

NEW SOLID FORMS OF *N*-[(1*S*,2*E*)-1-CYCLOPROPYL-3-(METHANESULFONYL)PROP-2-EN-1-YL]-2-(1,1-DIFLUOROETHYL)-4-PHENOXYPYRIMIDINE-5-CARBOXAMIDE

Field of the invention

The present invention provides new solid forms of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide, as
5 well as therapeutic uses thereof and pharmaceutical compositions comprising said forms.

Background art

RECQ helicases are 3' to 5' DNA unwinding DNA-dependent ATPases. Three RECQ helicases, BLM, Werner (WRN) and RECQL4, cause human syndromes that overlap, but are also distinct symptomatically, when their expression is altered or lost (de Renty C, Ellis N A.
10 Ageing Res Rev 2017; 33:36-51). WRN was identified as a potential synthetic lethal target for cancer that expresses high levels of microsatellite instability (MSI-H cancer) in 2019 by multiple groups independently (Chan, E.M. et al., Nature 2019, 568, 551-556; Behan, F.M. et al., Nature 2019, 568, 511-516; Lieb et al. eLife 2019, 8, e43333). There are a few reports describing identification of small molecules that inhibit WRN helicase activity with unknown mechanism
15 (Aggarwal et al., Cancer Res. 2013, 73, 5497; Aggarwal et al., PNAS 2011, 108, 4, 1525-1530; Sommers et al., PLoS ONE 2019, 14(1), e0210525).

There is accordingly a need for compounds that are inhibitors of WRN helicase for the treatment of MSI-H cancer. *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide satisfies these needs.

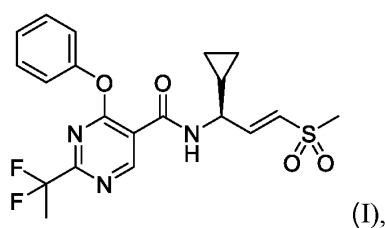
20 Polymorphs are different crystalline forms of the same compound. Polymorphs typically have a different crystal structure due to a different packing of the molecules in the lattice. Polymorphic forms are of interest to the pharmaceutical industry and especially to those involved in the development of suitable dosage forms. If the polymorphic form is not held constant during clinical studies, the exact dosage form used or studied may not be comparable

form one lot to another. It is also desirable to have processes for producing a compound with the selected polymorphic form in high purity when the compound is used in clinical studies or commercial products since any impurities may produce undesired effects (e.g. toxicity). Certain polymorphs may also exhibit enhanced stability or may be more readily manufactured in high
 5 purity in large quantities, and are more suitable for inclusion in pharmaceutical formulations. Certain polymorphs may display other advantageous physical properties such as lack of hygroscopic tendencies, improved solubility, and enhanced rates of dissolution due to different lattice energies.

N-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-
 10 phenoxy pyrimidine-5-carboxamide is an inhibitor of WRN helicase for the treatment of MSI-H cancer. Accordingly, for pharmaceutical development and commercialization, there is a need to identify solid forms of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide having desirable properties such as high crystallinity, high purity, and favourable physical stability, chemical stability, dissolution and
 15 mechanical properties. The present invention provides *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide in novel solid forms, namely crystalline polymorphic Form A, crystalline polymorphic Form E and an Form Amorphous.

Detailed description of the invention

20 The present invention relates to a solid form of a compound of formula (I)



wherein the solid form is crystalline polymorph Form A, crystalline polymorph Form E, or Form Amorphous.

The compound of formula (I) is also referred to as *N*-[(1*S*,2*E*)-1-cyclopropyl-3-
 25 (methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide

Crystalline polymorphic Form A is the thermodynamically stable form of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide. The crystalline polymorphic Form A is characterized by favourable biophysical properties.

- 5 Form Amorphous of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide is hygroscopic and is characterized by enhanced biophysical properties such as for instance solubility or bioavailability.

The terms “pharmaceutically acceptable carrier” and “pharmaceutically acceptable auxiliary substance” refer to carriers and auxiliary substances such as diluents or excipients that
10 are compatible with the other ingredients of the formulation.

The term “room temperature” refers to 18-30 °C, in particular 20-25 °C, more particular to 20 °C.

The terms “about” and “approximately” are interchangeably and refer to a range of values that fall within 5%, greater or less than the stated reference value. More particularly “about” or
15 “approximately” refers to $\pm 0.2^\circ$ degrees 2-theta or $\pm 0.5^\circ$ C.

The terms “substantial amounts” as used herein, can mean at least 50%, in particular at least 60%, and more particular at least 70% of the initially present amount of a specific substance in a defined fraction. For instance after a purification step, the fraction comprising a substantial amount of a specific substance will comprise at least 50%, in particular at least 60%,
20 more particularly at least 70% of the specific substance of the initially present amount of that specific substance prior to the purification step.

“Crystallization” and “recrystallization” may be used interchangeably; referring to a process that leads to a stable polymorph or crystalline form of a particular chemical compound wherein the chemical compound prior to the process can be in amorphous form, or dissolved or
25 suspended in a solvent system. For example, the crystallization steps can be done by forming a crystal with a solvent and an anti-solvent.

“XRPD” refers the analytical method of X-Ray Powder Diffraction. The repeatability of the angular values is in the range of 2-theta $\pm 0.2^\circ$. The term “approximately” given in combination with an angular value denotes the repeatability which is in the range of 2-theta. The
30 relative XRPD peak intensity is dependent upon many factors such as structure factor,

temperature factor, crystallinity, polarization factor, multiplicity, and Lorentz factor. Relative intensities may vary considerably from one measurement to another due to preferred orientation effects. According to USP 941 (US Pharmacopoeia, 37th Edition, General Chapter 941), relative intensities between two samples of the same material may vary considerably due to “preferred orientation” effects. Anisotropic materials adopting preferred orientation will lead to anisotropic distribution of properties such as modulus, strength, ductility, toughness, electrical conductivity, thermal expansion, etc., as described e. g. in Kocks U.F. et al. (Texture and Anisotropy: Preferred Orientations in Polycrystals and Their Effect on Materials Properties, Cambridge University Press, 2000). In XRPD but also Raman spectroscopy, preferred orientations cause a change in the intensity distribution. Preferred orientation effects are particularly pronounced with crystalline APIs of relatively large particle size.

"Characteristic peak" refers to the presence of the powder X-ray diffraction peak definitively identifies the *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide as the referenced crystalline form (Form A). Typically, the powder X-ray diffraction analysis is conducted at ambient conditions in transmission geometry with a STOE STADI P diffractometer (Cu K α_1 radiation, primary monochromator, silicon strip detector, angular range 3 to 42 degrees two-theta, approximately 30 minutes total measurement time). The samples (approximately 10 to 50 mg) are prepared between thin polymer films and are analyzed without further processing (e. g. grinding or sieving) of the substance.

"Polymorph" refers to crystalline forms having the same chemical composition but different spatial arrangements of the molecules, atoms, and/or ions forming the crystal. In general, reference throughout this specification will be to a polymorphic form of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide. The term “polymorphic form” as used herein may or may not include other crystalline solid state molecular forms including hydrates (e.g. bound water present in the crystalline structure) of the same compound. Polymorphs typically have a different crystal structure due to a different packing of the molecules in the lattice. This results in a different crystal symmetry and/or unit cell parameters which directly influences its physical properties such as the X-ray diffraction characteristics of crystals or powder.

“Amorphous” refers to solid materials that lack the long-range order that is characteristic of a crystalline solid.

The term “solvate” refers herein to a molecular complex comprising a compound of formula (I) and a stoichiometric or non-stoichiometric amount of one or more solvent molecules (e. g., ethanol). “Hydrate” refers herein to a solvate comprising a compound of formula (I) and a stoichiometric or non-stoichiometric amount of water.

5 The terms “pharmaceutically acceptable excipient”, “pharmaceutically acceptable carrier”, and “therapeutically inert excipient” can be used interchangeably and denote any pharmaceutically acceptable ingredient in a pharmaceutical composition having no therapeutic activity and being non-toxic to the subject administered, such as disintegrators, binders, fillers, solvents, buffers, tonicity agents, stabilizers, antioxidants, surfactants, carriers, diluents or
10 lubricants used in formulating pharmaceutical products.

The term “pharmaceutical composition” encompasses a product comprising specified ingredients in pre-determined amounts or proportions, as well as any product that results, directly or indirectly, from combining specified ingredients in specified amounts. Particularly it encompasses a product comprising one or more active ingredients, and an optional carrier
15 comprising inert ingredients, as well as any product that results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients.

The terms “pharmaceutically acceptable carrier” and “pharmaceutically acceptable
20 auxiliary substance” refer to carriers and auxiliary substances such as diluents or excipients that are compatible with the other ingredients of the formulation.

“Therapeutically effective amount” means an amount that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

The term “substantially pure” when used in reference to a solid form of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide refers to said solid being > 95% pure. The solid form of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide does not contain more than 5% of any other compound, in particular does not contain more than 5% of any other solid form of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide.
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More particular, the term “substantially pure” when used in reference to a solid form of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide refers to said solid form being > 97% pure. The solid form of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide does not contain more than 3% of any other compound, in particular does not contain more than 3% of any other solid form of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide.

Even more particular, the term “substantially pure” when used in reference to a solid form of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide refers to said polymorph being > 99% pure. The solid form of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide does not contain more than 1% of any other compound, in particular does not contain more than 1% of any other solid form of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide.

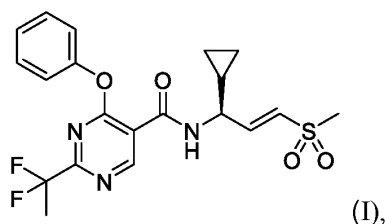
Most particular, the term “substantially pure” when used in reference to a solid form of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide refers to said polymorph being > 99.5% pure. The solid form of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide does not contain more than 1% of any other compound, in particular does not contain more than 1% of any other solid form of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes can be made and equivalents can be substituted without departing from the true spirit and scope of the invention. In addition, many modifications can be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto. All separate embodiments can be combined.

Specific numbered aspects of the invention are:

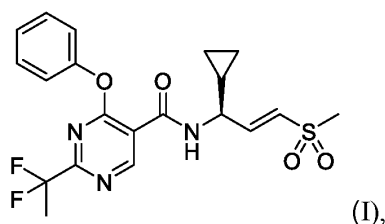
1. A solid form of a compound of formula (I)

- 7 -



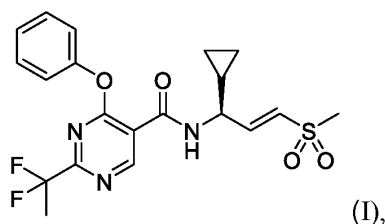
- wherein the solid form is crystalline polymorphic Form A characterized by a X-ray powder diffraction pattern comprising a peak at an angle of diffraction at about 18.31 degrees 2-theta and at least one additional peak expressed in values of degrees 2-theta at about 7.76, 19.23, 11.63, 18.58, 21.94, 17.09, 22.58, 11.16, 20.08, or 9.60.
2. A solid form according to aspect 1, characterized by an X-ray powder diffraction pattern comprising a peak at an angle of diffraction at about 18.31 degrees 2-theta and a peak at about 7.76 degrees 2-theta.
 3. A solid form according to aspect 1 or 2, characterized by an X-ray powder diffraction pattern comprising a peak at an angle of diffraction at about 18.31 degrees 2-theta and a peak at about 7.76 degrees 2-theta; wherein the pattern is further comprising at least one additional peak expressed in values of degrees 2-theta at about 19.23, 11.63, 18.58, 21.94, 17.09, 22.58, 11.16, 20.08, or 9.60.
 4. A solid form according to any one of aspects 1 to 3, characterized by an X-ray powder diffraction pattern comprising at least three of the peaks at an angle of diffraction at about 18.31, 7.76, 19.23, or 11.63 degrees 2-theta.
 5. A solid form according to any one of aspects 1 to 4, characterized by an X-ray powder diffraction pattern comprising peaks at an angle of diffraction at about 18.31, 7.76, 19.23, 11.63, 18.58, 21.94, 17.09, 22.58, 11.16, 20.08, and 9.60 degrees 2-theta.
 6. A solid form according to any one of aspects 1 to 5, which is further comprising a peak expressed in values of degrees 2-theta at about 17.94.
 7. A solid form characterized by an X-ray powder diffraction pattern according to any one of aspects 1 to 6, which is further comprising at least one additional peak expressed in values of degrees 2-theta at about 24.48, 9.60, 17.27, 20.81, 22.98, 25.68, 19.67, 18.91, 23.98, 23.37, 12.85, 13.26, 16.79, 21.37, 21.57, 9.12, 9.79, 21.09, or 25.88.

8. A solid form according to any one of aspects 1 to 7, characterized by an X-ray powder diffraction pattern as shown in Figure 1.
9. A solid form according to any one of aspects 1 to 8, characterized by having a melting point with an onset signal of about 132.0 – 134.0 °C, in particular with an onset signal at about 133 °C, using differential scanning calorimetry with a heating rate of 10 K/min.
10. A solid form according to any one of aspects 1 to 9, characterized by a differential scanning calorimetry thermogram as shown in Figure 2.
11. A solid form according to any one of aspects 1 to 9, characterized by a thermogravimetric analysis thermogram as shown in Figure 3.
12. A solid form of a compound of formula (I)



- wherein the solid form is crystalline polymorphic Form A characterized by an IR spectrum comprising at least one peak at one of the positions 1649 (± 2) cm^{-1} , 1313 (± 2) cm^{-1} , or 780 (± 2) cm^{-1} , in particular comprising at least two peaks at positions 1649 (± 2) cm^{-1} , 1313 (± 2) cm^{-1} , or 780 (± 2) cm^{-1} , more particularly comprising the peaks at positions 1649 (± 2) cm^{-1} , 1313 (± 2) cm^{-1} , and 780 (± 2) cm^{-1} .
13. A solid form according to any one of aspects 1 to 11, further characterized by an IR spectrum according to aspect 12.
14. A solid form according to any one of aspects 1 to 11, further characterized by an IR spectrum comprising a peak at the position of 1649 (± 2) cm^{-1} .
15. A solid form according to any one of aspects 1 to 14, characterized by an IR spectrum as shown in Figure 5.
16. A solid form of a compound of formula (I)

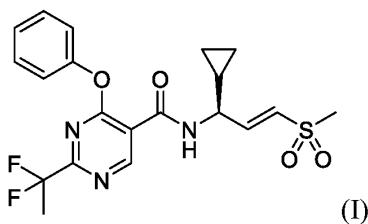
- 9 -



(I),

wherein the solid form is crystalline polymorphic Form A characterized by a Raman spectrum comprising at least one peak at one of the positions $2934 (\pm 2) \text{ cm}^{-1}$, $1648 (\pm 2) \text{ cm}^{-1}$, or $1124 (\pm 2) \text{ cm}^{-1}$, more particularly comprising the peaks at positions $2934 (\pm 2) \text{ cm}^{-1}$, and $1124 (\pm 2) \text{ cm}^{-1}$.

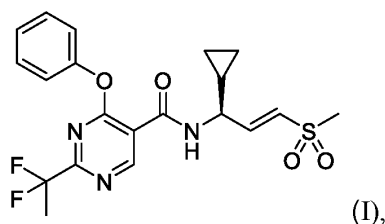
17. A solid form according to any one of aspects 1 to 15, further characterized by a Raman spectrum according to aspect 16.
18. A solid form according to any one of aspects 1 to 11, further characterized by a Raman spectrum comprising a peak at the position $1648 (\pm 2) \text{ cm}^{-1}$.
- 10 19. A solid form according to any one of aspects 1 to 18, characterized by a Raman spectrum as shown in Figure 4.
20. A substantially pure solid form according to any one of aspects 1 to 19.
21. A solid form of a compound of formula (I)



(I)

- 15 wherein the solid form is amorphous.
22. A solid form according to aspect 21, characterized by exhibiting an onset of a glass transition at a temperature of about 39.0°C to about 41.0°C , in particular of about 39.5°C to about 40.5°C , more particularly of about 40.0°C using differential scanning calorimetry with a heating rate of 10 K/min .

23. A solid form according to aspects 21 or 22, characterized by exhibiting an onset of recrystallization at a temperature of about 85 °C to about 95 °C, in particular between about 87 °C to about 93 °C, more particularly of about 90 °C using differential scanning calorimetry with a heating rate of 10 K/min.
- 5 24. A solid form according to any one of aspects 21 to 23, wherein the solid form is characterized by an IR spectrum comprising at least one peak at one of the positions 3416 (± 2) cm^{-1} or 1305 (± 2) cm^{-1} , more particular comprising the peaks at positions 3416 (± 2) cm^{-1} and 1305 (± 2) cm^{-1} .
- 10 25. A solid form according to any one of aspects 21 to 24, wherein the solid form is characterized by a Raman spectrum comprising at least one peak at one of the positions 2928 (± 2) cm^{-1} or 928 (± 2) cm^{-1} , more particular having the peaks at positions 2928 (± 2) cm^{-1} and 928 (± 2) cm^{-1} .
26. A substantially pure solid form according to any one of aspects 21 to 25.
27. A solid form of a compound of formula (I)



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wherein the solid form is crystalline polymorphic Form E characterized by the following unit cell parameters:

$a = 10.52 \text{ \AA}$;
 $b = 15.24 \text{ \AA}$;
20 $c = 13.06 \text{ \AA}$;
 $\alpha = 90 \text{ deg}$;
 $\beta = 99.30 \text{ deg}$;
 $\gamma = 90 \text{ deg}$.

- 25 28. A solid form according to aspect 27, characterized by an X-ray powder diffraction pattern comprising a peak at an angle of diffraction at about 6.75 degrees 2-theta and at least one

additional peak expressed in values of degrees 2-theta at about 10.23, 11.29, 24.20, 19.38, 17.66, 20.77, 18.28, 19.75, 21.14, or 23.71.

29. A solid form according to aspect 27 or 28, characterized by an X-ray powder diffraction pattern comprising a peak at an angle of diffraction at about 6.75 degrees 2-theta and a peak at about 10.23 degrees 2-theta.
30. A solid form according to aspect 27 to 29, characterized by an X-ray powder diffraction pattern comprising a peak at an angle of diffraction at about 6.75 degrees 2-theta and a peak at about 10.23 degrees 2-theta; wherein the pattern is further comprising at least one additional peak expressed in values of degrees 2-theta at about 11.29, 24.20, 19.38, 17.66, 20.77, 18.28, 19.75, 21.14, or 23.71.
31. A solid form according to any one of aspects 27 to 30, characterized by an X-ray powder diffraction pattern comprising at least three of the peaks at an angle of diffraction at about 6.75, 10.23, 11.29, 24.20, or 19.38 degrees 2-theta.
32. A substantially pure solid form according to any one of aspects 27 to 31.
33. A solid form according to any one of aspects 1 to 32 for use as a medicament.
34. A solid form according to any one of aspects 1 to 32 for the treatment or prophylaxis of a proliferative disease wherein the proliferative disease is cancer.
35. A solid form according to any one of aspects 1 to 32 for the treatment or prophylaxis of a cancer selected from the group consisting of colon cancer, colorectal cancer, gastric cancer, endometrium cancer, ovarian cancer, hepatobiliary tract cancer, urinary tract cancer, brain cancer, skin cancer, and MSI-H cancer.
36. A pharmaceutical composition comprising a solid form according to any one of aspects 1 to 32 and one or more pharmaceutically acceptable auxiliary substances.
37. Use of a solid form according to any one of aspects 1 to 32 for the treatment of cancer.
38. Use of a solid form according to any one of aspects 1 to 32 for the treatment of a cancer selected from the group consisting of colon cancer, colorectal cancer, gastric cancer, endometrium cancer, ovarian cancer, hepatobiliary tract cancer, urinary tract cancer, brain cancer, skin cancer, and MSI-H cancer.

39. Use of a solid form according to any one of aspects 1 to 32 for the preparation of a medicament for the treatment of cancer.
40. A method for therapeutic or prophylactic treatment of cancer, said method comprising administering an effective amount of a solid form according to any one of aspects 1 to 32 to a patient in need thereof.

In one embodiment, the crystalline polymorphic Form A of compound of formula (I) is anhydrous, i.e. free of water bound in the crystal lattice, and non-hygroscopic ($< 0.2\%$ water uptake according to European Pharmacopeia).

A certain embodiment relates to the crystalline polymorphic Form A of the compound of formula (I) as described herein, characterized by the dynamic water vapour sorption profile as shown in Figure 6.

A certain embodiment relates to the amorphous form of the compound of formula (I) as described herein, characterized by the dynamic water vapour sorption profile as shown in Figure 10.

The invention also relates to a compound according to the invention when manufactured according to a process of the invention.

Pharmaceutical compositions

The compound of formula (I) in its various solid forms can be used as therapeutically active substance, e.g. in the form of a pharmaceutical composition. The pharmaceutical composition can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatin capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compound of formula (I) can be processed with a pharmaceutically inert, inorganic or organic carriers for the production of a pharmaceutical composition. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatin capsules. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are however usually required

in the case of soft gelatin capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical composition can, moreover, contain pharmaceutically acceptable
5 auxiliary substances such as preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Pharmaceutical compositions comprising a compound of formula (I) alone or in combination, can be prepared for storage by mixing the active ingredient having the desired degree
10 of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. (ed.) (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives
15 (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as
20 glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g. Zn-protein complexes); and/or non-ionic surfactants such as TWEENTM, PLURONICSTM or polyethylene glycol (PEG).

25 Medicaments containing a solid form of the compound of formula (I) as described herein and a therapeutically inert carrier are also provided by the present invention, as is a process for their production, which comprises bringing one or more compounds of formula (I) and/or pharmaceutically acceptable solvates thereof and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically
30 inert carriers.

Pharmaceutical compositions of an inhibitor of WRN helicase include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration.

The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 200 mg to about 4000 mg per day of a compound of general formula (I) or of the corresponding amount of a pharmaceutically acceptable salt or a pharmaceutically acceptable solvate thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

The following examples illustrate the present invention without limiting it, but serve merely as representative thereof. The pharmaceutical preparations conveniently contain about 5-500 mg, particularly 100-500 mg, of a compound of formula (I). Examples of compositions according to the invention are:

Example A

Tablets of the following composition are manufactured in the usual manner:

ingredient	mg/tablet			
	5	25	100	500
1. Compound of formula (I)	5	25	100	500
2. Lactose Anhydrous DTG	125	105	30	150
3. Sta-Rx 1500	6	6	6	60
4. Microcrystalline Cellulose	30	30	30	450
5. Magnesium Stearate	1	1	1	1
Total	167	167	167	1161

Table 1: possible tablet composition

Manufacturing Procedure

1. Mix ingredients 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50 °C.
3. Pass the granules through suitable milling equipment.
4. Add ingredient 5 and mix for three minutes; compress on a suitable press.

Example B-1

Capsules of the following composition are manufactured:

ingredient	mg/capsule			
	5	25	100	500
1. Compound of formula (I)	5	25	100	500
2. Hydrous Lactose	159	123	148	-
3. Corn Starch	25	35	40	70
4. Talc	10	15	10	25
5. Magnesium Stearate	1	2	2	5
Total	200	200	300	600

Table 2: possible capsule ingredient composition

Manufacturing Procedure

1. Mix ingredients 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add ingredients 4 and 5 and mix for 3 minutes.
- 5 3. Fill into a suitable capsule.

The compound of formula (I), lactose and corn starch are firstly mixed in a mixer and then in a comminuting machine. The mixture is returned to the mixer; the talc is added thereto and mixed thoroughly. The mixture is filled by machine into suitable capsules, e.g. hard gelatin capsules.

10 Example B-2

Soft gelatin capsules of the following composition are manufactured:

ingredient	mg/capsule
Compound of formula (I)	5
Yellow wax	8
Hydrogenated Soya bean oil	8
Partially hydrogenated plant oils	34
Soya bean oil	110
Total	165

Table 3: possible soft gelatin capsule ingredient composition

ingredient	mg/capsule
Gelatin	75
Glycerol 85 %	32
Karion 83	8 (dry matter)
Titan dioxide	0.4
Iron oxide yellow	1.1
Total	116.5

Table 4: possible soft gelatin capsule composition

Manufacturing Procedure

The compound of formula (I) is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

Example C

Suppositories of the following composition are manufactured:

ingredient	mg/suppository
Compound of formula (I)	15
Suppository mass	1285
Total	1300

Table 5: possible suppository composition

Manufacturing Procedure

The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45 °C. Thereupon, the finely powdered compound of formula (I) is added thereto and stirred until it has dispersed completely. The mixture is poured into suppository moulds of suitable size, left to cool; the suppositories are then removed from the moulds and packed individually in wax paper or metal foil.

15 Example D

Injection solutions of the following composition are manufactured:

ingredient	mg/injection solution
Compound of formula (I)	3
Polyethylene Glycol 400	150
Acetic acid	q.s. ad pH 5.0
Water for injection solutions	ad 1.0 ml

Table 6: possible injection solution composition

Manufacturing Procedure

The compound of formula (I) is dissolved in a mixture of Polyethylene Glycol 400 and water for injection (part). The pH is adjusted to 5.0 by acetic acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Example E

Sachets of the following composition are manufactured:

ingredient	mg/sachet
Compound of formula (I)	50
Lactose, fine powder	1015
Microcrystalline cellulose (AVICEL PH 102)	1400
Sodium carboxymethyl cellulose	14
Polyvinylpyrrolidone K 30	10
Magnesium stearate	10
Flavoring additives	1
Total	2500

Table 7: possible sachet composition

10 *Manufacturing Procedure*

The compound of formula (I) is mixed with lactose, microcrystalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidone in water. The granulate is mixed with magnesium stearate and the flavoring additives and filled into sachets.

Brief description of the drawings

Figure 1 illustrates a X-ray powder diffraction pattern of the polymorphic Form A of *N*-[(1S,2E)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide.

Figure 2 is a thermogram of the polymorphic Form A of *N*-[(1S,2E)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide obtained by differential scanning calorimetry (DSC). A sharp melting signal was observed (onset 133 °C, peak 135 °C, enthalpy -72 J/g).

Figure 3 is a thermogram of the polymorphic Form A of *N*-[(1S,2E)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide obtained by thermogravimetric analysis (TGA). No significant mass loss was observed.

Figure 4 is a Raman spectrum of the polymorphic Form A of *N*-[(1S,2E)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide.

Figure 5 is a IR spectrum of the polymorphic Form A of *N*-[(1S,2E)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide.

Figure 6 is a water vapour sorption/desorption curve of the polymorphic Form A of *N*-[(1S,2E)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide obtained by dynamic vapour sorption (DVS). Masschange is < 0.1% from 0% - 90% RH ; Polymorphic Form A is not hygroscopic, no solid form change during the cycles.

Figure 7 illustrates a X-ray powder diffraction pattern of Form Amorphous of *N*-[(1S,2E)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide.

Figure 8 is a thermogram of Form Amorphous *N*-[(1S,2E)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxypyrimidine-5-carboxamide obtained by differential scanning calorimetry (DSC). The observed thermal events are glass transition (onset 40 °C, change of specific heat capacity 0.242 J/gK), recrystallization (onset 90 °C, Peak 99 °C, enthalpy 46 J/g) and melting (onset 130 °C).

Figure 9 is a thermogram of Form Amorphous of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide obtained by thermogravimetric analysis (TGA). A mass loss of 0.3% w/w was observed.

Figure 10 is a water vapour sorption/desorption curve of Form Amorphous of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide obtained by dynamic vapour sorption (DVS). Mass change is 2.2% from 0% - 90% RH; Form Amorphous is slightly hygroscopic at 80% RH (1.8% w/w) and hygroscopic at 90% RH (2.2% w/w).

Figure 11 is a Raman spectrum of Form Amorphous of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide.

Figure 12 is an IR spectrum of Form Amorphous of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide.

Figure 13 is the result of a simulated X-ray powder diffraction pattern of Form E based on the X-ray single crystal diffraction measurement of the polymorphic Form E of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide.

Experimental part

The following experiments are provided for illustration of the invention. They should not be considered as limiting the scope of the invention, but merely as being representative thereof.

Abbreviations:

ATR = attenuated total reflection; DSC = differential scanning calorimetry; DVS = dynamic vapour sorption; FT = fourier transform; FTIR = fourier-transform infrared; h = hour(s); HPLC = High Performance Liquid Chromatography; IR = infrared; LC-MS/MS = liquid chromatography-MS/MS; MS = mass spectrometry; NMM = N-Methylmorpholine; RH = relative humidity; rt = room temperature; TGA = thermogravimetry.

High Resolution X-Ray Powder Diffraction

X-ray powder diffraction patterns are recorded at ambient conditions in transmission geometry with a STOE STADI P diffractometer (Cu K α radiation, primary Ge-monochromator,

Mythen 1K silicon strip detector, angular range 3° to 42° 2Theta, 0.02° 2Theta step size, 20 seconds measurement time per step). The samples are prepared and analyzed without further processing (e.g. grinding or sieving) of the substance.

For polymorphic Form A the following peaks have been found by XRPD (expressed in values of degrees 2-theta) at approximately: 6.16, 7.76, 9.12, 9.60, 9.79, 11.16, 11.63, 12.35, 12.85, 13.26, 14.76, 15.76, 16.44, 16.79, 17.09, 17.27, 17.94, 18.31, 18.58, 18.91, 19.23, 19.42, 19.67, 20.08, 20.81, 21.09, 21.37, 21.57, 21.94, 22.58, 22.98, 23.37, 23.98, 24.48, 24.85, 25.43, 25.68, 25.88, and 26.24.

X-Ray Single Crystal Diffraction

X-ray single crystal diffraction is employed to measure and elucidation of the crystals structure of crystalline forms. A single crystal was mounted in a loop and measured at ambient temperature conditions. Data are collected on a XtaLAB Synergy-i diffractometer (Rigaku) with Cu-radiation ($1.54184 \text{ \AA}$). Data are processed with the Oxford Diffraction CRYSTALIS-software. The crystal structure is solved and refined with the software ShelXTL (Bruker AXS, Karlsruhe).

Form E has been characterized by single crystal X-ray diffraction. Polymorphic Form E is characterized by the following unit cell parameters found through single crystal structural data of polymorphic Form E:

$a = 10.52 \text{ \AA}$;
 $b = 15.24 \text{ \AA}$;
 $c = 13.06 \text{ \AA}$;
 $\alpha = 90 \text{ deg}$;
 $\beta = 99.30 \text{ deg}$;
 $\gamma = 90 \text{ deg}$.

The simulated peak list (rel. intensities $< 2\%$ omitted for clarity) of the polymorphic Form E based on single crystal data (expressed in values of degrees-2-theta) are identified as approximately: 6.75, 8.80, 10.23, 11.29, 13.17, 15.12, 15.87, 17.10, 17.38, 17.66, 18.02, 18.28, 18.29, 19.38, 19.75, 20.11, 20.20, 20.54, 20.56, 20.66, 20.77, 20.90, 21.14, 21.57, 21.77, 22.61, 23.33, 23.71, 24.19, 24.20, 24.29, 24.39, 24.51, 25.17, 25.60, 25.87, 25.99, 26.52, 26.62, 27.22, 27.25, 28.57, 29.14, 29.30, 29.78, 30.02, 30.67, 30.88, 32.28, 33.42, 35.75, 35.91, 36.38, and 36.84.

Differential Scanning Calorimetry (DSC)

DSC curves were recorded using a Mettler-Toledo™ differential scanning calorimeter DSC2. System suitability tests were performed with Indium as reference substance and calibrations were carried out using Indium, Benzoic acid, Biphenyl and Zinc as reference
5 substances.

For the measurements, approximately 2 to 6 mg of sample were placed in aluminum pans, accurately weighed and hermetically closed. Prior to measurement, the lids were pierced resulting in approx. 0.5 mm pin holes. The samples were then heated under a flow of nitrogen of about 100 mL/min using heating rate of 10 K/min to a maximum temperature of typically
10 180 °C to 350 °C depending on decomposition temperature.

Thermogravimetry (TGA)

Thermogravimetric analyses (TGA) were performed on a Mettler-Toledo™ thermogravimetric analyzer (TGA/DSC1 or TGA/DSC3+). System suitability tests were performed with Hydranal as reference substance and calibrations using Aluminum and Indium
15 as reference substances.

For the thermogravimetric analyses, approx. 5 to 15 mg of sample were placed in aluminum pans, accurately weighed and hermetically closed. Prior to measurement, the lids were automatically pierced resulting in approx. 0.5 mm pin holes. The samples were then heated under a flow of nitrogen of about 50 mL/min using a heating rate of 5 K/min to a maximum
20 temperature of typically 350 °C.

Moisture Sorption / Desorption

Moisture sorption/desorption data was collected on a DVS Advantage, a DVS Adventure, or a DVS Intrinsic (SMS Surface Measurements Systems) moisture balance system. The sorption/desorption isotherms were measured stepwise in a range from 0 %-RH to 90 %-RH at
25 typically 25 °C. A weight change of typically <0.001 %/min was chosen as criterion to switch to the next level of relative humidity (with a maximum equilibration time of typically 24 hours, if the weight change criterion was not met). The data were corrected for the initial moisture content of the samples by taking the weight after drying of the samples at 0 %-RH as zero point.

The hygroscopicity of a given substance was characterized (by close analogy with the European Pharmacopoeia) by the increase in mass when the relative humidity was raised from 0 %-RH to 90 %-RH:

- non-hygroscopic: weight increase $Dm < 0.2\%$
 5 slightly hygroscopic: weight increase $0.2\% \leq Dm < 2.0\%$
 hygroscopic: weight increase $2.0\% \leq Dm < 15.0\%$
 very hygroscopic: weight increase $Dm \geq 15.0\%$
 deliquescent: sufficient liquid is adsorbed to form a liquid

European Pharmacopoeia – 8th Edition (2014), Chapter 5.11.

10

IR Spectroscopy

- The ATR FTIR spectra were recorded without any sample preparation using a Thermo Nicolet iS5 FTIR spectrometer with ATR accessory. The spectral range is between 4000 cm^{-1} and 650 cm^{-1} , resolution 4 cm^{-1} and 32 co-added scans were collected. Happ-Genzel apodization was
 15 applied. Using ATR FTIR will cause the relative intensities of infrared bands to differ from those seen in a transmission FTIR spectrum using KBr disc or nujol mull sample preparations. Due to the nature of ATR FTIR, the bands at lower wavenumber are more intense than those at higher wavenumber.

- Peakpicking was performed using Thermo Scientific Omnic 8.3 software using the automated
 20 'Find Peaks' function. The 'threshold' and 'sensitivity' were manually adjusted to get a representative number of peaks.

675	833	1050	1222	1425	1649
694	903	1068	1267	1457	2933
715	914	1096	1300	1488	3008
728	935	1133	1313	1506	3056
761	967	1156	1335	1520	3339
780	982	1168	1383	1553	
812	1023	1185	1402	1582	

Table 8: list of peaks identified by infrared spectroscopy of polymorphic Form A (in cm^{-1}).

692	905	1071	1272	1489	2927
722	932	1130	1305	1521	3009

760	969	1159	1402	1553	3056
812	1024	1168	1425	1582	3371
831	1054	1187	1458	1658	3416

Table 9: list of peaks identified by infrared spectroscopy of Form Amorphous (in cm^{-1}).

Raman Spectroscopy

The FT-Raman spectrum was collected in the spectral range of $4000\text{--}50\text{ cm}^{-1}$ with a Bruker
 5 MultiRam FT-Raman spectrometer, equipped with a NdYAG 1064 nm laser and a liquid nitrogen cooled Germanium detector. The laser power was set to 300mW, 4 cm^{-1} resolution was used and 1024 scans (Form A) and 512 scans (Form Amorphous) were co-added. The apodization used was Blackman-Harris 4-term.

Peakpicking was performed using Thermo Scientific Omnic 8.3 software using the
 10 automated 'Find Peaks' function. The 'threshold' and 'sensitivity' were manually adjusted to get a representative number of peaks.

59	593	889	1158	1460
170	615	905	1194	1521
251	681	921	1222	1584
306	700	937	1270	1648
413	723	984	1317	2934
495	745	1007	1381	2948
511	762	1025	1412	3009
561	835	1124	1435	3071

Table 10: list of peaks identified by Raman spectroscopy of polymorphic Form A (in cm^{-1}).

61	616	981	1282	1584
168	637	1006	1319	1640
249	722	1025	1384	1662
304	760	1130	1411	2928
414	834	1159	1434	2949
510	906	1194	1461	3012
591	928	1219	1524	3073

Table 11: list of peaks identified by Raman spectroscopy of Form Amorphous (in cm^{-1}).

Synthesis and Crystallization Protocol

Procedure A: *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxamide was prepared according to the reaction sequence below:

5

Step 1: 2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxylic acid

Ethyl 2-(1,1-difluoroethyl)-4-hydroxy-pyrimidine-5-carboxylate (56.4 kg, 243 mol, 1.00 eq.), toluene (167 L) and acetonitrile (59 kg) were combined in a reaction vessel 1. *N,N*-dimethylformamide (530 g, 7.28 mol, 0.30 eq.) in acetonitrile (1.0 kg) was added, the flask
10 rinsed with acetonitrile (3.0 kg). The reaction mixture was heated to 30 °C and oxalyl chloride (34.5 kg, 97.4 mol) added over 45 minutes. The dosing equipment was rinsed with acetonitrile (24.0 kg). The reaction mixture was stirred at 30 °C until complete conversion, then cooled to 15 °C and a 12 % aqueous solution of potassium dihydrogen phosphate (243 kg) over 45 minutes and water (65 kg) was added over 30 minutes. Toluene (210 L) was added and the aqueous layer
15 separated. Water (280 kg) was added to the organic layer and the aqueous layer was separated. The organic layer was concentrated below 50 °C and a solvent exchange was performed with acetonitrile to a volume of 225 L.

In a second reaction vessel 2, potassium carbonate 325 mesh (44.3 kg, 321 mol, 1.32 eq.) and acetonitrile (86 kg) were combined, and phenol (24.2 kg, 257 mol, 1.06 eq.) in acetonitrile
20 (43 kg) was added at 15 – 30 °C, the addition vessel rinsed with acetonitrile (31 kg).

The content of the reaction vessel 1 was added onto the content of the reaction vessel 2 at 30 °C within 20 minutes, the vessel 1 rinsed with acetonitrile (110 kg). The reaction mixture was stirred at 30 °C until complete conversion, then an aqueous solution of sodium hydroxide 5.5 % (391 kg) was added within 10 minutes and water (60 kg) was added over 90 minutes. The
25 reaction mixture was concentrated below 50 °C to a volume of 440 L. Water (120 kg) was added, the mixture cooled to 15 °C and a 8 % aqueous solution of hydrochloric acid (~430 kg) added within 120 minutes to achieve pH = 1 – 1.5. The suspension was stirred at 15 °C and then filtered, the wet cake rinsed with water (total 420 kg). The product was dried under vacuum at 55 °C to yield 2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxylic acid (61.1 kg) as a
30 white solid.

Step 2: *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxamide

The preparation of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxamide from the reaction of 2-(1,1-difluoroethyl)-4-phenoxy-pyrimidine-5-carboxylic acid with (E,1*S*)-1-cyclopropyl-3-methylsulfonyl-prop-2-en-1-amine; 4-methylbenzenesulfonic acid can be performed as described below:

In a 200 mL reactor, 5.00 g (17.8 mmol) of acid were suspended at room temperature in 40 mL of ethyl acetate. 2.15 g (17.8 mmol) of pivaloyl chloride were added. The vessel was rinsed with 2.5 mL ethyl acetate. The mixture was cooled to 0-5 °C and 1.80 g (17.8 mmol) of NMM (N-Methylmorpholine) were added over 15 minutes. The vessel and the pipe were rinsed with 2.5 mL ethyl acetate. The resulting white suspension was stirred for 3 h at 0-5 °C.

In a 100 mL reactor, 6.20 g (17.8 mmol) of Tosylate ((E,1*S*)-1-cyclopropyl-3-methylsulfonyl-prop-2-en-1-amine; 4-methylbenzenesulfonic acid) were suspended in 30 mL of ethyl acetate at room temperature. The Tosylate ((E,1*S*)-1-cyclopropyl-3-methylsulfonyl-prop-2-en-1-amine; 4-methylbenzenesulfonic acid) suspension was transferred to the mixed anhydride suspension and the reactor and transfer line were rinsed with 2x10 mL of ethyl acetate. 3.61 g (35.7 mmol) of NMM were added over 20 minutes. The reaction mixture was stirred for 3 h at approx. 0-5 °C. The reaction mixture was quenched with water. The lower aqueous layer was separated. Water was added to the organic layer and the pH was adjusted between pH 7-8 with a sodium hydroxide (5.6%) solution. The lower aqueous layer was separated. The org. layer was washed with water. The pH was adjusted with a 4% citric acid solution to pH 2-3 after separating the layers the organic layer was washed with water.

The organic layer was concentrated to approx. 50 mL under reduced pressure at 50 °C. When the residual volume was reached, 80 g ethyl acetate were added. The organic layer was concentrated again to approx. 50 mL under reduced pressure at 50 °C. After reaching the level, 50 mL of n-heptane were added to the solution leading to the starting of crystallization at 60 °C. The crystal growing was kept for 30 minutes before proceeding slow dosage of 80 g of n-heptane and a cooling ramp to 20 °C within 4-6 h. The product was isolated by filtration at 20 °C and washed with 2x 20 g ethyl acetate/n-heptane (1:4 V/V). The crystals were dried for 28 h at 50 °C in a vacuum drying oven, whereby the amide 3 (6.62 g, 15.7 mmol, 85% yield) was obtained as white crystals. HPLC purity: 99.8% (254 nm).

Form Amorphous: General procedure for preparation of Form Amorphous by cooling from melt

- 5 A glass vial closed with a screw cap fitted with a septum was charged with 300 mg of *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide and inserted into an aluminium block placed on a heating plate. The aluminium block, fitted with a temperature sensor, was heated to 155 °C. After 10 minutes at 155 °C, the resulting melt was cooled by submerging the vial into liquid nitrogen for 3 minutes.
- 10 A glassy material was obtained and analyzed without further processing after gentle crushing with mortar and pestle.

During the entire preparation process, a slight flow of nitrogen was introduced via a needle inserted into the septum, which was itself equipped with a second needle to allow the gas flow to be evacuated.

15

Form A: General procedure for preparation of polymorphic Form A using slurry equilibration

- 100 mg of amorphous material was suspended in a closed vial, at 22 °C, in 2.0 mL of water and allowed to agitate at 22 °C. After 7 days equilibration at 22 °C, the slurry was filtered and Form A obtained in the wet stage. After drying at 50 °C under reduced pressure overnight
- 20 Form A remains unchanged.

Recrystallization to achieve polymorphic Form A in high quality:

- N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide (37.9 kg) and ethylacetate (266 L) were combined in a reaction vessel 1. The mixture was stirred till complete dissolution and filtered to a second
- 25 reaction vessel 2, the vessel 1 was rinsed with ethylacetate (67 L). The solution was concentrated below 50 °C under vacuum and a solvent exchange was performed with isopropanol to a volume of approx. 225 L. Isopropanol (446 kg) was added to the suspension and the mixture was heated to 65 °C till a clear solution was obtained, the solution cooled to 53 °C, seeded with polymorphic Form A, the suspension cooled to 45 °C within 4 hours, then cooled down to 20 °C
- 30 within 4 hours and stirred at 20 °C. The suspension was filtered, the wet cake rinsed with

isopropanol (total 104 kg). The product was dried under vacuum at 50 °C to yield *N*-[(1*S*,2*E*)-1-cyclopropyl-3-(methanesulfonyl)prop-2-en-1-yl]-2-(1,1-difluoroethyl)-4-phenoxy pyrimidine-5-carboxamide, recrystallized (32.7 kg) as a white solid.

- 5 **Form E:** General procedure for preparation of polymorphic Form E using evaporation crystallization

A glass vial was charged with 2.3 mg of polymorphic Form A and 200 µL of ethanol and then closed with a crimped lid.

- After vortexing for 10 seconds the sample remained mostly undissolved. The closed vial was
10 prepared with an injection needle of 0.8mm diameter and placed in a Thermoblock at 30 °C for regular evaporation.

The experiment led to single crystals of Form E suitable for single crystal structure analysis.

Procedure B: (E,1*S*)-1-cyclopropyl-3-methylsulfonyl-prop-2-en-1-amine;4-methylbenzenesulfonic acid was prepared according to the reaction sequence illustrated below.

- 15 Steps 1 and 2: methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-2-cyclopropyl-acetate

- A reaction vessel was charged with methanol (216 kg) and 2-cyclopropyl-L-glycine (109.1 kg, 948 mol, 1.00 eq.) at room temperature. The reactor was rinsed with additional methanol (216 kg). The inner temperature was adjusted to -10 to 5 °C. Then thionyl chloride (141.2 kg, 1187 mol, 1.25 eq) was charged into the reactor while keeping the inner temperature at -5 to 5 °C. After
20 the addition the inner temperature was raised to 15 to 25 °C and the reaction mixture was stirred for 15 hours at 15 to 25 °C. After completion of the reaction the mixture was concentrated at a temperature below 30 °C under vacuum. Then the inner temperature was adjusted to 15 to 25 °C before water (236 kg), triethylamine (99.8 kg, 986 mol, 1.04 eq.), sodium hydrogencarbonate (124 kg, 1476 mol, 1.5 eq.) followed by water (470 kg) was added to the mixture, while maintaining
25 the inner temperature at 15 to 25 °C. Then the inner temperature was lowered to -5 to 5 °C.

To a second tank tetrahydrofuran (106 kg) and di-*tert*-butyl dicarbonate (203.2 kg, 912 mol, 0.97 eq.) was added and mixed.

The di-*tert*-butyl dicarbonate solution in tetrahydrofuran was dosed slowly for 6 hours into the reactor while maintaining the inner temperature at -5 to 5 °C. After the addition the inner

temperature was adjusted 15 to 25 °C and the mixture was stirred for 15 hours. The reaction mixture was concentrated under vacuum to 975 to 1195 L at a temperature below 40 °C.

Then tetrahydrofuran (300 kg) was added into the reactor and the mixture was stirred for 1 hour, while the temperature was maintained at 15 to 25 °C. The obtained mixture was filtered, the filter was rinsed with tetrahydrofuran (89 kg) and the clear solution was transferred back into the reactor. The filter and piping were rinsed additionally with tetrahydrofuran (50 kg). Afterwards the aqueous layer was separated.

The organic layer was extracted with aqueous 25% sodium chloride solution (244 kg). After phase separation the organics were concentrated under vacuum at a temperature below 40 °C to a volume of 216 to 432 L. Then tetrahydrofuran (200 kg) was added into the reactor and the mixture was concentrated under vacuum at a temperature below 40 °C to a volume of 216 to 432 L. The addition and concentration procedure was repeated twice before the inner temperature in the reactor was adjusted to 15 to 25 °C to yield 470 kg of methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-2-cyclopropyl-acetate as a solution in tetrahydrofuran (assay 42.5 (w/w%)).

Step 3: *tert*-butyl *N*-[(1*S*)-1-cyclopropyl-2-hydroxy-ethyl]carbamate

In a 3000 L glass line reactor tetrahydrofuran (894 kg, Karl Fischer 0.01%) was added. The inner temperature was adjusted to -10 to 0 °C, followed by the addition of a 2.5 M solution of Lithium aluminum hydride in tetrahydrofuran (423.4 kg, 217 mol, 1.30 eq.), while maintaining the inner temperature at -10 to 0 °C. After the addition, the line was rinsed with tetrahydrofuran (34 kg) and the reaction mixture was stirred for 2.5 hours at -10 to 0 °C. The solution of methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-2-cyclopropyl-acetate in tetrahydrofuran (199.1 kg, 868 mol, 1.00 eq) was slowly added to the reactor for 11 hour while maintaining the inner temperature at -10 to 0 °C. After the addition, the feeding pipe was rinsed with tetrahydrofuran (190 kg) and the mixture was stirred for 10 hours at 15 to 25 °C.

After completion of the reaction the inner temperature was adjusted to 10 to 20 °C and the mixture was quenched with Na₂SO₄•10 H₂O (503 kg, 1561 mol, 1.80 eq) at 10 to 20 °C for 21 hours. The resulting slurry was filtered through a centrifuge and the filter cake has been washed with 5 portions tetrahydrofuran (in total 529 kg). The washed filter cake was transferred into the reactor. Then tetrahydrofuran (896 kg) was added into the reactor at inner temperature of 10 to 20°C. The slurry was stirred at 15 to 25 °C for 3 hours. The slurry was filtered again via

centrifuge and the filter cake was washed with 5 portions tetrahydrofuran (in total 529 kg). The filtrates were combined in a reactor and concentrated under vacuum at a temperature below 40 °C to appr. 200 kg. The concentrated product was diluted with dichloromethane (538 kg) and the mixture was concentrated under vacuum at inner temperature below 40 °C. This process of
5 dilution with dichloromethane and concentration under vacuum was repeated additional two times. The concentrated product in the reactor was diluted with dichloromethane (528 kg) to yield 721.4 kg of *tert*-butyl *N*-[(1*S*)-1-cyclopropyl-2-hydroxy-ethyl]carbamate as a solution in dichloromethane (assay 24.1 (w/w%)).

Step 4: *tert*-butyl *N*-[(1*S*)-1-cyclopropyl-2-oxo-ethyl]carbamate

10 **Preparation of starting material solution:**

In a reactor with the solution of *tert*-butyl *N*-[(1*S*)-1-cyclopropyl-2-hydroxy-ethyl]carbamate (86 kg, 427 mol, 1.00 eq., in 275 kg dichloromethane) was added dichloromethane (304 kg) followed by the addition of dimethyl sulfoxide (102 kg, 1306 mol, 3.00 eq.). The mixture was stirred for 0.5 h at 20 to 30 °C inner temperature until a clear solution was observed. The solution was filtered
15 into a storage tank under nitrogen.

Preparation of diisopropylethylamin solution

After the reactor was emptied, dichloromethane (574 kg) was charged, followed by the charging of diisopropylethylamine (222 kg, 1718 mol, 4.00 eq.). This mixture was stirred for 0.5 hours at 20 to 30 °C inner temperature until a clear solution was observed. The amine base solution in
20 dichloromethane was transferred under filtration into storage tank under nitrogen.

Preparation of citric acid solution

The empty reactor was charged with citric acid monohydrate (188.6 kg, 898 mol, 2.00 eq), followed by the addition of water (738 kg). The mixture was stirred for 0.5 h at 20 to 30 °C inner temperature until a clear solution was observed. The aqueous citric acid solution was filtered into
25 a storage tank under nitrogen.

Preparation of oxalyl chlorid solution

A reactor was charged with dichloromethane (620 kg), followed by the addition of oxalyl chloride (84 kg, 662 mol, 1.55 eq). The mixture was stirred for 0.5 hours at 20 to 30 °C inner

temperature until a clear solution was observed. The oxalyl chloride solution was filtered into a storage tank under nitrogen.

Work up (batch operation)

The obtained product solution in dichloromethane was transferred to a reactor.

- 5 The pH of the aqueous layer was adjusted with 20% aqueous citric acid solution at inner temperature -5 to 5 °C to pH 3.0 to 4.0, followed by phase separation and removal of the aqueous layer. Water (443 kg) was charged to the reactor and the pH adjusted with a 7% aqueous sodium hydrogen carbonate solution (70 kg) at 0 to 10 °C. After stirring, phases were separated and the aqueous layer was removed. Water (615 kg) was charged to the reactor,
- 10 followed by the addition of a 25% aqueous sodium chloride solution (258 kg) at 0 to 10 °C. After stirring, the phases were separated and the aqueous layer was removed. The product solution was concentrated under vacuum at inner temperature below 20 °C. The reactor and piping was rinsed with dichloromethane (87 kg) and 520 kg of *tert*-butyl *N*-[(1*S*)-1-cyclopropyl-2-oxo-ethyl]carbamate as a solution in dichloromethane was obtained (assay 13.4%)

15 Steps 5 & 6: *tert*-butyl *N*-[(*E*,1*S*)-1-cyclopropyl-3-methylsulfonyl-allyl]carbamate

- To a stainless steel tank charged with dichloromethane (110 kg), diethyl-(methylsulfonyl)methyl phosphonate (54.9 kg, 238 mol, 1.00 eq.) was added at 20 to 30°C inner temperature under stirring, followed by rinsing the tank and piping with dichloromethane (72 kg). The mixture was stirred at 20 to 30°C (inner temperature) for 1 hour. The solution was filtered
- 20 into a reactor and the filter and piping was rinsed with dichloromethane (42 kg). Potassium carbonate (70.7 kg, 512 mol, 2.15 eq) was added to the solution at 20 to 30 °C inner temperature, followed by rinsing with dichloromethane (44 kg). To this mixture the solution of *tert*-butyl *N*-[(1*S*)-1-cyclopropyl-2-oxo-ethyl]carbamate in dichloromethane (70.2 kg, 352 mol, 1.48 eq.) was added at 20 to 30°C. The reaction mixture was stirred for 7.5 hours, while maintaining the inner
- 25 temperature at 20 to 30°C.

- The inner temperature was adjusted to 10 to 20 °C and the organic solution was extracted with water (274 kg), followed by extraction with 3% aqueous hydrogen peroxide solution (276 kg) at 10 to 20 °C. Afterwards the organic layer was extracted with aqueous sodium sulfite solution (43.9 kg sodium sulfite in 248 kg water), followed by extraction with 15% aqueous sodium
- 30 chloride solution (188 kg).

The organic layers of two batches (2 x 54.9 kg = 109.8 kg, 476 mol) were combined for further work-up and isolation in a reactor. The obtained solution of product in dichloromethane was concentrated to dryness and diluted with iso-propanol (308 kg). The mixture was concentrated and diluted with iso-propanol (308 kg) two times in repetition.

5 To this mixture iso-propanol (44 kg) was added. The inner temperature was increased to 45 to 55 °C and the mixture was stirred for 1 hour at this temperature. Then the temperature of the solution was adjusted to 25 to 35 °C and seed crystals (1 kg) were added. The mixture was stirred for 1 hour at 25 to 35 °C, before n-heptane (300 kg) was dosed into the reactor over 5 hours. The temperature was lowered to -5 to 5 °C over 6 hours and the slurry was stirred for 6 hours at -5 to
10 5 °C. The slurry was filtered and washed with a mixture of iso-propanol and n-heptane (1:8, 165kg).

The wet filter cake was charged back into the reactor filled with tetrahydrofuran (62 kg). The reactor and piping was rinsed with tetrahydrofuran (44 kg). The mixture was stirred at 15 to 25 °C for 1 hour and n-heptane (52 kg) was charged over 1 hour. Seed crystals (1 kg) were charged
15 to the reactor, followed by dosing of n-heptane (52 kg) over 5 hours. The obtained slurry was filtered and washed with a mixture of tetrahydrofuran and n-heptane (1:4, 161 kg).

The wet solid was dried under vacuum at a temperature below 45 °C for not less than 24 hours to yield 76.75 kg of *tert*-butyl *N*-[(*E*,1*S*)-1-cyclopropyl-3-methylsulfonyl-allyl]carbamate.

Step 7: (*E*,1*S*)-1-cyclopropyl-3-methylsulfonyl-prop-2-en-1-amine;4-methylbenzenesulfonic
20 acid

To a stainless steel tank charged with acetonitrile (160 kg), *tert*-butyl *N*-[(*E*,1*S*)-1-cyclopropyl-3-methylsulfonyl-allyl]carbamate (66.9 kg, 243 mol, 1.00eq.) was added at 20 to 30 °C inner temperature under stirring, followed by rinsing the tank and piping with acetonitrile (27 kg). The mixture was stirred at 20 to 30 °C for 2 hours. The solution was filtered into a reactor,
25 the filter and piping was rinsed with acetonitrile (28 kg) and the inner temperature was adjusted to 20 to 30 °C. P-toluene sulfonic acid (pTSA x H₂O, 56.4 kg, 297 mol, 1.2 eq) was added to the solution at 20 – 30 °C inner temperature over a period of 3 hours, followed by addition of seed crystals (2.67 kg). The charging pipe was rinsed with acetonitrile (55.5 kg) into the reactor. The reaction mixture was heated to 50-60 °C (inner temperature) and stirred for 16 hours, while
30 maintaining the temperature at 50 to 60 °C. After the reaction, the mixture was cooled to 15 to

25 °C (inner temperature) and stirred for 3.5 hours at this temperature. The obtained slurry was filtered and washed with acetonitrile (260kg).

The wet solid was dried under vacuum at a product temperature of 40 to 45 °C for 20 hours to yield 68.1 kg (*E,1S*)-1-cyclopropyl-3-methylsulfonyl-prop-2-en-1-amine; 4-methylbenzenesulfonic acid as a white solid.

Procedure C: Ethyl 2-(1,1-difluoroethyl)-4-hydroxy-pyrimidine-5-carboxylate was prepared according to the reaction sequence below:.

Step 1: 2,2-difluoropropanamide

A reaction vessel was charged with n-heptane (280 kg) and 2,2-difluoropropionic acid ethyl ester (77.2 kg, 559 mol, 1.00 eq.) at room temperature. The pipe was rinsed with n-heptane (16 kg) into the reactor. The inner temperature was adjusted to -5 to 5 °C. Ammonia gas (17.0 kg, 998 mol, 1.75 eq.) was charged to the reactor over 14 hours while keeping the inner temperature at -5 to 5 °C. After the addition the reaction mixture was stirred for 16 hours at -5 to 5 °C, while the product began to precipitate from the reaction mixture. The temperature was adjusted to 15 to 25 °C (inner temperature) and the mixture was stirred for 1 hour at this temperature. After completion of the reaction, the mixture was concentrated at a temperature below 28 °C under vacuum to 3 to 4 volumes.

Then the inner temperature was adjusted to -15 to -5 °C and the mixture was cooled over 5 hours. The slurry was stirred for additional 8 hours at this temperature, before being filtered over a stainless steel centrifuge. The filtered product cake was washed with two portions of n-heptane (total amount 37 kg), before the product was transferred into single cone dryer. The product was dried at 30 to 40 °C (jacket temperature) for a total of 13 hours under nitrogen purging. After completion of drying 57.4 kg 2,2-difluoropropanamide were obtained.

Step 2: 2,2-Difluoropropanamidine

A reactor was charged with dichloromethane (188 kg) and 2,2-difluoropropionic amide (27.0 kg, 248 mol, 1.00 eq.) at room temperature. The pipe was rinsed with dichloromethane (10 kg) into the reactor. The inner temperature was set to 15 to 25 °C. Trimethyloxonium tetrafluoroborate (36.8 kg, 248 mol, 1.00 eq.) was charged to the reactor and the pipe was rinsed with dichloromethane (46 kg) into the reactor. After the addition the reaction mixture was stirred for 18 hours at 15 to 25 °C. The temperature was adjusted to -45 to -35 °C (inner temperature) and

ammonia gas (11.8 kg, 693 mol, 2.8 eq.) was charged into the reactor over 8 hours at internal temperature of -45 to -35 °C. After addition the mixture was stirred for 1 hour at this temperature and the inner temperature was then increased to 15 to 25 °C. The reaction mixture was stirred for further 16 hours at 15 to 25 °C inner temperature.

- 5 After completion of the reaction, the mixture was filtrated through a centrifuge to separate the product solution from the solids. The wet cake was washed with dichloromethane (40 kg) and the organic solution was transferred back into the reactor. The product solution was concentrated under vacuum at a temperature below 20 °C to 1 to 2 volumes. Dichloromethane (34 kg) was charged into the reactor and the product solution was concentrated again under vacuum at a temperature below 20 °C to 1 to 2 volumes. The transfer pipe was rinsed with dichloromethane (6 kg) into the reactor and 64.4 kg of 2,2-difluoropropanamidine in dichloromethane was obtained.

Step 3: Ethyl 2-(1,1-difluoroethyl)-4-hydroxy-pyrimidine-5-carboxylate

- A reactor was charged with acetonitrile (216.0 kg) and potassium carbonate (55.0 kg, 398 mol, 1.6 eq) at room temperature. The pipe was rinsed with acetonitrile (8 kg) into the reactor. 15 The inner temperature was set to 65 to 75 °C. Diethyl ethoxymethylenemalonate (53.8 kg, 249 mol, 1.00 eq.) was charged to the reactor and the pipe was rinsed with acetonitrile (10 kg) into the reactor. Then the solution of 2,2-difluoropropanamidine (64.4 kg solution, 27 kg starting material, 249 mol, 1.0 eq.) in dichloromethane was added into the reactor at inner temperature 65 to 75 °C. The charging pipe was rinsed with acetonitrile (14 kg) into the reactor. After the addition the 20 reaction mixture was stirred for 16 hours at 65 to 75 °C (inner temperature).

- The temperature was adjusted to 50 to 60 °C (inner temperature) and the reaction mixture was filtered. The filter was washed with acetonitrile (41.0 kg). The acetonitrile solution was transferred back into the reactor and the pipe was rinsed with acetonitrile (50 kg). The product solution was concentrated at an inner temperature below 40 °C under vacuum to 2.5 to 3.5 25 volumes. Then ethyl acetate (65 kg) was charged into the reactor. The product solution was concentrated at an inner temperature below 40 °C under vacuum to 2.5 to 3.5 volumes. Ethyl acetate (65 kg), water (287 kg) and methyl-tert-butyl ether (150 kg) were charged into the reactor. The product solution was concentrated at an inner temperature below 40 °C under vacuum to 2.5 to 3.5 volumes. Ethyl acetate (65 kg) was charged into the reactor.

- 30 The mixture was stirred for 1 hour at inner temperature 15 to 25 °C and the organic layer was separated and removed. Ethyl acetate (40 kg) and methyl-tert-butyl ether (79 kg) were added

to the aqueous layer in the reactor. The mixture was stirred for 1 hour at inner temperature 15 to 25 °C and the organic layer was separated and removed. Ethyl acetate (248 kg) was added to the aqueous layer in the reactor and the pH was adjusted to 2.5 through addition of 35% aq. HCl solution (22.4 kg) at inner temperature 15 to 25 °C. The mixture was stirred for 1 hour at inner
5 temperature 15 to 25 °C and the organic layer was separated and stored in plastic drums. The aqueous layer was extracted two times with ethyl acetate (50 kg each). After removal of the aqueous phase from the reactor, the separated organic layers were combined in the reactor. The combined organic layers were extracted with 25% brine solution (59 kg). The separated organic layer was concentrated at inner temperature below 40 °C under vacuum to 1 – 2 volumes and
10 methyl-tert-butyl ether (40 kg) was charged into the reactor. The solution was concentrated at inner temperature below 40 °C under vacuum to 1 to 2 volumes and methyl-tert-butyl ether (40 kg) was charged into the reactor. The solution was concentrated a third time at inner temperature below 40 °C under vacuum to 1 – 2 volumes and methyl-tert-butyl ether (38 kg) was charged into the reactor. The temperature was adjusted to 10 to 20 °C.

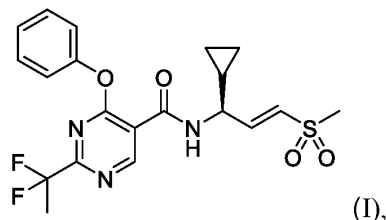
15 The mixture was further concentrated at inner temperature below 40 °C under vacuum to 1 to 2 volumes and the temperature was adjusted to 10 to 20 °C. The slurry was stirred at this temperature for 1 hour, filtered and the filter cake was washed with methyl-tert-butyl ether (26 kg).

The obtained filter cake was combined with a second batch for further purification. The
20 wet crude product cake was charged, together with a second batch into the reactor. Methyl-tert-butyl ether (80 kg) was added into the reactor. The inner temperature was adjusted to 10 to 20 °C and the slurry was stirred for 16 hours at this temperature. The slurry was filtered and washed with methyl-tert-butyl ether (59 kg) in two portions.

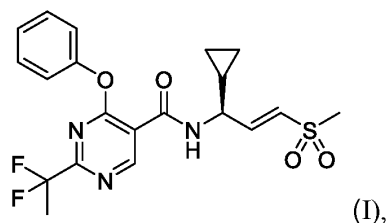
The product was dried in a single cone dryer to yield 57.2 kg of ethyl 2-(1,1-
25 difluoroethyl)-4-hydroxy-pyrimidine-5-carboxylate after sieving.

Claims

1. A solid form of a compound of formula (I)

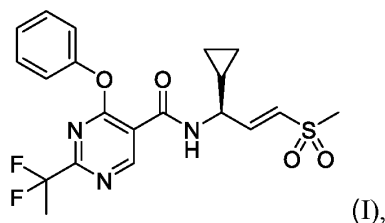


- 5 wherein the solid form is crystalline polymorphic Form A characterized by a X-ray powder diffraction pattern comprising a peak at an angle of diffraction at about 18.31 degrees 2-theta and at least one additional peak expressed in values of degrees 2-theta at about 7.76, 19.23, 11.63, 18.58, 21.94, 17.09, 22.58, 11.16, 20.08, or 9.60.
2. A solid form according to claim 1, characterized by an X-ray powder diffraction pattern
10 comprising at least three of the peaks at an angle of diffraction at about 18.31, 7.76, 19.23, or 11.63 degrees 2-theta.
3. A solid form according to any one of claims 1 to 2, characterized by an X-ray powder diffraction pattern comprising peaks at an angle of diffraction at about 18.31, 7.76, 19.23, 11.63, 18.58, 21.94, 17.09, 22.58, 11.16, 20.08, and 9.60 degrees 2-theta.
- 15 4. A solid form according to any one of claims 1-3, characterized by having a melting point with an onset signal of about 132.0 – 134.0 °C, in particular with an onset signal at about 133 °C, using differential scanning calorimetry with a heating rate of 10 K/min.
5. A solid form of a compound of formula (I)



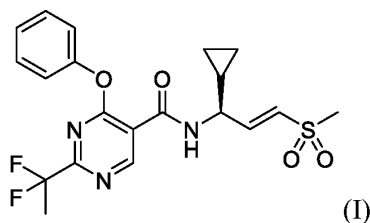
wherein the solid form is crystalline polymorphic Form A characterized by an IR spectrum comprising at least one peak at one of the positions $1649 (\pm 2) \text{ cm}^{-1}$, $1313 (\pm 2) \text{ cm}^{-1}$, or $780 (\pm 2) \text{ cm}^{-1}$, in particular comprising at least two peaks at positions $1649 (\pm 2) \text{ cm}^{-1}$, $1313 (\pm 2) \text{ cm}^{-1}$, or $780 (\pm 2) \text{ cm}^{-1}$, more particularly comprising the peaks at positions $1649 (\pm 2) \text{ cm}^{-1}$, $1313 (\pm 2) \text{ cm}^{-1}$, and $780 (\pm 2) \text{ cm}^{-1}$.

6. A solid form according to any one of claims 1 to 5, further characterized by an IR spectrum comprising a peak at the position of $1649 (\pm 2) \text{ cm}^{-1}$.
7. A solid form of a compound of formula (I)



wherein the solid form is crystalline polymorphic Form A characterized by a Raman spectrum comprising at least one peak at one of the positions $2934 (\pm 2) \text{ cm}^{-1}$, $1648 (\pm 2) \text{ cm}^{-1}$, or $1124 (\pm 2) \text{ cm}^{-1}$, more particularly comprising the peaks at positions $2934 (\pm 2) \text{ cm}^{-1}$, and $1124 (\pm 2) \text{ cm}^{-1}$.

8. A solid form according to any one of claims 1 to 7, further characterized by a Raman spectrum comprising a peak at the position $1648 (\pm 2) \text{ cm}^{-1}$.
9. A solid form of a compound of formula (I)

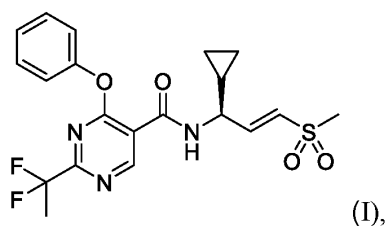


wherein the solid form is amorphous.

10. A solid form according to claim 9, characterized by exhibiting an onset of a glass transition at a temperature of about 39.0°C to about 41.0°C , in particular of about 39.5°C

to about 40.5 °C, more particularly of about 40.0 °C using differential scanning calorimetry with a heating rate of 10 K/min.

11. A solid form according to any one of claims 9 to 10, wherein the solid form is characterized by an IR spectrum comprising at least one peak at one of the positions 3416 (± 2) cm^{-1} or 1305 (± 2) cm^{-1} , more particular comprising the peaks at positions 3416 (± 2) cm^{-1} and 1305 (± 2) cm^{-1} .
12. A solid form according to any one of claims 9 to 11, wherein the solid form is characterized by a Raman spectrum comprising at least one peak at one of the positions 2928 (± 2) cm^{-1} or 928 (± 2) cm^{-1} , more particular having the peaks at positions 2928 (± 2) cm^{-1} and 928 (± 2) cm^{-1} .
13. A solid form of a compound of formula (I)



wherein the solid form is crystalline polymorphic Form E characterized by the following unit cell parameters:

- a = 10.52 Å;
b = 15.24 Å;
c = 13.06 Å;
alpha = 90 deg;
beta = 99.30 deg;
gamma = 90 deg.

14. A solid form according to any one of claims 1 to 13 for use as a medicament.
15. A solid form according to any one of claims 1 to 13 for the treatment or prophylaxis of a proliferative disease wherein the proliferative disease is cancer.

16. A solid form according to any one of claims 1 to 13 for the treatment or prophylaxis of a cancer selected from the group consisting of colon cancer, colorectal cancer, gastric cancer, endometrium cancer, ovarian cancer, hepatobiliary tract cancer, urinary tract cancer, brain cancer, skin cancer, and MSI-H cancer.
- 5 17. A pharmaceutical composition comprising a solid form according to any one of claims 1 to 13 and one or more pharmaceutically acceptable auxiliary substances.
18. Use of a solid form according to any one of claims 1 to 13 for the treatment of cancer.
19. Use of a solid form according to any one of claims 1 to 13 for the treatment of a cancer selected from the group consisting of colon cancer, colorectal cancer, gastric cancer,
10 endometrium cancer, ovarian cancer, hepatobiliary tract cancer, urinary tract cancer, brain cancer, skin cancer, and MSI-H cancer.
20. Use of a solid form according to any one of claims 1 to 13 for the preparation of a medicament for the treatment of cancer.
21. A method for therapeutic or prophylactic treatment of cancer, said method comprising
15 administering an effective amount of a solid form according to any one of claims 1 to 13 to a patient in need thereof.
