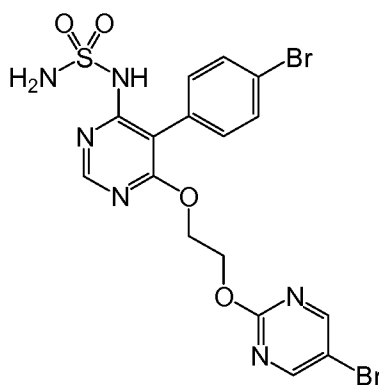


CRYSTALLINE FORMS OF THE 4-PYRIMIDINESULFAMIDE DERIVATIVE APROCITENTAN

The present invention concerns novel crystalline forms of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide (hereinafter also referred to as "COMPOUND"), processes for the preparation thereof, pharmaceutical compositions comprising said crystalline forms, pharmaceutical compositions prepared from such crystalline forms, and their use as endothelin receptor inhibitors and endothelin receptor antagonists. It also relates to uses of the COMPOUND for treating particular diseases or disorders, either alone or in combination with other active ingredients or therapeutic agents.

- 10 Aprocitentan, {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide has the formula I



I

- Aprocitentan, also known under the name ACT-132577, is an endothelin receptor inhibitor and useful as 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 to corresponding alkylated derivatives. This makes the compound of formula I particularly suitable for long-acting pharmaceutical compositions, as disclosed in WO 2009/024906. Certain manufacturing processes relating to aprocitentan are disclosed in WO2015/121397.
- 20 Because of its ability to inhibit the endothelin binding, COMPOUND can be used for treatment of endothelin related diseases which are associated with an increase in vasoconstriction, proliferation or inflammation due to endothelin. Examples of such endothelin related diseases are hypertension, pulmonary hypertension, coronary diseases,

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cardiac insufficiency, renal and myocardial ischemia, renal failure, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, Raynaud's syndrome, digital ulcers and portal hypertension. They can also be used in the treatment or prevention of chronic kidney disease (CKD), diabetes, diabetic nephropathy, diabetic retinopathy, diabetic vasculopathy, chronic heart failure and diastolic dysfunction. they can further be used in the treatment or prevention of atherosclerosis, restenosis after balloon or stent angioplasty, inflammation, stomach and duodenal ulcer, cancer, melanoma, prostate cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, pulmonary fibrosis, gram negative septicemia, shock, sickle cell anemia, glomerulonephritis, renal colic, glaucoma, connective tissue diseases, therapy and prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, hyperlipidemia as well as other diseases, presently known to be related to endothelin.

According to the 2014 American Society of Hypertension and International Society of Hypertension joint statement [Weber et al., "Clinical Practice Guidelines for the Management of Hypertension in the Community. A Statement by the American Society of Hypertension and the International Society of Hypertension." J Clin Hypertens (2014), 16(1), 14-26], the 2013 European Society of Hypertension and European Society of Cardiology joint guideline [Mancia et al, J. Hypertens. (2013), 31, 1281-1357], as well as several national guidelines [Denolle et al., J Hum Hypertens. (2016), 30(11), 657-663; McCormack et al., Br J Cardiol (2013), 20 (suppl 1), S1-S16], resistant hypertension (rHT) (or difficult to treat hypertension) is defined as uncontrolled blood pressure (BP) (i.e., failure to lower BP to a pre-defined threshold) despite concurrent administration of three antihypertensive therapies of different pharmacological classes at maximal or optimal doses, including a diuretic. Thus, 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)).

Clinical studies have shown that endothelin receptor antagonists (ERAs) may have significant treatment effect in patients suffering from hypertension and/ or renal disease. However, therapeutic benefit needs to be weighted against potential side effects, such as the potential risk of teratogenic activity. In addition, both, selective ET_A-antagonists and

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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, 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 rHT, chronic kidney disease 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 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.

WO2016/073846 provides a comprehensive summary of ERAs tested for various indications including chronic kidney disease (CKD) and rHT. Similarly to the observations made for darusentan mentioned above, also the ET_A-selective ERA avosentan, in a trial that investigated the use of avosentan to reduce proteinuria in patients with 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. The trial was terminated prematurely, and the authors conclude that "it may be that at dosages of 25 to 50 mg, avosentan is less selective

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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 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
5 were treated with ACEIs (Mann et al., J Am Soc Nephrol. 2010, 21(3): 527–535." 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
10 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 an acceptable level.

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
15 macitentan (Vercauteren et al., JPET 2017, 361, 322-333). On the other hand, 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). It has been shown in a phase 2 trial that aprocitentan, an ERA resulting in effective dual blockade of
20 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
25 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,
30 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.

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It has now been found that certain crystalline forms of COMPOUND may under certain conditions be found. Said crystalline forms of COMPOUND are novel and may have advantageous properties in view of the potential use of COMPOUND 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 COMPOUND may be particularly suitable in a process of manufacturing certain pharmaceutical compositions. It has also been found that COMPOUND 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, e.g. 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 a dichloromethane solvate of the COMPOUND in a crystalline form B, e.g. 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): 11.2° (16%), 16.2° (57%), 18.0° (21%), 18.6° (71%), 18.8° (36%), 19.8° (19%), 20.3° (100%), 22.4° (45%), 22.9° (28%), 24.3° (44%), 24.8° (11%), 25.0° (41%), 25.7° (22%), 26.1° (31%), 27.4° (20%), 29.4° (16%), 29.8° (38%) and 32.4° (12%).

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Figure 3 shows the X-ray powder diffraction diagram of COMPOUND in a crystalline form C, e.g. as obtained from Example 3. 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%).

Figure 4 shows the X-ray powder diffraction diagram of COMPOUND in a crystalline form D, e.g. as obtained from Example 4. 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): 4.6° (27%), 8.4° (15%), 8.6° (11%), 16.4° (17%), 16.8° (26%), 17.2° (10%), 18.6° (11%), 18.9° (18%), 19.3° (40%), 19.6° (45%), 20.1° (100%), 20.6° (55%), 20.8° (26%), 22.0° (10%), 22.7° (14%), 23.0° (24%), 23.5° (32%), 23.8° (12%), 24.2° (17%), 24.7° (20%), 25.1° (55%), 25.4° (22%), 25.6° (14%), 26.2° (16%), 26.8° (17%), 27.2° (28%), 28.1° (21%) and 28.1° (19%).

Figure 5 shows the X-ray powder diffraction diagram of an acetonitrile solvate of the COMPOUND in a crystalline form E, e.g. as obtained from Example 5. 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): 9.0° (21%), 9.5° (56%), 11.3° (61%), 14.5° (41%), 14.8° (15%), 15.6° (47%), 16.0° (26%), 16.5° (100%), 18.2° (84%), 18.7° (73%), 18.9° (56%), 20.2° (20%), 20.7° (56%), 22.8° (96%), 23.9° (22%), 24.5° (70%), 25.3° (77%), 25.6° (29%), 26.0° (14%), 26.6° (66%), 27.5° (27%), 29.6° (31%), 30.2° (66%) and 33.0° (13%).

Figure 6 shows the X-ray powder diffraction diagram of COMPOUND in a crystalline form J, e.g. as obtained from Example 6. The X-ray diffraction diagram shows peaks

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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): 4.0° (44%), 4.7° (14%), 6.5° (23%), 9.0° (27%),
5 16.1° (40%), 17.2° (11%), 18.7° (22%), 19.0° (58%), 19.4° (28%), 19.8° (46%), 20.7° (57%), 21.2° (17%), 21.9° (100%), 22.6° (14%), 23.2° (23%), 24.1° (37%), 24.8° (40%), 25.6° (42%), 27.0° (29%), 28.2° (27%), 29.0° (20%), 30.3° and 30.8° (10%).

Figure 7 shows the X-ray powder diffraction diagram of a dimethylsulfoxide solvate of the COMPOUND in a crystalline form K, e.g. as obtained from Example 7. The X-ray
10 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): 10.9° (16%), 16.9° (18%), 18.2° (26%), 18.4° (30%), 18.6° (29%), 18.7° (55%), 19.3° (100%), 20.8° (35%),
15 21.2° (47%), 21.9° (26%), 24.3° (21%), 24.8° (24%), 25.4° (29%), 25.8° (22%), 26.7° (34%), 27.7° (13%), 27.8° (14%), 28.6° (15%), 29.4° (18%), 31.5° (23%) and 31.8° (12%).

Figure 8 shows the X-ray powder diffraction diagram of an ethanol solvate of the COMPOUND in a crystalline form L, e.g. as obtained from Example 8. The X-ray
20 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): 9.1° (31%), 9.3° (34%), 11.3° (49%), 12.2° (10%), 14.6° (17%), 14.8° (46%), 15.7° (16%), 16.1° (10%),
25 16.4° (80%), 17.9° (17%), 18.2° (19%), 18.7° (96%), 20.0° (38%), 20.3° (100%), 22.6° (11%), 22.8° (76%), 23.2° (50%), 24.1° (14%), 24.5° (56%), 24.7° (68%), 25.4° (46%), 25.9° (32%), 26.4° (14%), 26.8° (22%), 27.7° (38%), 28.2° (12%), 29.7° (11%), 29.5° (64%), 29.8° (14%), 30.3° (14%), 30.5° (13%) and 32.4° (16%).

For avoidance of any doubt, the above-listed peaks describe the experimental results of the
30 X-ray powder diffraction shown in Figure 1 to Figure 8. It is understood that, in contrast to the above peak list, only a selection of characteristic peaks is required to fully and

unambiguously characterize of the COMPOUND in the respective crystalline form of the present invention.

In the X-ray diffraction diagrams of Fig. 1 to Fig 8 the angle of refraction 2θ (2θ) is plotted on the horizontal axis and the counts on the vertical axis.

5 **Figure 9** shows the acute effects of COMPOUND on mean arterial blood pressure ("MAP") in conscious, male hypertensive Dahl salt sensitive rats.

Figure 10 shows the acute effects of COMPOUND on MAP in conscious, male hypertensive deoxycorticosterone acetate salt rats.

10 **Figure 11** shows the acute effects of COMPOUND on MAP in conscious, male spontaneously hypertensive rats.

Figure 12 shows the acute effects of COMPOUND, used alone or in combination with valsartan, on MAP in conscious, male spontaneously hypertensive rats.

Figure 13 shows the acute effects of COMPOUND, used alone or in combination with valsartan, on MAP in conscious, male hypertensive deoxycorticosterone acetate salt rats.

15 **Figure 14** shows the acute effects of COMPOUND, used alone or in combination with enalapril, on MAP in conscious, male spontaneously hypertensive rats.

Figure 15 shows the acute effects of COMPOUND, used alone or in combination with amlodipine, on MAP in conscious, male hypertensive deoxycorticosterone acetate salt rats.

20 **Figure 16** shows the effects of chronic oral administration of COMPOUND on MAP in conscious, male hypertensive deoxycorticosterone acetate salt rats.

Figure 17 shows the effects of chronic oral administration of COMPOUND on renal vascular resistance in conscious, male hypertensive deoxycorticosterone acetate salt rats.

Figure 18 shows the effects of a single dose oral administration of COMPOUND on haematocrit (Hct) male Wistar rats.

25 **Figure 19** shows the gravimetric vapour sorption diagram of COMPOUND in a crystalline form A as obtained from Example 1.

Figure 20 shows the gravimetric vapour sorption diagram of COMPOUND in a crystalline form C as obtained from Example 3.

Detailed Description of the Invention

1) A first embodiment of the invention relates to crystalline forms of the COMPOUND {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide or of a solvate of that compound, characterized by:

- 5 • form A of the COMPOUND comprising 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° ; or
- form C of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.7° , 15.7° , and 22.0° ; or
- form D of the COMPOUND comprising the presence of peaks in the X-ray powder
10 diffraction diagram at the following angles of refraction 2θ : 4.6° , 16.8° , and 20.1° ; or
- form E of an acetonitrile solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.5° , 16.5° , and 18.2° ; or
- form J of the COMPOUND comprising the presence of peaks in the X-ray powder
15 diffraction diagram at the following angles of refraction 2θ : 4.0° , 16.1° , and 21.9° ; or
- form K of a dimethylsulfoxide solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 16.9° , 19.3° , and 24.8° ; or
- form L of an ethanol solvate of the COMPOUND comprising the presence of peaks in
20 the X-ray powder diffraction diagram at the following angles of refraction 2θ : 11.3° , 16.4° , and 20.3° ;

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 $2\theta \pm 0.2^\circ$.

- 25 It is understood, that the crystalline forms according to embodiment 1) 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

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(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 or ansolvate forms i.e. they comprise no coordinated water, but may comprise non-coordinated solvent such as isopropanol, methanol, ethanol and / or water, crystalline form B is a DCM solvate, crystalline form E is a MeCN solvate, crystalline form K is a DMSO solvate, and crystalline form L is an ethanol solvate.

It is to be understood that the present invention covers each of the forms A, C, D, E, J, K and L individually, as well as two, three, four, five, six or seven individual forms. Preferred are forms A and/or C, especially form A.

- 10 2) Another embodiment relates to a crystalline form of the COMPOUND or of a solvate of that compound, characterized by
- form A of the COMPOUND comprising 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° ; or
 - 15 • form C of the COMPOUND comprising 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° ; or
 - form D of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 4.6° , 16.8° , 19.6° , 20.1° and 20.6° ; or
 - 20 • form E of an acetonitrile solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.5° , 15.6° , 16.5° , 18.2° and 26.6° ; or
 - form J of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 4.0° , 16.1° , 19.0° , 20.7° and 21.9° ; or
 - 25 • form K of a dimethylsulfoxide solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 16.9° , 19.3° , 20.8° , 21.2° and 24.8° ; or

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- form L of an ethanol solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.3° , 11.3° , 16.4° , 20.0° and 20.3° ;

wherein said X-ray powder diffraction diagram is obtained by using combined Cu $K\alpha_1$ and

5 $K\alpha_2$ radiation, without $K\alpha_2$ stripping; and the accuracy of the 2θ values is in the range of $2\theta \pm 0.2^\circ$. Preferred are forms A and/or C, especially form A.

3) Another embodiment relates to a crystalline form of the COMPOUND or of a solvate of that compound, characterized by:

- form A of the COMPOUND comprising the presence of peaks in the X-ray powder
10 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° ; or
- form C of the COMPOUND comprising 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° ; or
- 15 • form D of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 4.6° , 16.4° , 16.8° , 19.3° , 19.6° , 20.1° , 20.6° , 23.0° , 23.5° , and 25.1° ; or
- form E of an acetonitrile solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.5° ,
20 15.6° , 16.0° , 16.5° , 18.2° , 18.7° , 25.3° , 26.6° , 29.6° , and 30.2° ; or
- form J of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 4.0° , 6.5° , 9.0° , 16.1° , 19.0° , 19.8° , 20.7° , 21.9° , 24.1° , and 24.8° ; or
- form K of a dimethylsulfoxide solvate of the COMPOUND comprising the presence of
25 peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 10.9° , 13.7° , 16.9° , 18.2° , 19.3° , 20.8° , 21.2° , 24.3° , 24.8° , and 26.7° ; or
- form L of an ethanol solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.1° , 9.3° , 11.3° , 14.8° , 16.4° , 20.0° , 20.3° , 22.8° , 24.5° , and 24.7° ;

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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 $2\theta \pm 0.2^\circ$. Preferred are forms A and/or C, especially form A.

4) Another embodiment relates to a crystalline form of the COMPOUND or of a solvate thereof, characterized by:

- form A of the COMPOUND comprising 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° ; or
- 10 • form C of the COMPOUND comprising 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° , 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° ; or
- form D of the COMPOUND comprising the presence of peaks in the X-ray powder
15 diffraction diagram at the following angles of refraction 2θ : 4.6° , 8.4° , 8.6° , 16.4° , 16.8° , 17.2° , 18.6° , 18.9° , 19.3° , 19.6° , 20.1° , 20.6° , 20.8° , 22.0° , 22.7° , 23.0° , 23.5° , 23.8° , 24.2° , 24.7° , 25.1° , 25.4° , 25.6° , 26.2° , 26.8° , 27.2° , 28.1° and 28.1° ; or
- form E of an acetonitrile solvate of the COMPOUND comprising the presence of peaks
20 in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.0° , 9.5° , 11.3° , 14.5° , 14.8° , 15.6° , 16.0° , 16.5° , 18.2° , 18.7° , 18.9° , 20.2° , 20.7° , 22.8° , 23.9° , 24.5° , 25.3° , 25.6° , 26.0° , 26.6° , 27.5° , 29.6° , 30.2° and 33.0° ; or
- form J of the COMPOUND comprising the presence of peaks in the X-ray powder
25 diffraction diagram at the following angles of refraction 2θ : 4.0° , 4.8° , 6.5° , 9.0° , 16.1° , 17.2° , 18.7° , 19.0° , 19.4° , 19.8° , 20.7° , 21.2° , 21.9° , 22.6° , 23.2° , 24.1° , 24.8° , 25.6° , 27.0° , 28.2° , 29.0° , 30.4° and 30.8° ; or
- form K of a dimethylsulfoxide solvate of the COMPOUND comprising the presence of
peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 10.9° , 16.9° , 18.2° , 18.4° , 18.6° , 18.7° , 19.3° , 20.8° , 21.2° , 21.9° , 24.3° , 24.8° , 25.4° , 25.8° , 26.7° , 27.7° , 27.8° , 28.6° , 29.4° , 31.5° and 31.8° ; or

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- form L of an ethanol solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.1° , 9.3° , 11.3° , 12.2° , 14.6° , 14.8° , 15.7° , 16.1° , 16.4° , 17.9° , 18.2° , 18.7° , 20.0° , 20.3° , 22.6° , 22.8° , 23.2° , 24.1° , 24.5° , 24.7° , 25.5° , 25.9° , 26.4° , 26.8° , 27.7° , 28.2° , 29.7° , 29.5° , 29.8° , 30.3° , 30.5° and 32.4° ;

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 $2\theta \pm 0.2^\circ$. Preferred are forms A and/or C, especially form A.

5) Another embodiment relates to a crystalline form of the COMPOUND or of a solvate thereof; characterized by:

- form A of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 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%); or
- form C of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 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%); or
- form D of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 4.6° (27%), 8.4° (15%), 8.6° (11%), 16.4° (17%), 16.8° (26%), 17.2° (10%), 18.6° (11%), 18.9° (18%), 19.3° (40%), 19.6° (45%), 20.1° (100%), 20.6° (55%), 20.8° (26%), 22.0° (10%), 22.7° (14%), 23.0° (24%), 23.5° (32%), 23.8° (12%), 24.2° (17%), 24.7° (20%), 25.1° (55%), 25.4° (22%), 25.6° (14%), 26.2° (16%), 26.8° (17%), 27.2° (28%), 28.1° (21%) and 28.1° (19%); or

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- form E of an acetonitrile solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.0° (21%), 9.5° (56%), 11.3° (61%), 14.5° (41%), 14.8° (15%), 15.6° (47%), 16.0° (26%), 16.5° (100%), 18.2° (84%), 18.7° (73%), 18.9° (56%), 20.2° (20%), 20.7° (56%), 22.8° (96%), 23.9° (22%), 24.5° (70%), 25.3° (77%), 25.6° (29%), 26.0° (14%), 26.6° (66%), 27.5° (27%), 29.6° (31%), 30.2° (66%) and 33.0° (13%); or
- form J of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 4.0° (44%), 4.8° (14%), 6.5° (23%), 9.0° (27%), 16.1° (40%), 17.2° (11%), 18.7° (22%), 19.0° (58%), 19.4° (28%), 19.8° (46%), 20.7° (57%), 21.2° (17%), 21.9° (100%), 22.6° (14%), 23.2° (23%), 24.1° (37%), 24.8° (40%), 25.6° (42%), 27.0° (29%), 28.2° (27%), 29.0° (20%), 30.4° and 30.8° (10%); or
- form K of a dimethylsulfoxide solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 10.9° (16%), 16.9° (18%), 18.2° (26%), 18.4° (30%), 18.6° (29%), 18.7° (55%), 19.3° (100%), 20.8° (35%), 21.2° (47%), 21.9° (26%), 24.3° (21%), 24.8° (24%), 25.4° (29%), 25.8° (22%), 26.7° (34%), 27.7° (13%), 27.8° (14%), 28.6° (15%), 29.4° (18%), 31.5° (23%) and 31.8° (12%); or
- form L of an ethanol solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.1° (31%), 9.3° (34%), 11.3° (49%), 12.2° (10%), 14.6° (17%), 14.8° (46%), 15.7° (16%), 16.1° (10%), 16.4° (80%), 17.9° (17%), 18.2° (19%), 18.7° (96%), 20.0° (38%), 20.3° (100%), 22.6° (11%), 22.8° (76%), 23.2° (50%), 24.1° (14%), 24.5° (56%), 24.7° (68%), 25.5° (46%), 25.9° (32%), 26.4° (14%), 26.8° (22%), 27.7° (38%), 28.2° (12%), 29.7° (11%), 29.5° (64%), 29.8° (14%), 30.3° (14%), 30.5° (13%) and 32.4° (16%);

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 $2\theta \pm 0.2^\circ$. Preferred are forms A and C, especially form A.

- 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

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parentheses) at the indicated angles of refraction 2θ (selected peaks from the range $3-33^\circ 2\theta$ with relative intensity larger than 10% are reported).

- 6) Another embodiment relates to a crystalline form of the COMPOUND or of a solvate thereof which essentially shows the X-ray powder diffraction pattern as depicted in any one of the Figures 1, 3, 4, 5, 6, 7 and 8, 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 $2\theta \pm 0.2^\circ$.

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.

- 7) A particular sub-embodiment of embodiment 6) relates to a crystalline form of COMPOUND 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 $K\alpha 1$ and $K\alpha 2$ radiation, without $K\alpha 2$ stripping; and the accuracy of the 2θ values is in the range of $2\theta \pm 0.2^\circ$.

- 8) In another embodiment the present invention relates to a crystalline form of the COMPOUND or of a solvate thereof wherein

- (a) form A is obtainable by crystallisation of the COMPOUND in an aqueous solution at pH 6.2 to 6.8;
- (b) form B is obtainable by crystallisation of the COMPOUND from DCM at pH 7;
- (c) form C is obtainable by crystallisation of the COMPOUND from MeOH, EtOH or propan-2-ol;
- (d) form D is obtainable by crystallisation of form A from methyl-ethylketone;
- (e) form E is obtainable by crystallisation of form A from MeCN;
- (j) form J is obtainable by crystallisation of form B from DMSO and water;
- (k) form K is obtainable by crystallisation of the COMPOUND in an aqueous solution;
- (l) form L is obtainable by crystallisation of form K from EtOH.

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- 9) Another embodiment of the present invention relates to a crystalline form A of the COMPOUND comprising 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° ; whereby it is an anhydrate or an solvate form. It is understood that the X-ray powder diffraction diagram may further
5 comprise the peaks as disclosed in embodiment 2), 3), 4), 5) or 6). It is further understood that said crystalline form may be further characterized by an endothermic event with a peak of the endotherm observed at about 159°C as determined by DSC, e.g. using the method disclosed in the experimental part.
- 10) Another embodiment of the present invention relates to a crystalline form A of the
10 COMPOUND comprising 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° ; whereby it is an anhydrate or an solvate form which is obtainable by crystallisation in an aqueous solution at pH 6.2 to 6.8. It is understood that the X-ray powder diffraction diagram may further comprise the peaks as disclosed in embodiment 2), 3), 4), 5) or 6).
- 15 11) Another embodiment of the present invention relates to a crystalline form B of a dichloromethane solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 16.2° , 18.6° , and 20.3° (notably 16.2° , 18.6° , 20.3° , 22.4° and 24.3° , especially 9.0° , 11.2° , 16.2° , 18.0° , 18.6° , 19.8° , 20.3° , 22.4° , 22.9° and 24.3°).
- 20 12) Another embodiment of the present invention relates to a crystalline form B of a dichloromethane solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 16.2° , 18.6° , and 20.3° (notably 16.2° , 18.6° , 20.3° , 22.4° and 24.3° , especially 9.0° , 11.2° , 16.2° , 18.0° , 18.6° , 19.8° , 20.3° , 22.4° , 22.9° and 24.3°); whereby this form is obtainable by
25 crystallisation from dichloromethane at pH 7.
- 13) Another embodiment of the present invention relates to a crystalline form C of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.7° , 15.7° , and 22.0° ; whereby it is an anhydrate or an solvate form. It is understood that the X-ray powder diffraction diagram may further
30 comprise the peaks as disclosed in embodiment 2), 3), 4), 5) or 6). It is further understood that said crystalline form may be further characterized by an endothermic event with a

peak of the endotherm observed at about 153°C as determined by DSC, e.g. using the method disclosed in the experimental part.

14) Another embodiment of the present invention relates to a crystalline form C of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.7°, 15.7°, and 22.0°; whereby it is an anhydrate or an solvate form which is obtainable by crystallisation MeOH, EtOH or propan-2-ol. It is understood that the X-ray powder diffraction diagram may further comprise the peaks as disclosed in embodiment 2), 3), 4), 5) or 6).

15) Another embodiment of the present invention relates to a crystalline form D of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 4.6°, 16.8°, and 20.1°; whereby it is obtainable by crystallisation of form A from methyl-ethylketone. It is understood that the X-ray powder diffraction diagram may further comprise the peaks as disclosed in embodiment 2), 3), 4), 5) or 6).

16) Another embodiment of the present invention relates to a crystalline form E of an acetonitrile solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.5°, 16.5°, and 18.2°. It is understood that the X-ray powder diffraction diagram may further comprise the peaks as disclosed in embodiment 2), 3), 4), 5) or 6).

17) Another embodiment of the present invention relates to a crystalline form E of an acetonitrile solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.5°, 16.5°, and 18.2°; whereby this form is obtainable by crystallisation of form A from acetonitrile. It is understood that the X-ray powder diffraction diagram may further comprise the peaks as disclosed in embodiment 2), 3), 4), 5) or 6).

18) Another embodiment of the present invention relates to a crystalline form J of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 4.0°, 16.1°, and 21.9°; whereby it is obtainable by crystallisation of form B of a dichloromethane solvate of the COMPOUND from DMSO and water. It is understood that the X-ray powder diffraction diagram may further comprise the peaks as disclosed in embodiment 2), 3), 4), 5) or 6).

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19) Another embodiment of the present invention relates to a crystalline form K of a dimethylsulfoxide solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 16.9° , 19.3° , and 24.8° . It is understood that the X-ray powder diffraction diagram may further comprise the peaks as disclosed in embodiment 2), 3), 4), 5) or 6).

20) Another embodiment of the present invention relates to a crystalline form K of a dimethylsulfoxide solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 16.9° , 19.3° , and 24.8° ; whereby this form is obtainable by crystallisation in an aqueous solution. It is understood that the X-ray powder diffraction diagram may further comprise the peaks as disclosed in embodiment 2), 3), 4), 5) or 6).

21) Another embodiment of the present invention relates to a crystalline form L of an ethanol solvate of the COMPOUND comprising the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 11.3° , 16.4° , and 20.3° ; whereby it is obtainable by crystallisation of form K from ethanol. It is understood that the X-ray powder diffraction diagram may further comprise the peaks as disclosed in embodiment 2), 3), 4), 5) or 6).

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 2θ ", 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 it should be understood that the accuracy of the 2θ values as provided herein is in the range of ± 0.1 - 0.2° . Notably, when specifying an angle of refraction 2θ for a peak in the invention embodiments and the claims, the 2θ 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 diagram depicted (S = signal, N = noise). According to this definition, when stating that a peak has 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 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 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 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.

22) Another embodiment of the present invention relates to an amorphous form of the COMPOUND {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide. Thus, the 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.

23) The crystalline forms, especially the essentially pure crystalline forms, of the COMPOUND according to any one of embodiments 1) to 21) can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral or parenteral administration.

The term “essentially pure” is understood in the context of the present invention to mean especially that at least 90, preferably at least 95, and most preferably at least 99 per cent by weight of COMPOUND is present in the respective crystalline form.

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24) Another embodiment thus relates to a crystalline form of COMPOUND according to any one of embodiments 1) to 21) for use as a medicament.

The crystalline solid, especially the essentially pure crystalline solid, of COMPOUND according to any one of embodiments 1) to 21) may be used as single component or as
5 mixtures with other crystalline forms or the amorphous form of COMPOUND.

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
10 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) Another embodiment of the present invention relates to a crystalline form of the
15 COMPOUND or of a solvate of that compound, according to any one of embodiments 1) to 21), for the use in the manufacture of a pharmaceutical composition, wherein said pharmaceutical composition comprises as active ingredient the compound {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide, and at least one therapeutically inert excipient.

20 Such pharmaceutical compositions according to embodiment 25) are especially useful for the treatment of hypertension, pulmonary hypertension, coronary diseases, cardiac insufficiency, renal and myocardial ischemia, renal failure, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, Raynaud's syndrome, digital ulcers or portal hypertension as well as for the treatment or prevention of atherosclerosis, restenosis after
25 balloon or stent angioplasty, inflammation, stomach and duodenal ulcer, cancer, melanoma, prostate cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, pulmonary fibrosis, gram negative septicemia, shock, sickle cell anemia, glomerulonephritis, renal colic, glaucoma, connective tissue diseases, diabetic complications, complications of vascular or cardiac surgery or after
30 organ transplantation, complications of cyclosporin treatment, pain or hyperlipidemia. The pharmaceutical compositions according to embodiment 25) are also useful for the treatment of Chronic Kidney Disease (CKD), especially CKD of stages 1 to 4 as defined

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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 essential hypertension.

Preferably, they are useful for in the treatment of a disease selected from the group
5 consisting of hypertension, pulmonary hypertension, diabetic arteriopathy, heart failure, erectile dysfunction, angina pectoris and 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 essential hypertension].

10 Moreover, they are useful in the treatment of a disease selected from the group consisting of essential hypertension, resistant hypertension, pulmonary hypertension and pulmonary arterial hypertension (and notably in the treatment of resistant hypertension).

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
15 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
20 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.

25 The term "resistant hypertension" in the present invention is defined as blood pressure that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes. One of the 3 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 3 medications. That is, patients
30 whose blood pressure is controlled but require 4 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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"Diuretic" in particular means in the present application a diuretic of the thiazide class (a thiazide-like diuretic) such as especially chlorthalidone, hydrochlorothiazide, chlorothiazide, indapamide, or metolazone. Preferred diuretics are chlorthalidone or hydrochlorothiazide.

5 The invention, thus, further relates to COMPOUND, especially a crystalline form of COMPOUND according to any one of embodiments 1) to 21) (in particular crystalline Form A or C), wherein COMPOUND / said crystalline form is used as a medicament, especially for the treatment of resistant hypertension; wherein COMPOUND / said crystalline form is used alone or (preferably) in combination (preferably for simultaneously
10 adminiatration, including a fixed dose combination) with a diuretic, in particular hydrochlorothiazide (HCTZ or HCT). In a sub-embodiment, said combination of COMPOUND / said crystalline form according to any one of embodiments 1) to 21) (in particular crystalline Form A or C) with a diuretic, in particular hydrochlorothiazide (HCTZ or HCT) for the treatment of resistant hypertension; may require further
15 combination (preferably for simultaneously adminiatration, including a fixed dose combination) with one or two additional active ingredients that are antihypertensive agents of different classes (especially a CCB and/or an ARB), in particular valsartan. The invention, thus, especially relates to pharmaceutical compositions comprising COMPOUND / the respective crystalline form of COMPOUND as defined in any one of
20 embodiments 26) to 31) below; comprising as active ingredients, in addition to COMPOUND / the respective crystalline form of COMPOUND, a diuretic, in particular hydrochlorothiazide (HCTZ or HCT); and optionally further comprising one or two active ingredients that are antihypertensive agents of different classes (especially a CCB and/or an ARB); in particular further comprising valsartan.

25 26) Another embodiment of the present invention relates to a pharmaceutical composition comprising as active ingredient a crystalline form of the COMPOUND according to any one of embodiments 1) to 21), and at least one therapeutically inert excipient.

27) The invention thus also relates to a solid pharmaceutical composition (in particular in the form of a tablet) comprising COMPOUND, especially a crystalline form of the
30 COMPOUND according to any one of embodiments 1) to 21) (especially solid form A of the COMPOUND, as described in any one of embodiments 1) to 7)), microcrystalline cellulose, lactose, hydroxypropylcellulose, croscarmellose sodium and magnesium

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stearate; it will in particular relate to a solid pharmaceutical composition (in particular in the form of a tablet) consisting of a crystalline form of the COMPOUND according to any one of embodiments 1) to 21) (especially solid form A thereof, as described in any one of embodiments 1) to 7)), microcrystalline cellulose, lactose, hydroxypropylcellulose, croscarmellose sodium and magnesium stearate.

28) Preferably, the solid pharmaceutical composition of embodiment 27) will comprise COMPOUND, especially the crystalline form of the COMPOUND according to any one of embodiments 1) to 21) (especially solid form A of the COMPOUND, as described in any one of embodiments 1) to 7)) in a total amount from 1 to 25% (especially 5 to 25%) in weight based on the total weight of the pharmaceutical composition, microcrystalline cellulose in a total amount from 20 to 35 % (especially 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.

Such pharmaceutical compositions according to any of embodiments 26) to 28) are especially useful for the treatment of endothelin related diseases and disorders, notably the diseases and disorders of embodiment 25).

29) A further embodiment of the invention relates to a pharmaceutical composition according to any one of embodiments 26) to 28), wherein said pharmaceutical composition is in form of a tablet.

30) In particular, the pharmaceutical composition of embodiment 29) will be in the form of a tablet consisting of the solid form A of the COMPOUND (as described in any one of embodiments 1) to 7)) in a total amount from 1 to 25% (especially 5 to 25%) in weight based on the total weight of the pharmaceutical composition, microcrystalline cellulose in a total amount from 20 to 35 % (especially 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

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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
5 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.

A tablet according to embodiment 29) or 30) can optionally be coated with a suitable protective pellicle. Said protective pellicle will notably prevent direct contact of the
10 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 Biogrand) or dimethylaminoethyl methacrylate (e.g. EUDRAGIT® E PO)).
15 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.

20 31) A further embodiment of the invention relates to a pharmaceutical composition according to any one of embodiments 26) to 28), wherein said pharmaceutical composition is in form of a capsule.

For avoidance of any doubt, embodiments 25), 26), 27), 28), 29), 30) or 31) especially refer to the crystalline forms according to any one of embodiments 1) to 21) which is
25 suitable / which is used as final isolation step of COMPOUND (e.g. in order to meet the purity requirements of pharmaceutical production), whereas the final pharmaceutical composition according to embodiment 25), 26), 27), 28) , 29), 30) or 31) may or may not contain said crystalline form (e.g. because the originally crystalline form of COMPOUND is further transformed during the manufacturing process and / or is dissolved in the
30 pharmaceutically acceptable carrier material(s); thus, in the final pharmaceutical composition, COMPOUND may be present in non-crystalline form, in another crystalline form, or in dissolved form, or the like).

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32) A further embodiment of the invention relates to COMPOUND or a pharmaceutically acceptable salt thereof, especially a crystalline form of COMPOUND according to any one of embodiments 1) to 21), for use in the treatment of hypertension, pulmonary hypertension, coronary diseases, cardiac insufficiency, renal and myocardial ischemia, renal failure, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, Raynaud's syndrome, digital ulcers or portal hypertension as well as for the treatment or prevention of atherosclerosis, restenosis after balloon or stent angioplasty, inflammation, stomach and duodenal ulcer, cancer, melanoma, prostate cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, pulmonary fibrosis, gram negative septicemia, shock, sickle cell anemia, glomerulonephritis, renal colic, glaucoma, connective tissue diseases, diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, hyperlipidemia or 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 essential hypertension].

33) A further embodiment of the invention relates to COMPOUND or a pharmaceutically acceptable salt thereof, especially a crystalline form of COMPOUND according to any one of embodiments 1) to 21), for use in the treatment of a disease selected from the group consisting of hypertension, pulmonary hypertension, diabetic arteriopathy, heart failure, erectile dysfunction, angina pectoris and 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 essential hypertension].

34) A further embodiment of the invention relates to COMPOUND or a pharmaceutically acceptable salt thereof, especially a crystalline form of COMPOUND according to any one of embodiments 1) to 21), for use in the treatment of a disease selected from the group consisting of essential hypertension, resistant hypertension, pulmonary hypertension and pulmonary arterial hypertension (and notably for use in the treatment of resistant hypertension).

For avoidance of any doubt, if a certain crystalline form of COMPOUND is described as useful for the prevention / prophylaxis or treatment of certain diseases, such compounds are likewise suitable for use in the preparation of a medicament for the prevention /

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prophylaxis or treatment of said diseases. Likewise, such compounds are also suitable in a method for the prevention / prophylaxis or treatment of such diseases, comprising administering to a subject (mammal, especially human) in need thereof, an effective amount of such compound.

- 5 35) A further embodiment of the invention relates to the use of COMPOUND or a pharmaceutically acceptable salt thereof, especially of a crystalline form of COMPOUND according to any one of embodiments 1) to 21), for the preparation of a medicament intended for the treatment of any one of the diseases or disorders mentioned in embodiment 32).
- 10 36) A further embodiment of the invention relates to the use of COMPOUND or a pharmaceutically acceptable salt thereof, especially of a crystalline form of COMPOUND according to any one of embodiments 1) to 21), for the preparation of a medicament intended for the treatment of any one of the diseases or disorders mentioned in embodiment 33).
- 15 37) A further embodiment of the invention relates to the use of COMPOUND or a pharmaceutically acceptable salt thereof, especially of a crystalline form of COMPOUND according to any one of embodiments 1) to 21), for the preparation of a medicament intended for the treatment of any one of the diseases or disorders mentioned in embodiment 34).
- 20 38) A further embodiment of the invention relates to a method for the treatment of any one of the diseases or disorders mentioned in embodiment 32), comprising administering to a patient an effective amount of COMPOUND or a pharmaceutically acceptable salt thereof, especially of a crystalline form of COMPOUND according to any one of embodiments 1) to 21), or of a pharmaceutical composition according to any one of embodiments 26) to 31).
- 25 39) A further embodiment of the invention relates to a method for the treatment of any one of the diseases or disorders mentioned in embodiment 33), comprising administering to a patient an effective amount of COMPOUND or a pharmaceutically acceptable salt thereof, especially of a crystalline form of COMPOUND according to any one of embodiments 1) to 21), or of a pharmaceutical composition according to any one of embodiments 26) to 31).
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40) A further embodiment of the invention relates to a method for the treatment of any one of the diseases or disorders mentioned in embodiment 34), comprising administering to a patient an effective amount of COMPOUND or a pharmaceutically acceptable salt thereof, especially of a crystalline form of COMPOUND according to any one of embodiments 1) to 21), or of a pharmaceutical composition according to embodiments 26) to 31).

41) Yet another embodiment of the invention relates to the COMPOUND or a pharmaceutically acceptable salt thereof, especially a crystalline form of COMPOUND according to any one of embodiments 1) to 21), for use in the treatment of a disorder selected from the group consisting of chronic kidney disease (CKD), diabetes, diabetic nephropathy, diabetic retinopathy, diabetic vasculopathy, chronic heart failure and diastolic dysfunction.

42) One sub-embodiment of embodiment 41) relates to the COMPOUND or a pharmaceutically acceptable salt thereof, especially a crystalline form of COMPOUND according to any one of embodiments 1) to 21), for use in the treatment of 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 essential hypertension.

43) Another sub-embodiment of embodiment 41) relates to the COMPOUND or a pharmaceutically acceptable salt thereof, especially a crystalline form of COMPOUND according to any one of embodiments 1) to 21), for use in the treatment of diabetes (that is, type 1 or type 2 diabetes).

44) Another sub-embodiment of embodiment 41) relates to the COMPOUND or a pharmaceutically acceptable salt thereof, especially a crystalline form of COMPOUND according to any one of embodiments 1) to 21), for use in the treatment of diabetic nephropathy.

45) Another sub-embodiment of embodiment 41) relates to the COMPOUND or a pharmaceutically acceptable salt thereof, especially a crystalline form of COMPOUND according to any one of embodiments 1) to 21), for use in the treatment of diabetic retinopathy.

46) Another sub-embodiment of embodiment 41) relates to the COMPOUND or a pharmaceutically acceptable salt thereof, especially a crystalline form of COMPOUND

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according to any one of embodiments 1) to 21), for use in the treatment of diabetic vasculopathy.

47) Another sub-embodiment of embodiment 41) relates to the COMPOUND or a pharmaceutically acceptable salt thereof, especially a crystalline form of COMPOUND according to any one of embodiments 1) to 21), for use in the treatment of chronic heart failure.

48) According to one variant of sub-embodiment 47), the chronic heart failure of sub-embodiment 47) will be heart failure with preserved ejection fraction.

49) According to another variant of sub-embodiment 47), the chronic heart failure of sub-embodiment 47) will be diastolic heart failure.

50) Another sub-embodiment of embodiment 41) relates to the COMPOUND or a pharmaceutically acceptable salt thereof, especially a crystalline form of COMPOUND according to any one of embodiments 1) to 21), for use in the treatment of diastolic dysfunction.

51) Preferably, the COMPOUND or a pharmaceutically acceptable salt thereof [especially a crystalline form of COMPOUND according to any one of embodiments 1) to 21)] according to any one of embodiments 41) to 50) will be comprised in a pharmaceutical unit dosage form suitable for the oral administration of 2.5 to 100 mg (in particular 5 or 10 to 50 mg, notably 25 or 50 mg) per day of the COMPOUND {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide or of a pharmaceutically acceptable salt thereof.

52) Preferably, the COMPOUND or pharmaceutically acceptable salt thereof [especially a crystalline form of COMPOUND according to any one of embodiments 1) to 21)] according to any one of embodiments 41) to 51) will be for use in combination with an Angiotensin Converting Enzyme (ACE) inhibitor, an Angiotensin Receptor Blocker (ARB) or a Calcium Channel Blocker (CCB), or with a pharmaceutically acceptable salt of one of these.

"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.

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"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.

- 5 "Calcium Channel Blocker" or "CCB" in particular means in the present application amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, cilnidipine, clevidipine, isradipine, efonidipine, felodipine, lacidipine, 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
- 10 amlodipine or a pharmaceutically acceptable salt thereof.

Accordingly, the COMPOUND or a pharmaceutically acceptable salt thereof [especially a crystalline form of COMPOUND according to any one of embodiments 1) to 21)] according to any one of embodiments 41) to 51) can be for use in combination with an ACE inhibitor, an ARB, and/or a CCB. The corresponding combined treatment may be

15 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

20 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

25 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. For example, when used in combination with an ACE inhibitor, an ARB, and/or a CCB, the COMPOUND would possibly be used "simultaneously". Likewise, when used in combination with a diuretic, the COMPOUND would possibly be

30 used "simultaneously".

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“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.

“Separately”, when referring to an administration type, means in the present application
5 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
10 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
15 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
20 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).

53) Also preferably, the COMPOUND or pharmaceutically acceptable salt thereof
25 [especially a crystalline form of COMPOUND according to any one of embodiments 1) to 21)] according to any one of embodiments 41) to 51) will be for use in combination with a diuretic (in particular for use in combination with hydrochlorothiazide (HCT)).

Accordingly, the COMPOUND or a pharmaceutically acceptable salt thereof [especially a crystalline form of COMPOUND according to any one of embodiments 1) to 21)]
30 according to any one of embodiments 41) to 51) can be for use in combination with a diuretic (in particular for use in combination with HCT). The corresponding combined

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treatment may be effected simultaneously, separately, or over a period of time (especially simultaneously), as defined hereabove.

54) Yet another embodiment of the invention relates to the use of the COMPOUND or of a pharmaceutically acceptable salt thereof [especially of a crystalline form of COMPOUND according to any one of embodiments 1) to 21)], for the manufacture of a medicament for use in the treatment of a disorder selected from the group consisting of chronic kidney disease (CKD), diabetes, diabetic nephropathy, diabetic retinopathy, diabetic vasculopathy, chronic heart failure and diastolic dysfunction.

55) One sub-embodiment of embodiment 54) relates to the use according to embodiment 54) which is for the manufacture of a medicament for use in the treatment of 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 essential hypertension.

56) Another sub-embodiment of embodiment 54) relates to the use according to embodiment 54) which is for the manufacture of a medicament for use in the treatment of diabetes (that is, type 1 or type 2 diabetes).

57) Another sub-embodiment of embodiment 54) relates to the use according to embodiment 54) which is for the manufacture of a medicament for use in the treatment of diabetic nephropathy.

58) Another sub-embodiment of embodiment 54) relates to the use according to embodiment 54) which is for the manufacture of a medicament for use in the treatment of diabetic retinopathy.

59) Another sub-embodiment of embodiment 54) relates to the use according to embodiment 54) which is for the manufacture of a medicament for use in the treatment of diabetic vasculopathy.

60) Another sub-embodiment of embodiment 54) relates to the use according to embodiment 54) which is for the manufacture of a medicament for use in the treatment of chronic heart failure.

61) According to one variant of sub-embodiment 60), the chronic heart failure of sub-embodiment 60) will be heart failure with preserved ejection fraction.

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62) According to another variant of sub-embodiment 60), the chronic heart failure of sub-embodiment 60) will be diastolic heart failure.

63) Another sub-embodiment of embodiment 54) relates to the use according to embodiment 54) which is for the manufacture of a medicament for use in the treatment of
5 diastolic dysfunction.

64) Preferably, the use according to any one of embodiments 54) to 63) will be such that it is for the manufacture of a pharmaceutical unit dosage form suitable for the oral administration of 2.5 to 100 mg (in particular 5 or 10 to 50 mg, notably 25 or 50 mg) per day of the COMPOUND or of a pharmaceutically acceptable salt thereof [especially of a
10 crystalline form of COMPOUND according to any one of embodiments 1) to 21)].

65) Preferably, the use according to any one of embodiments 54) to 64) will be for the manufacture of a medicament for use in combination with an Angiotensin Converting Enzyme (ACE) inhibitor, an Angiotensin Receptor Blocker (ARB) or a Calcium Channel Blocker (CCB) or with a pharmaceutically acceptable salt of one of these.

15 Accordingly, the use according to any one of embodiments 54) to 64) can be for the manufacture of a medicament for use in combination with an ACE inhibitor, an ARB or a CCB or with a pharmaceutically acceptable salt of one of these. The corresponding combined treatment may be effected simultaneously, separately, or over a period of time (especially simultaneously).

20 66) Also preferably, the use according to any one of embodiments 54) to 64) will be for the manufacture of a medicament for use in combination with a diuretic (in particular for the manufacture of a medicament for use in combination with hydrochlorothiazide (HCT)).

Accordingly, the use according to any one of embodiments 54) to 64) can be for the manufacture of a medicament for use in combination with a diuretic (in particular for the
25 manufacture of a medicament for use in combination with HCT). The corresponding combined treatment may be effected simultaneously, separately, or over a period of time (especially simultaneously), as defined hereabove.

67) Yet another embodiment of the invention relates to a method for treating a disorder selected from the group consisting of chronic kidney disease (CKD), diabetes, diabetic nephropathy, diabetic retinopathy, diabetic vasculopathy, chronic heart failure and diastolic
30 dysfunction in a patient, said method comprising the administration of a therapeutically

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effective amount of the COMPOUND or of a pharmaceutically acceptable salt thereof [especially of a crystalline form of COMPOUND according to any one of embodiments 1) to 21)], to a patient in need thereof.

5 68) One sub-embodiment of embodiment 67) relates to the method according to embodiment 67) which is for treating CKD in a patient, 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 essential hypertension.

10 69) Another sub-embodiment of embodiment 67) relates to the method according to embodiment 67) which is for treating diabetes (that is, type 1 or type 2 diabetes).

70) Another sub-embodiment of embodiment 67) relates to the method according to embodiment 67) which is for treating diabetic nephropathy.

71) Another sub-embodiment of embodiment 67) relates to the method according to embodiment 67) which is for treating diabetic retinopathy.

15 72) Another sub-embodiment of embodiment 67) relates to the method according to embodiment 67) which is for treating diabetic vasculopathy.

73) Another sub-embodiment of embodiment 67) relates to the method according to embodiment 67) which is for treating chronic heart failure.

20 74) According to one variant of sub-embodiment 73), the chronic heart failure of sub-embodiment 73) will be heart failure with preserved ejection fraction.

75) According to another variant of sub-embodiment 73), the chronic heart failure of sub-embodiment 73) will be diastolic heart failure.

76) Another sub-embodiment of embodiment 67) relates to the method according to embodiment 67) which is for treating diastolic dysfunction.

25 77) Preferably, the method according to any one of embodiments 67) to 76) will be such that a dose of 2.5 to 100 mg (in particular 5 or 10 to 50 mg, notably 25 or 50 mg) per day of the COMPOUND or of a pharmaceutically acceptable salt thereof [especially of a crystalline form of COMPOUND according to any one of embodiments 1) to 21)] is administered orally to a patient in need thereof.

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78) Preferably, the method according to any one of embodiments 67) to 77) will such that a therapeutically effective amount of the COMPOUND or of a pharmaceutically acceptable salt thereof [especially of a crystalline form of COMPOUND according to any one of embodiments 1) to 21)] is administered in combination with a therapeutically effective
5 amount of an Angiotensin Converting Enzyme (ACE) inhibitor, an Angiotensin Receptor Blocker (ARB) or a Calcium Channel Blocker (CCB) or of a pharmaceutically acceptable salt of one of these.

Accordingly, the method according to any one of embodiments 67) to 77) can be such that a therapeutically effective amount of the COMPOUND or of a pharmaceutically
10 acceptable salt thereof [especially of a crystalline form of COMPOUND according to any one of embodiments 1) to 21)] is administered in combination with a therapeutically effective amount of an ACE inhibitor, an ARB or a CCB or of a pharmaceutically acceptable salt of one of these. The corresponding combined treatment may be effected simultaneously, separately, or over a period of time (especially simultaneously).

15 79) Also preferably, the method according to any one of embodiments 67) to 77) will such that a therapeutically effective amount of the COMPOUND or of a pharmaceutically acceptable salt thereof [especially of a crystalline form of COMPOUND according to any one of embodiments 1) to 21)] is administered in combination with a therapeutically effective amount of a diuretic (in particular in combination with a therapeutically effective
20 amount of hydrochlorothiazide (HCT)).

Accordingly, the method according to any one of embodiments 67) to 77) can be such that a therapeutically effective amount of the COMPOUND or of a pharmaceutically acceptable salt thereof [especially of a crystalline form of COMPOUND according to any one of embodiments 1) to 21)] is administered in combination with a therapeutically
25 effective amount of a diuretic (in particular in combination with a therapeutically effective amount of HCT). The corresponding combined treatment may be effected simultaneously, separately, or over a period of time (especially simultaneously).

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:

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

EXAMPLES

Method for obtaining XRPD patterns

- 25 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 30 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 2θ values as provided herein is in the range of ± 0.1 - 0.2° as it is generally the case for conventionally recorded X-ray powder diffraction patterns.

Gravimetric vapour sorption (GVS)

- 5 Measurements are performed on a multi sample instrument SPS-100n (Projekt Messtechnik, Ulm, Germany) operated in stepping mode at 25°C . The sample is allowed to equilibrate at 40% RH before starting a pre-defined humidity program (40-0-95-0-95-40% RH, steps of 5% ΔRH and with a maximal equilibration time of 24 hours per step are applied. About 20 to 30 mg of each sample is used.
- 10 The hygroscopic classification is done according to the European Pharmacopeia Technical Guide (1999, page 86), e.g., slightly hygroscopic: increase in mass is less than 2% and equal to or greater than 0.2% mass/mass; hygroscopic: increase in mass is less than 15% and equal to or greater than 2% mass/mass. The mass change between 40% relative humidity and 80% relative humidity in the first adsorption scan is considered.

15 *Differential scanning calorimetry (DSC)*

- DSC data are collected on a Mettler Toledo STARe System (DSC822e module, measuring cell with ceramic sensor and STAR software version 9.20) equipped with a 34-position auto-sampler. The instrument is calibrated for energy and temperature using certified indium. Typically, 1-5 mg of each sample, in an automatically pierced aluminium pan, is
- 20 heated at $10^\circ\text{C min}^{-1}$, unless stated otherwise, from -20°C to 280°C . A nitrogen purge at 20 mL min^{-1} is maintained over the sample. Peak temperatures are reported for melting points.

Thermogravimetric analysis (TGA)

- TGA data are collected on a Mettler Toledo STARe System (TGA851e module and STAR
- 25 software version 9.20) equipped with a 34 position auto-sampler. Typically about 5 mg of a sample, in an automatically pierced aluminium pan, is heated at $10^\circ\text{C min}^{-1}$, unless stated otherwise, from 30°C to 250°C . A nitrogen purge at 10 mL min^{-1} is maintained over the sample.

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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. (WO2015/121397)), 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, 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-bromopyrimidin-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-(2-((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

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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
5 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 kg, 77% yield, XRPD pattern Form A).

Example 2: Form B (DCM solvate of the COMPOUND):

5-(4-bromophenyl)-4-(2-((5-bromopyrimidin-2-yl)oxy)ethoxy)-6 fluoropyrimidine (10.0 g, 21.3 mmol, 1.00 eq.), sulfamide (4.1 g, 42.5 mmol, 2.0 eq.) and K₂CO₃ (14.7 g, 106 mmol,
10 5.0 eq.) were suspended in DMSO (50 mL, 5 vol.) and heated to 70°C for 5 h. The mixture was cooled to rt and EtOAc (40 mL, 4 vol.) followed by water (100 mL, 10 vol.) were added. After separation of the layers (org. phase discarded), the aq. phase was extracted with DCM (100 mL, 10 vol.). The DCM layer was acidified from pH 11.5 to pH 7.0 with conc. AcOH (3 mL, 52 mmol, 2.5 eq.), resulting in crystallization of the product. The
15 suspension was cooled to 0°C for 1 h, then to -5°C for 15 min. The solid was filtered, washed with cold DCM (10 mL, 1 vol.) and dried to yield a DCM solvate of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide in Form B as a white solid (9.8 g, 84% yield).

Example 3: Form C:

0.2 mL of a stock solution of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-
20 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-
25 phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide in Form C was obtained for each of these solvents.

Example 4: Form D:

4.1. A reactor was charged with sulfamide (2.00 eq.), K₂CO₃ (5.00 eq.), 5-(4-bromophenyl)-4-(2-((5-bromopyrimidin-2-yl)oxy)ethoxy)-6-fluoropyrimidine
30 (1.00 eq.), DMSO (5.0 vol.) and water (0.02 vol.). The mixture was heated to 75°C for 2 h.

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After cooling to 23 °C, the suspension was filtered and rinsed with EtOAc/iPrOAc 1:1 (5.5 vol.) through the reactor. The filtrate was again filtered through an in-line filter and rinsed with EtOAc/iPrOAc 1:1 (1.5 vol.). A solution of 1M NaOAc in water (5.0 vol.) was added at 27°C, and the layers were separated. The aq. phase was washed with
5 EtOAc/iPrOAc 1:1 (5.0 vol.). The aq. phase was acidified to pH 5.8 using 0.5M H₂SO₄ in water (2.35 vol.) over 2.5 h, leading to crystallization. After 1 h stirring at 20°C, the suspension was filtered and washed with water (2 x 10 vol.). The solid was slurried twice in water (2 x 10 vol.) at 20°C for 3 h each, filtered, washed with water (10 vol.) and dried to give {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-
10 sulfamide in Form D.

4.2. 50 mg of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide in Form A was dissolved in 3 mL methyl-ethylketone in a new 7 mL glass vial. After sonication in an ultrasound bath for 1 min, the vial was allowed to stand open at rt for 3 days. The solid residue was {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide in Form D.
15

Example 5: Form E (MeCN solvate of the COMPOUND):

{5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide in Form A was heated to reflux in 10 volumes of MeCN. After 10 min it was allowed to cool down to 20°C within 1 h (heating bath removed). It was filtered off and
20 dried under reduced pressure and 45 °C. Solid residue was a MeCN solvate of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide in Form E.

Example 6: Form J:

The DCM solvate of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide Form B (9.4 g, 17.2 mmol, 1.00 eq.) was dissolved in DMSO (19 mL, 2 vol.). The solution was added into H₂O (94 mL, 10 vol.) and stirred at rt for 5 min. The resulting suspension was filtered, washed twice with H₂O (2 x 94 mL, 2 x 10 vol.) and dried to provide {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide Form J as a white solid (6.8 g, 72% yield).
25

Example 7: Form K (DMSO solvate of the COMPOUND):

7.1. {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide Form A (1.00 g, 1.83 mmol, 1.00 eq.) was dissolved in DMSO (2 mL, 2 vol.).
30

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To this solution, 10% H₂O in DMSO (10 mL, 10 vol.) was added slowly, followed by pure H₂O (2 mL, 2 vol.). Seeding with form K triggered crystallization of the product. The suspension was filtered, washed with H₂O (5 x 10 mL, 5 x 10 vol.) and dried to give a DMSO solvate {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide in Form K as a white solid (0.95 g, 95% yield).

7.2. 5-(4-bromophenyl)-4-(2-((5-bromopyrimidin-2-yl)oxy)ethoxy)-6-fluoropyrimidine (10.0 g, 21.3 mmol, 1.00 eq.), sulfamide (4.1 g, 42.5 mmol, 2.0 eq.) and K₂CO₃ (14.7 g, 106 mmol, 5.0 eq.) were suspended in DMSO (50 mL, 5 vol.) and heated to 50°C for 20 h. The mixture was cooled to rt and MIBK (100 mL, 10 vol.) followed by water (100 mL, 10 vol.) were added. After separation of the layers (org. phase discarded), the aq. phase was acidified from pH 11.4 to pH 6.5 with conc. AcOH (4 mL, 70 mmol, 3.3 eq.), resulting in crystallization of the product. The solid was filtered, washed with water (4 x 50 mL, 4 x 5 vol.) and dried to afford a DMSO solvate of {5-(4-bromo-phenyl)-6-[2-(5-bromopyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide in Form K as a beige solid (10.4 g, 90% yield).

Example 8: Form L (EtOH solvate of the COMPOUND):

The DMSO solvate of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide Form K (100 mg, 0.183 mmol, 1.00 eq.) was slurried in EtOH (0.5 mL, 5 vol.) at rt for 4 h. The suspension was filtered, washed twice with H₂O (2 x 0.5 mL, 2 x 5 vol.) and dried to afford an EtOH solvate of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide in Form L as a white solid (40 mg, 40% yield).

Example 9: ACT-132577 tablets:

Tablets containing each 50 mg of COMPOUND 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	COMPOUND (amorphous, or 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
<i>Total</i>		<i>250.00</i>	<i>100.00</i>

qs = quantity sufficient

- 5 Preferably, COMPOUND in crystalline Form A (as described herein) will be used for making the tablets.

Example 10: ACT-132577 tablets:

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

Example 11: ACT-132577 tablets:

Tablets containing each 50 mg of COMPOUND 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	COMPOUND (amorphous, or 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
Extra-granular	Croscarmellose sodium	5.00	2.00
	Magnesium stearate	1.25	0.50
<i>Total</i>		<i>250.00</i>	<i>100.00</i>

qs = quantity sufficient

- 5 Preferably, COMPOUND in crystalline Form A (as described herein) will be used for making the tablets.

Example 12

The tablets of Example 11 can be coated with a layer of Aquapolish® white MS or Aquapolish® white PVA (coating manufacturer: Biogrand).

Example 13: ACT-132577 tablets:

Tablets containing each 12.5 mg of COMPOUND 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	COMPOUND (amorphous, or 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
<i>Total</i>		<i>100.00</i>	<i>100.00</i>

qs = quantity sufficient

- 5 Preferably, COMPOUND in crystalline Form A (as described herein) will be used for making the tablets.

Example 14: ACT-132577 tablets:

The tablets of Example 13 can be coated with a layer of Aquapolish® white MS or Aquapolish® white PVA (coating manufacturer: Bioground).

Example 15: ACT-132577 tablets:

Tablets containing each 12.5 mg of COMPOUND 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	COMPOUND (amorphous, or 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

- 5 Preferably, COMPOUND in crystalline Form A (as described herein) will be used for making the tablets.

Example 16: ACT-132577 tablets:

The tablets of Example 15 can be coated with a layer of Aquapolish® white MS or Aquapolish® white PVA (coating manufacturer: Bioground).

10 **Properties of the crystalline forms**

Storage at room temperature

- 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 sample at the end of the 2 months showed that
- 15 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.

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A sample of Form B crystals of a dichloromethane solvate of the COMPOUND (as obtained according to Example 2 above) has been stored in a closed vial (20 mg of Form B crystals being placed in a closed 4 mL vial) at a temperature of 20-25°C for about 3 weeks. X-ray powder diffraction performed on that sample at the end of the 3 weeks showed that the Form B crystals were transformed into Form A crystals of the COMPOUND.

A sample of Form K crystals of a dimethylsulfoxide solvate of the COMPOUND (as obtained according to Example 7 above) has been stored in a closed vial (20 mg of Form K crystals being placed in a closed 4 mL vial) at a temperature of 20-25°C for about 3 weeks. X-ray powder diffraction performed on that sample at the end of the 3 weeks showed that the Form K crystals were transformed into Form A crystals of the COMPOUND.

DSC

Form A of COMPOUND (as obtained by example 1) melts and decomposes concomitantly. By DSC an endothermic/exothermic signal is observed, with a peak of the endotherm observed at about 159°C.

Form C of COMPOUND (as obtained by example 3) melts and decomposes concomitantly. By DSC an endothermic/exothermic signal is observed, with a peak of the endotherm observed at about 153°C.

Hygroscopicity

Form A e.g. as obtained from Example 1 is considered to be non-hygroscopic as determined by gravimetric vapor sorption (GVS) (see Figure 19).

Form C e.g. as obtained from Example 3 is considered to be slightly hygroscopic as determined by gravimetric vapor sorption (GVS) (see Figure 20).

Examples of therapeutic uses of aprocitentan

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

The acute effects of COMPOUND on blood pressure, in particular on mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR") were 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 were used for the vehicle (7.5% gelatin aqueous

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solution) and each dose of COMPOUND tested (0.3, 1, 3, 10, 30, 100, and 300 mg/kg). Effects of COMPOUND on HR and MAP were 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 9** (data are presented as mean $\pm$ standard error of the mean). In summary, a dose of 10 mg/kg COMPOUND decreased MAP by 19 ± 4 mm Hg in Dahl-S rats. In contrast to MAP, HR was not affected.

EXAMPLE B: acute effects of COMPOUND in deoxycorticosterone acetate salt rats:

The acute effects of COMPOUND on blood pressure, in particular on mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR") were 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 were used for the vehicle (7.5% gelatin aqueous solution) and each dose of COMPOUND tested (0.3, 1, 3, 10, 30, 100, and 300 mg/kg). Effects of COMPOUND on HR and MAP were 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 10** (data are presented as mean $\pm$ standard error of the mean). In summary, a dose of 10 mg/kg COMPOUND decreased MAP by 29 ± 6 mm Hg in DOCA-salt rats. In contrast to MAP, HR was not affected.

EXAMPLE C: acute effects of COMPOUND in spontaneously hypertensive rats:

The acute effects of COMPOUND on blood pressure, in particular on mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR") were 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 were used for the vehicle (7.5% gelatin aqueous solution) and each dose of COMPOUND tested (1, 3, 10, 30, 100, and 300 mg/kg). Effects of COMPOUND on HR and MAP were calculated for individual animals relative to the 24 h period before administering. The results obtained regarding MAP (maximal MAP decrease observed

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over 6 consecutive hours) are summarised in **Figure 11** (data are presented as mean $\pm$ standard error of the mean). In summary, a dose of 100 mg/kg COMPOUND decreased MAP by 18 ± 4 mm Hg in SHR. In contrast to MAP, HR was not affected.

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

The acute effects of COMPOUND 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 COMPOUND being used either alone or in combination with valsartan administered orally at a single dose of 10 mg/kg, were 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 were used for this test. The results obtained regarding MAP are summarised in **Figure 12** 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", was calculated by adding the decreases 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 COMPOUND 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 COMPOUND, alone or in combination with valsartan, in deoxycorticosterone acetate salt rats:

The acute effects of COMPOUND 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 COMPOUND being used either alone or in combination with valsartan administered orally at a single dose of 30 mg/kg, were 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

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of 1% sodium chloride in drinking water. 7-8 DOCA-salt rats per treatment group were used for this test. The results obtained regarding MAP are summarised in **Figure 13** 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", was 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 COMPOUND 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 COMPOUND, alone or in combination with enalapril, in spontaneously hypertensive rats:

The acute effects of COMPOUND 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 COMPOUND being used either alone or in combination with enalapril administered orally at a single dose of 3 mg/kg, were 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 were used for this test. The results obtained regarding MAP are summarised in **Figure 14** 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", was 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 COMPOUND 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 COMPOUND, alone or in combination with amlodipine, in deoxycorticosterone acetate salt rats:

The acute effects of COMPOUND administered orally at a single dose of 10 mg/kg on blood pressure, in particular on mean arterial blood pressure (hereafter "MAP"), and heart

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rate (hereafter "HR"), with COMPOUND being used either alone or in combination with amlodipine administered orally at a single dose of 1 mg/kg, were 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 were used for this test. The results obtained regarding MAP are summarised in **Figure 15** 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", was 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 COMPOUND 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 COMPOUND in deoxycorticosterone acetate salt rats:

The chronic effects of repeated administrations of doses of 1, 10 and 100 mg/kg/day of COMPOUND, in particular mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR"), were 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 COMPOUND were 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 16** 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], DOCA-salt control rats [2nd line from top at day 28] and DOCA-salt rats receiving repeated administrations of doses of 1 mg/kg/day [top line at day

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28], 10 mg/kg/day [3rd line from top at day 28] and 100 mg/kg/day [4th line from top at day 28] of COMPOUND). In brief, oral administration of COMPOUND 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 17** wherein:

- ❖ DOCA Ø 2w represents DOCA-salt rats sacrificed just before initiation of treatment with COMPOUND; 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.

10 In summary, based on these tests, chronic oral administration of COMPOUND to DOCA-salt rats dose-dependently increased renal blood flow and decreased renal vascular resistance. COMPOUND 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).

15 **EXAMPLE I: effects of COMPOUND, alone or in combination with an ACE inhibitor or an ARB, in animal models of diabetes:**

The effects of COMPOUND 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 COMPOUND, 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).

25 **EXAMPLE J: Evaluation of the effect of COMPOUND 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 aprocitentan (1-30 mg/kg) or vehicle (gelatin) was administered by gavage to male Wistar rats. Twenty-four hours after administration, sublingual blood was sampled under isoflurane-induced anesthesia. Haematocrit was measured using a hematology analyser. COMPOUND did not impact on haematocrit (Hct) suggesting low liability on fluid retention (**Figure 18**).

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COMPARISON EXAMPLE 1: acute effects of spironolactone used in combination with valsartan in spontaneously hypertensive rats:

The acute effects of spironolactone on blood pressure, in particular on mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR") in combination with valsartan, each administered orally as single doses, were also 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) using a protocol analog to that described in Example D.

Unlike for COMPOUND, no synergistic effect was seen on MAP reduction for the combination of spironolactone treatment with valsartan treatment.

COMPARISON EXAMPLE 2: acute effects of spironolactone used in combination with valsartan in deoxycorticosterone acetate salt rats:

The acute effects of spironolactone on blood pressure, in particular on mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR") in combination with valsartan, each administered orally as single doses, were also 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) using a protocol analog to that described in Example E.

Unlike for COMPOUND, no synergistic effect was seen on MAP reduction for the combination of spironolactone treatment with valsartan treatment.

COMPARISON EXAMPLE 3: acute effects of spironolactone used in combination with enalapril in spontaneously hypertensive rats:

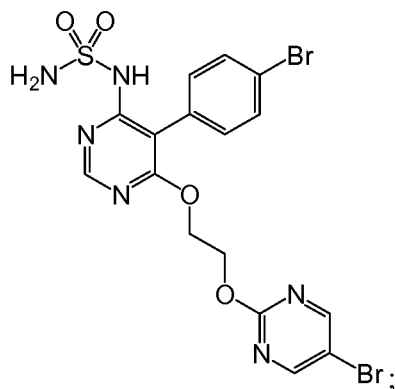
The acute effects of spironolactone on blood pressure, in particular on mean arterial blood pressure (hereafter "MAP"), and heart rate (hereafter "HR") in combination with valsartan, each administered orally as single doses, were also evaluated by means of telemetry in conscious, male spontaneously hypertensive rats (hereafter "SHRs" - see details about this model in Atanur et al., *Genome Res.* (2010), **20**, 791-803) using a protocol analog to that described in Example F.

Unlike for COMPOUND, no synergistic effect was seen on MAP reduction for the combination of spironolactone treatment with enalapril treatment.

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Claims

1. A crystalline form of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide:



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°; or
- the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.7°, 15.7°, and 22.0°; or
- the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 4.6°, 16.8°, and 20.1°; or
- the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 9.5°, 16.5°, and 18.2°; wherein said crystalline form is an acetonitrile solvate; or
- the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 4.0°, 16.1°, and 21.9°; or
- the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 16.9°, 19.3°, and 24.8°; wherein said crystalline form is a dimethylsulfoxide solvate; or
- the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction 2θ : 11.3°, 16.4°, and 20.3°; wherein said crystalline form is a ethanol solvate;

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 $2\theta \pm 0.2^\circ$.

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2. The crystalline form of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide according to claim 1, 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°; or
- 5 • 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°;

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 $2\theta \pm 0.2^\circ$.

- 10 3. The crystalline form of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide according to claim 1, 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
- 15 accuracy of the 2θ values is in the range of $2\theta \pm 0.2^\circ$.

4. The crystalline form of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide according to claim 1, 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
- 20 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 $2\theta \pm 0.2^\circ$.

5. The crystalline form of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide or of a solvate of that compound, according to claims 3 or 4, which essentially shows the X-ray powder diffraction pattern as depicted in Figure 1.

- 25 6. The crystalline form of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide, according to any one of claims 3 to 5, wherein said crystalline form is obtainable by crystallisation of the {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide in an aqueous solution at pH 6.2 to 6.8.

- 30 7. A crystalline form of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide, according to any one of claims 1 to 6, for use in the

manufacture of a pharmaceutical composition, wherein said pharmaceutical composition comprises as active ingredient the compound {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide, and at least one therapeutically inert excipient.

- 5 **8.** A pharmaceutical composition comprising as active ingredient a crystalline form of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide according to any one of claims 2 to 6, and at least one therapeutically inert excipient.
9. A pharmaceutical composition according to claim 8, which comprises as therapeutically inert excipient microcrystalline cellulose, lactose, hydroxypropylcellulose, croscarmellose
- 10 sodium and magnesium stearate.
- 10.** A crystalline form of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide according to any one of claims 2 to 6, for use in the treatment of hypertension, pulmonary hypertension, coronary diseases, cardiac insufficiency, renal and myocardial ischemia, renal failure, cerebral ischemia, dementia, migraine, subarachnoidal
- 15 hemorrhage, Raynaud's syndrome, digital ulcers or portal hypertension as well as for the treatment or prevention of atherosclerosis, restenosis after balloon or stent angioplasty, inflammation, stomach and duodenal ulcer, cancer, melanoma, prostate cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, pulmonary fibrosis, gram negative septicemia, shock, sickle cell anemia,
- 20 glomerulonephritis, renal colic, glaucoma, connective tissue diseases, diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain or hyperlipidemia.
- 11.** The crystalline form of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide according to claim 10, for use in the treatment of a
- 25 disease selected from the group consisting of hypertension, pulmonary hypertension, diabetic arteriopathy, heart failure, erectile dysfunction, angina pectoris and chronic kidney disease.
- 12.** The crystalline form of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide according to claim 10, for use in the treatment of a
- 30 disease selected from the group consisting of essential hypertension, resistant hypertension, pulmonary hypertension and pulmonary arterial hypertension.

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13. Use a crystalline form of the compound {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide according to any one of claims 2 to 6, for the preparation of a medicament for the treatment of hypertension, pulmonary hypertension, coronary diseases, cardiac insufficiency, renal and myocardial ischemia, renal failure, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, Raynaud's syndrome, digital ulcers or portal hypertension as well as for the treatment or prevention of atherosclerosis, restenosis after balloon or stent angioplasty, inflammation, stomach and duodenal ulcer, cancer, melanoma, prostate cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, pulmonary fibrosis, gram negative septicemia, shock, sickle cell anemia, glomerulonephritis, renal colic, glaucoma, connective tissue diseases, diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, hyperlipidemia or chronic kidney disease.

14. A method for the treatment of hypertension, pulmonary hypertension, coronary diseases, cardiac insufficiency, renal and myocardial ischemia, renal failure, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, Raynaud's syndrome, digital ulcers or portal hypertension as well as for the treatment or prevention of atherosclerosis, restenosis after balloon or stent angioplasty, inflammation, stomach and duodenal ulcer, cancer, melanoma, prostate cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, pulmonary fibrosis, gram negative septicemia, shock, sickle cell anemia, glomerulonephritis, renal colic, glaucoma, connective tissue diseases, diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, hyperlipidemia or chronic kidney disease, comprising administering to a patient an effective amount of a crystalline form of the compound {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide according to any one of claims 2 to 6, or of a pharmaceutical composition according to any one of claims 7 to 9.

15. A crystalline form of {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl}-sulfamide according to any one of claims 2 to 6, for use in the treatment of a disorder selected from the group consisting of chronic kidney disease (CKD), diabetes, diabetic nephropathy, diabetic retinopathy, diabetic vasculopathy, chronic heart failure and diastolic dysfunction.