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(54) Title: POLYMORPH OF LORLATINIB

(57) Abstract: The present invention relates to a polymorph of lorlatinib and to a process for its preparation. The present invention also relates to solvates of lorlatinib, which can be used as intermediates for the preparation of the polymorph of the present invention. Furthermore, the invention relates to a pharmaceutical composition comprising the polymorph of lorlatinib of the present invention, preferably in a predetermined and/or effective amount, and at least one pharmaceutically acceptable excipient. The pharmaceutical composition of the present invention can be used as a medicament, in particular for the treatment and/or prophylaxis of cancers such as non-small cell lung cancer (NSCLC).



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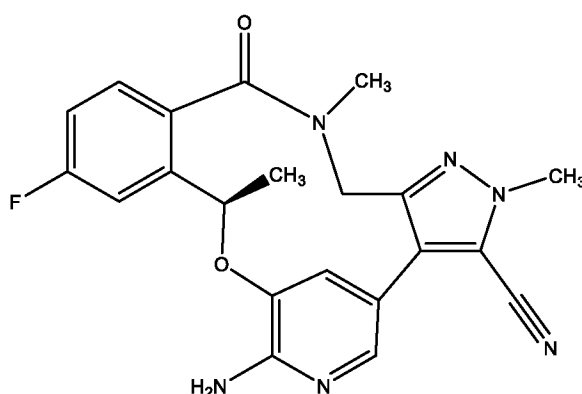
POLYMORPH OF LORLATINIB

FIELD OF THE INVENTION

The present invention relates to a polymorph of lorlatinib and to a process for its preparation. The present invention also relates to solvates of lorlatinib, which can be used as intermediates for the preparation of the polymorph of the present invention. Furthermore, the invention relates to a pharmaceutical composition comprising the polymorph of lorlatinib of the present invention, preferably in a predetermined and/or effective amount, and at least one pharmaceutically acceptable excipient. The pharmaceutical composition of the present invention can be used as a medicament, in particular for the treatment and/or prophylaxis of cancers such as non-small cell lung cancer (NSCLC).

BACKGROUND OF THE INVENTION

Lorlatinib is a potent, macrocyclic inhibitor of both wild type and resistance mutant forms of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) receptor tyrosine kinase. It is indicated for the treatment of patients with ALK-positive metastatic non-small cell lung cancer (NSCLC). Chemically, lorlatinib is designated as (10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-4,8-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile and it can be represented by the following chemical structure according to Formula (A)



Formula (A).

Lorlatinib and its preparation are disclosed in WO 2013/132376 A1 e.g. in Example 2, where lorlatinib is obtained as a white solid.

WO 2014/207606 A1 describes various crystalline forms of lorlatinib including a crystalline hydrate Form 1, a crystalline hydrate containing a non-stoichiometric amount of methanol designated as Form 2 and a crystalline acetic acid solvate containing about 1 molecule of acetic acid per one molecule of lorlatinib designated as Form 3. WO 2019/073347 A1 describes an additional hydrate of lorlatinib designated as Form 24.

WO 2017/021823 A1 discloses an anhydrous non-solvated Form 7 of lorlatinib. The marketed products (e.g. Lobrena® in US, Lorviqua® in EU) contain said Form 7.

Different solid-state forms of an active pharmaceutical ingredient often possess different properties. Differences in physicochemical properties of solid-state forms can play a crucial role for the improvement of pharmaceutical compositions, for example, pharmaceutical formulations with improved dissolution profile and bioavailability or with improved stability or shelf-life can become accessible due to an improved solid-state form of an active pharmaceutical ingredient. Also processing or handling of the active pharmaceutical ingredient during the formulation process may be improved. New solid-state forms of an active pharmaceutical ingredient can thus have desirable processing properties. They can be easier to handle, better suited for storage, and/or allow for better purification, compared to previously known solid forms.

The thermodynamically most stable polymorph of an active pharmaceutical ingredient is often used for the preparation of a drug product, since phase transitions during pharmaceutical standard processes like compaction, milling and granulation can be reduced to the extent possible. However, a huge drawback connected with the thermodynamically most stable form of a drug substance is the fact, that it is the least soluble form, which translates into decreased bioavailability. This is especially critical for low soluble compounds like lorlatinib, which is classified as a BCS class 4 substance with low solubility and low permeability (see Assessment report EMA/CHMP/182840/2019). Therefore, using a metastable polymorph of a drug substance is sometimes desirable on account of its special properties, in particular higher solubility and hence bioavailability. However, it is important to avoid any possible solid form transitions, which may occur for a metastable polymorph during pharmaceutical processing or storage, since this can have a huge impact on the safety and efficacy of a drug product. Therefore, not every metastable polymorph of an active pharmaceutical ingredient can be used for the production of a pharmaceutical composition.

Due to the low solubility of lorlatinib Form 7, the formulation of a bioavailable oral drug product requires special pretreatment of the drug substance, in this particular case the increase of the drug surface area e.g. by milling.

Aim of the present invention is therefore to address the above described issue connected with the low solubility of lorlatinib Form 7. In particular, the objective of the present invention is to provide an improved polymorph of lorlatinib, which shows high solubility and dissolution rates as well as good wettability and at the same time is kinetically stable e.g. does not undergo phase transformations during standard pharmaceutical processing and storage.

SUMMARY OF THE INVENTION

The present invention solves the above mentioned problems by providing a metastable polymorph of lorlatinib, which is hereinafter also referred to "Form B". Form B of the present invention was found to be monotropically related to the known Form 7 of WO 2017/021823 A1, with the latter being the higher melting form. No solid-state transformation from form B to form 7 was observed. The experimentally observed transition temperature at which Form B of the present invention transforms to Form 7 of WO 2017/021823 A1 is above the melting point of Form B, thus form 7 recrystallises from the melt of form B, which reflects the high kinetic stability of Form B of the present invention and indicates that the probability of solid form changes during standard pharmaceutical processing and during storage is vanishingly small. On the other hand Form B being the metastable polymorph in a monotropic system possesses by definition the higher solubility in the entire temperature range compared to the thermodynamically stable Form 7. Hence, lorlatinib Form B of the present invention combines the advantageous properties of high physical stability and high solubility and is therefore the preferred solid-state form of lorlatinib for the preparation of a pharmaceutical composition.

Another aspect of the present invention concerns solvates of lorlatinib with dimethylformamide (Form S-DMF) and 1,4-dioxane (Form S-DX), respectively. Having these solvates in hands, for the first time allowed the preparation of lorlatinib Form B of the present invention, which can be produced by desolvation of the solvates of the present invention.

Abbreviations

PXRD	powder X-ray diffractogram
FTIR	Fourier transform infrared

	DSC	differential scanning calorimetry
	TGA	thermogravimetric analysis
	HSM	hot stage microscope
	GC	gas chromatography
5	SXRD	single crystal X-ray diffraction
	NMR	nuclear magnetic resonance
	MS	mass spectrometry
	RT	room temperature
	RH	relative humidity
10	w-%	weight percent
	v	volume
	DMF	dimethylformamide
	BCS	Biopharmaceutical Classification System

Definitions

- 15 In the context of the present invention the following definitions have the indicated meaning, unless explicitly stated otherwise:

As used herein the term “room temperature” refers to a temperature in the range of from 20 to 30 °C.

- 20 As used herein, the term “measured at a temperature in the range of from 20 to 30 °C” refers to a measurement under standard conditions. Typically, standard conditions mean a temperature in the range of from 20 to 30 °C, i.e. at room temperature. Standard conditions can mean a temperature of about 22 °C. Typically, standard conditions can additionally mean a measurement under 20-80% RH, preferably 30-70% RH, more preferably 40-60% RH and most preferably 50% RH.

- 25 The term “Form 7” as used herein, when talking about a solid-state form of lorlatinib refers to the anhydrous non-solvated crystalline form of lorlatinib, which is disclosed in WO 2017/021823 A1. Form 7 of lorlatinib can be characterized by having a powder X-ray diffractogram comprising reflections at 2-Theta angles of $(9.6 \pm 0.2)^\circ$, $(10.1 \pm 0.2)^\circ$, $(14.3 \pm 0.2)^\circ$, $(16.2 \pm 0.2)^\circ$ and $(17.3 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20
30 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.

The term “reflection” with regard to powder X-ray diffraction as used herein, means peaks in an X-ray diffractogram, which are caused at certain diffraction angles (Bragg angles) by constructive interference from X-rays scattered by parallel planes of atoms in solid material, which are distributed in an ordered and repetitive pattern in a long-range positional order. Such a solid material is classified as crystalline material, whereas amorphous material is defined as solid material, which lacks long-range order and only displays short-range order, thus resulting in broad scattering. According to literature, long-range order e.g. extends over approximately 100 to 1000 atoms, whereas short-range order is over a few atoms only (see “*Fundamentals of Powder Diffraction and Structural Characterization of Materials*” by Vitalij K. Pecharsky and Peter Y. Zavalij, Kluwer Academic Publishers, 2003, page 3).

The term “essentially the same” with reference to powder X-ray diffraction means that variabilities in reflection positions and relative intensities of the reflections are to be taken into account. For example, a typical precision of the 2-Theta values is in the range of $\pm 0.2^\circ$ 2-Theta, preferably in the range of $\pm 0.1^\circ$ 2-Theta. Thus, a reflection that usually appears at 8.7° 2-Theta for example can appear between 8.5 and 8.9° 2-Theta, preferably between 8.6 and 8.8° 2-Theta on most X-ray diffractometers under standard conditions. Furthermore, one skilled in the art will appreciate that relative reflection intensities will show inter-apparatus variability as well as variability due to degree of crystallinity, preferred orientation, particle size, sample preparation and other factors known to those skilled in the art and should be taken as qualitative measure only.

The term “essentially the same” with reference to infrared spectrometry means that variabilities in peak positions and relative intensities of the peaks are to be taken into account. For example, a typical precision of the wavenumber values is in the range of $\pm 4\text{ cm}^{-1}$, preferably in the range of $\pm 2\text{ cm}^{-1}$. Thus, a peak at 2233 cm^{-1} for example can appear between (2229) and $(2237)\text{ cm}^{-1}$, preferably between (2231) and $(2235)\text{ cm}^{-1}$ on most infrared spectrometers under standard conditions. Peak intensities can be derived from according figures, but one skilled in the art will appreciate that differences in peak intensities due to degree of crystallinity, sample preparation, measurement method and other factors can also occur in infrared spectroscopy. Peak intensities should therefore be taken as qualitative measure only.

The anhydrous and non-solvated crystalline Form B of lorlatinib of the present invention may be referred to herein as being characterized by graphical data "as shown in" a figure. Such data

include, for example, powder X-ray diffraction and FTIR spectroscopy. The person skilled in the art understands that factors such as variations in instrument type, response and variations in sample directionality, sample concentration and sample purity may lead to small variations for such data when presented in graphical form, for example variations relating to the exact peak positions and intensities. However, a comparison of the graphical data in the figures herein with the graphical data generated for another or an unknown solid-state form and the confirmation that two sets of graphical data relate to the same crystal form is well within the knowledge of a person skilled in the art.

The terms “solid form” or “solid-state form” as used herein interchangeably refer to any crystalline and/or amorphous phase of a compound.

As used herein, the term “amorphous” refers to a solid form of a compound that is not crystalline. An amorphous compound possesses no long-range order and does not display a definitive X-ray diffraction pattern with reflections.

As used herein the term “polymorph” refers to crystalline forms having the same chemical composition but different spatial arrangements of the molecules, atoms, and/or ions forming the crystal.

The term “hydrate” as used herein, refers to a crystalline solid where either water is cooperated in or accommodated by the crystal structure e.g. is part of the crystal structure or entrapped into the crystal (water inclusions). Thereby, water can be present in a stoichiometric or non-stoichiometric amount. When water is present in stoichiometric amount, the hydrate may be referred to by adding greek numeral prefixes. For example, a hydrate may be referred to as a *hemihydrate* or as a *monohydrate* depending on the water/compound stoichiometry. The water content can be measured, for example, by Karl-Fischer-Coulometry.

The term “solvate” as used herein, refers to a crystalline solid where either one or more organic solvent(s) is/are cooperated in or accommodated by the crystal structure e.g. is/are part of the crystal structure or entrapped into the crystal (solvent inclusions). Thereby, the one or more organic solvent(s) can be present in a stoichiometric or non-stoichiometric amount. When the one or more organic solvent(s) is/are present in stoichiometric amount(s), the solvate may be referred to by adding greek numeral prefixes. For example, a solvate may be referred to as a

hemisolvate or as a *monosolvate* depending on the solvent(s)/compound stoichiometry. The solvent content can be measured, for example, by GC, NMR, SXRD and/or TGA/MS.

The terms “desolvating” or “desolvation” as used herein, describe the at least partial removal of organic solvent from the crystal structure of the host molecule.

- 5 The terms “anhydrous” or “anhydrate” as used herein refer to a crystalline solid where no water is cooperated in or accommodated by the crystal structure. Anhydrous forms may still contain residual water, which is not part of the crystal structure but may be adsorbed on the surface or absorbed in disordered regions of the crystal. Typically, an anhydrous form does not contain more than 2.0 w-%, preferably not more than 1.0 w-%, more preferably not more than 0.5 w-%
10 of water, based on the weight of the crystalline form.

- The term “non-solvated” as used herein, when talking about a crystalline solid indicates that no organic solvent is cooperated in or accommodated by the crystal structure. Non-solvated forms may still contain residual organic solvents, which are not part of the crystal structure but may be adsorbed on the surface or absorbed in disordered regions of the crystal. Typically, a non-
15 solvated form does not contain more than 2.0 w-%, preferably not more than 1.0 w-%, more preferably not more than 0.5 w-% of organic solvents, based on the weight of the crystalline form.

As used herein, the term “mother liquor” refers to the solution remaining after crystallization of a solid from said solution.

- 20 The term “antisolvent” as used herein refers to liquids which reduce the solubility of lorlatinib in a solvent.

A “predetermined amount” as used herein with regard to lorlatinib refers to the initial amount of lorlatinib used for the preparation of a pharmaceutical composition having a desired dosage strength of lorlatinib.

- 25 The term “effective amount” as used herein with regard to lorlatinib encompasses an amount of lorlatinib, which produces the desired therapeutic and/or prophylactic effect.

As used herein, the term “about” means within a statistically meaningful range of a value. Such a range can be within an order of magnitude, typically within 10%, more typically within 5%,

even more typically within 1% and most typically within 0.1% of the indicated value or range. Sometimes, such a range can lie within the experimental error, typical of standard methods used for the measurement and/or determination of a given value or range.

The term “pharmaceutically acceptable excipient” as used herein refers to substances, which do not show a significant pharmacological activity at the given dose and that are added to a pharmaceutical composition in addition to the active pharmaceutical ingredient. Excipients may take the function of vehicle, diluent, release agent, disintegrating agent, dissolution modifying agent, absorption enhancer, stabilizer or a manufacturing aid among others. Excipients may include fillers (diluent), binders, disintegrants, lubricants and glidants.

The term “filler” as used herein refers to substances that are used to dilute the active pharmaceutical ingredient prior to delivery. Fillers can also serve as stabilizers.

As used herein the term “binder” refers to substances which bind the active pharmaceutical ingredient and pharmaceutically acceptable excipient together to maintain cohesive and discrete portions.

The terms “disintegrant” or “disintegrating agent” as used herein refer to substances which, upon addition to a solid pharmaceutical composition, facilitate its break-up or disintegration after administration and permit the release of the active pharmaceutical ingredient as efficiently as possible to allow for its rapid dissolution.

The term “lubricant” as used herein refers to substances which are added to a powder blend to prevent the compacted powder mass from sticking to the equipment during tableting or encapsulation process. They aid the ejection of the tablet from the dies and can improve powder flow.

The term “glidant” as used herein refers to substances which are used for tablet and capsule formulations in order to improve flow properties during tablet compression and to produce an anti-caking effect.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: illustrates a representative PXRD of crystalline Form B of lorlatinib of the present invention. The x-axis shows the scattering angle in °2-Theta, the y-axis shows the intensity of the scattered X-ray beam in counts of detected photons.

Figure 2: illustrates a comparison of a representative PXRD of crystalline Form B of lorlatinib of the present invention (bottom) and a representative PXRD of Form 7 of lorlatinib of WO 2017/021823 A1 (top). The x-axis shows the scattering angle in $^{\circ}2\text{-Theta}$. The powder X-ray diffractogram of Form 7 was shifted along the y-axis to separate the diffractograms for clarity.

Figure 3: illustrates a representative FTIR spectrum of crystalline Form B of lorlatinib of the present invention. The x-axis shows the wavenumbers in cm^{-1} , the y-axis shows the relative intensity in percent transmittance.

Figure 4: illustrates a representative DSC curve of crystalline Form B of lorlatinib of the present invention. The x-axis shows the temperature in degree Celsius ($^{\circ}\text{C}$), the y-axis shows the heat flow rate in Watt per gram (W/g) with endothermic peaks going up.

Figure 5: illustrates a representative TGA curve of crystalline Form B of lorlatinib of the present invention. The x-axis shows the temperature in degree Celsius ($^{\circ}\text{C}$), the y-axis shows the mass (loss) of the sample in weight percent (w-%).

Figure 6: illustrates a representative PXRD of crystalline Form S-DMF of lorlatinib of the present invention. The x-axis shows the scattering angle in $^{\circ}2\text{-Theta}$, the y-axis shows the intensity of the scattered X-ray beam in counts of detected photons.

Figure 7: illustrates a representative PXRD of crystalline Form S-DX of lorlatinib of the present invention. The x-axis shows the scattering angle in $^{\circ}2\text{-Theta}$, the y-axis shows the intensity of the scattered X-ray beam in counts of detected photons.

Figure 8: illustrates comparative solubility curves of Form 7 of WO 2017/021823 A1 (bottom curve) and of Form B of the present invention (top curve) in *n*-heptane/toluene [1:3(v/v)]. The x-axis shows the temperature in degree Celsius ($^{\circ}\text{C}$), the y-axis shows the concentration in milligram per millilitre (mg/mL).

Figure 9: illustrates comparative solubility curves of Form 7 of WO 2017/021823 A1 (bottom curve) and of Form B of the present invention (top curve) in Fessif medium pH 5.0 at 37°C . The x-axis shows the time in hours (h), the y-axis shows the concentration in milligram per millilitre (mg/mL).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a metastable polymorph of lorlatinib, herein also designated as “Form B”.

Despite being a metastable polymorph, Form B of lorlatinib of the present invention possesses high physical stability, e.g. it is stable against temperature, moisture and/or mechanical stress (see Example 5 herein). The fact that Form B is monotropically related to the already known Form 7, with Form 7 being the higher melting form, implies that Form B of the present invention shows higher solubility, a fact which translates in higher bioavailability of a low soluble drug like lorlatinib (see Comparative Example 1 and 2 herein). Hence, Form B of the present invention combines the advantageous properties of high physical stability and high solubility and is therefore the ideal solid-state form of lorlatinib for the preparation of an improved pharmaceutical composition e.g. a pharmaceutical composition with increased bioavailability, which is safe and effective during its whole shelf-life.

Crystalline Form B of lorlatinib of the present invention may be characterized by analytical methods well known in the field of the pharmaceutical industry for characterizing solids. Such methods comprise but are not limited to powder X-ray diffraction, FTIR spectroscopy, DSC and TGA. It may be characterized by one of the aforementioned analytical methods or by combining two or more of them. In particular, Form B of lorlatinib of the present invention may be characterized by any one of the following embodiments or by combining two or more of the following embodiments.

Lorlatinib Form B, composition comprising Form B and process for preparing the same

In one embodiment the invention relates to an anhydrous and non-solvated crystalline form (Form B) of lorlatinib characterized by having a PXRD comprising reflections at 2-Theta angles of:

$(8.7 \pm 0.2)^\circ$, $(11.2 \pm 0.2)^\circ$ and $(11.8 \pm 0.2)^\circ$; or

$(8.7 \pm 0.2)^\circ$, $(11.2 \pm 0.2)^\circ$, $(11.8 \pm 0.2)^\circ$ and $(18.8 \pm 0.2)^\circ$; or

$(8.7 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$, $(11.2 \pm 0.2)^\circ$, $(11.8 \pm 0.2)^\circ$ and $(18.8 \pm 0.2)^\circ$; or

$(7.5 \pm 0.2)^\circ$, $(8.7 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$, $(11.2 \pm 0.2)^\circ$, $(11.8 \pm 0.2)^\circ$ and $(18.8 \pm 0.2)^\circ$; or

$(7.5 \pm 0.2)^\circ$, $(8.7 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$, $(11.2 \pm 0.2)^\circ$, $(11.8 \pm 0.2)^\circ$, $(16.7 \pm 0.2)^\circ$ and $(18.8 \pm 0.2)^\circ$; or

$(7.5 \pm 0.2)^\circ$, $(8.7 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$, $(11.2 \pm 0.2)^\circ$, $(11.8 \pm 0.2)^\circ$, $(15.7 \pm 0.2)^\circ$, $(16.7 \pm 0.2)^\circ$ and $(18.8 \pm 0.2)^\circ$; or

$(7.5 \pm 0.2)^\circ$, $(8.7 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$, $(11.2 \pm 0.2)^\circ$, $(11.8 \pm 0.2)^\circ$, $(13.3 \pm 0.2)^\circ$, $(15.7 \pm 0.2)^\circ$, $(16.7 \pm 0.2)^\circ$ and $(18.8 \pm 0.2)^\circ$; or

$(7.5 \pm 0.2)^\circ$, $(8.7 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$, $(11.2 \pm 0.2)^\circ$, $(11.8 \pm 0.2)^\circ$, $(13.3 \pm 0.2)^\circ$, $(15.2 \pm 0.2)^\circ$, $(15.7 \pm 0.2)^\circ$, $(16.7 \pm 0.2)^\circ$ and $(18.8 \pm 0.2)^\circ$; or

$(7.5 \pm 0.2)^\circ$, $(8.7 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$, $(11.2 \pm 0.2)^\circ$, $(11.8 \pm 0.2)^\circ$, $(13.3 \pm 0.2)^\circ$, $(15.2 \pm 0.2)^\circ$, $(15.7 \pm 0.2)^\circ$, $(16.7 \pm 0.2)^\circ$, $(18.8 \pm 0.2)^\circ$ and $(21.5 \pm 0.2)^\circ$; or

5 $(7.5 \pm 0.2)^\circ$, $(8.7 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$, $(11.2 \pm 0.2)^\circ$, $(11.8 \pm 0.2)^\circ$, $(13.3 \pm 0.2)^\circ$, $(15.2 \pm 0.2)^\circ$, $(15.7 \pm 0.2)^\circ$, $(16.7 \pm 0.2)^\circ$, $(18.8 \pm 0.2)^\circ$, $(21.5 \pm 0.2)^\circ$ and $(21.9 \pm 0.2)^\circ$; or

$(7.5 \pm 0.2)^\circ$, $(8.7 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$, $(11.2 \pm 0.2)^\circ$, $(11.8 \pm 0.2)^\circ$, $(13.3 \pm 0.2)^\circ$, $(15.2 \pm 0.2)^\circ$, $(15.7 \pm 0.2)^\circ$, $(16.7 \pm 0.2)^\circ$, $(18.8 \pm 0.2)^\circ$, $(21.5 \pm 0.2)^\circ$, $(21.9 \pm 0.2)^\circ$ and $(23.2 \pm 0.2)^\circ$,

when measured at a temperature in the range of from 20 to 30 °C with Cu-K α _{1,2} radiation

10 having a wavelength of 0.15419 nm.

In another embodiment, the invention relates to an anhydrous and non-solvated crystalline form (Form B) of lorlatinib characterized by having a PXRD comprising reflections at 2-Theta angles of $(8.7 \pm 0.2)^\circ$, $(11.2 \pm 0.2)^\circ$, $(11.8 \pm 0.2)^\circ$, $(15.2 \pm 0.2)^\circ$, $(17.2 \pm 0.2)^\circ$, $(18.8 \pm 0.2)^\circ$, $(21.5 \pm 0.2)^\circ$, $(21.9 \pm 0.2)^\circ$ and $(23.2 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20

15 to 30 °C with Cu-K α _{1,2} radiation having a wavelength of 0.15419 nm.

In a further embodiment, the present invention relates to an anhydrous and non-solvated crystalline form (Form B) of lorlatinib characterized by having a PXRD comprising reflections at 2-Theta angles of:

$(8.7 \pm 0.1)^\circ$, $(11.2 \pm 0.1)^\circ$ and $(11.8 \pm 0.1)^\circ$; or

20 $(8.7 \pm 0.1)^\circ$, $(11.2 \pm 0.1)^\circ$, $(11.8 \pm 0.1)^\circ$ and $(18.8 \pm 0.1)^\circ$; or

$(8.7 \pm 0.1)^\circ$, $(10.3 \pm 0.1)^\circ$, $(11.2 \pm 0.1)^\circ$, $(11.8 \pm 0.1)^\circ$ and $(18.8 \pm 0.1)^\circ$; or

$(7.5 \pm 0.1)^\circ$, $(8.7 \pm 0.1)^\circ$, $(10.3 \pm 0.1)^\circ$, $(11.2 \pm 0.1)^\circ$, $(11.8 \pm 0.1)^\circ$ and $(18.8 \pm 0.1)^\circ$; or

$(7.5 \pm 0.1)^\circ$, $(8.7 \pm 0.1)^\circ$, $(10.3 \pm 0.1)^\circ$, $(11.2 \pm 0.1)^\circ$, $(11.8 \pm 0.1)^\circ$, $(16.7 \pm 0.1)^\circ$ and $(18.8 \pm 0.1)^\circ$; or

25 $(7.5 \pm 0.1)^\circ$, $(8.7 \pm 0.1)^\circ$, $(10.3 \pm 0.1)^\circ$, $(11.2 \pm 0.1)^\circ$, $(11.8 \pm 0.1)^\circ$, $(15.7 \pm 0.1)^\circ$, $(16.7 \pm 0.1)^\circ$ and $(18.8 \pm 0.1)^\circ$; or

$(7.5 \pm 0.1)^\circ$, $(8.7 \pm 0.1)^\circ$, $(10.3 \pm 0.1)^\circ$, $(11.2 \pm 0.1)^\circ$, $(11.8 \pm 0.1)^\circ$, $(13.3 \pm 0.1)^\circ$, $(15.7 \pm 0.1)^\circ$, $(16.7 \pm 0.1)^\circ$ and $(18.8 \pm 0.1)^\circ$; or

$(7.5 \pm 0.1)^\circ$, $(8.7 \pm 0.1)^\circ$, $(10.3 \pm 0.1)^\circ$, $(11.2 \pm 0.1)^\circ$, $(11.8 \pm 0.1)^\circ$, $(13.3 \pm 0.1)^\circ$, $(15.2 \pm 0.1)^\circ$,

30 $(15.7 \pm 0.1)^\circ$, $(16.7 \pm 0.1)^\circ$ and $(18.8 \pm 0.1)^\circ$; or

$(7.5 \pm 0.1)^\circ$, $(8.7 \pm 0.1)^\circ$, $(10.3 \pm 0.1)^\circ$, $(11.2 \pm 0.1)^\circ$, $(11.8 \pm 0.1)^\circ$, $(13.3 \pm 0.1)^\circ$, $(15.2 \pm 0.1)^\circ$, $(15.7 \pm 0.1)^\circ$, $(16.7 \pm 0.1)^\circ$, $(18.8 \pm 0.1)^\circ$ and $(21.5 \pm 0.1)^\circ$; or

(7.5 ± 0.1)°, (8.7 ± 0.1)°, (10.3 ± 0.1)°, (11.2 ± 0.1)°, (11.8 ± 0.1)°, (13.3 ± 0.1)°, (15.2 ± 0.1)°, (15.7 ± 0.1)°, (16.7 ± 0.1)°, (18.8 ± 0.1)°, (21.5 ± 0.1)° and (21.9 ± 0.1)°; or

(7.5 ± 0.1)°, (8.7 ± 0.1)°, (10.3 ± 0.1)°, (11.2 ± 0.1)°, (11.8 ± 0.1)°, (13.3 ± 0.1)°, (15.2 ± 0.1)°, (15.7 ± 0.1)°, (16.7 ± 0.1)°, (18.8 ± 0.1)°, (21.5 ± 0.1)°, (21.9 ± 0.1)° and (23.2 ± 0.1)°,

5 when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.

In yet another embodiment, the invention relates to an anhydrous and non-solvated crystalline form (Form B) of lorlatinib characterized by having a PXRD comprising reflections at 2-Theta angles of (8.7 ± 0.1)°, (11.2 ± 0.1)°, (11.8 ± 0.1)°, (15.2 ± 0.1)°, (17.2 ± 0.1)°, (18.8 ± 0.1)°, 10 (21.5 ± 0.1)°, (21.9 ± 0.1)° and (23.2 ± 0.1)°, when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.

The PXRD of Form B of the present invention can be readily distinguished from the PXRD of Form 7 of WO 2017/021823 A1. Form B for example shows characteristic reflections at (8.7 ± 0.2)°, (13.3 ± 0.2)°, (16.7 ± 0.2)° and (18.8 ± 0.2)° 2-Theta, whereas Form 7 shows no 15 reflections in the same ranges. On the other hand Form 7 shows characteristic reflections at (9.6 ± 0.2)°, (12.6 ± 0.2)° and (16.2 ± 0.2)° 2-Theta, whereas Form B shows no reflections in the same ranges.

Hence, in another embodiment the present invention relates to an anhydrous and non-solvated crystalline form (Form B) of lorlatinib which can be characterized by having a PXRD as defined 20 in one of the above described embodiments, but not comprising reflections at 2-Theta angles of (9.6 ± 0.2)°, (12.6 ± 0.2)° and/or (16.2 ± 0.2)°, when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.

In yet another embodiment, the present invention relates to an anhydrous and non-solvated crystalline form (Form B) of lorlatinib characterized by having a PXRD essentially the same as 25 shown in Figure 1 of the present invention, when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.

In one embodiment, the present invention relates to an anhydrous and non-solvated crystalline form (Form B) of lorlatinib characterized by having an FTIR spectrum comprising peaks at wavenumbers of:

30 (3397 ± 4) cm⁻¹, (2233 ± 4) cm⁻¹ and (1633 ± 4) cm⁻¹ or;

$(3471 \pm 4) \text{ cm}^{-1}$, $(3397 \pm 4) \text{ cm}^{-1}$, $(2233 \pm 4) \text{ cm}^{-1}$ and $(1633 \pm 4) \text{ cm}^{-1}$; or
 $(3471 \pm 4) \text{ cm}^{-1}$, $(3397 \pm 4) \text{ cm}^{-1}$, $(2979 \pm 4) \text{ cm}^{-1}$, $(2233 \pm 4) \text{ cm}^{-1}$ and $(1633 \pm 4) \text{ cm}^{-1}$; or
 $(3471 \pm 4) \text{ cm}^{-1}$, $(3397 \pm 4) \text{ cm}^{-1}$, $(2979 \pm 4) \text{ cm}^{-1}$, $(2233 \pm 4) \text{ cm}^{-1}$, $(1633 \pm 4) \text{ cm}^{-1}$ and $(1588 \pm 4) \text{ cm}^{-1}$; or

- 5 $(3471 \pm 4) \text{ cm}^{-1}$, $(3397 \pm 4) \text{ cm}^{-1}$, $(2979 \pm 4) \text{ cm}^{-1}$, $(2233 \pm 4) \text{ cm}^{-1}$, $(1633 \pm 4) \text{ cm}^{-1}$, $(1588 \pm 4) \text{ cm}^{-1}$ and $(1417 \pm 4) \text{ cm}^{-1}$; or
 $(3471 \pm 4) \text{ cm}^{-1}$, $(3397 \pm 4) \text{ cm}^{-1}$, $(2979 \pm 4) \text{ cm}^{-1}$, $(2233 \pm 4) \text{ cm}^{-1}$, $(1633 \pm 4) \text{ cm}^{-1}$, $(1588 \pm 4) \text{ cm}^{-1}$, $(1417 \pm 4) \text{ cm}^{-1}$ and $(1197 \pm 4) \text{ cm}^{-1}$; or
 $(3471 \pm 4) \text{ cm}^{-1}$, $(3397 \pm 4) \text{ cm}^{-1}$, $(2979 \pm 4) \text{ cm}^{-1}$, $(2233 \pm 4) \text{ cm}^{-1}$, $(1633 \pm 4) \text{ cm}^{-1}$, $(1588 \pm 4) \text{ cm}^{-1}$, $(1486 \pm 4) \text{ cm}^{-1}$, $(1417 \pm 4) \text{ cm}^{-1}$ and $(1197 \pm 4) \text{ cm}^{-1}$; or
10 $(3471 \pm 4) \text{ cm}^{-1}$, $(3397 \pm 4) \text{ cm}^{-1}$, $(2979 \pm 4) \text{ cm}^{-1}$, $(2233 \pm 4) \text{ cm}^{-1}$, $(1633 \pm 4) \text{ cm}^{-1}$, $(1588 \pm 4) \text{ cm}^{-1}$, $(1486 \pm 4) \text{ cm}^{-1}$, $(1417 \pm 4) \text{ cm}^{-1}$, $(1197 \pm 4) \text{ cm}^{-1}$ and $(732 \pm 4) \text{ cm}^{-1}$,
when measured at a temperature in the range of from 20 to 30 °C with a diamond ATR cell.

In another embodiment, the present invention relates to an anhydrous and non-solvated crystalline form (Form B) of lorlatinib characterized by having an FTIR spectrum comprising
15 peaks at wavenumbers of:

- $(3397 \pm 2) \text{ cm}^{-1}$, $(2233 \pm 2) \text{ cm}^{-1}$ and $(1633 \pm 2) \text{ cm}^{-1}$ or;
 $(3471 \pm 2) \text{ cm}^{-1}$, $(3397 \pm 2) \text{ cm}^{-1}$, $(2233 \pm 2) \text{ cm}^{-1}$ and $(1633 \pm 2) \text{ cm}^{-1}$; or
 $(3471 \pm 2) \text{ cm}^{-1}$, $(3397 \pm 2) \text{ cm}^{-1}$, $(2979 \pm 2) \text{ cm}^{-1}$, $(2233 \pm 2) \text{ cm}^{-1}$ and $(1633 \pm 2) \text{ cm}^{-1}$; or
20 $(3471 \pm 2) \text{ cm}^{-1}$, $(3397 \pm 2) \text{ cm}^{-1}$, $(2979 \pm 2) \text{ cm}^{-1}$, $(2233 \pm 2) \text{ cm}^{-1}$, $(1633 \pm 2) \text{ cm}^{-1}$ and $(1588 \pm 2) \text{ cm}^{-1}$; or
 $(3471 \pm 2) \text{ cm}^{-1}$, $(3397 \pm 2) \text{ cm}^{-1}$, $(2979 \pm 2) \text{ cm}^{-1}$, $(2233 \pm 2) \text{ cm}^{-1}$, $(1633 \pm 2) \text{ cm}^{-1}$, $(1588 \pm 2) \text{ cm}^{-1}$ and $(1417 \pm 2) \text{ cm}^{-1}$; or
 $(3471 \pm 2) \text{ cm}^{-1}$, $(3397 \pm 2) \text{ cm}^{-1}$, $(2979 \pm 2) \text{ cm}^{-1}$, $(2233 \pm 2) \text{ cm}^{-1}$, $(1633 \pm 2) \text{ cm}^{-1}$, $(1588 \pm 2) \text{ cm}^{-1}$, $(1417 \pm 2) \text{ cm}^{-1}$ and $(1197 \pm 2) \text{ cm}^{-1}$; or
25 $(3471 \pm 2) \text{ cm}^{-1}$, $(3397 \pm 2) \text{ cm}^{-1}$, $(2979 \pm 2) \text{ cm}^{-1}$, $(2233 \pm 2) \text{ cm}^{-1}$, $(1633 \pm 2) \text{ cm}^{-1}$, $(1588 \pm 2) \text{ cm}^{-1}$, $(1486 \pm 2) \text{ cm}^{-1}$, $(1417 \pm 2) \text{ cm}^{-1}$ and $(1197 \pm 2) \text{ cm}^{-1}$; or
 $(3471 \pm 2) \text{ cm}^{-1}$, $(3397 \pm 2) \text{ cm}^{-1}$, $(2979 \pm 2) \text{ cm}^{-1}$, $(2233 \pm 2) \text{ cm}^{-1}$, $(1633 \pm 2) \text{ cm}^{-1}$, $(1588 \pm 2) \text{ cm}^{-1}$, $(1486 \pm 2) \text{ cm}^{-1}$, $(1417 \pm 2) \text{ cm}^{-1}$, $(1197 \pm 2) \text{ cm}^{-1}$ and $(732 \pm 2) \text{ cm}^{-1}$,
30 when measured at a temperature in the range of from 20 to 30 °C with a diamond ATR cell.

In yet another embodiment, the present invention relates to an anhydrous and non-solvated crystalline form (Form B) of lorlatinib characterized by having an FTIR spectrum essentially

the same as shown in Figure 3 of the present invention, when measured at a temperature in the range of from 20 to 30 °C with a diamond ATR cell.

In one embodiment, the present invention relates to an anhydrous and non-solvated crystalline form (Form B) of lorlatinib characterized by having a DSC curve comprising an endothermic peak having an onset at a temperature of (191 ± 5) °C, preferably of (191 ± 3) °C, more preferably of (191 ± 1) °C, when measured at a heating rate of 10 K/min.

In a further embodiment, the present invention relates to an anhydrous and non-solvated crystalline form (Form B) of lorlatinib characterized by having a DSC curve comprising an endothermic peak having a peak maximum at a temperature of (198 ± 5) °C, preferably of (198 ± 3) °C, more preferably of (198 ± 1) °C, when measured a heating rate of 10 K/min.

In still another embodiment, the invention relates to an anhydrous and non-solvated crystalline form (Form B) of lorlatinib characterized by having a melting point onset at a temperature of (191 ± 5) °C, preferably of (191 ± 3) °C, more preferably of (191 ± 1) °C, when measured with DSC at a heating rate of 10 K/min.

In another embodiment, the present invention relates to an anhydrous and non-solvated crystalline form (Form B) of lorlatinib characterized by having a TGA curve showing a mass loss of not more than 2.0 w-%, preferably of not more than 1.0 w-%, more preferably of not more than 0.5 w-%, based on the weight of the crystalline form, when heated from 25 to 200 °C at a rate of 10 K/min.

In another aspect, the present invention relates to a composition comprising the anhydrous and non-solvated crystalline form (Form B) of lorlatinib of the present invention as defined in any one of the above described embodiments, said composition being essentially free of any other solid-state form of lorlatinib. For example, a composition comprising the crystalline Form B of lorlatinib of the present invention comprises at most 20 w-%, preferably at most 10 w-%, more preferably at most 5, 4, 3, 2 or 1 w-% of any other solid-state form of lorlatinib, based on the weight of the composition. Preferably, the any other solid-state form of lorlatinib is form 7 of WO 2017/021823 A1 or amorphous lorlatinib. Form 7 of lorlatinib exhibits a PXRD comprising amongst others characteristic reflections at 2-Theta angles of $(9.6 \pm 0.2)^\circ$, $(12.6 \pm 0.2)^\circ$ and $(16.2 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm. Therefore, the absence of

reflections at 2-Theta angles of $(9.6 \pm 0.2)^\circ$, $(12.6 \pm 0.2)^\circ$ and $(16.2 \pm 0.2)^\circ$ in the PXRD confirms the absence of form 7 of lorlatinib in the composition.

Hence, in a preferred embodiment, the present invention relates to a composition comprising the anhydrous and non-solvated crystalline form (Form B) of lorlatinib of the present invention as defined in any one of the above described embodiments, said composition having a PXRD comprising no reflections at 2-Theta angles of $(9.6 \pm 0.2)^\circ$, $(12.6 \pm 0.2)^\circ$ and $(16.2 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20 to 30 °C with Cu-K α _{1,2} radiation having a wavelength of 0.15419 nm.

In another embodiment, the invention relates to a composition comprising at least 90 w-%, including at least 90, 91, 92, 93, 94, 95, 96, 97, 98 and 99 w-%, and also including equal to about 100 w-% of the anhydrous and non-solvated crystalline form (Form B) of lorlatinib as defined in any one of the above described embodiments, based on the total weight of the composition. The remaining material may comprise other solid-state form(s) of lorlatinib, and/or reaction impurities and/or processing impurities arising from the preparation of the composition.

In another aspect, the present invention relates to a process for the preparation of the anhydrous and non-solvated crystalline form (Form B) of lorlatinib of the present invention or the composition comprising the same as defined in any one of the above described aspects and their corresponding embodiments comprising:

- (a) providing the lorlatinib DMF solvate (Form S-DMF) or the lorlatinib 1,4-dioxane solvate (Form S-DX) of the present invention; and
- (b) desolvating the solvate provided in step (a);

The solvates of lorlatinib (Form S-DMF and Form S-DX) can be prepared according to the procedures disclosed hereinafter, in particular according to the procedures disclosed in Examples 2 and 3 herein, respectively.

Preferably, before desolvation, the solvates are subjected to a particle size reduction process such as milling, grinding, sieving and the like.

Desolvation of the solvates is performed by applying heat. Thereby the samples are heated to a temperature in the range of from 25 to 185 °C, preferably of from 100 to 185 °C and most preferably of from 160 to 185 °C. Heating rates selected from the group consisting of 2, 3, 4,

5, 10 and 20 K/min may be applied, most preferably the applied heating rate is 10 K/min. The heating step may be repeated.

Pharmaceutical compositions comprising lorlatinib Form B and their medical use

5 In a further aspect the present invention relates to the use of the anhydrous and non-solvated crystalline form (Form B) of lorlatinib of the present invention or the composition comprising the crystalline form B of lorlatinib as defined in any one of the above described aspects and their corresponding embodiments for the preparation of a pharmaceutical composition.

10 In yet another aspect, the present invention relates to a pharmaceutical composition comprising the anhydrous and non-solvated crystalline form (Form B) of lorlatinib or the composition comprising the crystalline form B of lorlatinib as defined in any one of the above described aspects and their corresponding embodiments, preferably in a predetermined and/or effective amount, and at least one pharmaceutically acceptable excipient.

15 Preferably, the predetermined and/or effective amount of the anhydrous and non-solvated crystalline form (Form B) of lorlatinib or the composition comprising the crystalline form B of lorlatinib as defined in any one of the above described aspects and their corresponding embodiments is selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg and 200 mg, calculated as anhydrous and non-solvated lorlatinib. More preferably, the predetermined and/or effective amount of the anhydrous and non-solvated crystalline form (Form B) of lorlatinib or the composition comprising the crystalline form B of lorlatinib as defined in any one of the above described aspects and their corresponding
20 embodiments is selected from the group consisting of 25 mg, 50 mg, 75 mg and 100 mg calculated as anhydrous and non-solvated lorlatinib. Most preferably, the predetermined and/or effective amount of the anhydrous and non-solvated crystalline form (Form B) of lorlatinib or
25 the composition comprising the crystalline form B of lorlatinib as defined in any one of the above described aspects and their corresponding embodiments is 25 mg or 100 mg calculated as anhydrous and non-solvated lorlatinib.

The at least one pharmaceutically acceptable excipient, which is comprised in the pharmaceutical composition of the present invention, is preferably selected from the group
30 consisting of fillers, binders, disintegrants, lubricants, glidants and combinations thereof.

Preferably, the at least one pharmaceutically acceptable excipient is selected from the group consisting of one or more fillers, a disintegrant and a lubricant. More preferably, the at least one pharmaceutically acceptable excipient is selected from the group consisting of microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, magnesium stearate and combinations thereof. Most preferably, all of these pharmaceutically acceptable excipients are comprised by the pharmaceutical composition of the present invention.

In a preferred embodiment, the pharmaceutical composition comprising the anhydrous and non-solvated crystalline form (Form B) of lorlatinib or the composition comprising the crystalline form B of lorlatinib as defined in any one of the above described aspects and their corresponding embodiments is an oral solid dosage form. More preferably, the oral solid dosage form is a tablet or a capsule, most preferably a tablet. In a particular embodiment, the pharmaceutical composition of the present invention as described above is a tablet, preferably a film-coated tablet, even more preferably an immediate-release film-coated tablet.

The pharmaceutical compositions of the present invention as defined in any one of the above described embodiments may be produced by standard manufacturing processes, which are well-known to the skilled person including e.g. blending, granulation (wet or dry granulation), tablet compression, film-coating or capsule filling and packaging.

For example, the tablet may be prepared by mixing the anhydrous and non-solvated crystalline form (Form B) of lorlatinib or the composition comprising the crystalline form B of lorlatinib as defined in any one of the above described aspects and their corresponding embodiments with at least one excipient such as fillers, binders, disintegrants, lubricants, glidants or combinations thereof. Optionally, a granulation step such as a dry or wet granulation step is performed before compression. The tablet cores may be additionally film-coated.

For example, the capsule may be prepared by mixing the anhydrous and non-solvated crystalline form (Form B) of lorlatinib or the composition comprising the crystalline form B of lorlatinib as defined in any one of the above described aspects and their corresponding embodiments with at least one excipient such as fillers, binders, disintegrants, lubricants, glidants or combinations thereof and filling the blend into a capsule. The capsule shell may be a gelatin shell or a hydroxypropylmethylcellulose (HPMC) shell.

In a further aspect, the present invention relates to the anhydrous and non-solvated crystalline form (Form B) of lorlatinib or the composition comprising the crystalline form B of lorlatinib or the pharmaceutical composition comprising the same as defined in any one of the above described aspects and their corresponding embodiments for use as a medicament.

- 5 In yet another aspect, the present invention relates to the anhydrous and non-solvated crystalline form (Form B) of lorlatinib or the composition comprising the crystalline form B of lorlatinib or the pharmaceutical composition comprising the same as defined in any one of the above described aspects and their corresponding embodiments for use in the treatment and/or prophylaxis of cancer.
- 10 Alternatively, the invention concerns a method of treating and/or preventing cancer, said method comprising administering an effective amount of the anhydrous and non-solvated crystalline form (Form B) of lorlatinib or the composition comprising the crystalline form B of lorlatinib or the pharmaceutical composition comprising the same as defined in any one of the above described aspects and their corresponding embodiments to a patient in need of such a
- 15 treatment.

In some embodiments, the cancer is selected from the group consisting of lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, carcinoma of the fallopian tubes, carcinoma of the

20 endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney

25 or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, or pituitary adenoma, and combinations thereof.

In other embodiments, the cancer is selected from the group consisting of non-small cell lung cancer (NSCLC), squamous cell carcinoma, hormone-refractory prostate cancer, papillary renal

30 cell carcinoma, colorectal adenocarcinoma, neuroblastoma, anaplastic large cell lymphoma (ALCL) and gastric cancer. In a particular embodiment, the cancer is ALK-positive NSCLC.

In another particular embodiment the cancer is NSCLC mediated by ALK or ROS1, and more particularly, NSCLC mediated by a genetically altered ALK and/or a genetically altered ROS1.

Lorlatinib dimethylformamide solvate (Form S-DMF), process for preparing the same and its use

In one embodiment the invention relates to a crystalline DMF-solvate (Form S-DMF) of lorlatinib characterized by having a PXRD comprising reflections at 2-Theta angles of:

$(5.7 \pm 0.2)^\circ$, $(7.6 \pm 0.2)^\circ$ and $(10.3 \pm 0.2)^\circ$; or

$(5.7 \pm 0.2)^\circ$, $(7.6 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$ and $(12.6 \pm 0.2)^\circ$; or

10 $(5.7 \pm 0.2)^\circ$, $(7.6 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$, $(12.1 \pm 0.2)^\circ$ and $(12.6 \pm 0.2)^\circ$; or

$(5.7 \pm 0.2)^\circ$, $(7.6 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$, $(12.1 \pm 0.2)^\circ$, $(12.6 \pm 0.2)^\circ$ and $(21.9 \pm 0.2)^\circ$; or

$(5.7 \pm 0.2)^\circ$, $(7.6 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$, $(12.1 \pm 0.2)^\circ$, $(12.6 \pm 0.2)^\circ$, $(21.3 \pm 0.2)^\circ$ and $(21.9 \pm 0.2)^\circ$; or

$(5.7 \pm 0.2)^\circ$, $(7.6 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$, $(12.1 \pm 0.2)^\circ$, $(12.6 \pm 0.2)^\circ$, $(20.2 \pm 0.2)^\circ$, $(21.3 \pm 0.2)^\circ$

15 and $(21.9 \pm 0.2)^\circ$; or

$(5.7 \pm 0.2)^\circ$, $(7.6 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$, $(12.1 \pm 0.2)^\circ$, $(12.6 \pm 0.2)^\circ$, $(17.2 \pm 0.2)^\circ$, $(20.2 \pm 0.2)^\circ$, $(21.3 \pm 0.2)^\circ$ and $(21.9 \pm 0.2)^\circ$; or

$(5.7 \pm 0.2)^\circ$, $(7.6 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$, $(12.1 \pm 0.2)^\circ$, $(12.6 \pm 0.2)^\circ$, $(16.8 \pm 0.2)^\circ$, $(17.2 \pm 0.2)^\circ$, $(20.2 \pm 0.2)^\circ$, $(21.3 \pm 0.2)^\circ$ and $(21.9 \pm 0.2)^\circ$,

20 when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.

In another embodiment, the invention relates to a crystalline DMF solvate (Form S-DMF) of lorlatinib characterized by having a PXRD comprising reflections at 2-Theta angles of $(7.6 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$, $(12.6 \pm 0.2)^\circ$, $(16.8 \pm 0.2)^\circ$, $(17.2 \pm 0.2)^\circ$, $(20.2 \pm 0.2)^\circ$, $(21.3 \pm 0.2)^\circ$, $(21.9 \pm 0.2)^\circ$, $(23.4 \pm 0.2)^\circ$ and $(23.6 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.

In a further embodiment, the present invention relates to a crystalline DMF solvate (Form S-DMF) of lorlatinib characterized by having a PXRD comprising reflections at 2-Theta angles of:

30 $(5.7 \pm 0.1)^\circ$, $(7.6 \pm 0.1)^\circ$ and $(10.3 \pm 0.1)^\circ$; or

$(5.7 \pm 0.1)^\circ$, $(7.6 \pm 0.1)^\circ$, $(10.3 \pm 0.1)^\circ$ and $(12.6 \pm 0.1)^\circ$; or

$(5.7 \pm 0.1)^\circ$, $(7.6 \pm 0.1)^\circ$, $(10.3 \pm 0.1)^\circ$, $(12.1 \pm 0.1)^\circ$ and $(12.6 \pm 0.1)^\circ$; or
 $(5.7 \pm 0.1)^\circ$, $(7.6 \pm 0.1)^\circ$, $(10.3 \pm 0.1)^\circ$, $(12.1 \pm 0.1)^\circ$, $(12.6 \pm 0.1)^\circ$ and $(21.9 \pm 0.1)^\circ$; or
 $(5.7 \pm 0.1)^\circ$, $(7.6 \pm 0.1)^\circ$, $(10.3 \pm 0.1)^\circ$, $(12.1 \pm 0.1)^\circ$, $(12.6 \pm 0.1)^\circ$, $(21.3 \pm 0.1)^\circ$ and $(21.9 \pm 0.1)^\circ$; or
5 $(5.7 \pm 0.1)^\circ$, $(7.6 \pm 0.1)^\circ$, $(10.3 \pm 0.1)^\circ$, $(12.1 \pm 0.1)^\circ$, $(12.6 \pm 0.1)^\circ$, $(20.2 \pm 0.1)^\circ$, $(21.3 \pm 0.1)^\circ$
and $(21.9 \pm 0.1)^\circ$; or
 $(5.7 \pm 0.1)^\circ$, $(7.6 \pm 0.1)^\circ$, $(10.3 \pm 0.1)^\circ$, $(12.1 \pm 0.1)^\circ$, $(12.6 \pm 0.1)^\circ$, $(17.2 \pm 0.1)^\circ$, $(20.2 \pm 0.1)^\circ$,
 $(21.3 \pm 0.1)^\circ$ and $(21.9 \pm 0.1)^\circ$; or
 $(5.7 \pm 0.1)^\circ$, $(7.6 \pm 0.1)^\circ$, $(10.3 \pm 0.1)^\circ$, $(12.1 \pm 0.1)^\circ$, $(12.6 \pm 0.1)^\circ$, $(16.8 \pm 0.1)^\circ$, $(17.2 \pm 0.1)^\circ$,
10 $(20.2 \pm 0.1)^\circ$, $(21.3 \pm 0.1)^\circ$ and $(21.9 \pm 0.1)^\circ$,
when measured at a temperature in the range of from 20 to 30 °C with Cu-K α _{1,2} radiation
having a wavelength of 0.15419 nm.

In yet another embodiment, the invention relates to a crystalline DMF solvate (Form S-DMF)
of lorlatinib characterized by having a PXRD comprising reflections at 2-Theta angles of $(7.6$
15 $\pm 0.1)^\circ$, $(10.3 \pm 0.1)^\circ$, $(12.6 \pm 0.1)^\circ$, $(16.8 \pm 0.1)^\circ$, $(17.2 \pm 0.1)^\circ$, $(20.2 \pm 0.1)^\circ$, $(21.3 \pm 0.1)^\circ$,
 $(21.9 \pm 0.1)^\circ$, $(23.4 \pm 0.1)^\circ$ and $(23.6 \pm 0.1)^\circ$, when measured at a temperature in the range of
from 20 to 30 °C with Cu-K α _{1,2} radiation having a wavelength of 0.15419 nm.

In yet another embodiment, the present invention relates to a crystalline DMF solvate (Form S-
DMF) of lorlatinib characterized by having a PXRD essentially the same as shown in Figure 6
20 of the present invention, when measured at a temperature in the range of from 20 to 30 °C with
Cu-K α _{1,2} radiation having a wavelength of 0.15419 nm.

In another aspect, the present invention relates to a process for the preparation of the crystalline
DMF solvate (Form S-DMF) of lorlatinib of the present invention comprising:

- a) contacting solid lorlatinib with DMF;
- 25 b) separating at least a part of the crystalline lorlatinib DMF solvate from DMF and
- c) optionally drying the crystalline lorlatinib DMF solvate.

Any solid form of lorlatinib can be used as starting material in step (a) of the above described
process e.g. crystalline lorlatinib, amorphous lorlatinib or mixtures thereof. Suitable crystalline
forms may for example be selected from the group consisting of Form 1-3 of
30 WO 2014/207606 A1, Form 24 of WO 2019/073347 A1 and Form 7 of WO 2017/021823 A1,
which may be prepared according to the teachings provided in the descriptions of the

respective patent applications. Preferably, the starting material is amorphous lorlatinib, which can be prepared according to the procedure described in Example 2 of WO 2013/132376 A1.

Contacting lorlatinib with DMF includes dissolving, crystallizing, evaporating, suspending, slurring, stirring, granulating, grinding, milling and the like of lorlatinib in the presence of DMF. It also includes contacting lorlatinib with DMF vapour. Most preferably, the solid lorlatinib starting material is dissolved in DMF, followed by solvent evaporation under reduced pressure until crystallization occurs.

Separating at least part, preferably all of the crystalline lorlatinib DMF solvate crystals from DMF encompasses any conventional method such as filtration, centrifugation, solvent evaporation or decantation.

The obtained crystals may then optionally be dried. Drying is performed at a temperature in the range of from about 15 to 25 °C. Drying may be performed for a period in the range of from about 1 to 48 hours, preferably of from about 1 to 24 hours. Drying is performed at ambient pressure. For example, the Form S-DMF crystals may be air-dried for 16 to 24 hours.

In another aspect, the invention relates to the use of the crystalline lorlatinib DMF solvate (Form S-DMF) as defined in anyone of the above described embodiments for the preparation of the anhydrous and non-solvated crystalline form (Form B) of lorlatinib or the composition comprising the crystalline form B of lorlatinib as defined in any one of the above described aspects and their corresponding embodiments.

Lorlatinib 1,4-dioxane solvate (Form S-DX), process for preparing the same and its use

In one embodiment the invention relates to a crystalline 1,4-dioxane solvate (Form S-DX) of lorlatinib characterized by having a PXRD comprising reflections at 2-Theta angles of:

$(5.5 \pm 0.2)^\circ$, $(7.0 \pm 0.2)^\circ$ and $(21.8 \pm 0.2)^\circ$; or

$(5.5 \pm 0.2)^\circ$, $(7.0 \pm 0.2)^\circ$, $(9.0 \pm 0.2)^\circ$ and $(21.8 \pm 0.2)^\circ$; or

$(5.5 \pm 0.2)^\circ$, $(7.0 \pm 0.2)^\circ$, $(8.6 \pm 0.2)^\circ$, $(9.0 \pm 0.2)^\circ$ and $(21.8 \pm 0.2)^\circ$; or

$(5.5 \pm 0.2)^\circ$, $(7.0 \pm 0.2)^\circ$, $(8.6 \pm 0.2)^\circ$, $(9.0 \pm 0.2)^\circ$, $(10.0 \pm 0.2)^\circ$ and $(21.8 \pm 0.2)^\circ$; or

$(5.5 \pm 0.2)^\circ$, $(7.0 \pm 0.2)^\circ$, $(8.6 \pm 0.2)^\circ$, $(9.0 \pm 0.2)^\circ$, $(10.0 \pm 0.2)^\circ$, $(15.0 \pm 0.2)^\circ$ and $(21.8 \pm 0.2)^\circ$;

or

$(5.5 \pm 0.2)^\circ$, $(7.0 \pm 0.2)^\circ$, $(8.6 \pm 0.2)^\circ$, $(9.0 \pm 0.2)^\circ$, $(10.0 \pm 0.2)^\circ$, $(15.0 \pm 0.2)^\circ$, $(18.8 \pm 0.2)^\circ$ and $(21.8 \pm 0.2)^\circ$; or

$(5.5 \pm 0.2)^\circ$, $(7.0 \pm 0.2)^\circ$, $(8.6 \pm 0.2)^\circ$, $(9.0 \pm 0.2)^\circ$, $(10.0 \pm 0.2)^\circ$, $(15.0 \pm 0.2)^\circ$, $(18.8 \pm 0.2)^\circ$, $(20.2 \pm 0.2)^\circ$ and $(21.8 \pm 0.2)^\circ$; or

5 $(5.5 \pm 0.2)^\circ$, $(7.0 \pm 0.2)^\circ$, $(8.6 \pm 0.2)^\circ$, $(9.0 \pm 0.2)^\circ$, $(10.0 \pm 0.2)^\circ$, $(15.0 \pm 0.2)^\circ$, $(18.8 \pm 0.2)^\circ$, $(20.2 \pm 0.2)^\circ$, $(20.6 \pm 0.2)^\circ$ and $(21.8 \pm 0.2)^\circ$,

when measured at a temperature in the range of from 20 to 30 °C with Cu-K α _{1,2} radiation having a wavelength of 0.15419 nm.

10 In another embodiment, the invention relates to a crystalline 1,4-dioxane solvate (Form S-DX) of lorlatinib characterized by having a PXRD comprising reflections at 2-Theta angles of $(5.5 \pm 0.2)^\circ$, $(7.0 \pm 0.2)^\circ$, $(8.6 \pm 0.2)^\circ$, $(9.0 \pm 0.2)^\circ$, $(10.0 \pm 0.2)^\circ$, $(15.0 \pm 0.2)^\circ$, $(17.1 \pm 0.2)^\circ$, $(18.8 \pm 0.2)^\circ$, $(21.8 \pm 0.2)^\circ$ and $(22.2 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20 to 30 °C with Cu-K α _{1,2} radiation having a wavelength of 0.15419 nm.

15 In a further embodiment, the present invention relates to a crystalline 1,4-dioxane solvate (Form S-DX) of lorlatinib characterized by having a PXRD comprising reflections at 2-Theta angles of:

$(5.5 \pm 0.1)^\circ$, $(7.0 \pm 0.1)^\circ$ and $(21.8 \pm 0.1)^\circ$; or

$(5.5 \pm 0.1)^\circ$, $(7.0 \pm 0.1)^\circ$, $(9.0 \pm 0.1)^\circ$ and $(21.8 \pm 0.1)^\circ$; or

$(5.5 \pm 0.1)^\circ$, $(7.0 \pm 0.1)^\circ$, $(8.6 \pm 0.1)^\circ$, $(9.0 \pm 0.1)^\circ$ and $(21.8 \pm 0.1)^\circ$; or

20 $(5.5 \pm 0.1)^\circ$, $(7.0 \pm 0.1)^\circ$, $(8.6 \pm 0.1)^\circ$, $(9.0 \pm 0.1)^\circ$, $(10.0 \pm 0.1)^\circ$ and $(21.8 \pm 0.1)^\circ$; or

$(5.5 \pm 0.1)^\circ$, $(7.0 \pm 0.1)^\circ$, $(8.6 \pm 0.1)^\circ$, $(9.0 \pm 0.1)^\circ$, $(10.0 \pm 0.1)^\circ$, $(15.0 \pm 0.1)^\circ$ and $(21.8 \pm 0.1)^\circ$; or

$(5.5 \pm 0.1)^\circ$, $(7.0 \pm 0.1)^\circ$, $(8.6 \pm 0.1)^\circ$, $(9.0 \pm 0.1)^\circ$, $(10.0 \pm 0.1)^\circ$, $(15.0 \pm 0.1)^\circ$, $(18.8 \pm 0.1)^\circ$ and $(21.8 \pm 0.1)^\circ$; or

25 $(5.5 \pm 0.1)^\circ$, $(7.0 \pm 0.1)^\circ$, $(8.6 \pm 0.1)^\circ$, $(9.0 \pm 0.1)^\circ$, $(10.0 \pm 0.1)^\circ$, $(15.0 \pm 0.1)^\circ$, $(18.8 \pm 0.1)^\circ$, $(20.2 \pm 0.1)^\circ$ and $(21.8 \pm 0.1)^\circ$; or

$(5.5 \pm 0.1)^\circ$, $(7.0 \pm 0.1)^\circ$, $(8.6 \pm 0.1)^\circ$, $(9.0 \pm 0.1)^\circ$, $(10.0 \pm 0.1)^\circ$, $(15.0 \pm 0.1)^\circ$, $(18.8 \pm 0.1)^\circ$, $(20.2 \pm 0.1)^\circ$, $(20.6 \pm 0.1)^\circ$ and $(21.8 \pm 0.1)^\circ$,

30 when measured at a temperature in the range of from 20 to 30 °C with Cu-K α _{1,2} radiation having a wavelength of 0.15419 nm.

In yet another embodiment, the invention relates to a crystalline 1,4-dioxane solvate (Form S-DX) of lorlatinib characterized by having a PXRD comprising reflections at 2-Theta angles of $(5.5 \pm 0.1)^\circ$, $(7.0 \pm 0.1)^\circ$, $(8.6 \pm 0.1)^\circ$, $(9.0 \pm 0.1)^\circ$, $(10.0 \pm 0.1)^\circ$, $(15.0 \pm 0.1)^\circ$, $(17.1 \pm 0.1)^\circ$, $(18.8 \pm 0.1)^\circ$, $(21.8 \pm 0.1)^\circ$ and $(22.2 \pm 0.1)^\circ$, when measured at a temperature in the range of from 20 to 30 °C with Cu-K α _{1,2} radiation having a wavelength of 0.15419 nm.

In yet another embodiment, the present invention relates to a crystalline 1,4-dioxane solvate (Form S-DX) of lorlatinib characterized by having a PXRD essentially the same as shown in Figure 7 of the present invention, when measured at a temperature in the range of from 20 to 30 °C with Cu-K α _{1,2} radiation having a wavelength of 0.15419 nm.

In another aspect, the present invention relates to a process for the preparation of the crystalline 1,4-dioxane solvate (Form S-DX) of lorlatinib of the present invention comprising:

- a) contacting solid lorlatinib with a solvent comprising 1,4-dioxane and optionally at least one antisolvent;
- b) separating at least a part of the crystalline lorlatinib 1,4-dioxane solvate from the solvent and
- c) optionally drying the crystalline lorlatinib 1,4-dioxane solvate.

Any solid form of lorlatinib can be used as starting material in step (a) of the above described process e.g. crystalline lorlatinib, amorphous lorlatinib or mixtures thereof. Suitable crystalline forms may for example be selected from the group consisting of Form 1-3 of WO 2014/207606 A1, Form 24 of WO 2019/073347 A1 and Form 7 of WO 2017/021823 A1, which may be prepared according to the teachings provided in the descriptions of the respective patent applications. Preferably, the starting material is amorphous lorlatinib, which can be prepared according to the procedure described in Example 2 of WO 2013/132376 A1.

Contacting lorlatinib with a solvent comprising 1,4-dioxane and optionally at least one antisolvent includes dissolving, crystallizing, evaporating, suspending, slurrying, stirring, granulating, grinding, milling and the like of lorlatinib in the presence of 1,4-dioxane and optionally at least one antisolvent. The at least one optional antisolvent is preferably an alkane, most preferably *n*-heptane. The 1,4-dioxane/*n*-heptane ratio may range from (v/v): 1:3, 1:2, 1:1, 2:1 and 3:1, most preferably the 1,4-dioxane/*n*-heptane ratio is (v/v): 1:3.

Separating at least a part, preferably all of the crystalline lorlatinib 1,4-dioxanes solvate crystals from the solvent mixture comprising 1,4-dioxane and optionally at least one antisolvent encompasses any conventional method such as filtration, centrifugation or decantation.

5 The obtained wet crystals may then optionally be dried. Drying is performed carefully at a temperature in the range of from about 15 to 25 °C. Drying may be performed for a period in the range of from about 0.5 to 4 hours, preferably of from about 0.5 to 2 hours. Drying is performed at ambient pressure. For example, the Form S-DX crystals may be air-dried for 0.5 to 1 hour.

10 In another aspect, the invention relates to the use of the crystalline lorlatinib 1,4-dioxane solvate (Form S-DX) as defined in anyone of the above described embodiments for the preparation of the anhydrous and non-solvated crystalline form (Form B) of lorlatinib or the composition comprising the crystalline form B of lorlatinib as defined in any one of the above described aspects and their corresponding embodiments.

EXAMPLES

15 The following non-limiting examples are illustrative for the disclosure and are not to be construed as to be in any way limiting for the scope of the invention.

Example 1: Preparation of lorlatinib Form B

Method A:

20 Lorlatinib Form S-DMF (e.g. prepared according to one of the procedures described in Example 2 herein) was air-dried for 24 hours at RT, then ground using a mortar and pestle. The sample was then air-dried for another 24 hours at RT. The solvate (approximately 200 mg) was then heated from RT to 180 °C using a heating rate of ~10 K/min. Heating was performed using a hot-stage microscope. The resulting solid form was characterised with powder X-ray diffraction and TGA and consisted of Form B. The sample was heated a second time from RT to 180 °C,
25 heating rate ~10 K/min (HSM) and confirmed to still be form B using powder X-ray diffraction.

Method B:

Lorlatinib Form S-DX (e.g. prepared according to one of the procedures described in Example 3 herein) was air-dried for 30 minutes at RT, then ground using a mortar and pestle. The solvate (approximately 150 mg) was then heated from RT to 180 °C using a heating rate of ~10 K/min.

Heating was performed using a hot-stage microscope. The resulting solid form was characterised with powder X-ray diffraction and TGA and consisted of Form B. The sample was heated a second time from RT to 180 °C, heating rate ~10 K/min (HSM) and confirmed to still be form B using powder X-ray diffraction.

5

Example 2: Preparation of lorlatinib DMF solvate (Form S-DMF)Method A:

Amorphous lorlatinib (250 mg, e.g. prepared according to the procedure described in Example 2 of WO 2013/132376 A1) was placed in a round-bottom flask and dissolved in DMF (2 mL).

10 The solvent was evaporated using a rotary evaporator (40 °C/8-10 mbar) until crystallization of a white solid had occurred. The obtained solid was air-dried for 24 hours to obtain lorlatinib Form S-DMF.

Method B:

15 DMF (0.05 mL) was added to lorlatinib Form 7 (20 mg, e.g. prepared according to the procedure described in Example 1 of WO 2017/021823 A1). The mixture was stirred for one day at ambient conditions. The solid obtained was collected by filtration and air-dried for 24 hours to obtain lorlatinib Form S-DMF.

Method C:

20 Two drops of DMF were added to amorphous lorlatinib (35 mg e.g. prepared according to the procedure described in Example 2 of WO 2013/132376 A1). The mixture was transferred either into a ball-mill jar and ground for 10 minutes at 30 Hz or transferred into a mortar and ground manually. After air drying both procedures produced lorlatinib Form S-DMF.

Example 3: Preparation of lorlatinib 1,4-dioxane solvate (Form S-DX)Method A:

25 Amorphous lorlatinib (50 mg e.g. prepared according to the procedure described in Example 2 of WO 2013/132376 A1) was placed into glass vials. Up to five drops of different mixtures of 1,4-dioxane and *n*-heptane (v/v): 1:3, 1:2, 1:1, 2:1 and 3:1 were added and the mixtures were stirred for 12 hours at RT. After filtration all experiments produced lorlatinib Form S-DX.

Method B:

Two drops of a mixture consisting of either 1,4-dioxane or a mixture of 1,4-dioxane and *n*-heptane (v/v): 1:3, 1:2, 1:1, 2:1 and 3:1 were added to amorphous lorlatinib (30 mg e.g. prepared according to the procedure described in Example 2 of WO 2013/132376 A1). The mixtures were transferred either into a ball-mill jar and ground for 10 minutes at 30 Hz or transferred into a mortar and ground manually to produce lorlatinib Form S-DX.

Example 4: Characterization of the solid-state forms of the present invention (Form B, Form S-DMF and Form S-DX)

Powder X-ray diffraction

PXRDs of Form B, S-DMF and Form S-DX were recorded (at 25 °C) with an X'Pert PRO diffractometer (PANalytical, Almelo, The Netherlands) equipped with a Theta/Theta coupled goniometer in transmission geometry, programmable XYZ stage with well plate holder, Cu-K $\alpha_{1,2}$ radiation source with a focussing mirror, a 0.5° divergence slit, a 0.02° soller slit collimator and a 1° anti-scattering slit on the incident beam side, a 2 mm anti-scattering slit, a 0.04° soller slit collimator, a Ni-filter and a solid-state PIXcel detector on the diffracted beam side. The patterns were recorded at a tube voltage of 40 kV, tube current of 40 mA, applying a step-size of 0.013° 2-Theta with 1000 s or 2400 s per step (255 channels) in the angular range of 2° to 40° 2-Theta.

A representative diffractogram of crystalline form B of lorlatinib is displayed in Figure 1 herein.

The corresponding reflection list is provided in Table 1 below.

Reflection position [° 2-Theta]	Reflection position [° 2-Theta]	Reflection position [° 2-Theta]	Reflection position [° 2-Theta]
7.5	15.2	20.1	24.4
8.7	15.7	20.4	25.3
10.3	16.7	20.8	26.4
11.2	17.2	21.5	26.9
11.5	17.5	21.9	27.7
11.8	18.2	22.4	28.6
13.3	18.8	23.2	28.9
14.0	19.3	23.8	29.7

Table 1: PXRD reflection positions of crystalline Form B of lorlatinib in the range of from 2 to 30° 2-Theta; a typical precision of the 2-Theta values is in the range of $\pm 0.2^\circ$ 2-Theta, preferably of $\pm 0.1^\circ$ 2-Theta.

Figure 2 illustrates an overlay of the PXRDs of lorlatinib Form B of the present invention (bottom) and Form 7 of WO 2017/021823 A1 (top). As can be seen both forms can be readily distinguished from each other by powder X-ray diffractometry. For example, the PXRD of lorlatinib Form B possesses reflections at $(8.7 \pm 0.2)^\circ$, $(13.3 \pm 0.2)^\circ$, $(16.7 \pm 0.2)^\circ$ and $(18.8 \pm 0.2)^\circ$ 2-Theta, whereas no reflections are visible in the PXRD of lorlatinib Form 7 in this range. On the other hand, the PXRD of lorlatinib Form 7 displays *i.a.* reflections at $(9.6 \pm 0.2)^\circ$, $(12.6 \pm 0.2)^\circ$ and $(16.2 \pm 0.2)^\circ$ 2-Theta, whereas the PXRD of lorlatinib Form 7 shows no reflection in these ranges.

A representative diffractogram of the crystalline DMF solvate (Form S-DMF) of lorlatinib is displayed in Figure 6 herein. The corresponding reflection list is provided in Table 2 below.

Reflection position [° 2-Theta]	Reflection position [° 2-Theta]	Reflection position [° 2-Theta]	Reflection position [° 2-Theta]
5.7	12.1	19.2	22.8
7.6	12.6	20.2	23.4
10.0	16.8	20.8	23.6
10.3	17.2	21.3	24.0
11.0	17.6	21.9	26.1
11.5	18.5	22.4	28.7

Table 2: PXRD reflection positions of crystalline Form S-DMF of lorlatinib in the range of from 2 to 30° 2-Theta; a typical precision of the 2-Theta values is in the range of $\pm 0.2^\circ$ 2-Theta, preferably of $\pm 0.1^\circ$ 2-Theta.

A representative diffractogram of the crystalline 1,4-dioxane solvate of lorlatinib (Form S-DX) is displayed in Figure 7 herein. The corresponding reflection list is provided in Table 3 below.

Reflection position [° 2-Theta]	Reflection position [° 2-Theta]	Reflection position [° 2-Theta]	Reflection position [° 2-Theta]
5.5	11.5	17.3	21.8
7.0	11.8	18.1	22.2
8.3	14.0	18.8	22.8
8.6	15.0	19.3	23.2

9.0	15.2	19.5	23.5
10.0	15.8	20.2	24.0
10.2	16.0	20.6	24.4
11.2	17.1	21.4	25.2

Table 3: PXRD reflection positions of crystalline Form S-DX of lorlatinib in the range of from 2 to 30° 2-Theta; a typical precision of the 2-Theta values is in the range of $\pm 0.2^\circ$ 2-Theta, preferably of $\pm 0.1^\circ$ 2-Theta.

5 Fourier transform infrared spectroscopy

The FTIR spectrum was recorded (obtained) on an MKII Golden Gate™ Single Reflection Diamond ATR cell with a Bruker Tensor 27 FTIR spectrometer with 4 cm⁻¹ resolution at RT. To record a spectrum a spatula tip of the sample was applied to the surface of the diamond in powder form. Then the sample was pressed onto the diamond with a sapphire anvil and the spectrum was recorded. A spectrum of the clean diamond was used as background spectrum

A representative FTIR spectrum of the crystalline Form B of lorlatinib according to the present invention is displayed in Figure 3 and the corresponding peak list is provided in Table 4 below.

Wavenumber [cm ⁻¹]	Wavenumber [cm ⁻¹]	Wavenumber [cm ⁻¹]
3471	1417	972
3397	1395	936
2979	1367	888
2935	1335	824
2233	1291	764
1633	1237	732
1622	1197	691
1588	1164	666
1486	1067	630
1444	1049	

Table 4: FTIR peak list of crystalline Form B of lorlatinib according to the present invention; a typical precision of the wavenumbers is in the range of ± 4 cm⁻¹, preferably of ± 2 cm⁻¹.

15 Differential scanning calorimetry

DSC was performed on a Mettler Polymer DSC R instrument. The sample (4.46 mg) was heated in a 40 microL aluminium pan with a pierced aluminium lid from 25 to 250 °C at a rate of 10 K/min. Nitrogen (purge rate 50 mL/min) was used as purge gas.

5 A representative DSC curve (excerpt from 25 to 220 °C) is displayed in Figure 4 hereinafter and shows an endotherm with an onset temperature of about 191 °C and a peak temperature of about 198 °C, which is due to the melting of the sample.

Thermogravimetric analysis

10 TGA was carried out with a TGA7 system (Perkin-Elmer, Norwalk, Connecticut, USA) using Pyris 2.0 software. Approximately 4 mg of sample was weighed into a platinum pan. Two-point calibration of the temperature was performed with ferromagnetic materials (Alumel and Ni, Curie-point standards, Perkin-Elmer). The sample was heated to 225 °C at a rate of 10 K/min and dry nitrogen was used as a purge gas (sample purge: 20 mL/min, balance purge: 40 mL/min).

15 A representative TGA curve is displayed in Figure 5. The sample shows a weight loss of only 0.3 w-% up to a temperature of 200 °C, which is due to sublimation and decomposition. TGA demonstrates the anhydrous and non-solvated nature of polymorph B.

Example 5: Stability of lorlatinib Form B

Stress Condition A:

20 Form B was stored at ambient condition and the phase consistency analysed periodically using powder X-ray diffraction. No transformation to Form 7 or any other solid form was seen within 59 days.

Stress Condition B:

25 Form B was stored at 40 °C (drying oven) and the phase identity checked periodically with powder X-ray diffraction. Within 47 days no transformation to Form 7 or any other form was seen.

Stress Condition C:

Form B was stored at 98% RH (RT) and the phase identity checked periodically with powder X-ray diffraction. Within 55 days no transformation to Form 7 or any other form was seen.

Stress Condition D:

An FTIR heating experiment was performed with a temperature-controlled diamond ATR (PIKE GaldiATR) crystal on a Bruker Vertex 70 FTIR spectrometer (Bruker Analytische Messtechnik GmbH, Germany). The spectra were recorded between 4000 and 400 cm^{-1} at an instrument resolution of 2 cm^{-1} (38 scans per spectrum). Heating experiments performed with lorlatinib Form B of the present invention revealed that Form B is stable upon heating in the temperature range of 25 to 180 °C.

Stress Condition E:

A manual laboratory press (PW10, P/O Weber, D-Remshalden) equipped with force and displacement sensors (Hottinger Baldwin, D-Darmstadt) was used for producing tablets consisting of neat lorlatinib Form B, whereat a tableting pressure of 4 kN was applied. According to powder X-ray diffraction, no phase transformation to Form 7 or any other form occurred.

Example 6: Immediate release film-coated tablets comprising lorlatinib Form B

Immediate release film-coated tablets were prepared in 25 mg, 50 mg and 100 mg strengths using a dry granulation manufacturing process prior to compression. Lorlatinib Form B was blended with some proportion of the excipients and the blend was dry granulated using a roller compactor. After milling the granules were blended with the remainder of the excipients and tablets were compressed. The compositions of the tablets are provided in Table 5:

*removed during processing; does not appear in final product

Component	Component Role	25 mg tablet [mg/tablet]	50 mg tablet [mg/tablet]	100 mg tablet [mg/tablet]
Lorlatinib Form B	Active ingredient	25.000	50.000	100.000
Microcrystalline cellulose	Filler	143.325	286.650	355.540
Dibasic calcium phosphate anhydrous	Filler	71.675	143.350	177.800

Sodium starch glycolate	Disintegrant	7.500	15.000	20.000
Magnesium stearate	Lubricant	2.500	5.000	13.330
Tablet core weight		250.000	500.000	666.670
Opadry II tan or lavender	Coating agent	7.500	15.000	20.000
Sterile water for irrigation*		(42.500)	(85.000)	(113.330)
Total weight [mg]		257.500	515.000	686.670

Table 5: Immediate release tablets comprising lorlatinib Form B

Example 7: Scale-up of lorlatinib Form B

Lorlatinib (45.9 g) was charged in a glass reactor and dissolved in 1,4-dioxane (305 mL) at 25 °C. Subsequently, *n*-heptane (250 mL) was slowly added to the solution. After complete *n*-heptane addition the mixture was seeded with lorlatinib dioxane solvate (50 mg, e.g. prepared according to one of the procedures described in example 3 herein) and further stirred for 1 hour at 25 °C followed by 3 hours at 0 °C. The obtained solid was collected by filtration, washed with *n*-heptane and dried under vacuum (10 mbar) at 100 °C for 17 hours to yield lorlatinib Form B (43.5 g).

Comparative Example 1: Solubility of Form B and Form 7

The solubility of the two polymorphs, Form 7 of WO 2017/021823 A1 and Form B of the present invention, was estimated in a 1:3 (v/v) *n*-heptane / toluene mixture using the Crystal16 parallel-reactor system. A heating rate of 0.3 K/min was applied. In the entire investigated temperature range of 15-87 °C Form B shows on average a solubility which is 60% higher than that of Form 7. Due to the fact that the solubility ratio of two polymorphs is independent of the solvent, a solvent mixture in which approx. 4 to 20 mg of lorlatinib dissolve in 1 mL has been chosen for the experiments. The corresponding solubility curves are displayed in Figure 8.

Comparative Example 2: Solubility of Form B and Form 7 in biorelevant medium

The solubility of the two polymorphs, Form 7 of WO 2017/021823 A1 and Form B of the present invention, was determined in Fessif medium pH 5.0 at 37 °C. In the entire investigated time range Form B shows on average a solubility which is 60% higher than that of Form 7. The corresponding solubility curves are displayed in Figure 9.

Comparative Example 3: Water wettability of Form B and Form 7

Drop shape analysis (DSA) gives information about the wetting behaviour of a compound. The shadow images of the sessile water drops were captured by a *Kruess DSA25E* instrument (*Kruess, D-Hamburg, Germany*), equipped with illumination, a manual lift table (z-axis) and a video camera. The software *Kruess Advance 1.6.2* was used for measuring the contact angle. The results are displayed in Table 6 below:

	Contact angle (wettability)
Lorlatinib Form B	79.7° - 82.4°
Lorlatinib Form 7	83.4° - 89.9°

Table 6: Comparison of contact angles (wettability)

A smaller contact angle indicates higher wettability. Hence Form B shows better water wettability than Form 7.

CLAIMS

- 1) An anhydrous and non-solvated crystalline form (Form B) of (10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-4,8-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (lorlatinib) characterized by having a powder X-ray diffractogram comprising reflections at 2-Theta angles of $(8.7 \pm 0.2)^\circ$, $(11.2 \pm 0.2)^\circ$ and $(11.8 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.
- 2) The crystalline form of claim 1 characterized by having a powder X-ray diffractogram comprising additional reflections at 2-Theta angles of $(10.3 \pm 0.2)^\circ$ and/or $(18.8 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.
- 3) The crystalline form according to claim 1 or 2 characterized by having a Fourier transform infrared spectrum comprising peaks at wavenumbers of $(3471 \pm 4) \text{ cm}^{-1}$, $(3397 \pm 4) \text{ cm}^{-1}$, $(2979 \pm 4) \text{ cm}^{-1}$, $(2233 \pm 4) \text{ cm}^{-1}$ and $(1633 \pm 4) \text{ cm}^{-1}$, when measured at a temperature in the range of from 20 to 30 °C with a diamond ATR cell.
- 4) The crystalline form according to any one of the preceding claims characterized by having a differential scanning calorimetry curve comprising an endothermic peak having an onset at a temperature of $(191 \pm 5)^\circ\text{C}$, when measured at a heating rate of 10 K/min.
- 5) The crystalline form according to any one of the preceding claims characterized by having a thermogravimetric analysis curve showing a mass loss of not more than 0.5 w-% based on the weight of the crystalline form, when heated from 25 to 200 °C at a rate of 10 K/min.
- 6) A composition comprising the crystalline form as defined in any one of the preceding claims and at most 20 w-%, 10 w-%, 5 w-%, 4 w-%, 3 w-%, 2 w-% or 1 w-% of any other solid-state form of lorlatinib, based on the weight of the composition.
- 7) The composition according to claim 6, wherein the other solid-state form of lorlatinib is Form 7 characterized by having a powder X-ray diffractogram comprising reflections at 2-Theta angles of $(9.6 \pm 0.2)^\circ$, $(10.1 \pm 0.2)^\circ$, $(14.3 \pm 0.2)^\circ$, $(16.2 \pm 0.2)^\circ$ and $(17.3 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.

- 8) The composition as defined in claim 6 or 7, characterized by having a PXRD comprising no reflections at 2-Theta angles of $(9.6 \pm 0.2)^\circ$, $(12.6 \pm 0.2)^\circ$ and $(16.2 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.
- 5 9) Use of the crystalline form as defined in any one of claims 1 to 5 or the composition as defined in any one of claims 6 to 8 for the preparation of a pharmaceutical composition.
- 10) A pharmaceutical composition comprising the crystalline form as defined in any one of claims 1 to 5 or the composition as defined in any one of claims 6 to 8 and at least one pharmaceutically acceptable excipient.
- 10 11) The pharmaceutical composition of claim 10, which is an oral solid dosage form.
- 12) The crystalline form as defined in any one of claims 1 to 5, the composition as defined in any one of claims 6 to 8 or the pharmaceutical composition of claim 10 or 11 for use in the treatment and/or prophylaxis of cancer.
- 13) A crystalline dimethylformamide solvate (Form S-DMF) of (10*R*)-7-amino-12-fluoro-
15 2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-4,8-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (lorlatinib) characterized by having a powder X-ray diffractogram comprising reflections at 2-Theta angles of $(5.7 \pm 0.2)^\circ$, $(7.6 \pm 0.2)^\circ$ and $(10.3 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.
- 20 14) A crystalline 1,4-dioxane solvate (Form S-DX) of (10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-4,8-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (lorlatinib) characterized by having a powder X-ray diffractogram comprising reflections at 2-Theta angles of $(5.5 \pm 0.2)^\circ$, $(7.0 \pm 0.2)^\circ$ and $(21.8 \pm 0.2)^\circ$, when measured at a temperature in the range of
25 from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.
- 15) Use of the solvate as defined in claim 13 or 14 for the preparation of the crystalline form as defined in any one of claims 1 to 5 or the composition as defined in any one of claims 6 to 8.

Figure 1

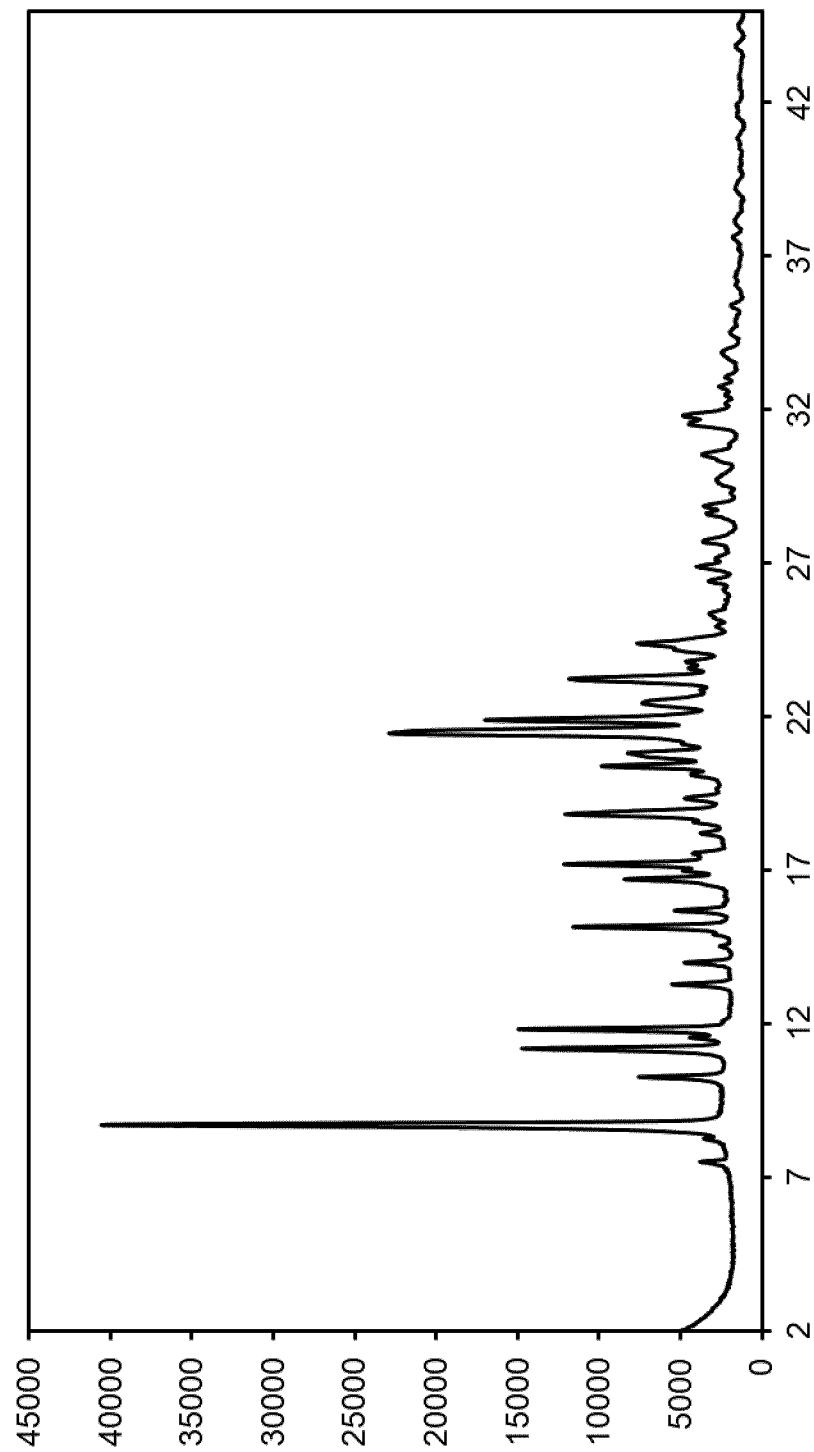


Figure 2

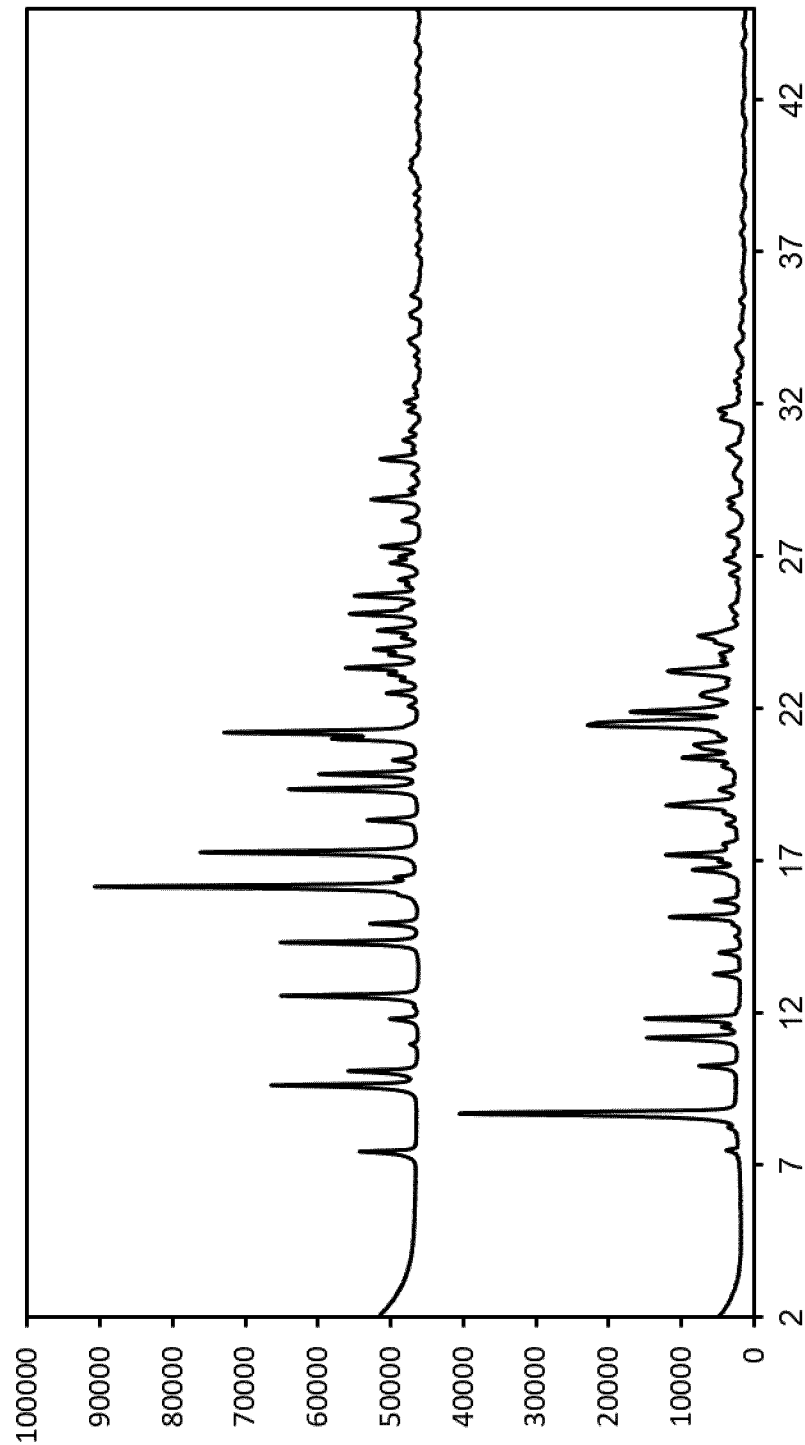


Figure 3

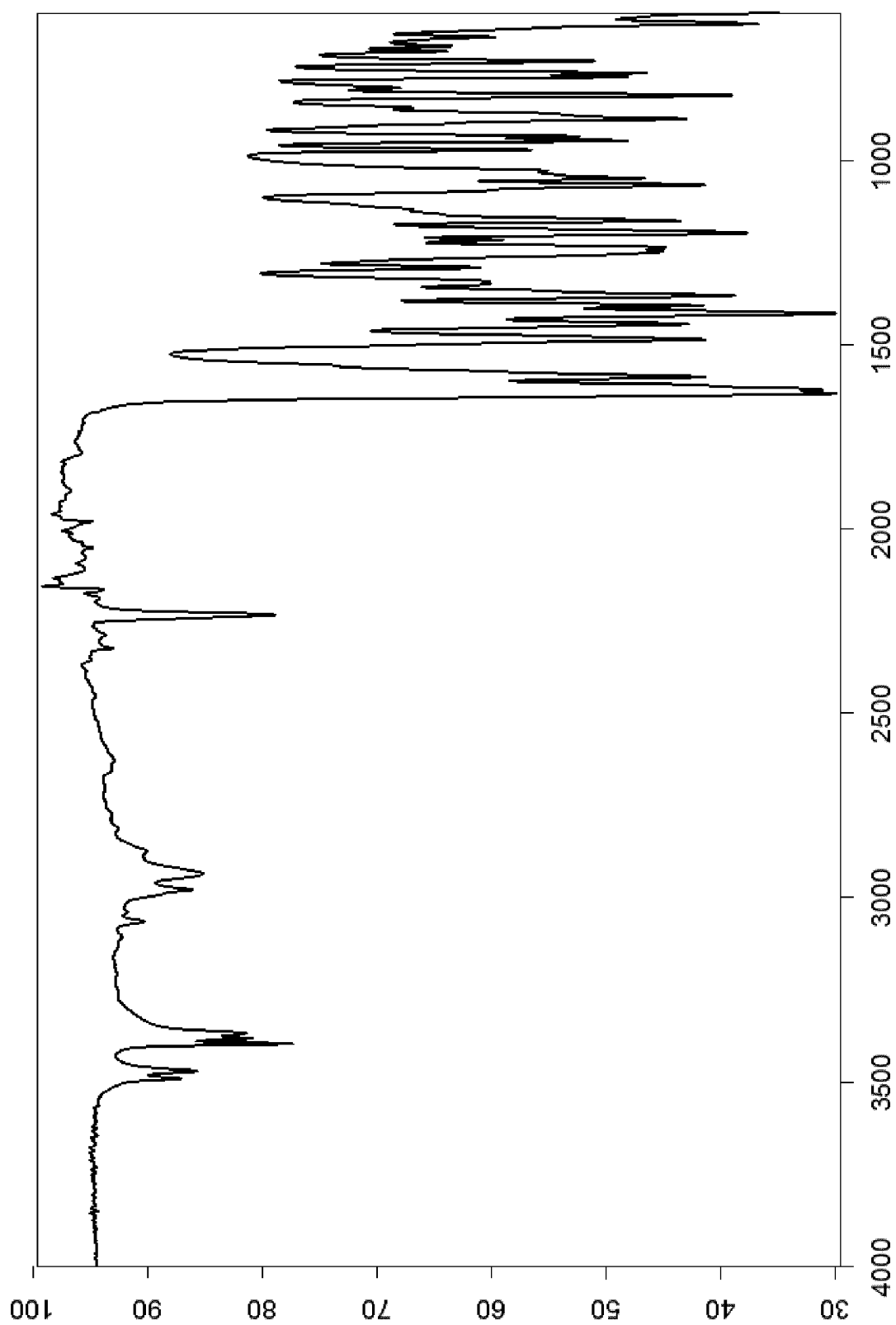


Figure 4

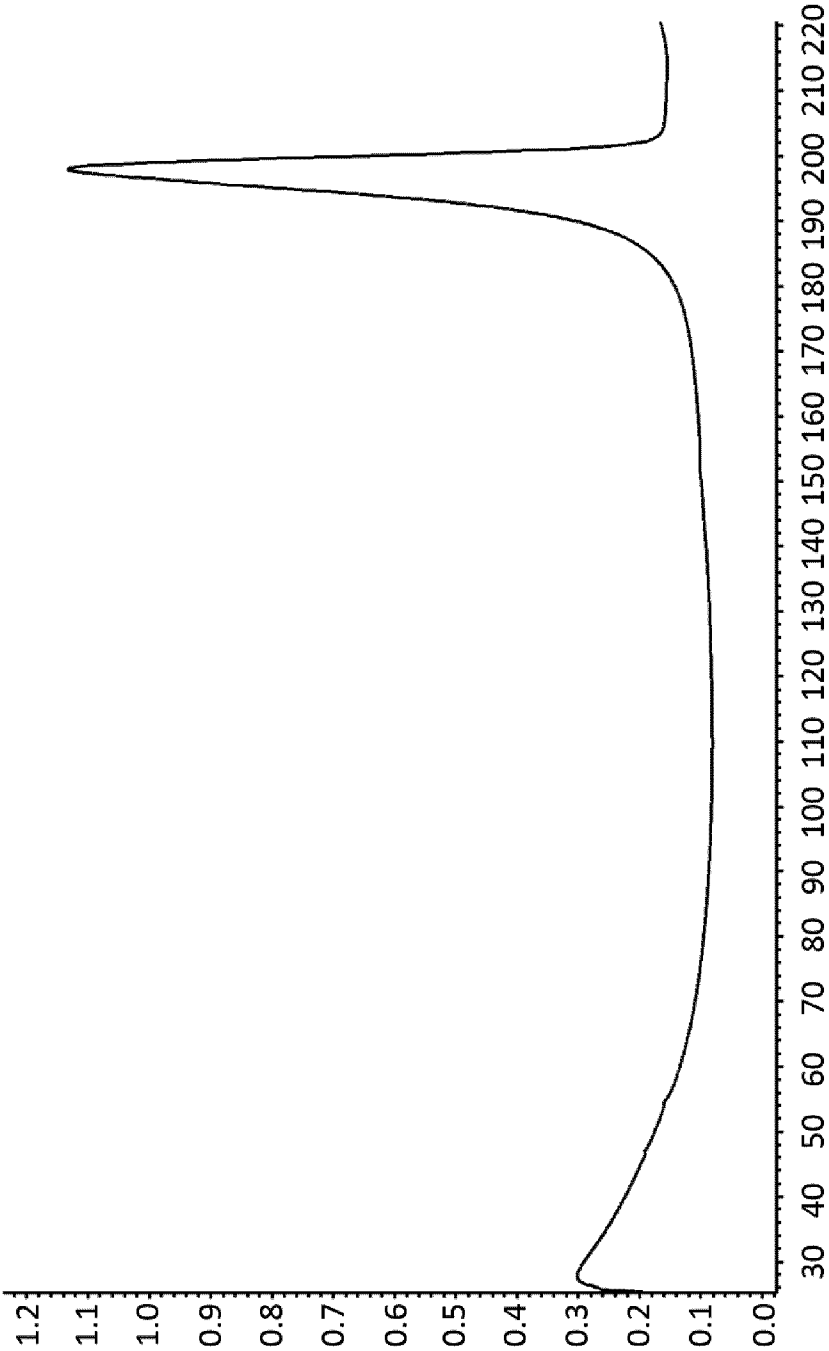


Figure 5

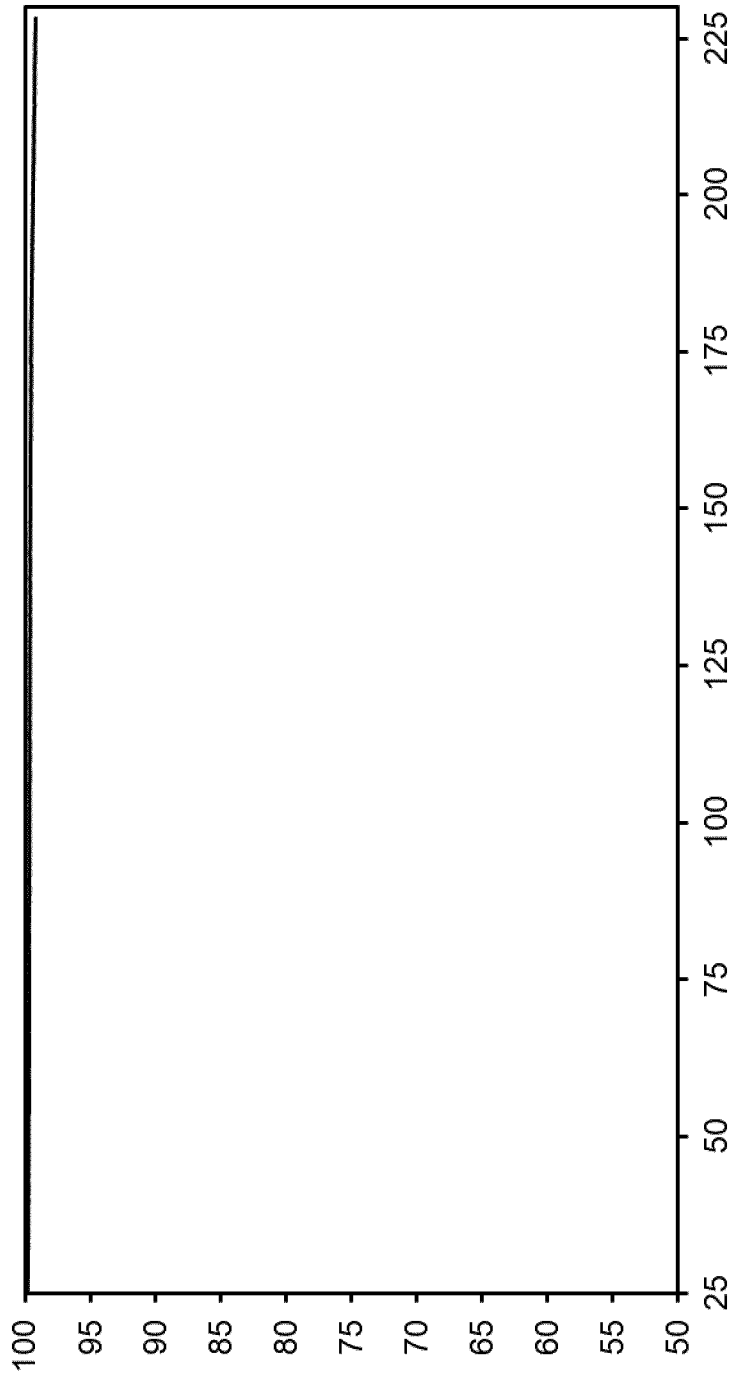


Figure 6

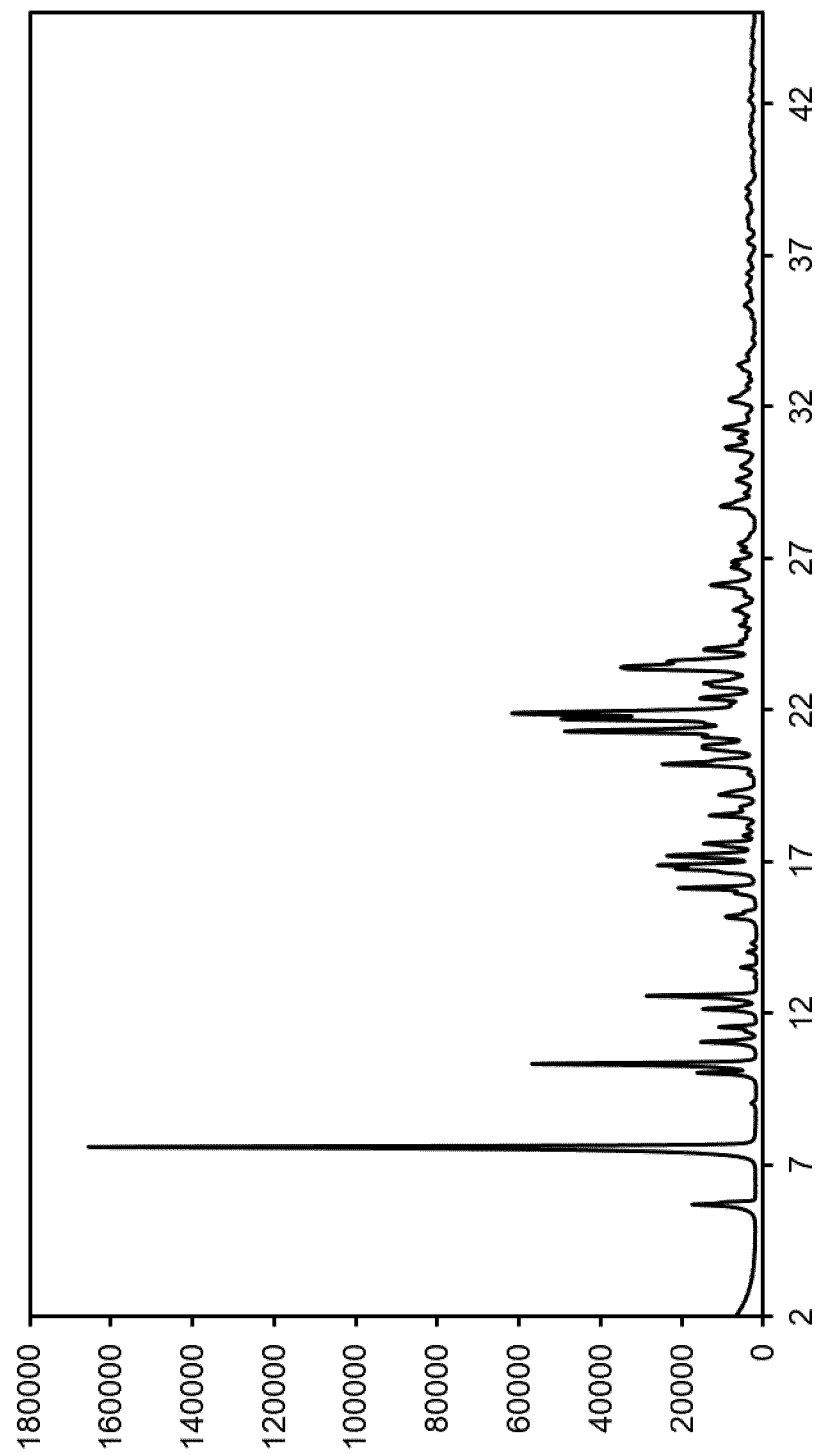


Figure 7

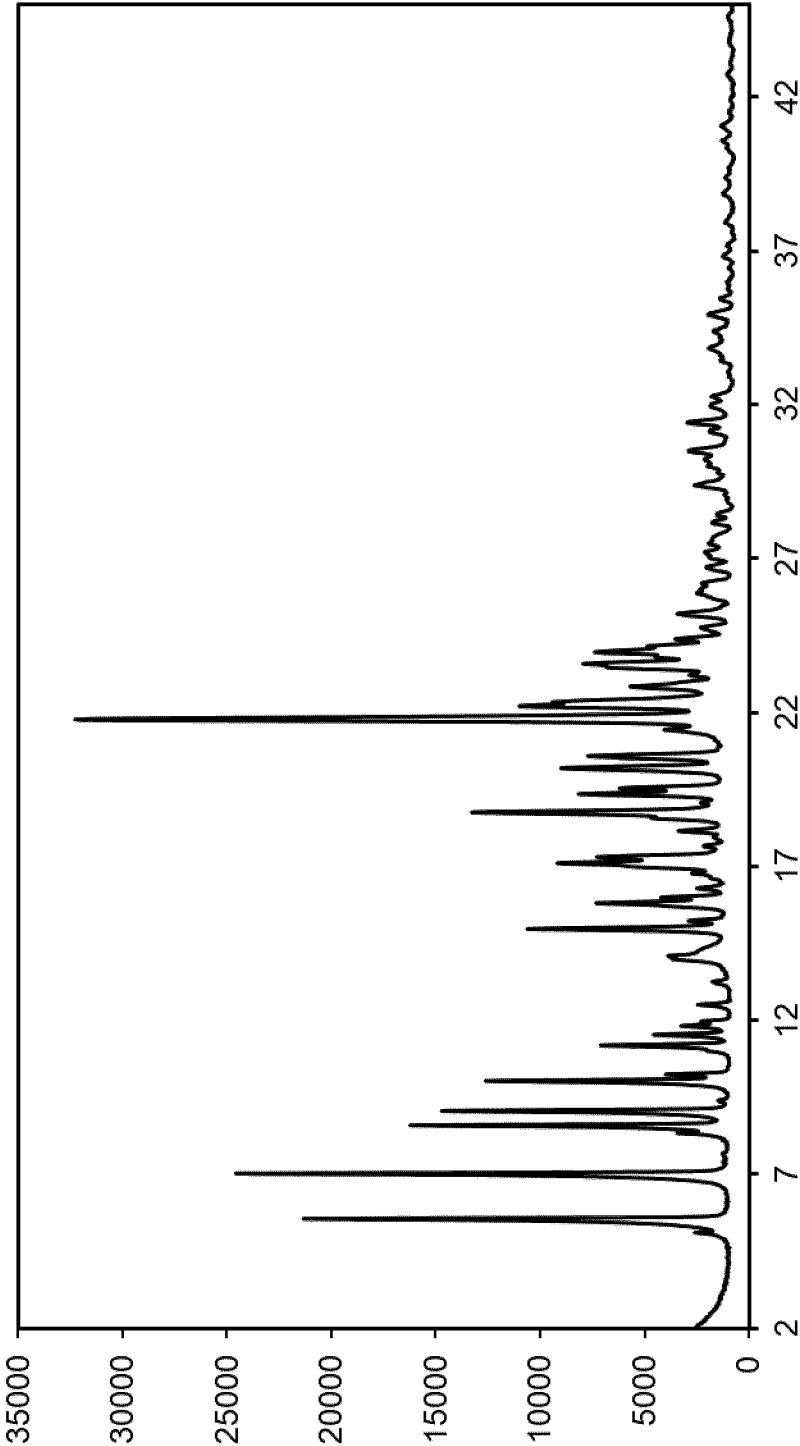


Figure 8

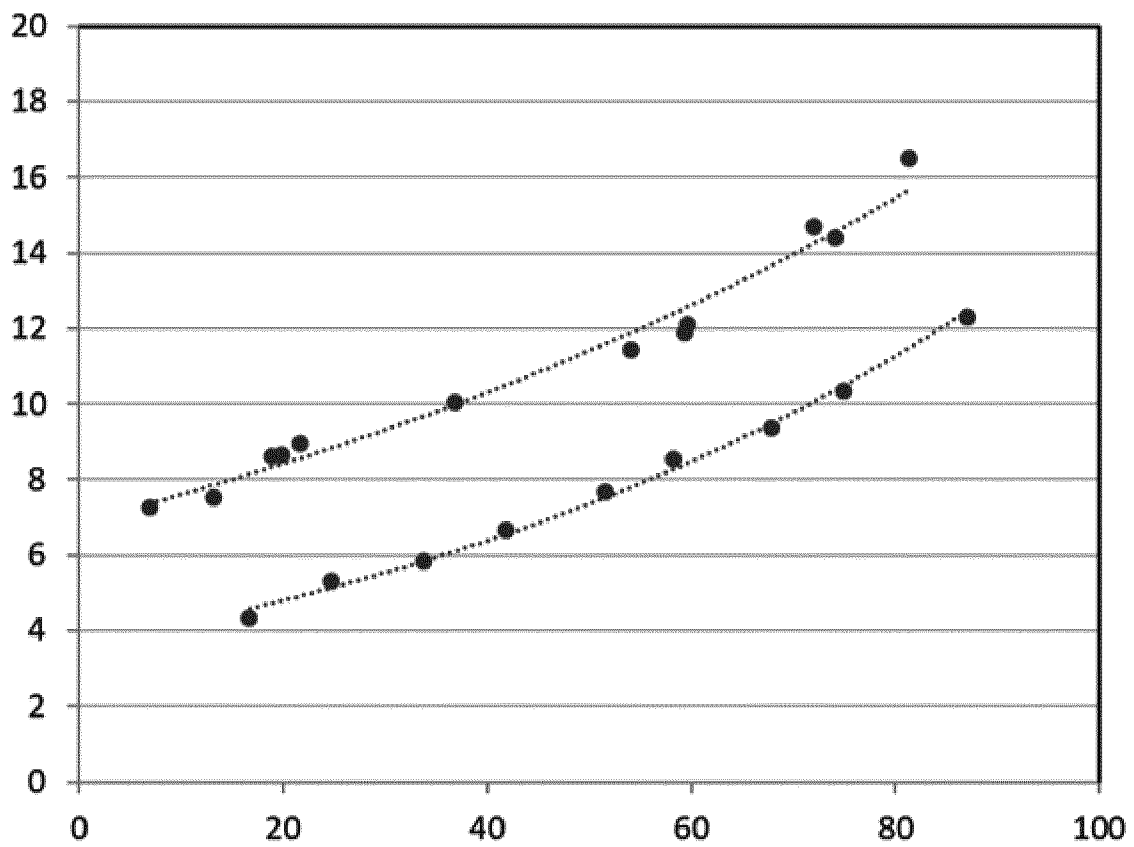
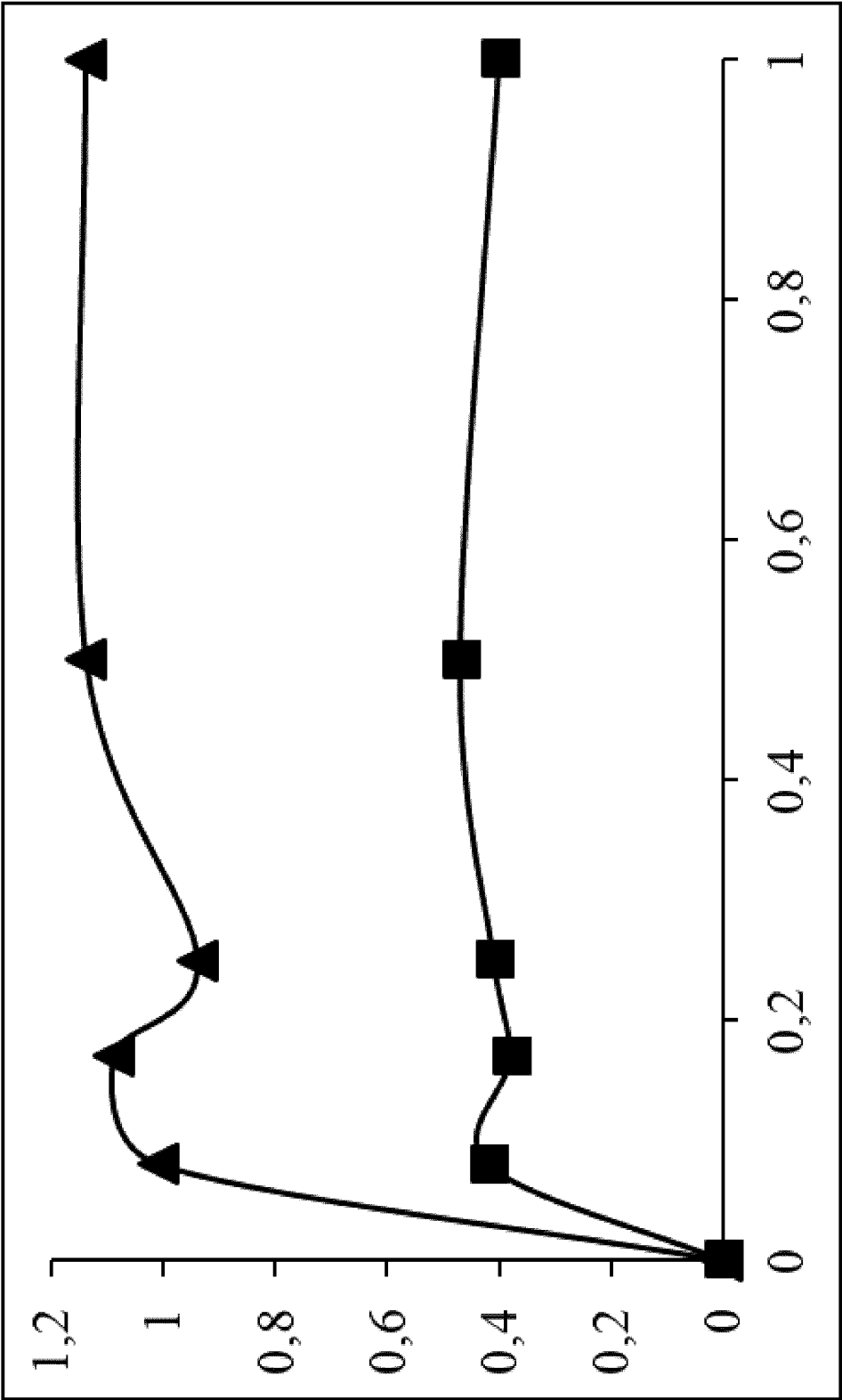


Figure 9



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/078254

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61P35/00 C07D498/18 A61K31/439
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61P C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2017/021823 A1 (PFIZER [US]) 9 February 2017 (2017-02-09) cited in the application claims; examples -----	1-15
X,P	WO 2019/209633 A1 (PLIVA HRVATSKA D O O [HR]; TEVA PHARMA [US]) 31 October 2019 (2019-10-31) claims; figures; examples -----	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

23 October 2020

Date of mailing of the international search report

13/11/2020

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2020/078254

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