer at 25–30°C over 2 hours to reach pH 6.4. The contents were then cooled to 15–20°C for 1 h. The solids were filtered off and washed twice with water (2 x 24 L, 2 x 1 vol.). The solid was slurried twice in water (2 x 242 kg, 2 x 10 vol.) at 15–20°C for 3 hours each, filtered and dried, to yield 5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide as a white solid (21.6 g, 77% yield, XRPD pattern Form A).

Example 2: Form C:

0.2 mL of a stock solution of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide dissolved in THF at 50 mg/mL was dispensed to 3 vials. The solvent was evaporated for 90 min in a Combidancer device from Hettich AG (Bäch, Switzerland) operated at 35 °C and 200 mbar. Immediately thereafter 0.015 mL of MeOH for the first vial, EtOH for the second vial and iPrOH for the third vial was added and the vials were allowed to stand closed for 3 days. Solid residue of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide in Form C was obtained for each of these solvents.

Example 3: ACT-132577 tablets:

Tablets containing each 50 mg of ACT-132577 can be prepared using a wet granulation process. The tablet composition is the following:

ACT-132577 tablets (250 mg)			
MATERIAL (CHEMICAL NAME)		mg / tablet	Weight % / tablet
Intra-granular	ACT-132577 (amorphous, solid form A or solid form C, as described herein)	50.00	20.00
	Microcrystalline cellulose	61.50	24.60
	Lactose (200M)	122.25	48.90
	Hydroxypropylcellulose	5.50	2.20
	Croscarmellose sodium	4.50	1.80
	Water	qs	qs
Extra-granular	Croscarmellose sodium	5.00	2.00
	Magnesium stearate	1.25	0.50
Total		250.00	100.00

qs = quantity sufficient

Preferably, ACT-132577 Form A (as described herein) will be used for making the tablets.

Example 4: ACT-132577 tablets:

The tablets of Example 3 can be coated with a layer of Aquapolish® white MS or Aquapolish® white PVA (coating manufacturer: Biogrand).

5

Example 5: ACT-132577 tablets:

Tablets containing each 50 mg of ACT-132577 can be prepared using a wet granulation process. The tablet composition is the following:

ACT-132577 tablets (250 mg)			
MATERIAL (CHEMICAL NAME)		mg / tablet	Weight % / tablet
Intra-granular	ACT-132577 (amorphous, solid form A or solid form C, as described herein)	50.00	20.00
	Microcrystalline cellulose	61.25	24.50
	Lactose (200M)	122.50	49.00
	Hydroxypropylcellulose	5.00	2.00
	Croscarmellose sodium	5.00	2.00
	Water	qs	qs

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Extra-granular	Croscarmellose sodium	5.00	2.00
	Magnesium stearate	1.25	0.50
Total		250.00	100.00

qs = quantity sufficient

Preferably, ACT-132577 Form A (as described herein) will be used for making the tablets.

Example 6

The tablets of Example 5 can be coated with a layer of Aquapolish® white MS or Aquapolish® white PVA (coating manufacturer: Biogrand).

Example 7: ACT-132577 tablets:

Tablets containing each 12.5 mg of ACT-132577 can be prepared using a wet granulation process. The tablet composition is the following:

ACT-132577 tablets (100 mg)			
Material (Chemical name)		mg / tablet	Weight % / tablet
Intra-granular	ACT-132577 (amorphous, solid form A or solid form C, as described herein)	12.50	12.50
	Microcrystalline cellulose	27.00	27.00
	Lactose (200M)	54.00	54.00
	Hydroxypropylcellulose	2.00	2.00
	Croscarmellose sodium	2.00	2.00
	Water	qs	qs
Extra-granular	Croscarmellose sodium	2.00	2.00
	Magnesium stearate	0.50	0.50
Total		100.00	100.00

qs = quantity sufficient

10 Preferably, ACT-132577 Form A (as described herein) will be used for making the tablets.

Example 8: ACT-132577 tablets:

The tablets of Example 7 can be coated with a layer of Aquapolish® white MS or Aquapolish® white PVA (coating manufacturer: Bioground).

Example 9: ACT-132577 tablets:

- 5 Tablets containing each 12.5 mg of ACT-132577 can be prepared using a wet granulation process. The tablet composition is the following:

ACT-132577 tablets (100 mg)			
MATERIAL (CHEMICAL NAME)		mg / tablet	Weight % / tablet
Intra-granular	ACT-132577 (amorphous, solid form A or solid form C, as described herein)	12.50	12.50
	Microcrystalline cellulose	27.50	27.50
	Lactose (200M)	53.50	53.50
	Hydroxypropylcellulose	2.20	2.20
	Croscarmellose sodium	1.80	1.80
	Water	qs	qs
Extra-granular	Croscarmellose sodium	2.00	2.00
	Magnesium stearate	0.50	0.50
Total		100.00	100.00

qs = quantity sufficient

Preferably, ACT-132577 Form A (as described herein) will be used for making the tablets.

Example 10: ACT-132577 tablets:

- 10 The tablets of Example 9 can be coated with a layer of Aquapolish® white MS or Aquapolish® white PVA (coating manufacturer: Bioground).

Properties of the crystal forms**Example 11: Storage at room temperature**

- 15 A sample of Form A crystals of the COMPOUND (as obtained according to Example 1 above) has been stored at a temperature of 20-25°C at 92% relative humidity for 2 months. X-ray powder diffraction performed on that

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sample at the end of the 2 months showed that the sample was still consisting only in Form A crystals of the COMPOUND. The same result was obtained after storage for 8 weeks under the above conditions. HPLC control of the sample after 8 weeks storage revealed no significant change in peak area%, i.e. no significant degradation was observed under such conditions.

5 **Example 12: Hygroscopicity**

Form A is considered to be slightly hygroscopic as determined by gravimetric vapor sorption (GVS). Mass increase of a sample as obtained according to Example 1 in the first cycle from 40% r.h. to 80% r.h. corresponds to 0.4%. At 95% r.h. 2.2% moisture were taken up in a reversible way without hysteresis upon drying.

10 **Examples of therapeutic uses of ACT-132577**

Therapeutic effects can be modeled in multiple animal models. For example, the spontaneously hypertensive rat (SHR) is the most extensively used animal model for genetic hypertension. It is characterized by increased stroke damage, insulin resistance syndrome and renal impairment. Renal impairment comprises arteriolar damage, glomerular injury and proteinuria. Therefore, the SHR model can be used to mimic a cardiovascular condition associated with several risk factors, namely hypertension, insulin resistance and renal failure (M.A. Poteza et al. Am J Physiol Heart Circ Physiol (2005) 289: H813-H822; L.G. Feld et al. Kidney International (1981), 20, 606-614). The Dahl salt-sensitive rat and DOCA-salt rat are models of salt-sensitive hypertension associated with either strong mineralocorticoid receptors stimulation (DOCA-salt model) or low/moderate mineralocorticoid receptors stimulation (Dahl-salt model). Both models are characterized by high blood pressure, endothelial dysfunction, end organ damage involving the heart, the brain and the kidney (Y.M. Pinto et al. Cardiovascular Research 1998, 39, 77-88).

EXAMPLE A: acute effects of ACT-132577 in Dahl salt-sensitive rats:

The acute effects of ACT-132577 on blood pressure, in particular on mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR") can be evaluated by means of telemetry in conscious, male hypertensive Dahl salt-sensitive rats (hereafter "Dahl-S rats" - see details about this model in Rapp, *Hypertension* (1982), 4, 753-763).

Elevated blood pressure is induced in Dahl-S rats by providing 1% sodium chloride in drinking water. Groups of 6-7 Dahl-S rats are used for the vehicle (7.5% gelatin aqueous solution) and each dose of ACT-132577 tested (0.3, 1, 3, 10, 30, 100, and 300 mg/kg). Effects of ACT-132577 on HR and MAP are calculated for individual animals relative to the 24 h period before administering. The results obtained regarding MAP (maximal MAP decrease observed over 6 consecutive hours) are summarised in **Figure 3** (data are presented as mean $\pm$ standard error of the mean). In summary, a dose of 10 mg/kg ACT-132577 decreased MAP by 19 ± 4 mm Hg in Dahl-S rats. In contrast to MAP, HR was not affected.

EXAMPLE B: acute effects of ACT-132577 in deoxycorticosterone acetate salt rats:

The acute effects of ACT-132577 on blood pressure, in particular on mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR") can be evaluated by means of telemetry in conscious, male hypertensive deoxycorticosterone acetate salt rats (hereafter "DOCA-salt rats" - see details about this model in Gavras et al., *Circ. Res.* (1975), **36**, 300-309).

In the DOCA-salt rats, hypertension is induced by the combination of unilateral nephrectomy, implantation of pellets of the mineralocorticoid analog DOCA, and provision of 1% sodium chloride in drinking water. Groups of 6-11 DOCA-salt rats are used for the vehicle (7.5% gelatin aqueous solution) and each dose of ACT-132577 tested (0.3, 1, 3, 10, 30, 100, and 300 mg/kg). Effects of ACT-132577 on HR and MAP are calculated for individual animals relative to the 24 h period before administering. The results obtained regarding MAP (maximal MAP decrease observed over 6 consecutive hours) are summarised in **Figure 4** (data are presented as mean $\pm$ standard error of the mean). In summary, a dose of 10 mg/kg ACT-132577 decreased MAP by 29 ± 6 mm Hg in DOCA-salt rats. In contrast to MAP, HR was not affected.

EXAMPLE C: acute effects of ACT-132577 in spontaneously hypertensive rats:

The acute effects of ACT-132577 on blood pressure, in particular on mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR") can be evaluated by means of telemetry in conscious, male spontaneously hypertensive rats (hereafter "SHRs" - see details about this model in Atanur et al., *Genome Res.* (2010), **20**, 791-803).

Groups of 4-6 SHRs are used for the vehicle (7.5% gelatin aqueous solution) and each dose of ACT-132577 tested (1, 3, 10, 30, 100, and 300 mg/kg). Effects of ACT-132577 on HR and MAP are calculated for individual animals relative to the 24 h period before administering. The results obtained regarding MAP (maximal MAP decrease observed over 6 consecutive hours) are summarised in **Figure 5** (data are presented as mean $\pm$ standard error of the mean). In summary, a dose of 100 mg/kg ACT-132577 decreased MAP by 18 ± 4 mm Hg in SHRs. In contrast to MAP, HR was not affected.

EXAMPLE D: acute effects of ACT-132577, alone or in combination with valsartan, in spontaneously hypertensive rats:

The acute effects of ACT-132577 administered orally at a single dose of 100 mg/kg on blood pressure, in particular on mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR"), with ACT-132577 being used either alone or in combination with valsartan administered orally at a single dose of 10 mg/kg, can be evaluated by means of telemetry in conscious, male spontaneously hypertensive rats (hereafter "SHRs" - see details about this model in Atanur et al., *Genome Res.* (2010), **20**, 791-803).

6 SHRs per treatment group are used for this test. The results obtained regarding MAP are summarised in **Figure 6** wherein each data point is presented as a 6-hour mean (NB: the expected additive effect of the combination of the two drugs, referred to as "Predicted additive effect", is calculated by adding the decreases

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in blood pressure values obtained after administration of each compound separately); the vehicle (7.5% gelatin aqueous solution) treatment had no effect on MAP or HR and the results obtained are therefore not represented in the figure. In brief, co-administration of ACT-132577 and valsartan decreased MAP beyond the predicted (calculated) values, demonstrating synergism between the two molecules. In contrast to MAP, HR was not affected in any of the treatment groups.

EXAMPLE E: acute effects of ACT-132577, alone or in combination with valsartan, in deoxycorticosterone acetate salt rats:

The acute effects of ACT-132577 administered orally at a single dose of 10 mg/kg on blood pressure, in particular on mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR"), with ACT-132577 being used either alone or in combination with valsartan administered orally at a single dose of 30 mg/kg, can be evaluated by means of telemetry in conscious, male hypertensive deoxycorticosterone acetate salt rats (hereafter "DOCA-salt rats" - see details about this model in Gavras et al., *Circ. Res.* (1975), **36**, 300-309).

In the DOCA-salt rats, hypertension is induced by the combination of unilateral nephrectomy, implantation of pellets of the mineralocorticoid analog DOCA, and provision of 1% sodium chloride in drinking water. 7-8 DOCA-salt rats per treatment group are used for this test. The results obtained regarding MAP are summarised in **Figure 7** wherein each data point is presented as a 6-hour mean (NB: the expected additive effect of the combination of the two drugs, referred to as "Predicted additive effect", is calculated by adding the decreases in blood pressure values obtained after administration of each compound separately); the vehicle (4% gelatin aqueous solution) treatment had no effect on MAP or HR and the results obtained are therefore not represented in the figure. In brief, co-administration of ACT-132577 and valsartan decreased MAP beyond the predicted (calculated) values, demonstrating synergism between the two molecules. In contrast to MAP, HR was not affected in any of the treatment groups.

EXAMPLE F: acute effects of ACT-132577, alone or in combination with enalapril, in spontaneously hypertensive rats:

The acute effects of ACT-132577 administered orally at a single dose of 100 mg/kg on blood pressure, in particular on mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR"), with ACT-132577 being used either alone or in combination with enalapril administered orally at a single dose of 3 mg/kg, can be evaluated by means of telemetry in conscious, male spontaneously hypertensive rats (hereafter "SHRs" - see details about this model in Atanur et al., *Genome Res.* (2010), **20**, 791-803).

7 SHRs per treatment group are used for this test. The results obtained regarding MAP are summarised in **Figure 8** wherein each data point is presented as a 6-hour mean (NB: the expected additive effect of the combination of the two drugs, referred to as "Predicted additive effect", is calculated by adding the decreases in blood pressure values obtained after administration of each compound separately); the vehicle (4% gelatin aqueous solution) treatment had no effect on MAP or HR and the results obtained are therefore not represented

in the figure. In brief, co-administration of ACT-132577 and enalapril decreased MAP beyond the predicted (calculated) values, demonstrating synergism between the two molecules. In contrast to MAP, HR was not affected in any of the treatment groups.

EXAMPLE G: acute effects of ACT-132577, alone or in combination with amlodipine, in deoxycorticosterone acetate salt rats:

The acute effects of ACT-132577 administered orally at a single dose of 10 mg/kg on blood pressure, in particular on mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR"), with ACT-132577 being used either alone or in combination with amlodipine administered orally at a single dose of 1 mg/kg, can be evaluated by means of telemetry in conscious, male hypertensive deoxycorticosterone acetate salt rats (hereafter "DOCA-salt rats" - see details about this model in Gavras et al., *Circ. Res.* (1975), **36**, 300-309).

In the DOCA-salt rats, hypertension is induced by the combination of unilateral nephrectomy, implantation of pellets of the mineralocorticoid analog DOCA, and provision of 1% sodium chloride in drinking water. 6-8 DOCA-salt rats per treatment group are used for this test. The results obtained regarding MAP are summarised in **Figure 9** wherein each data point is presented as a 6-hour mean (NB: the expected additive effect of the combination of the two drugs, referred to as "Predicted additive effect", is calculated by adding the decreases in blood pressure values obtained after administration of each compound separately); the vehicle (4% gelatin aqueous solution) treatment had no effect on MAP or HR and the results obtained are therefore not represented in the figure. In brief, co-administration of ACT-132577 and amlodipine decreased MAP beyond the predicted (calculated) values, demonstrating synergism between the two molecules. In contrast to MAP, HR was not affected in any of the treatment groups.

EXAMPLE H: chronic effects of ACT-132577 in deoxycorticosterone acetate salt rats:

The chronic effects of repeated administrations of doses of 1, 10 and 100 mg/kg/day of ACT-132577, in particular mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR"), can be evaluated in conscious, male hypertensive deoxycorticosterone acetate salt rats (hereafter "DOCA-salt rats" - see details about this model in Gavras et al., *Circ. Res.* (1975), **36**, 300-309). In the DOCA-salt rats, hypertension is induced by the combination of unilateral nephrectomy, implantation of pellets of the mineralocorticoid analog DOCA, and provision of 1% sodium chloride in drinking water. The results of the DOCA-salt rats treated with ACT-132577 can be compared to those obtained for Wistar rats or for DOCA-salt rats that received only the vehicle (4% gelatin aqueous solution).

a) The results obtained regarding MAP are summarised in **Figure 10** wherein each data point is presented as a 24-hour mean. 6 rats were used for each of the 5 test groups (Wistar control rats (bottom line in Figure 10), DOCA-salt control rats (top line in Figure 10) and DOCA-salt rats receiving repeated administrations of doses of 1, 10 and 100 mg/kg/day of ACT-132577 (second to third line from top, respectively, in Figure 10)). In brief,

oral administration of ACT-132577 for 4 weeks dose-dependently attenuated the DOCA-salt-induced increase in MAP without changing HR.

b) The results obtained regarding renal vascular resistance are summarised in **Figure 11** wherein:

- ❖ DOCA Ø 2w represents DOCA-salt rats sacrificed just before initiation of treatment with ACT-132577; and
- ❖ the "***" symbol in represents a statistical significance factor $p < 0.05$ when using a one way ANOVA followed by a Newmal-Keuls multiple comparisons post-hoc test.

In summary, based on these tests, chronic oral administration of ACT-132577 to DOCA-salt rats dose-dependently increased renal blood flow and decreased renal vascular resistance. ACT-132577 also tended to decrease left ventricular hypertrophy, as suggested by the dose-dependent decrease in plasma concentrations of *N*-terminal pro-brain natriuretic peptide (NTproBNP).

EXAMPLE I: effects of ACT-132577, alone or in combination with an ACE inhibitor or an ARB, in animal models of diabetes:

The effects of ACT-132577 can be assessed in diabetic rodent models (in this regard, see the models described in the following references: Sen et al, *Life Sci.* (2012), 91(13-14), 658-668; Janiak et al., *Eur. J. Pharmacol.* (2006), **534**, 271-279; and Iglarz et al, *J. Pharmacol. Exp. Ther.* (2008), **327**(3), 736-745). In particular, the effect of ACT-132577, alone or in combination, on glucose tolerance, insulinemia and end organ damage can be investigated. End organ damage includes: vascular function, renal function (e.g. proteinuria), cardiac function and remodelling and any other target organ affected by diabetes (e.g. the eye).

EXAMPLE J: Evaluation of the effect of ACT-132577 on fluid retention

A decrease in haematocrit (Hct) or haemoglobin occurs secondary to an increase in plasma volume and can be used as a marker of fluid retention. A single oral dose of ACT 132577 (1-30 mg/kg) or vehicle (gelatin) is administered by gavage to male Wistar rats. Twenty-four hours after administration, sublingual blood was sampled under isoflurane-induced anesthesia. Haematocrit is measured using a hematology analyser. ACT-132577 did not impact on haematocrit (Hct) in this assay, suggesting low liability on fluid retention (**Fig 12**).

EXAMPLE K: Hematocrit measurements, effects of an SGLT-2 inhibitor, alone or in combination with ACT-132577

Eight- to 12-week-old Male Wistar rats [healthy or diseased (streptozotocyn diabetic rats), or under diuretic treatment (loop diuretic, e.g. furosemide)] are assigned to groups (n=12) in a stratified random manner according to their body weight and baseline Hematocrit (Hct). SGLT-2 inhibitor (e.g. canagliflozin) is administered orally daily at a dose of 30 mg/kg (for canagliflozin) for one week. Then the combination of the same dose of SGLT-2 inhibitor and ACT-132577 (1 to 30 mg/kg) or vehicle (gelatin), n=6/group, is administered by gavage. Sublingual blood is sampled twice a week under isoflurane-induced anesthesia (AttaneTM, MINRAD INC. Buffalo, New York). Hematocrit (Hct), hemoglobin (Hb) and erythrocyte indices are measured using a

hematology analyzer (Coulter AcT, Beckman Coulter, Nyon, Switzerland and Advia 2120i, Siemens Healthcare Diagnostics GmbH, Zurich, Switzerland).

EXAMPLE L: Blood pressure measurements, effects of an SGLT-2 inhibitor, alone or in combination with ACT-132577

- 5 Spontaneously hypertensive rats (SHR) are instrumented micro-surgically with a telemetry pressure transmitter implanted in the peritoneal cavity (Data Science International, Minnesota, USA) under isoflurane-induced narcosis. In brief, the pressure catheter is inserted into the aorta, below the renal artery pointing upstream. The abdomen is closed and the transmitter sutured to the abdominal musculature. Blood pressure is collected continuously using the Dataquest ART Platinum acquisition system (version 4.36). Drugs (ACT-132577 or
- 10 SGLT2 inhibitors) or vehicle are administered by gavage (n=4-7 per group) alone or in combination. Systolic, mean and diastolic arterial pressures, and heart rate are collected at 5-minute intervals until the blood pressure curve comes back to baseline.

- Results: Maximal effects on MAP are summarized on figures 13 and 14. Because it takes several days for the SGLT2 inhibitors to exert an effect on blood pressure, rats are treated first for 12 days with either vehicle (5
- 15 ml/kg/day), or canagliflozin (30 mg/kg/day) or empagliflozin (30 mg/kg/day), then ACT-132577 (30 mg/kg/day) is co-administered for 3 additional days. Canagliflozin and empagliflozin decreased MAP by -9 ± 1 and -13 ± 3 mmHg, respectively. Data demonstrate that ACT-132577, when administered on top of canagliflozin or empagliflozin, further decreased blood pressure by -14 ± 1 and -18 ± 3 mmHg, respectively. These decreases in blood pressure were similar to those obtained when ACT-132577 was administered on top of vehicle without
- 20 canagliflozin or empagliflozin (-16 ± 2 and -14 ± 2 mmHg respectively).

In summary, based on these results, ACT-132577 at least maintained its hemodynamic efficacy when combined with two different SGLT2 inhibitors in a model of hypertension associated with insulinoreistance.

EXAMPLE M: Isolated kidney preparation, effects of an SGLT-2 inhibitor, alone or in combination with ACT-132577

- 25 Kidneys from healthy or diabetic rats are removed and mounted in a perfusion system to monitor renal pressures. Male Wistar rats are euthanized, the lower abdomen is exposed and surrounding fatty tissue excised around the left kidney and major vessels (aorta, vena cava, renal artery and vein). The kidney and associated vessels are removed en bloc, and the renal vein and then renal artery are cannulated using inox cannulae (O.D. 1mm, I.D. 0.7 mm, Hugo Sachs) and secured with silk suture. The cannulated kidney is then connected to the
- 30 perfusion system equipped with pressure sensors (perfused kidney apparatus size 2, Hugo Sachs, Germany). The perfusion buffer is a modified Krebs-Henseleit buffer. The initial perfusion flow rate is 2ml/minute which is then increased incrementally to 5ml/minute. Experimental protocols are performed when the perfusion pressure has stabilized at 15-25 mm Hg. Drugs (SGLT2 inhibitor, ACT-132577, their combination) are administered to the perfusion buffer via the perfusion reservoir (200ml volume) and pressure is recorded continuously.

EXAMPLE N: Acute effects of EXFORGE HCT® alone, and EXFORGE HCT® in combination with ACT-132577 or spironolactone, in spontaneously hypertensive rats

The acute effects of Exforge HCT® (i.e. a fixed dose combination of valsartan / amlodipine / hydrochlorothiazide; dosage adapted for 1.6 mg/kg / 0.1 mg/kg / 0.25 mg/kg for valsartan / amlodipine / hydrochlorothiazide, respectively) on blood pressure, in particular on mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR") in combination with ACT-132577 or spironolactone can be evaluated by means of telemetry in conscious, male spontaneously hypertensive rats (hereafter "SHRs" - see details about this model in Atanur et al., *Genome Res.* (2010), **20**, 791-803).

9 SHRs per treatment group are used for this test. To match the maximal effect on blood pressure of co-administered drug in this model, aprocitentan 100 mg/kg is administered orally on the 3rd day following 3-day oral administration of Exforge HCT® mg/kg and spironolactone 300 mg/kg is co-administered orally with Exforge HCT® on the 1st day followed by 2 days of Exforge HCT® administration. The results obtained regarding MAP are summarised in **Figure 15** and **16** wherein each data point is presented as a 6-hour mean.

When added on top of Exforge HCT®, aprocitentan or spironolactone further reduced blood pressure. However, aprocitentan induced a greater blood pressure reduction than spironolactone. In contrast to MAP, HR was not affected in any of the treatment groups.

EXAMPLE O: Acute effects of EXFORGE HCT® alone, and EXFORGE HCT® in combination with ACT-132577 or spironolactone, in deoxycorticosterone acetate salt rats

The acute effects of Exforge HCT® (dosage adapted for 3.2 mg/kg / 0.2 mg/kg / 0.5 mg/kg for valsartan / amlodipine / hydrochlorothiazide, respectively) on blood pressure, in particular on mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR") in combination with ACT-132577 (10 mg/kg) or spironolactone (300 mg/kg), each administered orally as single doses, can be evaluated by means of telemetry in conscious, male hypertensive deoxycorticosterone acetate salt rats (hereafter "DOCA-salt rats" - see details about this model in Gavras et al., *Circ. Res.* (1975), **36**, 300-309).

In the DOCA-salt rats, hypertension is induced by the combination of unilateral nephrectomy, implantation of pellets of the mineralocorticoid analog DOCA, and provision of 1% sodium chloride in drinking water. 7-9 DOCA-salt rats per treatment group are used for this test. The results obtained regarding MAP are summarised in **Figure 17** and **18** wherein each data point is presented as a 6-hour mean.

When added on top of Exforge HCT®, aprocitentan 10 mg/kg or spironolactone 300 mg/kg further reduced blood pressure. However, aprocitentan induced a greater blood pressure reduction than spironolactone. In contrast to MAP, HR was not affected in any of the treatment groups.

EXAMPLE P: Effects of ACT-132577, alone or in combination with a SGLT2 inhibitor, in an animal model of diabetic kidney disease

The effects of ACT-132577, alone or in combination with a SGLT2 inhibitor, can be assessed in an animal model of diabetic kidney disease such as the ZDF-1 rat (Su et al. Am J Nephrol. 2016 Nov; 44(5): 339–353), a
5 diabetic rodent model with renal impairment. In particular, the effect of ACT-132577, alone or in combination with a SGLT2 inhibitor, on blood pressure, glycemia and blood HBA1c, insulinemia and renal damage can be investigated. Renal damage includes: proteinuria, measurement of glomerular filtration rate via metabolic cages, biomarkers (e.g. Kim-1), urinary and plasma ketone bodies and creatinine, terminal hispothological examination of the kidney (glomerular damage, vasculopathy, fibrosis).

Claims

1. A pharmaceutical composition containing, as active principles, aprocitentan, or a pharmaceutically acceptable salt thereof, in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, as well as at least one pharmaceutically acceptable excipient.
- 5 2. A pharmaceutical composition according to claim 1, wherein the SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, is atigliflozin, bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, henagliflozin, ipragliflozin, luseogliflozin, remogliflozin, sotagliflozin, or tofogliflozin, or a pharmaceutically acceptable salt thereof.
3. A pharmaceutical composition according to claim 1, wherein the SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof, is canagliflozin, or a pharmaceutically acceptable salt thereof.
- 10 4. A pharmaceutical composition according to any one of claims 1 to 3 wherein aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 10 to 50 mg per day of aprocitentan.
5. A pharmaceutical composition according to claim 3, wherein
 - 15 • aprocitentan, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 10 to 50 mg per day of aprocitentan; and
 - canagliflozin, or a pharmaceutically acceptable salt thereof, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 50 to 400 mg per day of canagliflozin.
6. A pharmaceutical composition according to any one of claims 1 to 5, said composition comprising aprocitentan in crystalline form, wherein said crystalline form is characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 17.8° , 18.6° , 20.0° , 23.2° and 23.5° ; wherein said X-ray powder diffraction diagram is obtained by using combined Cu $K\alpha 1$ and $K\alpha 2$ radiation, without $K\alpha 2$ stripping; and the accuracy of the 2θ values is in the range of $2\theta \pm 0.2^\circ$.
- 20 7. Aprocitentan, or a pharmaceutically acceptable salt thereof,
 - 25 • for use in the prevention or treatment of CKD, including CKD caused by / associated with hypertension, and/or caused by / associated with diabetes; acute or chronic renal failure; diabetic nephropathy; or glomerulonephritis;
 - for use in the prevention or treatment of diabetes, and diabetes related diseases including diabetic arteriopathy, diabetic retinopathy, or diabetic vasculopathy; diabetic complications; for reducing the risk of developing a major cardiovascular event in patients who have diabetes, including patients who have diabetes that is accompanied by at least one other cardiovascular risk factor; or for use in the prevention or treatment of diabetic foot ulcers and/or for reducing the risk of lower extremity amputations in patients who have diabetes;
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- for use in the prevention or treatment of heart failure including systolic heart failure and diastolic heart failure; for reducing the risk of developing a major cardiovascular event in patients who are at cardiovascular risk; or for use in the prevention or treatment of ischemic heart diseases including angina pectoris, coronary diseases, and myocardial ischemia; cardiac insufficiency; or diastolic dysfunction;
- for use in the treatment of hypertension including resistant hypertension;
- for use in the prevention or treatment of atherosclerosis; or peripheral arterial obliterant disease including chronic peripheral arteriopathy;
- for use in the prevention or treatment of digital ulcers; or
- for use in the prevention or treatment of connective tissue diseases;

wherein aprocitentan is to be administered in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof.

8. Aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to claim 7, wherein aprocitentan is

- for use in the prevention or treatment of CKD caused by / associated with hypertension;
- for use in the prevention or treatment of diabetic kidney disease (DKD);
- for use in the prevention or treatment of chronic renal failure caused by / associated with hypertension or caused by / associated with diabetes; diabetic nephropathy; or glomerulonephritis caused by / associated with hypertension;
- for reducing the risk of developing a major cardiovascular event in patients who have diabetes, including in patients who have diabetes that is accompanied by at least one other cardiovascular risk factor;
- for use in the prevention or treatment of diabetic foot ulcers and/or for reducing the risk of lower extremity amputations in patients who have diabetes; or
- for use in the prevention or treatment of heart failure including systolic heart failure and diastolic heart failure;

wherein aprocitentan is to be administered in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof.

9. Aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to claim 7, wherein aprocitentan is for use in the treatment of diabetic kidney disease (DKD) associated, in addition, with hypertension.

10. Aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 7, 8 or 9; wherein said SGLT-2 inhibitor is atigliflozin, bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, henagliflozin, ipragliflozin, luseogliflozin, remogliflozin, sotagliflozin, or tofogliflozin, or a pharmaceutically acceptable salt thereof.

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11. Aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 7, 8 or 9; wherein said the SGLT-2 inhibitor is canagliflozin, dapagliflozin, or empagliflozin, or a pharmaceutically acceptable salt thereof.
12. Aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 7, 8 or 9; wherein said the SGLT-2 inhibitor is canagliflozin, or a pharmaceutically acceptable salt thereof.
13. Aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 7 to 12; wherein aprocitentan, or a pharmaceutically acceptable salt thereof, is to be administered in a pharmaceutical unit dosage form suitable for the oral administration of 10 to 50 mg per day of aprocitentan.
14. Aprocitentan, or a pharmaceutically acceptable salt thereof, for use according to claim 11; wherein aprocitentan, or a pharmaceutically acceptable salt thereof, is to be administered in a pharmaceutical unit dosage form suitable for the oral administration of 10 to 50 mg per day of aprocitentan; and
- canagliflozin, or a pharmaceutically acceptable salt thereof, if present, is to be administered in a pharmaceutical unit dosage form suitable for the oral administration of 50 to 400 mg per day of canagliflozin;
 - dapagliflozin, or a pharmaceutically acceptable salt thereof, if present, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 1 to 20 mg per day of dapagliflozin; and
 - empagliflozin, or a pharmaceutically acceptable salt thereof, if present, is comprised in a pharmaceutical unit dosage form suitable for the oral administration of 5 to 50 mg per day of empagliflozin.
15. Aprocitentan for use according to any one of claims 7 to 14; wherein aprocitentan in crystalline form is used, wherein said crystalline form is characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 17.8°, 18.6°, 20.0°, 23.2° and 23.5°; wherein said X-ray powder diffraction diagram is obtained by using combined Cu K α 1 and K α 2 radiation, without K α 2 stripping; and the accuracy of the 2θ values is in the range of $2\theta \pm 0.2^\circ$.
16. A method
- for the prophylaxis or treatment of CKD, including CKD caused by / associated with hypertension, or caused by / associated with diabetes; acute or chronic renal failure; diabetic nephropathy; or glomerulonephritis;
 - for the prophylaxis or treatment of diabetes, and diabetes related diseases including diabetic arteriopathy, diabetic retinopathy, or diabetic vasculopathy; diabetic complications; for reducing the risk of developing a major cardiovascular event in patients who have diabetes, including patients who have diabetes that is accompanied by at least one other cardiovascular risk factor; or for the

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prophylaxis or treatment of diabetic foot ulcers and/or for reducing the risk of lower extremity amputations in patients who have diabetes;

- for the prophylaxis or treatment of heart failure including systolic heart failure and diastolic heart failure; for reducing the risk of developing a major cardiovascular event in patients who are at cardiovascular risk; or for the prophylaxis or treatment of ischemic heart diseases including angina pectoris, coronary diseases, and myocardial ischemia; cardiac insufficiency; or diastolic dysfunction;
- for the treatment of hypertension including resistant hypertension;
- for the prophylaxis or treatment of atherosclerosis; or peripheral arterial obliterant disease including chronic peripheral arteriopathy;
- for the prophylaxis or treatment of digital ulcers; or
- for the prophylaxis or treatment of connective tissue diseases;

said method comprising the administration of a pharmaceutically effective amount of apocritentan, or of a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein apocritentan is administered in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof.

15 **17. A method**

- for the prophylaxis or treatment of CKD caused by / associated with hypertension;
- for the prophylaxis or treatment of diabetic kidney disease (DKD);
- for the prophylaxis or treatment of chronic renal failure caused by / associated with hypertension and/or caused by / associated with diabetes; diabetic nephropathy; or glomerulonephritis caused by / associated with hypertension;
- for reducing the risk of developing a major cardiovascular event in patients who have diabetes, including in patients who have diabetes that is accompanied by at least one other cardiovascular risk factor;
- for the prophylaxis or treatment of diabetic foot ulcers and/or for reducing the risk of lower extremity amputations in patients who have diabetes; or
- for use in the prophylaxis or treatment of heart failure including systolic heart failure and diastolic heart failure;

said method comprising the administration of a pharmaceutically effective amount of apocritentan, or of a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein apocritentan is administered in combination with an SGLT-2 inhibitor, or a pharmaceutically acceptable salt thereof.