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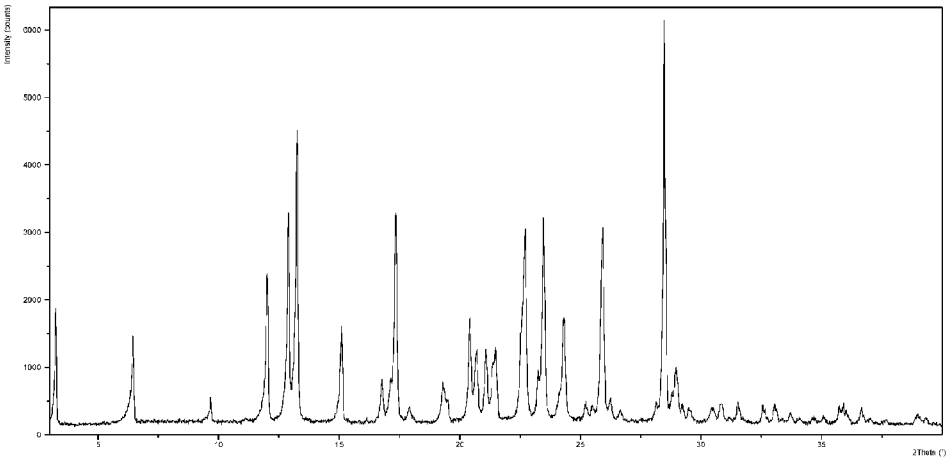
(54) Title: SOLID STATE FORMS OF AFICAMTEN AND PROCESS FOR PREPARATION THEREOF

Figure 1: crystalline Form M1 of Aficamten: maleic acid



(57) Abstract: The present disclosure encompasses solid state forms of Aficamten, in embodiments crystalline polymorphs of Aficamten, processes for preparation thereof, and pharmaceutical compositions thereof.

[Continued on next page]

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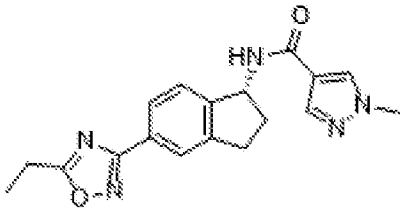
SOLID STATE FORMS OF AFICAMTEN AND PROCESS FOR PREPARATION THEREOF

FIELD OF THE DISCLOSURE

[0001] The present disclosure encompasses solid state forms of Aficamten, in embodiments crystalline polymorphs of Aficamten, processes for preparation thereof, and pharmaceutical compositions thereof.

BACKGROUND OF THE DISCLOSURE

[0002] Aficamten, *N*-[(1*R*)-5-(5-ethyl-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-inden-1-yl]-1-methylpyrazole-4-carboxamide, has the following structure:



[0003] Aficamten is a cardiac myosin inhibitor, developed for the treatment of cardiovascular disease, especially obstructive hypertrophic cardiomyopathy (oHCM). The compound is disclosed in US10836755. International publication No. WO2021/011807 describes different polymorphs of Aficamten; including Form I.

[0004] Polymorphism, the occurrence of different crystalline forms, is a property of some molecules and molecular complexes. A single molecule may give rise to a variety of polymorphs having distinct crystal structures and physical properties like melting point, thermal behaviors (e.g., measured by thermogravimetric analysis ("TGA"), or differential scanning calorimetry ("DSC")), X-ray diffraction (XRD) pattern, infrared absorption fingerprint, and solid state (^{13}C) NMR spectrum. One or more of these techniques may be used to distinguish different polymorphic forms of a compound.

[0005] Different salts and solid state forms (including solvated forms) of an active pharmaceutical ingredient may possess different properties. Such variations in the properties of different salts and solid state forms and solvates may provide a basis for improving formulation, for example, by facilitating better processing or handling characteristics, changing the

dissolution profile in a favorable direction, or improving stability (polymorph as well as chemical stability) and shelf-life. These variations in the properties of different salts and solid state forms may also offer improvements to the final dosage form, for instance, if they serve to improve bioavailability. Different salts and solid state forms and solvates of an active pharmaceutical ingredient may also give rise to a variety of polymorphs or crystalline forms, which may in turn provide additional opportunities to assess variations in the properties and characteristics of a solid active pharmaceutical ingredient.

[0006] Discovering new salts, solid state forms and solvates of a pharmaceutical product may yield materials having desirable processing properties, such as ease of handling, ease of processing, storage stability, and ease of purification or as desirable intermediate crystal forms that facilitate conversion to other polymorphic forms. New solid state forms of a pharmaceutically useful compound can also provide an opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for formulation optimization, for example by providing a product with different properties, including a different crystal habit, higher crystallinity, or polymorphic stability, which may offer better processing or handling characteristics, improved dissolution profile, or improved shelf-life (chemical/physical stability). For at least these reasons, there is a need for additional salts and solid state forms (including solvated forms) of Aficamten.

SUMMARY OF THE DISCLOSURE

[0007] The present disclosure provides crystalline polymorphs of Aficamten, processes for preparation thereof, and pharmaceutical compositions thereof. These crystalline polymorphs can be used to prepare other solid state forms of Aficamten, other Aficamten salts and their solid state forms.

[0008] The present disclosure also provides uses of the said solid state forms of Aficamten in the preparation of other solid state forms of Aficamten or other salts and their solid state forms thereof.

[0009] The present disclosure provides crystalline polymorphs of Aficamten for use in medicine, including for the treatment of cardiovascular disease, especially obstructive hypertrophic cardiomyopathy (oHCM).

[0010] The present disclosure also encompasses the use of crystalline polymorphs of Aficamten of the present disclosure for the preparation of pharmaceutical compositions and/or formulations, particularly pharmaceutical compositions or formulations for oral administration.

[0011] In another aspect, the present disclosure provides pharmaceutical compositions comprising crystalline polymorphs of Aficamten according to the present disclosure. Pharmaceutical compositions according to any aspect of the present disclosure may include oral dosage forms.

[0012] The present disclosure includes processes for preparing the above mentioned pharmaceutical compositions. The processes include combining any one or a combination of the crystalline polymorphs of Aficamten with at least one pharmaceutically acceptable excipient. Particularly, the pharmaceutical compositions may comprise pharmaceutically acceptable excipient suitable for preparing an oral dosage form.

[0013] The crystalline polymorph of Aficamten as defined herein and the pharmaceutical compositions or formulations of the crystalline polymorph of Aficamten may be used as medicaments, such as for treatment of cardiovascular disease, especially obstructive hypertrophic cardiomyopathy (oHCM).

[0014] The present disclosure also provides methods for treating cardiovascular disease, especially obstructive hypertrophic cardiomyopathy (oHCM), by administering a therapeutically effective amount of any one or a combination of the crystalline polymorphs of Aficamten of the present disclosure, or at least one of the above pharmaceutical compositions, to a subject suffering from cardiovascular disease, especially obstructive hypertrophic cardiomyopathy (oHCM), or otherwise in need of the treatment.

[0015] The present disclosure also provides uses of crystalline polymorphs of Aficamten of the present disclosure, or at least one of the above pharmaceutical compositions, for the manufacture of medicaments for treating e.g., cardiovascular disease, especially obstructive hypertrophic cardiomyopathy (oHCM). The medicament may be administered as an intranasal dosage form, or may be administered as an oral dosage form.

[0016] According to any aspect or embodiment of the present disclosure, pharmaceutical compositions or formulations for the treatment of cardiovascular disease, especially obstructive hypertrophic cardiomyopathy (oHCM), are preferably in the form of oral dosage form.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] Figure 1 shows a characteristic XRPD of Crystalline Form M1 of Aficamten: maleic acid.

[0018] Figure 2 shows a characteristic X-ray powder diffraction pattern (XRPD) of pure Form I of Aficamten.

[0019] Figure 3 shows a characteristic ^{13}C CP-MAS NMR spectra of Aficamten: maleic acid form M1.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0020] The present disclosure encompasses solid state forms of Aficamten, including crystalline polymorphs of Aficamten, processes for preparation thereof, and pharmaceutical compositions thereof.

[0021] Solid state properties of Aficamten and crystalline polymorphs thereof can be influenced by controlling the conditions under which Aficamten and crystalline polymorphs thereof are obtained in solid form.

[0022] A solid state form (or polymorph) may be referred to herein as polymorphically pure or as substantially free of any other solid state (or polymorphic) forms. As used herein in this context, the expression "substantially free of any other forms" will be understood to mean that the solid state form contains about 20% (w/w) or less, about 10% (w/w) or less, about 5% (w/w) or less, about 2% (w/w) or less, about 1% (w/w) or less, or about 0% of any other forms of the subject compound as measured, for example, by XRPD. Thus, a crystalline polymorph of Aficamten described herein as substantially free of any other solid state forms would be understood to contain greater than about 80% (w/w), greater than about 90% (w/w), greater than about 95% (w/w), greater than about 98% (w/w), greater than about 99% (w/w), or about 100% of the subject crystalline polymorph of Aficamten. In some embodiments of the disclosure, the described crystalline polymorph of Aficamten may contain from about 1% to about 20% (w/w), from about 5% to about 20% (w/w), or from about 5% to about 10% (w/w) of one or more other crystalline polymorph of the same Aficamten.

[0023] A compound may be referred to herein as chemically pure or purified compound or as substantially free of any other compounds. As used herein in this context, the expression "substantially free of any other compounds " will be understood to mean that the pure compound

contains about 20% (w/w) or less, about 10% (w/w) or less, about 5% (w/w) or less, about 2% (w/w) or less, about 1% (w/w) or less, or about 0% of any other compound as measured, for example, by HPLC. Thus, pure or purified Aficamten described herein as substantially free of any compounds would be understood to contain greater than about 80% (w/w), greater than about 90% (w/w), greater than about 95% (w/w), greater than about 98% (w/w), greater than about 99% (w/w), or about 100% of the subject Aficamten. In some embodiments of the disclosure, the described pure or purified Aficamten may contain from about 1% to about 20% (w/w), from about 5% to about 20% (w/w), or from about 5% to about 10% (w/w) of one or more other compounds.

[0024] In specific embodiments, the above described pure or purified Aficamten may relate to enantiomeric purity, i.e. pure or purified Aficamten refers to Aficamten that is substantially free of enantiomers of Aficamten.

[0025] Depending on which other crystalline polymorphs a comparison is made, the crystalline polymorphs of Aficamten of the present disclosure may have advantageous properties selected from at least one of the following: chemical purity, flowability, solubility, dissolution rate, morphology or crystal habit, stability, such as chemical stability as well as thermal and mechanical stability with respect to polymorphic conversion, stability towards dehydration and/or storage stability, low content of residual solvent, a lower degree of hygroscopicity, flowability, and advantageous processing and handling characteristics such as compressibility and bulk density.

[0026] A solid state form, such as a crystal form or an amorphous form, may be referred to herein as being characterized by graphical data "as depicted in" or "as substantially depicted in" a Figure. Such data include, for example, powder X-ray diffractograms and solid state NMR spectra. As is well-known in the art, the graphical data potentially provides additional technical information to further define the respective solid state form (a so-called "fingerprint") which cannot necessarily be described by reference to numerical values or peak positions alone. In any event, the skilled person will understand that such graphical representations of data may be subject to small variations, e.g., in peak relative intensities and peak positions due to certain factors such as, but not limited to, variations in instrument response and variations in sample concentration and purity, which are well known to the skilled person. Nonetheless, the skilled person would readily be capable of comparing the graphical data in the Figures herein with

graphical data generated for an unknown crystal form and confirm whether the two sets of graphical data are characterizing the same crystal form or two different crystal forms. A crystal form of Aficamten referred to herein as being characterized by graphical data “as depicted in” or “as substantially depicted in” a Figure will thus be understood to include any crystal forms of Aficamten characterized with the graphical data having such small variations, as are well known to the skilled person, in comparison with the Figure.

[0027] As used herein, and unless stated otherwise, the term “anhydrous” in relation to crystalline forms of Aficamten, relates to a crystalline form of Aficamten, which does not include any crystalline water (or other solvents) in a defined, stoichiometric amount within the crystal. Moreover, unless otherwise indicated, an “anhydrous” form would generally not contain more than 1% (w/w), of either water or organic solvents as measured for example by TGA.

[0028] The term "solvate," as used herein and unless indicated otherwise, refers to a crystal form that incorporates a solvent in the crystal structure. When the solvent is water, the solvate is often referred to as a "hydrate." The solvent in a solvate may be present in either a stoichiometric or in a non-stoichiometric amount.

[0029] As used herein, the term "isolated" in reference to crystalline polymorph of Aficamten of the present disclosure corresponds to a crystalline polymorph of Aficamten that is physically separated from the reaction mixture in which it is formed.

[0030] "Co-Crystal" or "Co-crystal" as used herein is defined as a crystalline material including two or more molecules in the same crystalline lattice and associated by non-ionic and non-covalent bonds.

[0031] As used herein, unless stated otherwise, the XRPD measurements are taken using copper Kα radiation wavelength 1.5418 Å. XRPD peaks reported herein are measured using CuK α radiation, λ = 1.5418 Å, typically at a temperature of 25 ± 3°C.

[0032] As used herein, unless stated otherwise, ^{13}C NMR reported herein are measured at 16.4 T at a magic angle spinning frequency $w_r/2p$ = 18 kHz, preferably at a temperature of at 293 K ± 3 K, preferably wherein the ^{13}C scale is referenced to α-glycine (176.03 ppm for ^{13}C).

[0033] As used herein, unit cell data is obtained at a temperature of 25 ± 3°C.

[0034] A thing, e.g., a reaction mixture, may be characterized herein as being at, or allowed to come to “room temperature” or “ambient temperature,” often abbreviated as “RT.” This means that the temperature of the thing is close to, or the same as, that of the space, e.g., the

room or fume hood, in which the thing is located. Typically, room temperature is from about 20°C to about 30°C, or about 22°C to about 27°C, or about 25°C.

[0035] The amount of solvent employed in a chemical process, e.g., a reaction or crystallization, may be referred to herein as a number of "volumes" or "vol" or "V." For example, a material may be referred to as being suspended in 10 volumes (or 10 vol or 10V) of a solvent. In this context, this expression would be understood to mean milliliters of the solvent per gram of the material being suspended, such that suspending 5 grams of a material in 10 volumes of a solvent means that the solvent is used in an amount of 10 milliliters of the solvent per gram of the material that is being suspended or, in this example, 50 mL of the solvent. In another context, the term "v/v" may be used to indicate the number of volumes of a solvent that are added to a liquid mixture based on the volume of that mixture. For example, adding solvent X (1.5 v/v) to a 100 ml reaction mixture would indicate that 150 mL of solvent X was added.

[0036] A process or step may be referred to herein as being carried out "overnight." This refers to a time interval, e.g., for the process or step, that spans the time during the night, when that process or step may not be actively observed. This time interval is from about 8 to about 20 hours, or about 10-18 hours, in some cases about 16 hours.

[0037] As used herein, the term "reduced pressure" refers to a pressure that is less than atmospheric pressure. For example, reduced pressure is about 10 mbar to about 50 mbar.

[0038] As used herein and unless indicated otherwise, the term "ambient conditions" refer to atmospheric pressure and a temperature of 22-24°C.

[0039] The present disclosure describes polymorphically pure Form I of Aficamten. Polymorphically pure Form I can be characterized by an XRPD pattern having characteristic peaks at 14.9, 18.6, 23.3, 25.6 and 29.0 degrees 2-theta ± 0.2 degrees 2-theta, by an XRPD pattern as depicted in Figure 2; or by combinations thereof. Polymorphically pure Form I of Aficamten can be characterized by an XRPD pattern having the above-described characteristic peaks, and having an absence of a peak at 13.5 degrees 2-theta ± 0.2 degrees 2-theta; or an XRPD pattern having the above-described characteristic peaks, and having an absence of a peak at 17.8 degrees 2-theta ± 0.2 degrees 2-theta; or an XRPD pattern having the above-described characteristic peaks and having an absence of a peak at 30.6 degrees 2-theta ± 0.2 degrees 2-theta. Alternatively, according to any embodiment of the present disclosure, the polymorphically pure Form I of Aficamten may be characterized by an XRPD pattern having characteristic peaks

at 14.9, 18.6, 23.3, 25.6 and 29.0 degrees 2-theta ± 0.2 degrees 2-theta, and having an absence of one, two or three peaks at 13.5, 17.8 and 30.6 degrees 2-theta ± 0.2 degrees 2-theta. Alternatively, according to any embodiment of the present disclosure, the polymorphically pure Form I of Aficamten may be characterized by an XRPD pattern having characteristic peaks at 14.9, 18.6, 23.3, 25.6 and 29.0 degrees 2-theta ± 0.2 degrees 2-theta, and having an absence of peaks at 13.5, 17.8 and 30.6 degrees 2-theta ± 0.2 degrees 2-theta.

[0040] Polymorphically pure Form I of Aficamten may be prepared by a process comprising crystallization of Aficamten from a hot solution in toluene. Preferably, the process comprises: (a) providing a hot solution of Aficamten in toluene, (b) cooling the solution, and optionally (c) isolating the resulting crystals. According to any embodiment of the process, the solution in step (a) may be at a temperature of: about 80°C to about 130°C, about 85°C to about 120°C, about 90°C to about 115°C, about 95°C to about 110°C, or about 105°C. According to any embodiment of the process, the toluene is used in an amount of about 10 ml to about 50 ml, about 10 ml to about 40 ml, about 12 ml to about 35 ml, about 15 ml to about 30 ml, about 18 ml to about 25 ml, or about 20 ml, per gram of Aficamten. According to any embodiment of the disclosed process, step (b) can comprise allowing the solution to cool to about 30°C to about 20°C, about 27°C to about 22°C, or about 25°C. The product may be isolated from the suspension by any suitable method, such as filtration, decantation, or centrifugation, preferably by filtration. Advantageously, the process of the present disclosure can provide Form I of Aficamten which is polymorphically pure.

[0041] Preferably, according to any aspect or embodiment of the present invention, Form I of Aficamten may be substantially free of any other solid state (or polymorphic) forms of Aficamten, and particularly contains about 20% (w/w) or less, about 10% (w/w) or less, about 5% (w/w) or less, about 2% (w/w) or less, about 1% (w/w) or less, or about 0% of any other crystalline and/or amorphous forms of Aficamten, for example, as measured by XRPD. Particularly, the Form I of Aficamten may contain less than about 5% (w/w), less than about 2% (w/w), or less than about 1% (w/w) of any other crystalline forms of Aficamten. More particularly, the Form I of Aficamten as described in any embodiment may comprise less than about 0.5% (w/w) or less than about 0.2% (w/w) or less than about 0.1% (w/w) of any other crystalline and/or amorphous forms of Aficamten, or about 0% of any other crystalline and/or amorphous forms of Aficamten.

[0042] The present disclosure includes a crystalline polymorph of Aficamten: maleic acid, designated Form M1. Crystalline Form M1 may be described by data selected from one or more of the following: an XRPD pattern having characteristic peaks at 3.2, 12.0, 13.2, 17.3 and 25.9 degrees 2-theta ± 0.2 degrees 2-theta, by an XRPD pattern as depicted in Figure 1; or by combinations thereof. Crystalline Form M1 may be further described by an XRPD pattern having characteristic peaks at 3.2, 12.0, 13.2, 17.3 and 25.9 degrees 2-theta ± 0.2 degrees 2-theta, and any one, two, three, four or five additional peaks at 6.4, 15.1, 20.4, 22.7 and 23.4 degrees 2-theta ± 0.2 degrees 2-theta.

[0043] Crystalline Form M1 may be described by an XRPD pattern having characteristic peaks at 3.2, 6.4, 12.0, 13.2, 15.1, 17.3, 20.4, 22.7, 23.4 and 25.9 degrees 2-theta ± 0.2 degrees 2-theta.

[0044] According to any aspect or embodiment of the present disclosure, crystalline Form M1 may be additionally described by an XRPD pattern which has an absence of peaks at 4.0 to 5.6 degrees 2-theta ± 0.2 degrees 2-theta; and or an absence of peaks at 7.0 to 8.0 degrees 2-theta ± 0.2 degrees 2-theta; and/or an absence of peaks at 10.0 to 10.8 degrees 2-theta ± 0.2 degrees 2-theta.

[0045] Alternatively or additionally, according to any aspect or embodiment of the present disclosure, crystalline Form M1 may be characterized by a solid state ^{13}C NMR spectrum having peaks at: 170.1, 161.8, 117.6, 53.5 and 40.2 ± 0.2 ppm, and/or a solid state ^{13}C NMR spectrum having the following chemical shift absolute differences between the characteristic peaks at 170.1, 161.8, 117.6, 53.5 and 40.2 ± 0.2 ppm and a reference peak at 11.0 ppm ± 0.2 ppm peaks of 159.1, 150.8, 106.6, 42.5 and 29.2 ± 0.1 ppm. Alternatively or additionally, crystalline Form M1 may be characterized by a solid state ^{13}C NMR spectrum having peaks in the range of 100-200 ppm at: 179.7, 170.1, 167.4, 166.7, 161.8, 146.9, 143.4, 138.8, 137.4, 132.5, 126.9, 125.5, 124.8, 124.0, 121.7, and 117.5 ± 0.2 ppm. Alternatively or additionally, crystalline Form M1 may be characterized by a solid state ^{13}C NMR spectrum having peaks in the range of 0-200 ppm at: 179.7, 170.1, 167.4, 166.7, 161.8, 146.9, 143.4, 138.8, 137.4, 132.5, 126.9, 125.5, 124.8, 124.0, 121.7, 117.5, 53.5, 40.2, 32.3, 31.0, 20.3, and 11.0 ± 0.2 ppm; or a solid state ^{13}C NMR spectrum substantially as depicted in Figure 3. Optionally, crystalline Form M1 may be characterized; by a solid state ^{13}C NMR spectrum having the following peaks as the only peaks in the range of 100-200 ppm: 179.7, 170.1, 167.4, 166.7, 161.8, 146.9, 143.4, 138.8, 137.4,

132.5, 126.9, 125.5, 124.8, 124.0, 121.7, and 117.5 ± 0.2 ppm; or by a solid state ^{13}C NMR spectrum having the following peaks as the only peaks in the range of 0-200 ppm: 179.7, 170.1, 167.4, 166.7, 161.8, 146.9, 143.4, 138.8, 137.4, 132.5, 126.9, 125.5, 124.8, 124.0, 121.7, 117.5, 53.5, 40.2, 32.3, 31.0, 20.3, and 11.0 ± 0.2 ppm. According to any aspect or embodiment of the disclosure, crystalline Form M1 may be additionally characterized by a ^{13}C NMR spectrum having an absence of peaks at 150 to 160 ppm ± 0.2 ppm; and/or an absence of peaks at 172.0 to 178 ppm ± 0.2 ppm.

[0046] Alternatively or additionally, according to any aspect or embodiment of the present disclosure, crystalline Form M1 may be characterized by the following unit cell data:

Cell length a	5.2906 Å
Cell length b	7.6606 Å
Cell length c	27.4900 Å
Cell angle alpha	90°
Cell angle beta	90.6790 °
Cell angle gamma	90°
Cell volume	1114.07 $Å^3$
Symmetry cell setting	Monoclinic
Symmetry space group	$P2_1$

[0047] According to any aspect or embodiment, crystalline Form M1 may be characterized by any of the XRPD data described herein for Form M1, and optionally in combination with any of the solid state ^{13}C NMR data described herein for Form M1.

[0048] According to any aspect or embodiment of the present disclosure, crystalline Form M1 of Aficamten: maleic acid is preferably isolated.

[0049] According to another embodiment, crystalline Form M1 is anhydrous.

[0050] Crystalline Form M1 of Aficamten: maleic acid may be a co-crystal of Aficamten and maleic acid. Alternatively, crystalline Aficamten: maleic acid may be a salt. Preferably, crystalline Aficamten: maleic acid according to the invention is a co-crystal of Aficamten with maleic acid.

[0051] The molar ratio between Aficamten and maleic acid may be between about 2:1 to about 1:1; or about 1.5:1 to about 1:1.5 or about 1.1:1 to about 1:1.1, and preferably 1:1.

[0052] Aficamten: maleic acid as described in any aspect or embodiment herein may have particular advantages which makes it highly suitable as an active agent. For example, the Aficamten: maleic acid according to any aspect or embodiment as described herein may have superior processability characteristics, such as compressibility and wettability. Alternatively, the Aficamten: maleic acid according to any aspect or embodiment as described herein may particularly have superior morphological characteristics. Alternatively or additionally, Aficamten: maleic acid according to any aspect or embodiment as described herein may be particularly stable, for example to elevated temperatures or to high relative humidity conditions, or. In embodiments, Aficamten: maleic acid may be desirably provided as an anhydrous form, which avoids potential issues, particularly stability problems, that can be associated with solvated or hydrated forms.

[0053] The above crystalline polymorphs can be used to prepare other crystalline polymorphs of Aficamten, other Aficamten salts and their solid state forms. Solid state forms may be crystalline polymorphs, co-crystals and complexes of Aficamten or of Aficamten salt.

[0054] The present disclosure encompasses a process for preparing other solid state forms of Aficamten. The process includes preparing any one of the crystalline polymorphs of Aficamten by the processes of the present disclosure. The process may further comprise converting said crystalline polymorph of Aficamten to other crystalline polymorph of Aficamten or to other Aficamten salt.

[0055] The present disclosure provides the above described crystalline polymorphs of Aficamten for use in the preparation of pharmaceutical compositions comprising Aficamten and/or crystalline polymorphs thereof.

[0056] The present disclosure also encompasses the use of crystalline polymorphs of Aficamten of the present disclosure for the preparation of pharmaceutical compositions of crystalline polymorph Aficamten and/or crystalline polymorphs thereof. Particularly, the pharmaceutical compositions may be used for oral administration.

[0057] The present disclosure includes processes for preparing the above mentioned pharmaceutical compositions. The processes include combining any one or a combination of the crystalline polymorphs of Aficamten of the present disclosure with at least one pharmaceutically

acceptable excipient. Particularly, the pharmaceutical compositions may comprise pharmaceutically acceptable excipient suitable for making formulation for oral administration. Pharmaceutical combinations or formulations of the present disclosure contain any one or a combination of the solid state forms of Aficamten of the present disclosure. In addition to the active ingredient, the pharmaceutical formulations of the present disclosure can contain one or more excipients. Excipients are added to the formulation for a variety of purposes. For example, excipients may be added to assist in formation of formulation suitable for oral administration.

[0058] Diluents increase the bulk of a solid pharmaceutical composition, and can make a pharmaceutical dosage form containing the composition easier for the patient and caregiver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g., Avicel®), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g., Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol, and talc.

[0059] Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, can include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginic acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate, and starch.

[0060] The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach can be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g., Ac-Di-Sol®, Primellose®), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g., Kollidon®, Polyplasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g., Explotab®), and starch.

[0061] Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that can function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc, and tribasic calcium phosphate.

[0062] When a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, and zinc stearate.

[0063] Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that can be included in the composition of the present disclosure include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, and tartaric acid.

[0064] Solid and liquid compositions can also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

[0065] In liquid pharmaceutical compositions of the present invention, Aficamten and any other solid excipients can be dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol, or glycerin.

[0066] Liquid pharmaceutical compositions can contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that can be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol, and cetyl alcohol.

[0067] Liquid pharmaceutical compositions of the present invention can also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose,

gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth, xanthan gum and combinations thereof.

[0068] Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol, and invert sugar can be added to improve the taste.

[0069] Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxyl toluene, butylated hydroxyanisole, and ethylenediamine tetraacetic acid can be added at levels safe for ingestion to improve storage stability.

[0070] According to the present disclosure, a liquid composition can also contain a buffer such as gluconic acid, lactic acid, citric acid, or acetic acid, sodium gluconate, sodium lactate, sodium citrate, or sodium acetate. Selection of excipients and the amounts used can be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

[0071] The solid compositions of the present disclosure include powders, granulates, aggregates, and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant, intranasal and ophthalmic administration. Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, in embodiments the route of administration is oral. The dosages can be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

[0072] Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches, and lozenges, as well as liquid syrups, suspensions, and elixirs.

[0073] The dosage form of the present disclosure can be a capsule containing the composition, such as a powdered or granulated solid composition of the disclosure, within either a hard or soft shell. The shell can be made from gelatin and optionally contain a plasticizer such as glycerin and/or sorbitol, an opacifying agent and/or colorant.

[0074] The active ingredient and excipients can be formulated into compositions and dosage forms according to methods known in the art.

[0075] A composition for tableting or capsule filling can be prepared by wet granulation. In wet granulation, some or all of the active ingredients and excipients in powder form are blended

and then further mixed in the presence of a liquid, typically water, that causes the powders to clump into granules. The granulate is screened and/or milled, dried, and then screened and/or milled to the desired particle size. The granulate can then be tableted, or other excipients can be added prior to tableting, such as a glidant and/or a lubricant.

[0076] A tableting composition can be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients can be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules can subsequently be compressed into a tablet.

[0077] As an alternative to dry granulation, a blended composition can be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited for direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate, and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

[0078] A capsule filling of the present disclosure can include any of the aforementioned blends and granulates that were described with reference to tableting, but they are not subjected to a final tableting step.

[0079] A pharmaceutical formulation of Aficamten can be administered. For example, it can be administrated orally. Aficamten may be formulated for administration to a mammal, in embodiments to a human.

[0080] The crystalline polymorphs of Aficamten and the pharmaceutical compositions and/or formulations of Aficamten of the present disclosure can be used as medicaments, in embodiments in the treatment of cardiovascular disease, especially obstructive hypertrophic cardiomyopathy (oHCM). The medicament may preferably be administrated in oral form.

[0081] The present disclosure also provides methods of treating of cardiovascular disease, especially obstructive hypertrophic cardiomyopathy (oHCM) by administering a therapeutically effective amount of any one or a combination of the crystalline polymorphs of Aficamten of the present disclosure, or at least one of the above pharmaceutical compositions and/or formulations, to a subject in need of the treatment.

[0082] Having thus described the disclosure with reference to particular preferred embodiments and illustrative examples, those in the art can appreciate modifications to the disclosure as described and illustrated that do not depart from the spirit and scope of the disclosure as disclosed in the specification. The Examples are set forth to aid in understanding the disclosure but are not intended to, and should not be construed to limit its scope in any way.

Powder X-ray Diffraction ("XRPD") method

[0083] Sample is applied directly on a silicon plate holder. The X-ray powder diffraction pattern was measured with Philips X'Pert PRO X-ray powder diffractometer, equipped with Cu irradiation source=1.5418 Å (Ångström), X'Celerator (2.022° 2θ) detector. Scanning parameters: angle range: 3-40 deg., step size 0.0167, time per step 37 s, continuous scan.
The described peak positions were determined with using silicon powder as an internal standard in an admixture with the sample measured.
The position of the silicon (Si) peak was corrected to silicone theoretical peak: 28.45 degrees two theta, and the positions of the measured peaks were corrected respectively.

Solid State ^{13}C NMR Method

[0084] Solid-state NMR spectra are measured at 16.4 T using a Bruker Avance NEO 700 SB NMR spectrometer (Karlsruhe, Germany, 2021) with 3.2 mm probe head.
The ^{13}C CP/MAS NMR spectra employing cross-polarization are acquired using the standard cross-polarization pulse scheme at spinning frequency of 18 kHz. The dipolar decoupling SPINAL64 is applied during the data acquisition. The number of scans is set for the signal-to-noise ratio SINO reaches at least the value ca. 50. The ^{13}C scale is referenced to α-glycine (176.03 ppm for ^{13}C).

[0085] Frictional heating of the spinning samples is compensated by active cooling, and the temperature calibration is performed with $Pb(NO_3)_2$. The NMR spectrometer is always completely calibrated and all experimental parameters are carefully optimized prior the recording of the spectra. Magic angle is set using KBr during the standard optimization procedure and homogeneity of magnetic field is optimized using adamantane sample (resulting line-width at half-height $Dn_{1/2}$ was less than 3.5 Hz at 250 ms of acquisition time).

Unit Cell Measurement Method

XRPD data collection

[0086] Sample was ground and placed to the borosilicate-glass capillary. Powder diffraction data were collected using the Debye-Scherrer transmission configuration on the powder diffractometer Empyrean using Cu $K\alpha_{12}$ radiation (primary monochromator not used).

XRPD structure solution

[0087] The $K\alpha_2$ contribution to the record was stripped by Rachinger correction. The peaks positions were determined in DASH software. Indexing was done in DICVOL14 software. The molecular model of Aficamten was generated by molecular modeling and QM structure optimization in vacuum. The model of maleic acid was taken from known structure (CSD record MALIAC14).

[0088] The hydrogen atoms in the final model were manually placed in position giving sense according H-bond creation. The result of SA solution was geometry/energy minimized by CASTEP software (DFT rSCAN functional). The energy minimized structure was used for final Rietveld refinement

EXAMPLES

Preparation of starting materials

[0089] Aficamten can be prepared according to methods known from the literature, for example WO2019144041.

Example 1: Preparation of Crystalline Form M1 of Aficamten: maleic acid

[0090] Aficamten (420.8 mg) and maleic acid (579.2 mg) were dissolved in ethyl acetate (10 ml) at 49 °C. Heating was discontinued. The solution was cooled down to 0 °C and crystallization occurred. The obtained suspension was filtered off, washed with diethyl ether (3 ml) and analyzed by XRPD. Crystalline Form M1 of Aficamten: maleic acid was obtained, as shown in Figure 1.

Example 2: Preparation of polymorphically pure Form I of Aficamten

[0091] Aficamten (1000 mg) was dissolved in toluene (20 ml) at 105°C. The solution was left to cool down to room temperature (crystallization started at about 98°C) and immediately

filtered. The product was dried under vacuum at 80°C, for 4 hours and analyzed by XRPD. Pure crystalline Form I was obtained, as shown in Figure 2.

Further aspects and embodiments of the present disclosure are set out in the following numbered clauses:

1. Form I of Aficamten which is characterized by:
   (a) an XRPD pattern having peaks at 14.9, 18.6, 23.3, 25.6 and 29.0 degrees 2-theta ± 0.2 degrees 2-theta; or
   (b) an XRPD pattern as depicted in Figure 2.

2. Form I of Aficamten according to Clause 1, which is further characterized by having an absence of a peak at 13.5 degrees 2-theta ± 0.2 degrees 2-theta.

3. Form I of Aficamten according to Clause 1 or Clause 2, which is further characterized by having an absence of a peak at 17.8 degrees 2-theta ± 0.2 degrees 2-theta.

4. Form I of Aficamten according to any of Clauses 1, 2 and 3, which is further characterized by having an absence of a peak at 30.6 degrees 2-theta ± 0.2 degrees 2-theta.

5. Form I of Aficamten according to Clause 1, which is characterized by an XRPD pattern having peaks at 14.9, 18.6, 23.3, 25.6 and 29.0, and further characterized by having an absence of peaks at 13.5, 17.8 and 30.6 degrees 2-theta ± 0.2 degrees 2-theta.

6. Form I of Aficamten according to any of Clauses 1, 2, 3, 4, and 5, wherein the Form I of Aficamten is polymorphically pure.

7. Form I of Aficamten according Clause 6, which contains: about 20% (w/w) or less, about 10% (w/w) or less, about 5% (w/w) or less, about 2% (w/w) or less, about 1% (w/w) or less, about 0.5% (w/w) or less, about 0.2% (w/w) or less, about 0.1% (w/w) or less, or about 0% of any other crystalline forms of Aficamten.

8. Form I of Aficamten according to Clause 6 or Clause 7, which contains about 20% (w/w) or less, about 10% (w/w) or less, about 5% (w/w) or less, about 2% (w/w) or less, about 1% (w/w) or less, about 0.5% (w/w) or less, about 0.2% (w/w) or less, about 0.1% (w/w) or less, or about 0% of amorphous forms of Aficamten.

9. A process for preparing Form I of Aficamten according to any of Clauses 1, 2, 3, 4, 5, 6, 7, or 8, comprising crystallization of Aficamten from a hot solution in toluene.

10. A process according to Clause 9, comprising:
(a) providing a hot solution of Aficamten in toluene;
(b) cooling the solution; and optionally
(c) isolating the resulting crystals.

11. A process according to Clause 10, wherein the solution in step (a) is at a temperature of: about 80°C to about 130°C, about 85°C to about 120°C, about 90°C to about 115°C, about 95°C to about 110°C, or about 105°C.

12. A process according to any of Clauses 9, 10 or 11, wherein the toluene is used in an amount of: about 10 ml to about 50 ml, about 10 ml to about 40 ml, about 12 ml to about 35 ml, about 15 ml to about 30 ml, about 18 ml to about 25 ml, or about 20 ml, per gram of Aficamten.

13. A process according to any of Clauses 10, 11 or 12, wherein step (b) comprises allowing the solution to cool to about 30°C to about 20°C, about 27°C to about 22°C, or 25 °C.

14. A process according to any of Clauses 10, 11, 12, or 13, wherein the product is isolated from the suspension by filtration, decantation, or centrifugation, preferably by filtration.

15. A crystalline polymorph of Aficamten: maleic acid, designated Form M1, which is characterized by:
(a) an XRPD pattern having characteristic peaks at: 3.2, 12.0, 13.2, 17.3 and 25.9 degrees 2-theta ± 0.2 degrees 2-theta; or

(b) an XRPD pattern as depicted in Figure 1.

16. Crystalline Form M1 of Aficamten according to Clause 15, which is characterized by XRPD pattern having peaks at 3.2, 12.0, 13.2, 17.3 and 25.9 degrees 2-theta ± 0.2 degrees 2-theta, and any one, two, three, four or five additional peaks at 6.4, 15.1, 20.4, 22.7 and 23.4 degrees 2-theta ± 0.2 degrees 2-theta.

17. Crystalline Form M1 of Aficamten according to Clause 16, which is characterized by XRPD pattern having peaks at: 3.2, 6.4, 12.0, 13.2, 15.1, 17.3, 20.4, 22.7, 23.4 and 25.9 degrees 2-theta ± 0.2 degrees 2-theta.

18. Crystalline Form M1 of Aficamten: maleic acid according to Clause 15, 16 or 17, which is isolated.

19 Crystalline Form M1 of Aficamten: maleic acid according to any of Clauses 15, 16, 17, or 18, which is anhydrous.

20. Crystalline Form M1 of Aficamten: maleic acid according to any of Clauses 15, 16, 17, 18, or 19, which is a co-crystal of Aficamten and maleic acid; or which is a salt, and preferably a co-crystal of Aficamten with maleic acid.

21 Crystalline Form M1 of Aficamten: maleic acid according to any of Clauses 15, 16, 17, 18, 19, or 20, wherein the molar ratio of Aficamten to maleic acid is: about 2:1 to about 1:1; or about 1.5:1 to about 1:1.5 or about 1.1:1 to about 1:1.1, and preferably 1:1.

22. Crystalline Form M1 of Aficamten: maleic acid according to any of Clauses 15, 16, 17, 18, 19, 20 or 21, which is polymorphically pure.

23. Crystalline Form M1 of Aficamten: maleic acid according to Clause 22, which contains: about 20% (w/w) or less, about 10% (w/w) or less, about 5% (w/w) or less, about 2% (w/w) or less, about 1% (w/w) or less, about 0.5% (w/w) or less, about 0.2% (w/w) or

less, about 0.1% (w/w) or less, or about 0% of any other crystalline forms of Aficamten: maleic acid.

24. Crystalline Form M1 of Aficamten: maleic acid according to Clause 22 or Clause 23, which contains: about 20% (w/w) or less, about 10% (w/w) or less, about 5% (w/w) or less, about 2% (w/w) or less, about 1% (w/w) or less, about 0.5% (w/w) or less, about 0.2% (w/w) or less, about 0.1% (w/w) or less, or about 0% of amorphous forms of Aficamten: maleic acid.

25. Crystalline Form I of Aficamten, or crystalline Form M1 of Aficamten: maleic acid as defined in any of Clauses 1 to 24, wherein the Aficamten is enantiomerically pure.

26. Crystalline Form I of Aficamten, or crystalline Form M1 of Aficamten: maleic acid as defined in Clause 25, wherein the Aficamten contains about 20% (w/w) or less, about 10% (w/w) or less, about 5% (w/w) or less, about 2% (w/w) or less, about 1% (w/w) or less, about 0.5% (w/w) or less, about 0.2% (w/w) or less, or about 0% of any other enantiomer of Aficamten.

27. Use of crystalline Form I of Aficamten, or crystalline Form M1 of Aficamten: maleic acid as defined in any preceding clause for the preparation of other solid state forms of Aficamten, Aficamten co-crystals, Aficamten salts and their solid state forms.

28. A process for preparing other solid state forms of Aficamten, comprising preparing crystalline Form I of Aficamten, or crystalline Form M1 of Aficamten: maleic acid as defined in any of Clauses 1 to 26, and converting the crystalline Form I of Aficamten, or crystalline Form M1 of Aficamten: maleic acid to another crystalline form of Aficamten or to an Aficamten salt.

29. Crystalline Form I of Aficamten, or crystalline Form M1 of Aficamten: maleic acid as defined in any of Clauses 1 to 26, for use in the preparation of a pharmaceutical

composition comprising Aficamten, Aficamten salt, and/or crystalline polymorphs thereof.

30. A pharmaceutical composition comprising crystalline Form I of Aficamten, or crystalline Form M1 of Aficamten: maleic acid as defined in any of Clauses 1 to 26 and at least one pharmaceutically acceptable excipient, preferably wherein the pharmaceutical composition is for oral administration.

31. Use of crystalline Form I of Aficamten, or crystalline Form M1 of Aficamten: maleic acid as defined in any of Clauses 1 to 26 for the preparation of a pharmaceutical composition.

32. A process for preparing the pharmaceutical composition according to Clause 30, comprising combining a crystalline Form I of Aficamten, or crystalline Form M1 of Aficamten: maleic acid as defined in any of Clauses 1 to 26, with at least one pharmaceutically acceptable excipient.

33. A crystalline Form I of Aficamten, or crystalline Form M1 of Aficamten: maleic acid as defined in any of Clauses 1 to 26 or a pharmaceutical composition according to Clause 30, for use as a medicament.

34. A crystalline Form I of Aficamten, or crystalline Form M1 of Aficamten: maleic acid as defined in any of Clauses 1 to 26 or a pharmaceutical composition according to Clause 30, for use in the treatment of cardiovascular disease, preferably obstructive hypertrophic cardiomyopathy (oHCM).

CLAIMS

1. Crystalline Aficamten: maleic acid.

2. Crystalline Aficamten: maleic acid according to Claim 1, which is a co-crystal of Aficamten with maleic acid.

3. A crystalline polymorph of Aficamten: maleic acid according to Claim 1 or Claim 2, designated Form M1, which is characterized by:
   (a) an XRPD pattern having characteristic peaks at: 3.2, 12.0, 13.2, 17.3 and 25.9 degrees 2-theta ± 0.2 degrees 2-theta, or an XRPD pattern substantially as depicted in Figure 1; and/or
   (b) a solid state ^{13}C NMR spectrum having peaks at: 170.1, 161.8, 117.6, 53.5 and 40.2 ± 0.2 ppm, or a solid state ^{13}C NMR spectrum having peaks in the range of 100-200 ppm at: 179.7, 170.1, 167.4, 166.7, 161.8, 146.9, 143.4, 138.8, 137.4, 132.5, 126.9, 125.5, 124.8, 124.0, 121.7, and 117.5 ± 0.2 ppm, or a solid state ^{13}C NMR spectrum having peaks in the range of 0-200 ppm at: 179.7, 170.1, 167.4, 166.7, 161.8, 146.9, 143.4, 138.8, 137.4, 132.5, 126.9, 125.5, 124.8, 124.0, 121.7, 117.5, 53.5, 40.2, 32.3, 31.0, 20.3, and 11.0 ± 0.2 ppm, or a solid state ^{13}C NMR spectrum substantially as depicted in Figure 3; and/or
   (c) a solid state ^{13}C NMR spectrum having the following chemical shift absolute differences between the characteristic peaks at 170.1, 161.8, 117.6, 53.5 and 40.2 ± 0.2 ppm and a reference peak at 11.0 ppm ± 0.2 ppm peaks of 159.1, 150.8, 106.6, 42.5 and 29.2 ± 0.1 ppm; and/or
   (d) the following unit cell data:

Cell length a	5.2906 Å
Cell length b	7.6606 Å
Cell length c	27.4900 Å
Cell angle alpha	90°
Cell angle beta	90.6790

Cell angle gamma	90°
Cell volume	1114.07 Å^3
Symmetry cell setting	Monoclinic
Symmetry space group	$P2_1$

4. Crystalline Form M1 of Aficamten according to any of Claims 1, 2 or 3, which is characterized by XRPD pattern having peaks at 3.2, 12.0, 13.2, 17.3 and 25.9 degrees 2-theta ± 0.2 degrees 2-theta, and optionally further characterized by any one, two, three, four or five additional peaks at 6.4, 15.1, 20.4, 22.7 and 23.4 degrees 2-theta ± 0.2 degrees 2-theta.

5. Crystalline Form M1 of Aficamten according to any of Claims 1, 2, 3, or 4, which is characterized by XRPD pattern having peaks at: 3.2, 6.4, 12.0, 13.2, 15.1, 17.3, 20.4, 22.7, 23.4 and 25.9 degrees 2-theta ± 0.2 degrees 2-theta; or which is characterised by an XRPD pattern substantially as depicted in Figure 1.

6. A crystalline polymorph of Aficamten: maleic acid according to any of Claims 1, 2, 3, 4, or 5, which is further characterized by:
   (i) a solid state ^{13}C NMR spectrum having peaks at: 170.1, 161.8, 117.6, 53.5 and 40.2 ± 0.2 ppm; and/or
   (ii) a solid state ^{13}C NMR spectrum having the following chemical shift absolute differences between the characteristic peaks at 170.1, 161.8, 117.6, 53.5 and 40.2 ± 0.2 ppm and a reference peak at 11.0 ppm ± 0.2 ppm peaks of 159.1, 150.8, 106.6, 42.5 and 29.2 ± 0.1 ppm; and/or
   (iii) a solid state ^{13}C NMR spectrum having peaks in the range of 100-200 ppm at: 179.7, 170.1, 167.4, 166.7, 161.8, 146.9, 143.4, 138.8, 137.4, 132.5, 126.9, 125.5, 124.8, 124.0, 121.7, and 117.5 ± 0.2 ppm, a solid state ^{13}C NMR spectrum having peaks in the range of 0-200 ppm at: 179.7, 170.1, 167.4, 166.7, 161.8, 146.9, 143.4, 138.8, 137.4, 132.5, 126.9, 125.5, 124.8, 124.0, 121.7, 117.5, 53.5, 40.2, 32.3, 31.0, 20.3, and 11.0 ± 0.2 ppm; or a solid state ^{13}C NMR spectrum substantially as depicted in Figure 3.

7. A crystalline polymorph of Aficamten: maleic acid according to any of Claims 1, 2, 3, 4, 5, or 6, which is further characterized by the following unit cell data:

Cell length a	5.2906 Å
Cell length b	7.6606 Å
Cell length c	27.4900 Å
Cell angle alpha	90°
Cell angle beta	90.6790
Cell angle gamma	90°
Cell volume	1114.07 $Å^3$
Symmetry cell setting	Monoclinic
Symmetry space group	$P2_1$

8. A crystalline product according to any of Claims 1, 2, 3, 4, 5, 6, or 7, which is isolated.

9. A crystalline product according to any of Claims 1, 2, 3, 4, 5, 6, 7, or 8, which is anhydrous.

10. A crystalline product according to any of Claims 1, 2, 3, 4, 5, 6, 7, 8, or 9, which is a co-crystal of Aficamten and maleic acid; or which is a salt, and preferably a co-crystal of Aficamten with maleic acid.

11. A crystalline product according to any of Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein the molar ratio of Aficamten to maleic acid is: about 2:1 to about 1:1; or about 1.5:1 to about 1:1.5 or about 1.1:1 to about 1:1.1, and preferably 1:1.

12. Crystalline Form M1 of Aficamten: maleic acid according to any of Claims 3, 4, 5, 6, 7, 8, 9, 10, or 11, which is polymorphically pure.

13. Crystalline Form M1 of Aficamten: maleic acid according to Claim 12, which contains: about 20% (w/w) or less, about 10% (w/w) or less, about 5% (w/w) or less, about 2% (w/w) or less, about 1% (w/w) or less, about 0.5% (w/w) or less, about 0.2% (w/w) or less, about 0.1% (w/w) or less, or about 0% of any other crystalline forms of Aficamten: maleic acid.

14. Crystalline Form M1 of Aficamten: maleic acid according to Claim 12 or Claim 13, which contains: about 20% (w/w) or less, about 10% (w/w) or less, about 5% (w/w) or less, about 2% (w/w) or less, about 1% (w/w) or less, about 0.5% (w/w) or less, about 0.2% (w/w) or less, about 0.1% (w/w) or less, or about 0% of amorphous forms of Aficamten: maleic acid.

15. A product as defined in any of Claims 1 to 14, wherein the Aficamten is enantiomerically pure.

16. A product according to Claim 15, wherein the Aficamten contains about 20% (w/w) or less, about 10% (w/w) or less, about 5% (w/w) or less, about 2% (w/w) or less, about 1% (w/w) or less, about 0.5% (w/w) or less, about 0.2% (w/w) or less, or about 0% of any other enantiomer of Aficamten.

17. Use of a product as defined in any of Claims 1 to 16, for the preparation of other solid state forms of Aficamten, Aficamten co-crystals, Aficamten salts and their solid state forms.

18. A process for preparing other solid state forms of Aficamten, comprising preparing a product as defined in any of Claims 1 to 16, and converting the product to another crystalline form of Aficamten or to an Aficamten salt.

19. A product as defined in any of Claims 1 to 16, for use in the preparation of a pharmaceutical composition comprising Aficamten, Aficamten salt, and/or crystalline polymorphs thereof.

20. A pharmaceutical composition comprising a product as defined in any of Claims 1 to 16 and at least one pharmaceutically acceptable excipient, preferably wherein the pharmaceutical composition is for oral administration.

21. Use of a product as defined in any of Claims 1 to 16 for the preparation of a pharmaceutical composition.

22. A process for preparing the pharmaceutical composition according to Claim 20, comprising combining a product as defined in any of Claims 1 to 16, with at least one pharmaceutically acceptable excipient.

23. A product as defined in any of Claims 1 to 16 or a pharmaceutical composition according to Claim 20, for use as a medicament.

24. A product as defined in any of Claims 1 to 16, or a pharmaceutical composition according to Claim 20, for use in the treatment of cardiovascular disease, preferably obstructive hypertrophic cardiomyopathy (oHCM).

25. A method of treating cardiovascular disease, preferably obstructive hypertrophic cardiomyopathy (oHCM), comprising administration of a therapeutically effective amount of a product as defined in any of Claims 1 to 16, or a pharmaceutical composition according to Claim 20, to a subject in need thereof.

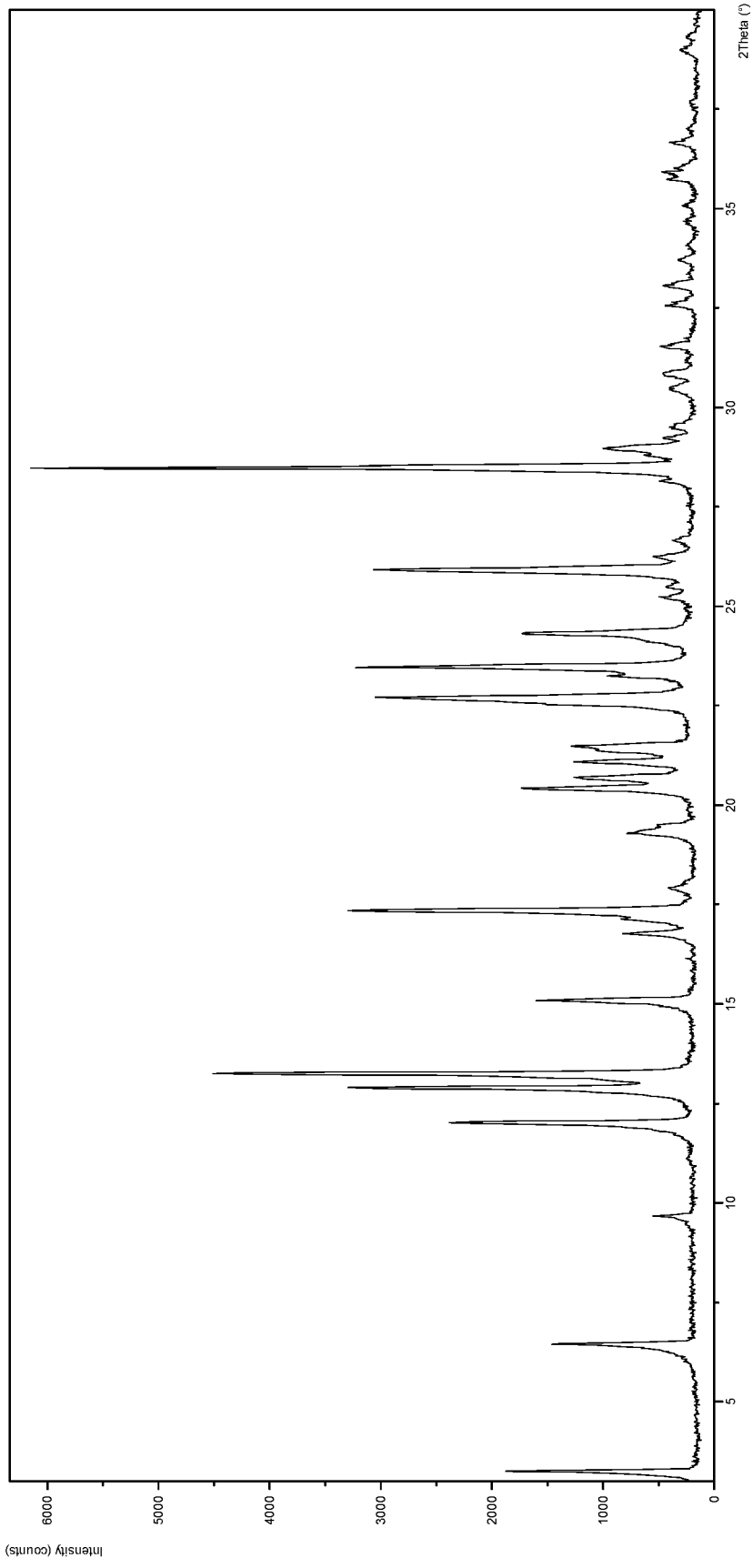


Figure 1: crystalline Form M1 of Aficamten: maleic acid

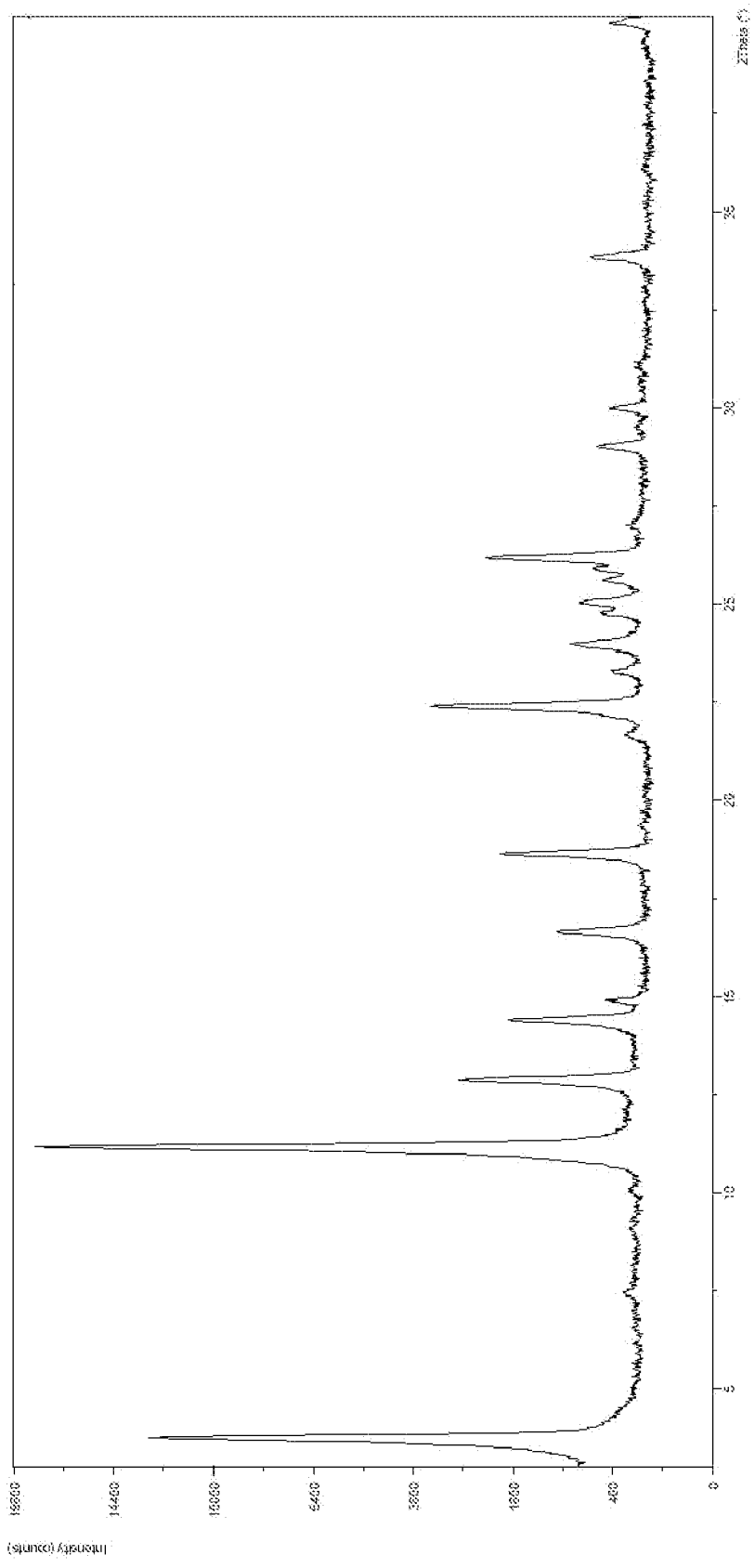


Figure 2: Polymorphically pure Form I of Aficamten

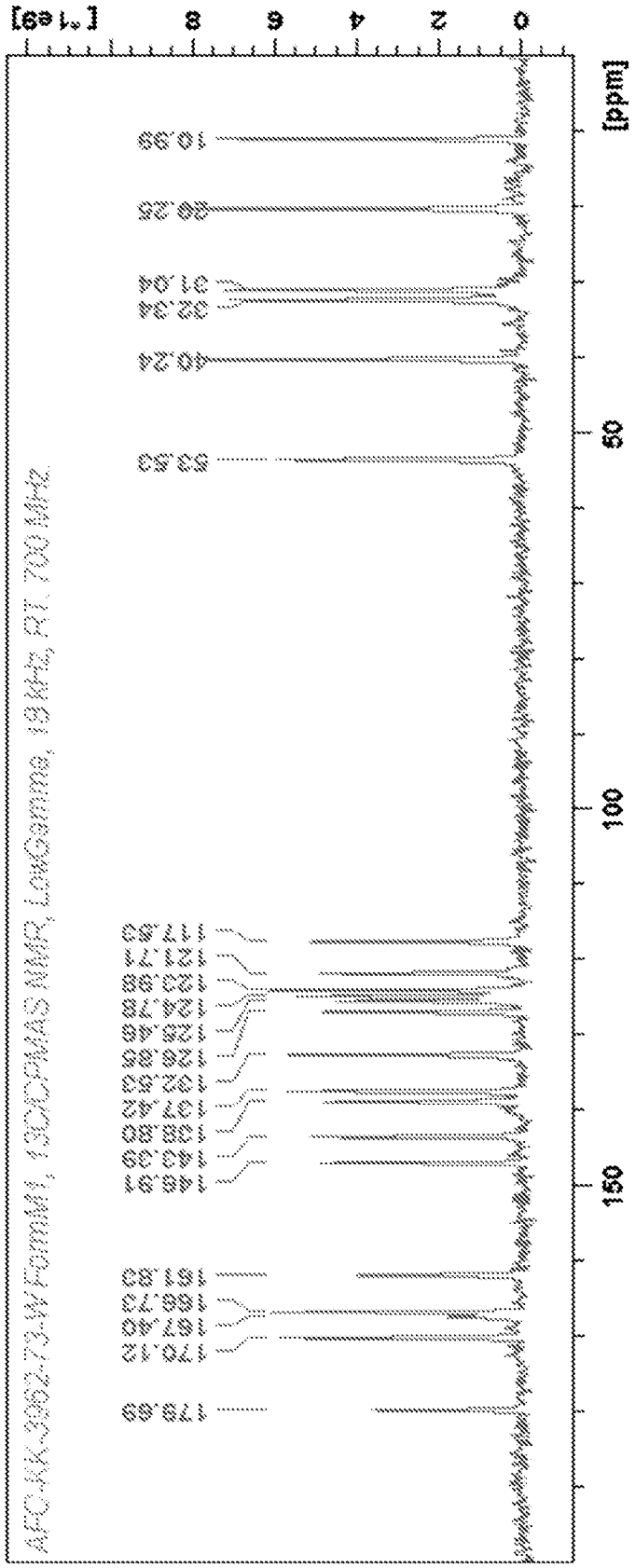


Figure 3. ^{13}C CP-MAS NMR spectra of Aficamten: maleic acid form M1

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2023/062945

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/12 A61P9/00 A61K31/4245
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)
C07D A61P A61K

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/144041 A1 (CYTOKINETICS INC [US]) 25 July 2019 (2019-07-25) cited in the application	1,2
Y	page 83, example 184; paragraph [0033]; claims 1-53	3-25
A	WO 2021/011807 A1 (CYTOKINETICS INC [US]) 21 January 2021 (2021-01-21) paragraph [0161]; claims 1-62	1-25

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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2024	23/04/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kleidernigg, Oliver

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2023/062945

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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