

POLYMORPHIC FORMS OF RAD1901-2HCL

PRIORITY CLAIM

[0001] This application claims priority under 35 U.S.C. § 119(e) to United States Provisional Patent Application No. 62/694,003, filed July 4, 2018, the contents of which are incorporated by reference herein in its entirety, including drawings.

BACKGROUND

[0002] RAD1901 is a selective estrogen receptor down-regulator/degrader, or SERD, that crosses the blood-brain barrier and is particularly useful for the treatment of metastatic breast cancer. RAD1901 has been shown to bind with good selectivity to the estrogen receptor (ER) and to have both estrogen-like and estrogen-antagonistic effect in different tissues. In many cancers, hormones, like estrogen, stimulate tumor growth, and thus a desired therapeutic goal is to block this estrogen-dependent growth while inducing apoptosis of the cancer cells. SERDs have the potential to be an emerging class of endocrine therapies that could directly induce ER degradation, thus potentially enabling them to remove the estrogen growth signal in ER-dependent tumors without allowing ligand-independent resistance to develop.

SUMMARY OF THE INVENTION

[0003] Various polymorphic forms of RAD1901-2HCl are disclosed herein, along with pharmaceutical compositions thereof, preparation methods thereof, and uses thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0004] Figure 1: Conversion among Forms 1, 2, and 3 of RAD1901-2HCl.

[0005] Figure 2A: RP-HPLC Chromatogram of Sample 1 collected at 255 nm.

[0006] Figure 2B: ¹H NMR of Sample 1 collected in d₆-DMSO.

[0007] Figure 3A: RP-HPLC Chromatogram of Sample 2 collected at 255 nm.

[0008] Figure 3B: ¹H NMR of Sample 2 collected in d₆-DMSO.

[0009] Figure 4A: XRPD diffraction pattern of Sample 1 at ambient RH (e.g., 40-65% RH).

[0010] Figure 4B: Overlay of XRPD patterns obtained for Sample 1 pre- (bottom) and post-storage (top) at elevated condition analysis.

[0011] Figure 4C: Overlay of VH-XRPD patterns of Sample 1 collected at varied RH.

[0012] Figure 4D: Overlay of XRPD patterns obtained for Sample 1 pre- (bottom) and post-storage (top) GVS (uptake 0-90% RH) analysis.

[0013] Figure 4E: Overlay of XRPD patterns obtained for Sample 1 pre- (Sample 1) and post-GVS (HighRH_Desorp_3 and HighRH methods).

[0014] Figure 4F: Overlay of XRPD patterns obtained for Sample 1 pre- and post-GVS (HighRH_Desorp_3's 1 cycle and HighRH_Double_Cycle's 2 cycles), and post storage at 25 °C /97% RH.

[0016] Figure 4G: XRPD diffraction pattern of Sample 1 at 0% RH.

[0017] Figure 4H: Overlay of XRPD diffraction pattern of Forms 1-3.

[0018] Figure 5A: XRPD patterns obtained for Sample 2.

[0019] Figure 5B: Overlay of XRPD patterns obtained for Sample 2 and post-storage at elevated condition analysis.

[0020] Figure 5C: Overlay of XRPD patterns obtained for Sample 1 (top) and Sample 2 (bottom 2 plots) post-storage at elevated condition analysis.

[0021] Figure 5D: Overlay of VT-XRPD patterns of Sample 2 collected upon heating to 200 °C and Sample 1.

[0022] Figure 5E: Overlay of VH-XRPD patterns of Sample 2 collected at high RH (>90%) and Sample 1 post storage at high RH.

[0023] Figure 5F: Overlay of VH-XRPD patterns of Sample 2 collected at dry condition (0% RH).

[0024] Figure 5G: Overlay of XRPD patterns obtained for Sample 2 pre- and post-GVS (uptake 0-90% RH).

[0025] Figure 5H: XRPD patterns obtained for Sample 2 at 0% RH (Form 2).

[0026] Figure 5I: XRPD patterns obtained for Sample 2 at 92% RH (Form 3).

[0027] Figure 6A: GVS Isotherm Plot for Sample 1 collected from 0 to 90% RH.

[0028] Figure 6B: GVS Kinetic Plot for Sample 1 collected from 0 to 90% RH.

[0029] Figure 6C: GVS Isotherm Plot for Sample 1 collected from 40 to 95% RH with GVS method HighRH.

[0030] Figure 6D: GVS Kinetic Plot for Sample 1 collected from 40 to 95% RH with GVS method HighRH.

[0031] Figure 6E: GVS Isotherm Plot for Sample 1 collected over a single cycle with GVS method HighRH_Desorp_3.

[0032] Figure 6F: GVS Kinetic Plot for Sample 1 collected over a single cycle with GVS method HighRH_Desorp_3.

[0033] Figure 6G: GVS Isotherm Plot for Sample 1 collected over a double cycle with GVS method HighRH_DoubleCycle_2.

[0034] Figure 6H: GVS Kinetic Plot for Sample 1 collected over a double cycle with GVS method HighRH_DoubleCycle_2.

[0035] Figure 7A: GVS Isotherm Plot for Sample 2 collected from 0 to 90% RH.

[0036] Figure 7B: GVS Kinetic Plot for Sample 2 collected from 0 to 90% RH.

[0037] Figure 8: Thermal analysis of Sample 1 by TGA (top) and DSC (bottom).

[0038] Figure 9: Thermal analysis of Sample 2 by TGA (top) and DSC (bottom).

[0039] Figure 10A: PLM images of Sample 1.

[0040] Figure 10B: PLM images of crystals isolated from solubility assessment of Sample 1, produced platelet crystals upon cooling in methanol.

[0041] Figure 11: PLM images of Sample 2.

[0042] Figure 12A: SEM images of Sample 1 (295x).

[0043] Figure 12B: SEM images of Sample 1 (1050x).

[0044] Figure 12C: SEM images of Sample 1 (5100x).

[0045] Figure 13A: SEM images of Sample 2 (730x).

[0046] Figure 13B: SEM images of Sample 2 (1650x).

[0047] Figure 13C: SEM images of Sample 2 (3400x).

[0048] Figure 14A: Overlay of XRPD patterns obtained from the polymorph screen on crystalline Sample 1, which are substantially consistent with Form 1.

[0049] Figure 14B: Overlay of XRPD patterns obtained from the polymorph screen on crystalline Sample 1, which are substantially consistent with Form 1.

[0050] Figure 14C: Overlay of XRPD patterns obtained from the polymorph screen on crystalline Sample 1, which are substantially consistent with Form 3.

[0051] Figure 15A: Overlay of XRPD patterns obtained for Sample 1 pre- and post-lyophilisation in water or t-butanol/water.

[0052] Figure 15B: Overlay of XRPD patterns obtained for samples obtained by lyophilization of Sample 1 from water or t-butanol/water and crystalline samples of Sample 1 post-storage at 25 °C/97 % RH.

[0053] Figure 15C: Overlay of XRPD patterns obtained for samples obtained by lyophilization from water or t-butanol/water of Sample 1 post-storage at 25 °C/97 % RH and 40 °C/97 % RH.

[0054] Figure 16: ¹H NMR spectra of Sample 1 pre- and post-lyophilisation in water or t-butanol/water.

[0055] Figure 17A: DSC analysis of samples of Sample 1 obtained by lyophilization from water (solid line) or t-butanol/water (dashed line).

[0056] Figure 17B: TGA analysis of samples of Sample 1 obtained by lyophilization from water (solid line) or t-butanol/water (dashed line).

[0057] Figure 17C: mDSC analysis of a sample of Sample 1 obtained by lyophilization from water (solid line).

[0058] Figure 18A: Overlay of XRPD patterns obtained from the polymorph screen on Sample 1 obtained by lyophilization from nitromethane, acetonitrile, THF, ethanol, or propan-1-ol, which are substantially consistent with (anhydrous) Form 1.

[0059] Figure 18B: Overlay of XRPD patterns obtained from the polymorph screen on Sample 1 obtained by lyophilization from dichloromethane (DCM), toluene, methyl isobutyl ketone (MIBK), isopropyl acetate, ethyl acetate or propyl acetate, which are substantially consistent with Form 3 (Sample 2, 90% RH) or a mixture of Form 2 and Form 3 (sample 2 post 25/97).

[0060] Figure 18C: Overlay of XRPD patterns obtained from the polymorph screen on Sample 1 obtained by lyophilization from 10% water/THF, 10% water/IPA, 10% water/EtOH, water, dimethoxyethane, or methanol, which are substantially consistent with Form 3 (hydrate, Sample 2, 90% RH) or a mixture of Form 2 (anhydrous) and Form 3 (sample 2 post 25/97).

[0061] Figure 18D: Overlay of XRPD patterns obtained from the polymorph screen on Sample 1 obtained by lyophilization from 1,4-dioxane, t-butyl methyl ether (TBME),

acetone, methyl ethyl ketone (MEK), propan-2-ol, or n-heptane, which are too poorly crystalline to assign polymorph, but appear to be Form 1 or a mixture of Form 2 and Form 3 (sample 2 post 25/97).

[0062] Figure 19A: PLM images of crystals obtained during polymorph screens prepared by cooling a lyophilized sample of Sample 1-methanol.

[0063] Figure 19B: PLM images of crystals obtained during polymorph screens prepared by maturation of a lyophilized sample of Sample 1 in water.

[0064] Figure 19C: PLM images of crystals obtained during polymorph screens prepared by maturation of a lyophilized sample of Sample 1 in nitromethane.

[0065] Figure 20A: Overlay of XRPD patterns of samples prepared by maturation of a lyophilized sample of Sample 1 in different water/ethanol solvent mixtures, which are substantially consistent with Form 1 or Form 3 (hydrate) (sample 1 post 25/97).

[0066] Figure 20B: Overlay of XRPD patterns of samples prepared by maturation of a lyophilized sample of Sample 1 in different water/methanol solvent mixtures, which are substantially consistent with Form 2 or Form 3 (hydrate) (sample 1 post 25/97).

[0067] Figure 20C: Overlay of XRPD patterns of samples prepared by maturation of a lyophilized sample of Sample 1 in anhydrous or water-saturated ethyl acetate, which are substantially consistent with Form 1 or Form 3 (sample 1 post 25/97).

[0068] Figure 21A: DSC and TGA Thermal analysis of Form 1B (Pattern B).

[0069] Figure 21B: XRPD analysis of Form 1B pre- and post-GVS.

[0070] Figure 22A: XRPD overlay of Form 1 (Form 1) and Form 1B (Pattern B).

[0071] Figure 22B: XRPD of Form 1.

[0072] Figure 22C: XRPD of Form 1B (Pattern B).

[0073] Figure 23: ¹³C solid-state CPMAS NMR of Form 1, Form 1B (Pattern B), and a mixture of Form 1 with a trace amount of Form 1B.

[0074] Figure 24: ¹H solid-state MAS NMR of Form 1 and Form 1B (Pattern B).

[0075] Figure 25A: FT-IR of Form 1 and Form 1B (Pattern B).

[0076] Figure 25B: FT-IR of Form 1.

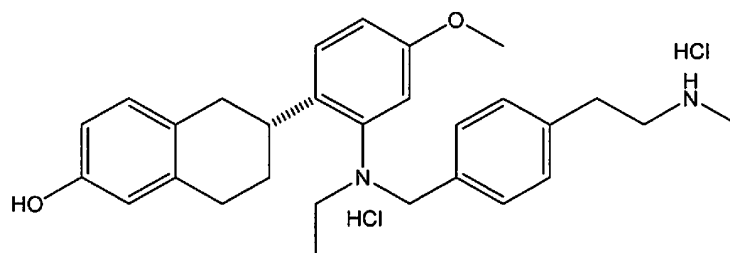
[0077] Figure 25C: FT-IR of Form 1B (Pattern B).

[0078] Figure 26: Raman Spectra of Form 1 and Form 1B (Pattern B).

DETAILED DESCRIPTION

I. Polymorphic Forms of RAD1901-2HCl

[0079] As set forth in the Examples section below, three crystalline and amorphous forms of RAD1901-2HCl were prepared and characterized.



RAD1901-2HCl

[0080] The definitions provided herein are meant to clarify, but not limit, the terms defined. If a term used herein is not specifically defined, such term should not be considered indefinite. Rather, terms are used within their accepted meanings.

[0081] As used herein, RAD1901-2HCl refers to a salt form wherein the molar ratio of RAD1901 and HCl is approximately 2, e.g., from about 1.7 to about 2.1, or from 1.8 to about 2.0. Small changes in the amount of assayed HCl can be attributed to, without limitation, measurement variability and loss of small amounts of HCl through storage and/or processing.

[0082] As used herein, "crystalline" refers to a solid having a highly regular chemical structure. In particular, a crystalline free base or salt form may be produced as one or more single crystalline forms. For the purposes of this application, the terms "crystalline form", "single crystalline form" and "polymorph" are synonymous; the terms distinguish between crystals that have different properties (e.g., different XRPD patterns and/or different DSC scan results). The term "polymorph" includes pseudopolymorphs, which are typically different solvates of a material, and thus their properties differ from one another. Thus, each distinct polymorph and pseudopolymorph of a free base or salt form is considered to be a distinct single crystalline form herein.

[0083] The term "substantially crystalline" refers to forms that may be at least a particular weight percent crystalline. Particular weight percentages are 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or any percentage between 10% and 100%. In some

embodiments, substantially crystalline refers to a free base or salt form that is at least 70% crystalline. In other embodiments, substantially crystalline refers to a free base or salt form that is at least 90% crystalline.

[0084] As used herein, "amorphous" refers to a solid material comprising non-crystalline materials. In certain embodiments, an amorphous sample of a material may be prepared by lyophilization of a mixture of the material with a solvent, wherein the mixture may be homogeneous (e.g., solution) or heterogeneous (e.g., a slurry).

[0085] The term "substantially free" refers to forms and compositions that may be at least a particular weight percent free of impurities and/or crystalline compound. Particular weight percentages are 60%, 70%, 75%, 80%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or any percentage between 60% and 100% free of impurities and/or crystalline compound. In some embodiments, substantially free refers to a free base or salt form that is at least 70% pure. In other embodiments, substantially crystalline refers to a free base or salt form that is at least 90% pure. In other embodiments, substantially free of crystalline compound refers to a composition having less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1% of crystalline compound.

[0086] The term "hydrate" is a solvate wherein the solvent molecule is H₂O that is present in a defined stoichiometric or non-stoichiometric amount. Stoichiometric solvates may, for example, include hemihydrate, monohydrate, dihydrate, or trihydrate forms, among others. Non-stoichiometric solvates may include, for example, channel hydrates, including where water content may change depending on humidity of the environment.

[0087] The term "solvate or solvated" means a physical association of a compound, including a crystalline form thereof, of this invention with one or more solvent molecules. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate or solvated" encompasses both solution-phase and isolable solvates. Representative solvates include, for example, a hydrate, ethanolate or a methanolate.

[0088] The term "stable" in the context of a polymorphic form disclosed herein refers to the stability of the polymorphic form relative to heat and/or humidity.

[0089] The relationship among the three crystalline forms of RAD1901 is provided in Figure 1. As used herein, the crystalline forms of RAD1901-2HCl are referred to as Forms 1, 1A, 2, and 3, respectively. Forms 1 and 2 are anhydrous forms of RAD1901-2HCl, and Form 3 is a hydrated form of RAD1901-2HCl. Forms 1, 1A, 2, and 3 each exhibit different X-ray powder diffraction (XRPD) patterns. In certain embodiments, another crystalline form of RAD1901-2HCl provided herein is referred to as Form 1B. As used herein, the term “Form 1B” is synonymous and can be interchanged with the term “Pattern B”. The RAD1901-2HCl Form 1B has an XRPD pattern different from the XRPD patterns characterizing Forms 1, 2, or 3 of RAD1901-2HCl. See Figure 22A for an XRPD overlay of Form 1 and Form 1B, Figure 22B for an XRPD of Form 1, and Figure 22C for an XRPD of Form 1B.

[0090] Sample 1 refers to an initially uncharacterized batch of RAD1901-2HCl that was subsequently determined to be predominately Form 1. Sample 2 refers to an initially uncharacterized batch of RAD1901-2HCl that was subsequently determined to be a mixture of Form 2 and Form 3

[0091] GVS experiments showed that Form 2 was hygroscopic with a mass uptake from 0-40% RH, and the mass uptake plateaued above 40% RH. Thus, an equilibrium existed between the anhydrous Form 2 and hydrate Form 3 at near ambient RH. Anhydrous Form 1 demonstrated low hygroscopicity between 0-90% RH, and started converting to the hydrate Form 3 at above 90% RH.

[0092] In many embodiments disclosed herein, RAD1901-2HCl is disclosed as having a crystalline structure.

[0093] In certain embodiments, crystalline structures in this disclosure can be identified by having one or more characteristics peaks in an XRPD spectrum, as disclosed herein.

[0094] In some embodiments, crystalline structures in this disclosure have one or more characteristics endothermic peaks in differential scanning calorimetry, as disclosed herein.

[0095] In certain embodiments, methods of preparing and/or interconverting one or more crystalline forms of RAD1901-2HCl are provided. Further embodiments describe the conversion to, and preservation of a crystalline form of RAD1901-2HCl that has desired stability under expected storage conditions.

[0096] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising a peak, in terms of 2θ , at 7.1 degrees $2\theta \pm 0.2$ degrees 2θ at about relative humidity 0%, e.g., Form 1.

[0097] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ , at 7.1 degrees $2\theta \pm 0.2$ degrees 2θ , and/or 14.3 degrees $2\theta \pm 0.2$ degree 2θ at about relative humidity 0%, e.g., Form 1.

[0098] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having an X-Ray powder diffraction pattern comprising at least two peaks, in terms of 2-theta, selected from the group consisting of 7.1 degrees $2\theta \pm 0.2$ degree 2θ , 14.3 degrees $2\theta \pm 0.2$ degree 2θ and 18.3 degrees $2\theta \pm 0.2$ degree 2θ at about relative humidity 0%, e.g., Form 1.

[0099] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having an X-Ray powder diffraction pattern comprising at least three peaks, in terms of 2-theta, selected from the group consisting of 7.1 degrees $2\theta \pm 0.2$ degree 2θ , 14.3 degrees $2\theta \pm 0.2$ degree 2θ , 18.3 degrees $2\theta \pm 0.2$ degree 2θ , 13.8 degrees $2\theta \pm 0.2$ degree 2θ and 12.0 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%, e.g., Form 1.

[00100] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having an X-Ray powder diffraction pattern comprising at least four peaks, in terms of 2-theta, selected from the group consisting of 7.1 degrees $2\theta \pm 0.2$ degree 2θ , 14.3 degrees $2\theta \pm 0.2$ degree 2θ , 18.3 degrees $2\theta \pm 0.2$ degree 2θ , 13.8 degrees $2\theta \pm 0.2$ degree 2θ , 12.0 degrees $2\theta \pm 0.2$ degree 2θ , 25.1 degrees $2\theta \pm 0.2$ degree 2θ and 18.9 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%, e.g., Form 1.

[00101] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having an X-Ray powder diffraction pattern comprising at least five peaks, in terms of 2-theta, selected from the group consisting of 7.1 degrees $2\theta \pm 0.2$ degree 2θ , 14.3 degrees $2\theta \pm 0.2$ degree 2θ , 18.3 degrees $2\theta \pm 0.2$ degree 2θ , 13.8 degrees $2\theta \pm 0.2$ degree 2θ , 12.0 degrees $2\theta \pm 0.2$ degree 2θ , 25.1 degrees $2\theta \pm 0.2$ degree 2θ , 18.9 degrees $2\theta \pm 0.2$ degree 2θ , 27.2 degrees $2\theta \pm 0.2$ degree 2θ and 11.0 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%, e.g., Form 1.

[00102] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having an X-Ray powder diffraction pattern comprising at least seven peaks, in terms of 2-theta, selected from the group consisting of 7.1 degrees $2\theta \pm 0.2$ degree 2θ , 14.3 degrees $2\theta \pm 0.2$ degree 2θ , 18.3 degrees $2\theta \pm 0.2$ degree 2θ , 13.8 degrees $2\theta \pm 0.2$ degree 2θ , 12.0 degrees $2\theta \pm 0.2$ degree 2θ , 25.1 degrees $2\theta \pm 0.2$ degree 2θ , 18.9 degrees $2\theta \pm 0.2$ degree 2θ

2 θ , 27.2 degrees 2 θ $\pm$ 0.2 degree 2 θ , 11.0 degrees 2 θ $\pm$ 0.2 degree 2 θ , and 16.2 degrees 2 θ $\pm$ 0.2 degree 2 θ , at about relative humidity 0%, e.g., Form 1.

[00103] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having an X-Ray powder diffraction pattern comprising at least eight peaks, in terms of 2-theta, selected from the group consisting of 7.1 degrees 2 θ $\pm$ 0.2 degree 2 θ , 14.3 degrees 2 θ $\pm$ 0.2 degree 2 θ , 18.3 degrees 2 θ $\pm$ 0.2 degree 2 θ , 13.8 degrees 2 θ $\pm$ 0.2 degree 2 θ , 12.0 degrees 2 θ $\pm$ 0.2 degree 2 θ , 25.1 degrees 2 θ $\pm$ 0.2 degree 2 θ , 18.9 degrees 2 θ $\pm$ 0.2 degree 2 θ , 27.2 degrees 2 θ $\pm$ 0.2 degree 2 θ , 11.0 degrees 2 θ $\pm$ 0.2 degree 2 θ , and 16.2 degrees 2 θ $\pm$ 0.2 degree 2 θ , at about relative humidity 0%, e.g., Form 1.

[00104] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having an X-Ray powder diffraction pattern comprising at least nine peaks, in terms of 2-theta, selected from the group consisting of 7.1 degrees 2 θ $\pm$ 0.2 degree 2 θ , 14.3 degrees 2 θ $\pm$ 0.2 degree 2 θ , 18.3 degrees 2 θ $\pm$ 0.2 degree 2 θ , 13.8 degrees 2 θ $\pm$ 0.2 degree 2 θ , 12.0 degrees 2 θ $\pm$ 0.2 degree 2 θ , 25.1 degrees 2 θ $\pm$ 0.2 degree 2 θ , 18.9 degrees 2 θ $\pm$ 0.2 degree 2 θ , 27.2 degrees 2 θ $\pm$ 0.2 degree 2 θ , 11.0 degrees 2 θ $\pm$ 0.2 degree 2 θ , and 16.2 degrees 2 θ $\pm$ 0.2 degree 2 θ , at about relative humidity 0%, e.g., Form 1.

[00105] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising the peaks, in terms of 2-theta, of 7.1 degrees 2 θ $\pm$ 0.2 degree 2 θ , 14.3 degrees 2 θ $\pm$ 0.2 degree 2 θ , 18.3 degrees 2 θ $\pm$ 0.2 degree 2 θ , 13.8 degrees 2 θ $\pm$ 0.2 degree 2 θ , 12.0 degrees 2 θ $\pm$ 0.2 degree 2 θ , 25.1 degrees 2 θ $\pm$ 0.2 degree 2 θ , 18.9 degrees 2 θ $\pm$ 0.2 degree 2 θ , 27.2 degrees 2 θ $\pm$ 0.2 degree 2 θ , 11.0 degrees 2 θ $\pm$ 0.2 degree 2 θ , and 16.2 degrees 2 θ $\pm$ 0.2 degree 2 θ , at about relative humidity 0%, e.g., Form 1.

[00106] Certain embodiments disclosed herein provide a solid form (Form 1) having an X-ray powder diffraction pattern substantially as shown in Figure 4G at about relative humidity 0%.

[00107] Certain embodiments disclosed herein provide a solid form (Form 1) having an X-ray powder diffraction pattern substantially as shown in Figure 22B.

[00108] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1) having an X-ray powder diffraction pattern comprising one or more peaks of the peaks of Table 7A. In certain embodiments, the solid form (Form 1) of RAD1901-2HCl has

an X-ray powder diffraction pattern comprising one peak, two peaks, three peaks, four peaks, five peaks, six peaks, seven peaks, eight peaks, nine peaks, ten peaks, eleven peaks, twelve peaks, thirteen peaks, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, or at least thirteen peaks, in terms of 2-theta, at 7.14 degrees $2\theta \pm 0.2$ degree 2θ , 12.02 degrees $2\theta \pm 0.2$ degree 2θ , 13.78 degrees $2\theta \pm 0.2$ degree 2θ , 14.24 degrees $2\theta \pm 0.2$ degree 2θ , 16.13 degrees $2\theta \pm 0.2$ degree 2θ , 17.79 degrees $2\theta \pm 0.2$ degree 2θ , 18.35 degrees $2\theta \pm 0.2$ degree 2θ , 18.88 degrees $2\theta \pm 0.2$ degree 2θ , 22.08 degrees $2\theta \pm 0.2$ degree 2θ , 22.94 degrees $2\theta \pm 0.2$ degree 2θ , 23.63 degrees $2\theta \pm 0.2$ degree 2θ , 24.01 degrees $2\theta \pm 0.2$ degree 2θ , 25.08 degrees $2\theta \pm 0.2$ degree 2θ , or any combinations thereof, at about relative humidity 0%.

[00109] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1) having an X-ray powder diffraction pattern comprising one peak, two peaks, three peaks, four peaks, five peaks, six peaks, seven peaks, eight peaks, nine peaks, ten peaks, eleven peaks, twelve peaks, thirteen peaks, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, or at least thirteen peaks, in terms of 2-theta, at 7.14 degrees $2\theta \pm 0.02$ degree 2θ , 12.02 degrees $2\theta \pm 0.02$ degree 2θ , 13.78 degrees $2\theta \pm 0.02$ degree 2θ , 14.24 degrees $2\theta \pm 0.02$ degree 2θ , 16.13 degrees $2\theta \pm 0.02$ degree 2θ , 17.79 degrees $2\theta \pm 0.02$ degree 2θ , 18.35 degrees $2\theta \pm 0.02$ degree 2θ , 18.88 degrees $2\theta \pm 0.02$ degree 2θ , 22.08 degrees $2\theta \pm 0.02$ degree 2θ , 22.94 degrees $2\theta \pm 0.02$ degree 2θ , 23.63 degrees $2\theta \pm 0.02$ degree 2θ , 24.01 degrees $2\theta \pm 0.02$ degree 2θ , 25.08 degrees $2\theta \pm 0.02$ degree 2θ , or any combinations thereof, at about relative humidity 0%.

[00110] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1) having an X-ray powder diffraction pattern comprising one peak, two peaks, three peaks, four peaks, five peaks, six peaks, seven peaks, eight peaks, nine peaks, ten peaks, eleven peaks, twelve peaks, thirteen peaks, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, or at least thirteen peaks, in terms of 2-theta, at 7.14 degrees $2\theta \pm 0.01$ degree 2θ , 12.02 degrees $2\theta \pm 0.01$ degree 2θ , 13.78 degrees $2\theta \pm 0.01$ degree 2θ , 14.24 degrees $2\theta \pm 0.01$ degree 2θ , 16.13 degrees $2\theta \pm 0.01$ degree 2θ , 17.79 degrees $2\theta \pm 0.01$ degree 2θ , 18.35 degrees $2\theta \pm 0.01$ degree 2θ , 18.88 degrees $2\theta \pm 0.01$ degree 2θ , 22.08 degrees $2\theta \pm 0.01$ degree 2θ , 22.94 degrees $2\theta \pm 0.01$ degree 2θ , 23.63 degrees $2\theta \pm 0.01$

degree 2θ , 24.01 degrees $2\theta \pm 0.01$ degree 2θ , 25.08 degrees $2\theta \pm 0.01$ degree 2θ , or any combinations thereof, at about relative humidity 0%.

[00111] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1B) having an X-ray powder diffraction pattern substantially as shown in Figure 22C.

[00112] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1B) having an X-ray powder diffraction pattern comprising one or more peaks of the peaks provided in Table 7B.

[00113] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1B) having an X-ray powder diffraction pattern comprising one peak, two peaks, three peaks, four peaks, five peaks, six peaks, seven peaks, eight peaks, nine peaks, ten peaks, eleven peaks, at least one peak, at least two peaks, at least three peaks, at least four peaks, at least five peaks, at least six peaks, at least seven peaks, at least eight peaks, at least nine peaks, at least ten peaks, or at least eleven peaks, in terms of 2-theta, at 8.9 degrees $2\theta \pm 0.2$ degree 2θ , at 11.53 degrees $2\theta \pm 0.2$ degree 2θ , at 14.04 degrees $2\theta \pm 0.2$ degree 2θ , at 19.23 degrees $2\theta \pm 0.2$ degree 2θ , at 21.66 degrees $2\theta \pm 0.2$ degree 2θ , at 22.39 degrees $2\theta \pm 0.2$ degree 2θ , at 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 24.80 degrees $2\theta \pm 0.2$ degree 2θ , at 25.58 degrees $2\theta \pm 0.2$ degree 2θ , at 26.84 degrees $2\theta \pm 0.2$ degree 2θ , 28.76 degrees $2\theta \pm 0.2$ degree 2θ , or any combinations thereof, at about relative humidity 0%.

[000114] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1B) having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 11.53 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00115] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1B), having an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at 11.53 degrees $2\theta \pm 0.2$ degree 2θ and 22.63 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00116] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1B), having an X-ray powder diffraction pattern comprising at least one peak, in terms of 2-theta, selected from the group consisting of 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , and 19.23 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00117] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1B), having an X-ray powder diffraction pattern comprising at least two peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , 19.23 degrees $2\theta \pm 0.2$ degree 2θ , and 26.84 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00118] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1B), having an X-ray powder diffraction pattern comprising at least three peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , 19.23 degrees $2\theta \pm 0.2$ degree 2θ , 26.84 degrees $2\theta \pm 0.2$ degree 2θ , and 8.94 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00119] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1B), having an X-ray powder diffraction pattern comprising at least four peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , 19.23 degrees $2\theta \pm 0.2$ degree 2θ , 26.84 degrees $2\theta \pm 0.2$ degree 2θ , 8.94 degrees $2\theta \pm 0.2$ degree 2θ , and 22.39 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00120] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1B), having an X-ray powder diffraction pattern comprising at least five peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , 19.23 degrees $2\theta \pm 0.2$ degree 2θ , 26.84 degrees $2\theta \pm 0.2$ degree 2θ , 8.94 degrees $2\theta \pm 0.2$ degree 2θ , 22.39 degrees $2\theta \pm 0.2$ degree 2θ , and 24.80 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00121] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1B), having an X-ray powder diffraction pattern comprising at least five peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , 19.23 degrees $2\theta \pm 0.2$ degree 2θ , 26.84 degrees $2\theta \pm 0.2$ degree 2θ , 8.94 degrees $2\theta \pm 0.2$ degree 2θ , 22.39 degrees $2\theta \pm 0.2$ degree 2θ , 24.80 degrees $2\theta \pm 0.2$ degree 2θ , and 25.58 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00122] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1B), having an X-ray powder diffraction pattern comprising at least six peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 14.04

degrees $2\theta \pm 0.2$ degree 2θ , 19.23 degrees $2\theta \pm 0.2$ degree 2θ , 26.84 degrees $2\theta \pm 0.2$ degree 2θ , 8.94 degrees $2\theta \pm 0.2$ degree 2θ , 22.39 degrees $2\theta \pm 0.2$ degree 2θ , 24.80 degrees $2\theta \pm 0.2$ degree 2θ , 25.58 degrees $2\theta \pm 0.2$ degree 2θ , and 21.66 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00123] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1B), having an X-ray powder diffraction pattern comprising at least seven peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , 19.23 degrees $2\theta \pm 0.2$ degree 2θ , 26.84 degrees $2\theta \pm 0.2$ degree 2θ , 8.94 degrees $2\theta \pm 0.2$ degree 2θ , 22.39 degrees $2\theta \pm 0.2$ degree 2θ , 24.80 degrees $2\theta \pm 0.2$ degree 2θ , 25.58 degrees $2\theta \pm 0.2$ degree 2θ , 21.66 degrees $2\theta \pm 0.2$ degree 2θ , and 28.76 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00124] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1B), having an X-ray powder diffraction pattern comprising the peaks, in terms of 2-theta, of 8.94 degrees $2\theta \pm 0.2$ degree 2θ , 11.53 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , 19.23 degrees $2\theta \pm 0.2$ degree 2θ , 21.66 degrees $2\theta \pm 0.2$ degree 2θ , 22.39 degrees $2\theta \pm 0.2$ degree 2θ , 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 24.80 degrees $2\theta \pm 0.2$ degree 2θ , 25.58 degrees $2\theta \pm 0.2$ degree 2θ , 26.84 degrees $2\theta \pm 0.2$ degree 2θ , and 28.76 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00125] In certain embodiments disclosed herein, a solid form of RAD1901-2HCl (Form 1B) has an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 11.53 degrees $2\theta \pm 0.02$ degree 2θ , at about relative humidity 0%.

[00126] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1B), having an X-ray powder diffraction pattern comprising one peak, two peaks, three peaks, four peaks, five peaks, six peaks, seven peaks, eight peaks, nine peaks, ten peaks, eleven peaks, at least one peak, at least two peaks, at least three peaks, at least four peaks, at least five peaks, at least six peaks, at least seven peaks, at least eight peaks, at least nine peaks, at least ten peaks, at least eleven peaks, in terms of 2-theta, at 8.9 degrees $2\theta \pm 0.02$ degree 2θ , at 11.53 degrees $2\theta \pm 0.02$ degree 2θ , at 14.04 degrees $2\theta \pm 0.02$ degree 2θ , at 19.23 degrees $2\theta \pm 0.02$ degree 2θ , at 21.66 degrees $2\theta \pm 0.02$ degree 2θ , at 22.39 degrees $2\theta \pm 0.02$ degree 2θ , at 22.63 degrees $2\theta \pm 0.02$ degree 2θ , 24.80 degrees $2\theta \pm 0.02$ degree 2θ , at 25.58 degrees $2\theta \pm 0.02$ degree 2θ , at 26.84 degrees $2\theta \pm 0.02$ degree 2θ , 28.76 degrees $2\theta \pm 0.02$ degree 2θ , or any combinations thereof, at about relative humidity 0%.

[00127] In certain embodiments disclosed herein, a solid form of RAD1901-2HCl (Form 1B) has an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 11.53 degrees $2\theta \pm 0.01$ degree 2θ , at about relative humidity 0%.

[00128] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl (Form 1B), having an X-ray powder diffraction pattern comprising one peak, two peaks, three peaks, four peaks, five peaks, six peaks, seven peaks, eight peaks, nine peaks, ten peaks, eleven peaks, at least one peak, at least two peaks, at least three peaks, at least four peaks, at least five peaks, at least six peaks, at least seven peaks, at least eight peaks, at least nine peaks, at least ten peaks, at least eleven peaks, selected from the peaks, in terms of 2-theta, at 8.9 degrees $2\theta \pm 0.01$ degree 2θ , at 11.53 degrees $2\theta \pm 0.01$ degree 2θ , at 14.04 degrees $2\theta \pm 0.01$ degree 2θ , at 19.23 degrees $2\theta \pm 0.01$ degree 2θ , at 21.66 degrees $2\theta \pm 0.01$ degree 2θ , at 22.39 degrees $2\theta \pm 0.01$ degree 2θ , at 22.63 degrees $2\theta \pm 0.01$ degree 2θ , 24.80 degrees $2\theta \pm 0.01$ degree 2θ , at 25.58 degrees $2\theta \pm 0.01$ degree 2θ , at 26.84 degrees $2\theta \pm 0.01$ degree 2θ , and 28.76 degrees $2\theta \pm 0.01$ degree 2θ , or any combinations thereof, at about relative humidity 0%.

[00129] In certain embodiments disclosed herein, a solid form of RAD1901-2HCl having a mixture of Form 1 and Form 1B has an X-ray powder diffraction pattern comprising one peak, two peaks, three peaks, four peaks, five peaks, six peaks, seven peaks, eight peaks, nine peaks, ten peaks, eleven peaks, twelve peaks, thirteen peaks, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, or at least thirteen peaks, in terms of 2-theta, at 7.14 degrees $2\theta \pm 0.2$ degree 2θ , 12.02 degrees $2\theta \pm 0.2$ degree 2θ , 13.78 degrees $2\theta \pm 0.2$ degree 2θ , 14.24 degrees $2\theta \pm 0.2$ degree 2θ , 16.13 degrees $2\theta \pm 0.2$ degree 2θ , 17.79 degrees $2\theta \pm 0.2$ degree 2θ , 18.35 degrees $2\theta \pm 0.2$ degree 2θ , 18.88 degrees $2\theta \pm 0.2$ degree 2θ , 22.08 degrees $2\theta \pm 0.2$ degree 2θ , 22.94 degrees $2\theta \pm 0.2$ degree 2θ , 23.63 degrees $2\theta \pm 0.2$ degree 2θ , 24.01 degrees $2\theta \pm 0.2$ degree 2θ , 25.08 degrees $2\theta \pm 0.2$ degree 2θ ; 8.9 degrees $2\theta \pm 0.2$ degree 2θ , at 11.53 degrees $2\theta \pm 0.2$ degree 2θ , at 14.04 degrees $2\theta \pm 0.2$ degree 2θ , at 19.23 degrees $2\theta \pm 0.2$ degree 2θ , at 21.66 degrees $2\theta \pm 0.2$ degree 2θ , at 22.39 degrees $2\theta \pm 0.2$ degree 2θ , at 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 24.80 degrees $2\theta \pm 0.2$ degree 2θ , at 25.58 degrees $2\theta \pm 0.2$ degree 2θ , at 26.84 degrees $2\theta \pm 0.2$ degree 2θ , 28.76 degrees $2\theta \pm 0.2$ degree 2θ ; or any combinations thereof, at about relative humidity 0%.

[00130] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having a differential scanning calorimetry (DSC) thermogram displaying a melting onset at 218.2 °C and an endothermic peak at 232.1 °C, e.g., Form 1.

[00131] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having a differential scanning calorimetry (DSC) thermogram substantially as shown in the bottom graph of Figure 8, e.g., Form 1.

[00132] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having a differential scanning calorimetry (DSC) thermogram substantially as shown in the bottom graph of Figure 21A, e.g., Form 1B.

[00133] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having a differential scanning calorimetry (DSC) thermogram (Figure 21A) displaying a melting onset at 210.3 °C and an endothermic peak at 233.8 °C, e.g., Form 1A.

[00134] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having a thermogravimetric analysis (TGA) substantially as shown in the top graph of Figure 8, e.g., Form 1.

[00135] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having a thermogravimetric analysis (TGA) substantially as shown in the top graph of Figure 21A, e.g., Form 1B.

[00136] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl having a ¹³C solid-state CPMAS NMR pattern substantially as Form 1B shown in Figure 23.

[00137] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl having a ¹H solid-state MAS NMR pattern substantially as Form 1B shown in Figure 24.

[00138] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl having an FT-IR pattern substantially as Form 1B as shown in Figure 25C.

[00139] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl having a Raman spectra pattern substantially as Form 1B shown in Figure 26.

[00140] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl having an XRPD pattern substantially as shown in Figure 22B.

[00141] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl having a ¹³C solid-state CPMAS NMR pattern substantially as Form 1 shown in Figure 23.

[00142] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl having a ^1H solid-state MAS NMR pattern substantially as Form 1 shown in Figure 24.

[00143] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl having an FT-IR pattern substantially as Form 1 as shown in Figure 25B.

[00144] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl having a Raman pattern substantially as Form 1 shown in Figure 26.

[00145] Certain embodiments disclosed herein provide a solid form of RAD1901 as disclosed herein (e.g., Form 1, Form 1B, or a combination of Form 1 and Form 1B) wherein said solid form comprises at least 1% w/w of a total sample of RAD1901-2HCl.

[00146] Certain embodiments disclosed herein provide a composition comprising RAD1901 wherein at least 5% w/w of the total amount of RAD1901 is a solid form of RAD1901 as disclosed herein (e.g., Form 1, Form 1B, or a combination of Form 1 and Form 1B).

[00147] Certain embodiments disclosed herein provide a composition comprising RAD1901 wherein at least 10% w/w of the total amount of RAD1901 is a solid form of RAD1901 as disclosed herein (e.g., Form 1, Form 1B, or a combination of Form 1 and Form 1B).

[00148] Certain embodiments disclosed herein provide a composition comprising RAD1901 wherein at least 25% w/w of the total amount of RAD1901 is a solid form of RAD1901 as disclosed herein (e.g., Form 1, Form 1B, or a combination of Form 1 and Form 1B).

[00149] Certain embodiments disclosed herein provide a composition comprising RAD1901 wherein at least 50% w/w of the total amount of RAD1901 is a solid form of RAD1901 as disclosed herein (e.g., Form 1, Form 1B, or a combination of Form 1 and Form 1B).

[00150] Certain embodiments disclosed herein provide a composition comprising RAD1901 wherein at least 90% w/w of the total amount of RAD1901 is a solid form of RAD1901 as disclosed herein (e.g., Form 1, Form 1B, or a combination of Form 1 and Form 1B).

[00151] Certain embodiments disclosed herein provide a composition comprising RAD1901 wherein at least 95% w/w of the total amount of RAD1901 is a solid form of RAD1901 as disclosed herein (e.g., Form 1, Form 1B, or a combination of Form 1 and Form 1B).

[00152] Certain embodiments disclosed herein provide a composition comprising RAD1901 wherein at least 98% w/w of the total amount of RAD1901 is a solid form of RAD1901 as disclosed herein (e.g., Form 1, Form 1B, or a combination of Form 1 and Form 1B).

[00153] Certain embodiments disclosed herein provide a composition comprising RAD1901 wherein at least 99% w/w of the total amount of RAD1901 is a solid form of RAD1901 as disclosed herein (e.g., Form 1, Form 1B, or a combination of Form 1 and Form 1B).

[00154] Certain embodiments disclosed herein provide a pharmaceutical composition comprising Form 1 in any of its specified embodiments and one or more pharmaceutically acceptable excipients.

[00155] Certain embodiments disclosed herein provide a pharmaceutical composition comprising Form 1B in any of its specified embodiments and one or more pharmaceutically acceptable excipients.

[00156] Certain embodiments disclosed herein provide a pharmaceutical composition comprising a combination of Form 1 and Form 1B in any of their specified embodiments and one or more pharmaceutically acceptable excipients.

[00157] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl having an X-Ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 6.3 degrees $2\theta \pm 0.2$ degree 2θ at about relative humidity 0%, e.g., Form 2.

[00158] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 6.3 degrees $2\theta \pm 0.2$ degree 2θ , and/or 12.5 degrees $2\theta \pm 0.2$ degree 2θ at about relative humidity 0%, e.g., Form 2.

[00159] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising at least two peaks, in terms of 2-theta, selected from the group consisting of 6.3 degrees $2\theta \pm 0.2$ degree 2θ , 12.5 degrees $2\theta \pm 0.2$ degree 2θ , and 15.4 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%, e.g., Form 2.

[00160] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising at least two peaks, in terms of 2-theta, selected from the group consisting of 6.3 degrees $2\theta \pm 0.2$ degree 2θ , 12.5 degrees $2\theta \pm 0.2$ degree 2θ , and 15.4 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%, e.g., Form 2.

[00161] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising at least three peaks, in terms of 2-theta, selected from the group consisting of 6.3 degrees $2\theta \pm 0.2$ degree 2θ , 12.5 degrees $2\theta \pm$

0.2 degree 2θ , 15.4 degrees $2\theta \pm 0.2$ degree 2θ , 18.3 degrees $2\theta \pm 0.2$ degree 2θ , and 13.4 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%, e.g., Form 2.

[00162] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern substantially as shown in Figure 5H at about relative humidity 0%, e.g., Form 2.

[00163] Certain embodiments disclosed herein provide a pharmaceutical composition comprising a solid form of RAD1901-2HCl disclosed herein (e.g., Form 2), and one or more pharmaceutically acceptable excipients.

[00164] In some embodiments, a solid form RAD1901-2HCl is a crystalline mixture comprising less than 1% Form 2.

[00165] In certain embodiments, a solid form RAD1901-2HCl is a crystalline mixture comprising more than 0.1% of Form 2 but less than 2%.

[00166] In some embodiments, a solid form RAD1901-2HCl comprises at least 10% Form 2.

[00167] In some embodiments, a solid form RAD1901-2HCl comprises at least 25% Form 2.

[00168] In some embodiments, a solid form RAD1901-2HCl comprises at least 50% Form 2.

[00169] In some embodiments, a solid form RAD1901-2HCl comprises at least 75% Form 2.

[00170] In some embodiments, a solid form RAD1901-2HCl comprises at least 95% Form 2.

[00171] In some embodiments, a solid form RAD1901-2HCl comprises at least 97% Form 2.

[00172] In some embodiments, a solid form RAD1901-2HCl comprises at least 99% Form 2.

[00173] Certain embodiments disclosed herein provide a solid, hydrated form of RAD1901-2HCl, e.g., Form 3. In some embodiments the solid hydrated form of RAD1901-2HCl is a dihydrate.

[00174] Certain embodiments disclosed herein provide a solid, hydrated form of RAD1901-2HCl having an X-Ray powder diffraction comprising a peak, in terms of 2-theta, at 5.8 degrees $2\theta \pm 0.2$ degree 2θ at about relative 92%, e.g., Form 3.

[00175] Certain embodiments disclosed herein provide a solid hydrated form of RAD901-2HCl having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 5.8 degrees $2\theta \pm 0.2$ degree 2θ , and/or 21.3 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 92%, e.g., Form 3.

[00176] Certain embodiments disclosed herein provide a solid hydrated form of RAD1901-2HCl having an X-ray powder diffraction pattern comprising at least two peaks, in terms of 2-theta, selected from the group consisting of 5.8 degrees $2\theta \pm 0.2$ degree 2θ , 21.3 degrees $2\theta \pm 0.2$ degree 2θ , and 24.8 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 92%, e.g., Form 3.

[00177] Certain embodiments disclosed herein provide a solid hydrated form of RAD1901-2HCl having an X-Ray powder diffraction pattern comprising at least three peaks, in terms of 2-theta, selected from the group consisting of 5.8 degrees $2\theta \pm 0.2$ degree 2θ , 21.3 degrees $2\theta \pm 0.2$ degree 2θ , 24.8 degrees $2\theta \pm 0.2$ degree 2θ , 23.3 degrees $2\theta \pm 0.2$ degree 2θ , and 9.5 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 92%, e.g., Form 3.

[00178] Certain embodiments disclosed herein provide a solid hydrated form of RAD1901-2HCl having an X-Ray powder diffraction pattern comprising at least four peaks, in terms of 2-theta, selected from the group consisting of 5.8 degrees $2\theta \pm 0.2$ degree 2θ , 21.3 degrees $2\theta \pm 0.2$ degree 2θ , 24.8 degrees $2\theta \pm 0.2$ degree 2θ , 23.3 degrees $2\theta \pm 0.2$ degree 2θ , and 9.5 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 92%, e.g., Form 3.

[00179] Certain embodiments disclosed herein provide a solid form of RAD1901-2HCl that is amorphous.

[00180] Certain embodiments disclosed herein provide one or more crystalline and/or amorphous form of RAD1901-2HCl dispersed into a matrix.

[00181] Certain embodiments are disclosed comprising a dosage form of RAD1901-2HCl comprising 50 gm, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, or 600 mg of RAD1901-2HCl in one or more crystalline and/or amorphous forms, wherein said one or more crystalline and/or amorphous forms are dispersed in a solid or liquid matrix.

II. Pharmaceutical compositions and/or formulas of Polymorphic Forms of RAD1901-2HCl

[00182] Provided herein are pharmaceutical compositions comprising one or more polymorphous and/or amorphous forms of RAD1901-2HCl disclosed herein, and a physiologically acceptable carrier (also referred to as a pharmaceutically acceptable carrier or solution or diluent). Such carriers and solutions include pharmaceutically acceptable salts and solvates of compounds used in the methods of the instant invention, and mixtures comprising two or more of such compounds, pharmaceutically acceptable salts of the

compounds and pharmaceutically acceptable solvates of the compounds. Such compositions are prepared in accordance with acceptable pharmaceutical procedures such as described in Remington's Pharmaceutical Sciences, 17th edition, ed. Alfonso R. Gennaro, Mack Publishing Company, Eaton, Pa. (1985), which is incorporated herein by reference.

[00183] The term "pharmaceutically acceptable carrier" refers to a carrier that does not cause an allergic reaction or other untoward effect in a subject to whom it is administered and are compatible with the other ingredients in the formulation. Pharmaceutically acceptable carriers include, for example, pharmaceutical diluents, excipients or carriers suitably selected with respect to the intended form of administration, and consistent with conventional pharmaceutical practices. For example, solid carriers/diluents include, but are not limited to, a gum, a starch (e.g., corn starch, pregelatinized starch), a sugar (e.g., lactose, mannitol, sucrose, dextrose), a cellulosic material (e.g., microcrystalline cellulose), an acrylate (e.g., polymethylacrylate), calcium carbonate, magnesium oxide, talc, or mixtures thereof. Pharmaceutically acceptable carriers may further comprise minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the therapeutic agent.

[00184] The term "patient" refers to a human subject.

[00185] The one or more polymorphous and/or amorphous forms of RAD1901-2HCl disclosed herein and pharmaceutical composition thereof may be formulated into unit dosage forms, meaning physically discrete units suitable as unitary dosage for subjects undergoing treatment, with each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, optionally in association with a suitable pharmaceutical carrier. The unit dosage form can be for a single daily dose or one of multiple daily doses (e.g., about 1 to 4 or more times per day). When multiple daily doses are used, the unit dosage form can be the same or different for each dose. In certain embodiments, the compounds may be formulated for controlled release.

[00186] The one or more polymorphous and/or amorphous forms of RAD1901-2HCl disclosed herein and pharmaceutical composition thereof may be formulated according to any available conventional method. Examples of preferred dosage forms include a tablet, a powder, a suble granule, a granule, a coated tablet, a capsule, a syrup, a troche, and the like. In the formulation, generally used additives such as a diluent, a binder, a disintegrant, a lubricant, a colorant, a flavoring agent, and if necessary, a stabilizer, an emulsifier, an absorption enhancer, a surfactant, a pH adjuster, an antiseptic, an antioxidant and the like can

be used. In addition, the formulation is also carried out by combining compositions that are generally used as a raw material for pharmaceutical formulation, according to the conventional methods. Examples of these compositions include, for example, (1) an oil such as a soybean oil, a beef tallow and synthetic glyceride; (2) hydrocarbon such as liquid paraffin, squalane and solid paraffin; (3) ester oil such as octyldodecyl myristic acid and isopropyl myristic acid; (4) higher alcohol such as cetostearyl alcohol and biphenyl alcohol; (5) a silicon resin; (6) a silicon oil; (7) a surfactant such as polyoxyethylene fatty acid ester, sorbitan fatty acid ester, glycerin fatty acid ester, polyoxyethylene sorbitan fatty acid ester, a solid polyoxyethylene castor oil and polyoxyethylene polyoxypropylene block co-polymer; (8) water soluble macromolecule such as hydroxyethyl cellulose, polyacrylic acid, carboxyvinyl polymer, polyethyleneglycol, polyvinylpyrrolidone and methylcellulose; (9) lower alcohol such as ethanol and isopropanol; (10) multivalent alcohol such as glycerin, propyleneglycol, dipropyleneglycol and sorbitol; (11) a sugar such as glucose and cane sugar; (12) an inorganic powder such as anhydrous silicic acid, aluminum magnesium silicate and aluminum silicate; (13) purified water, and the like. Additives for use in the above formulations may include, for example, 1) lactose, corn starch, sucrose, glucose, mannitol, sorbitol, crystalline cellulose and silicon dioxide as the diluent; 2) polyvinyl alcohol, polyvinyl ether, methyl cellulose, ethyl cellulose, gum arabic, tragacanth, gelatin, shellac, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, polypropylene glycol-poly oxyethylene-block co-polymer, meglumine, calcium citrate, dextrin, pectin and the like as the binder; 3) starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium bicarbonate, calcium citrate, dextrin, pectic, carboxymethylcellulose/calcium and the like as the disintegrant; 4) magnesium stearate, talc, polyethyleneglycol, silica, condensed plant oil and the like as the lubricant; 5) any colorants whose addition is pharmaceutically acceptable is adequate as the colorant; 6) cocoa powder, menthol, aromatizer, peppermint oil, cinnamon powder as the flavoring agent; 7) antioxidants whose addition is pharmaceutically accepted such as ascorbic acid or alpha-tophenol.

[00187] Some embodiments disclosed herein provide a pharmaceutical dosage form comprising RAD1901-2HCl Form 1 in an amount of 50 gm, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, or 600 mg.

[00188] Certain embodiments disclosed herein provide a drug dosage form as a tablet comprising 50 gm, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, or 600 mg RAD1901-2HCl crystalline Form 1. In certain embodiments, at least 80%, at least 85%, at least 90%, at least

95%, at least 98%, or at least 99.5% of RAD1901 in the table is RAD1901-2HCl crystalline Form 1.

[00189] Some embodiments disclosed herein provide a pharmaceutical dosage form comprising RAD1901-2HCl Form 1B in an amount of 50 gm, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, or 600 mg.

[00190] Certain embodiments disclosed herein provide a drug dosage form as a tablet comprising 50 gm, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, or 600 mg RAD1901-2HCl crystalline Form 1B. In certain embodiments, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99.5% of RAD1901 in the tablet is RAD1901-2HCl crystalline Form 1B.

[00191] Certain embodiments disclosed herein provide a drug dosage form as a tablet comprising 50 gm, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, or 600 mg RAD1901-2HCl of a mixture of crystalline Form 1 and crystalline Form 1B. In certain embodiments, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99.5% of RAD1901 in the tablet is RAD1901-2HCl in a mixture of crystalline Form 1 and crystalline Form 1B.

[00192] Certain embodiments disclosed herein provide a pharmaceutical composition comprising 50 gm, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, or 600 mg of a solid form of RAD1901-2HCl disclosed herein (e.g., comprising Form 2 and/or Form 3), and one or more pharmaceutically acceptable excipients.

[00193] In certain embodiments, a pharmaceutical dosage form comprises Form 2 as disclosed herein.

III. Use of the Polymorphic Forms of RAD1901-2HCl

[00194] Provided herein are methods of treating and/or preventing one or more conditions of a subject that can benefit from administration of RAD1901, the methods comprise administering to the subject with therapeutically effective amount of one or more polymorphic forms of RAD1901-2HCl disclosed herein, or a pharmaceutical composition thereof.

[00195] In certain embodiments, the one or more conditions treated/prevented by the methods disclosed herein are breast, uterus, and ovary tumors and/or cancers having overexpression of estrogen receptors, and metastatic cancer and/or tumor. In certain embodiments, the cancer and/or tumor treated in the methods disclosed herein are resistant ER-driven cancers or tumors, (e.g. having mutant ER binding domains (e.g. ER α comprising

one or more mutations including, but not limited to, Y537X₁ wherein X₁ is S, N, or C, D538G, L536X₂ wherein X₂ is R or Q, P535H, V534E, S463P, V392I, E380Q and combinations thereof), overexpressors of the ERs or tumor and/or cancer proliferation becomes ligand independent, or tumors and/or cancers that progress after endocrinological treatment, such as with treatment of SERD (e.g., fulvestrant, TAS-108 (SR16234), ZK191703, RU58668, GDC-0810 (ARN-810), GW5638/DPC974, SRN-927, and AZD9496), aromatase inhibitor (e.g., anastrozole, exemestane, and letrozole), selective estrogen receptor modulators (e.g., tamoxifen, raloxifene, lasofoxifene, and/or toremifene), Her2 inhibitors (e.g., trastuzumab, lapatinib, ado-trastuzumab emtansine, and/or pertuzumab), chemo therapy (e.g., abraxane, adriamycin, carboplatin, cytoxan, daunorubicin, doxil, ellence, fluorouracil, gemzar, helaven, lxempra, methotrexate, mitomycin, micoxantrone, navelbine, taxol, taxotere, thiotepa, vincristine, and xeloda), angiogenesis inhibitor (e.g., bevacizumab), cdk4/6 inhibitors, m-TOR inhibitors and/or rituximab.

[00196] Provided herein are methods of modulating estrogen receptors of a subject, the methods comprise administering to the subject with therapeutically effective amount of one or more polymorphic forms of RAD1901-2HCl disclosed herein, or a pharmaceutical composition thereof; and the one or more polymorphic forms of RAD1901-2HCl disclosed herein demonstrate an estrogen-like action in the central nervous system, bone tissue and lipid metabolism, and/or estrogen antagonism in a reproductive organ and a mammary gland.

[00197] A therapeutically effective amount of the one of more polymorphic forms of RAD1901-2HCl for use in the methods disclosed herein is an amount that, when administered over a particular time interval, results in achievement of one or more therapeutic benchmarks (e.g., slowing or halting of tumor growth, cessation of symptoms, etc.). The skilled artisan can readily determine this amount, on either an individual subject basis (e.g., the amount of the one of more polymorphic forms of RAD1901-2HCl necessary to achieve a particular therapeutic benchmark in the subject being treated) or a population basis (e.g., the amount of the one of more polymorphic forms of RAD1901-2HCl necessary to achieve a particular therapeutic benchmark in the average subject from a given population). Ideally, the therapeutically effective amount does not exceed the maximum tolerated dosage at which 50% or more of treated subjects experience nausea or other toxicity reactions that prevent further drug administrations. A therapeutically effective amount may vary for a subject depending on a variety of factors, including variety and extent of the symptoms, sex, age, body weight, or general health of the subject, administration mode and salt or solvate type, variation in susceptibility to the drug, the specific type of the disease, and the like.

[00198] The one of more polymorphic forms of RAD1901-2HCl or the pharmaceutical composition thereof for use in the presently disclosed methods may be administered to a subject one time or multiple times. In those embodiments wherein the compounds are administered multiple times, they may be administered at a set interval, e.g., daily, every other day, weekly, or monthly. Alternatively, they can be administered at an irregular interval, for example on an as-needed basis based on symptoms, patient health, and the like.

[00199] Some embodiments disclosed herein provide a method of treating ER+ breast cancer comprising a daily administration of 400 mg of RAD1901-2HCl crystalline Form 1 in a dosage form wherein said dosage form is a tablet or capsule and said administration is oral.

[00200] Some embodiments disclosed herein provide a method of treating ER+ breast cancer in a subject, wherein: the ER+ breast cancer is resistant to one or more endocrinological therapies or the subject has progressed after prior treatment with one or more endocrinological therapies; the treatment comprises a daily administration of 400 mg of RAD1901-2HCl crystalline Form 1 in a dosage form; and the dosage form is a tablet or capsule and said administration is oral.

[00201] Some embodiments disclosed herein provide a method of treating ER+ breast cancer in a subject wherein: the ER+ breast cancer is resistant to one or more endocrinological therapies or the subject has progressed after prior treatment with one or more endocrinological therapies; the treatment comprises a first administration of 400 mg daily of RAD1901-2HCl crystalline Form 1 in a dosage form; the dosage form is a tablet or capsule; the administration is oral; the administration of RAD1901-2HCl crystalline Form 1 is in combination with a second administration of a cdk4/6 inhibitor and/or an m-TOR inhibitor; and the second administration is an administration method suitable for the cdk4/6 inhibitor and/or m-TOR inhibitor.

[00202] Some embodiments disclosed herein provide a method of treating ER+ breast cancer in a subject wherein: the ER+ breast cancer is resistant to one or more endocrinological therapies or the subject has progressed after prior treatment with one or more endocrinological therapies; the treatment comprises a first administration of 400 mg daily of RAD1901-2HCl crystalline Form 1 in a dosage form; the dosage form is a tablet or capsule; the administration is oral; and the first administration is in combination with a second administration of palbociclib, ribociclib, abemaciclib and/or everolimus.

[00203] Some embodiments disclosed herein provide a method of treating ER+ breast cancer in a subject wherein: the ER+ breast cancer is resistant to one or more cdk4/6 inhibitors

and/or m-TOR inhibitors; the treatment comprises a daily administration of 400 mg of RAD1901-2HCl crystalline Form 1 in a dosage form; the dosage form is a tablet or capsule; and the administration is oral.

[00204] Certain embodiments disclosed herein provide a method of treating breast cancer comprising an administration to a subject in need thereof a crystalline form of RAD1901-2HCl (e.g., Form 1 as disclosed herein). In some embodiments, the breast cancer is ER+.

[00205] Certain embodiments disclosed herein provide a method of treating ovarian cancer comprising an administration to a subject in need thereof RAD1901-2HCl (Form 1). In some embodiments, the ovarian cancer is ER+.

[00206] Some embodiments disclosed herein provide a method of treating ER+ breast cancer comprising a daily administration of 400 mg of RAD1901-2HCl crystalline Form 1B in a dosage form wherein said dosage form is a tablet or capsule and said administration is oral.

[00207] Some embodiments disclosed herein provide a method of treating ER+ breast cancer in a subject, wherein: the ER+ breast cancer is resistant to one or more endocrinological therapies or the subject has progressed after prior treatment with one or more endocrinological therapies; the treatment comprises a daily administration of 400 mg of RAD1901-2HCl crystalline Form 1B in a dosage form; and the dosage form is a tablet or capsule and said administration is oral.

[00208] Some embodiments disclosed herein provide a method of treating ER+ breast cancer in a subject wherein: the ER+ breast cancer is resistant to one or more endocrinological therapies or the subject has progressed after prior treatment with one or more endocrinological therapies; the treatment comprises a first administration of 400 mg daily of RAD1901-2HCl crystalline Form 1B in a dosage form; the dosage form is a tablet or capsule; the administration is oral; the administration of RAD1901-2HCl crystalline Form 1B is in combination with a second administration of a cdk4/6 inhibitor and/or an m-TOR inhibitor; and the second administration is an administration method suitable for the cdk4/6 inhibitor and/or m-TOR inhibitor.

[00209] Some embodiments disclosed herein provide a method of treating ER+ breast cancer in a subject wherein: the ER+ breast cancer is resistant to one or more endocrinological therapies or the subject has progressed after prior treatment with one or more endocrinological therapies; the treatment comprises a first administration of 400 mg daily of RAD1901-2HCl crystalline Form 1B in a dosage form; the dosage form is a tablet or capsule;

the administration is oral; and the first administration is in combination with a second administration of palbociclib, ribociclib, abemaciclib and/or everolimus.

[00210] Some embodiments disclosed herein provide a method of treating ER+ breast cancer in a subject wherein: the ER+ breast cancer is resistant to one or more cdk4/6 inhibitors and/or m-TOR inhibitors; the treatment comprises a daily administration of 400 mg of RAD1901-2HCl crystalline Form 1B in a dosage form; the dosage form is a tablet or capsule; and the administration is oral.

[00211] Certain embodiments disclosed herein provide a method of treating breast cancer comprising an administration to a subject in need thereof a crystalline form of RAD1901-2HCl (e.g., Form 1B as disclosed herein). In some embodiments, the breast cancer is ER+.

[00212] Certain embodiments disclosed herein provide a method of treating ovarian cancer comprising an administration to a subject in need thereof RAD1901-2HCl (Form 1B). In some embodiments, the ovarian cancer is ER+.

[00213] Some embodiments disclosed herein provide a method of treating ER+ breast cancer comprising a daily administration of 400 mg of RAD1901-2HCl having a mixture of crystalline Form 1 and crystalline Form 1B in a dosage form wherein said dosage form is a tablet or capsule and said administration is oral.

[00214] Some embodiments disclosed herein provide a method of treating ER+ breast cancer in a subject, wherein: the ER+ breast cancer is resistant to one or more endocrinological therapies or the subject has progressed after prior treatment with one or more endocrinological therapies; the treatment comprises a daily administration of 400 mg of RAD1901-2HCl having a mixture of crystalline Form 1 and crystalline Form 1B in a dosage form; and the dosage form is a tablet or capsule and said administration is oral.

[00215] Some embodiments disclosed herein provide a method of treating ER+ breast cancer in a subject wherein: the ER+ breast cancer is resistant to one or more endocrinological therapies or the subject has progressed after prior treatment with one or more endocrinological therapies; the treatment comprises a first administration of 400 mg daily of RAD1901-2HCl having a mixture of crystalline Form 1 and crystalline Form 1B in a dosage form; the dosage form is a tablet or capsule; the administration is oral; the administration of RAD1901-2HCl having a mixture of crystalline Form 1 and crystalline Form 1B is in combination with a second administration of a cdk4/6 inhibitor and/or an m-TOR inhibitor;

and the second administration is an administration method suitable for the cdk4/6 inhibitor and/or m-TOR inhibitor.

[00216] Some embodiments disclosed herein provide a method of treating ER+ breast cancer in a subject wherein: the ER+ breast cancer is resistant to one or more endocrinological therapies or the subject has progressed after prior treatment with one or more endocrinological therapies; the treatment comprises a first administration of 400 mg daily of RAD1901-2HCl having a mixture of crystalline Form 1 and crystalline Form 1B in a dosage form; the dosage form is a tablet or capsule; the administration is oral; and the first administration is in combination with a second administration of palbociclib, ribociclib, abemaciclib and/or everolimus.

[00217] Some embodiments disclosed herein provide a method of treating ER+ breast cancer in a subject wherein: the ER+ breast cancer is resistant to one or more cdk4/6 inhibitors and/or m-TOR inhibitors; the treatment comprises a daily administration of 400 mg of RAD1901-2HCl having a mixture of crystalline Form 1 and crystalline Form 1B in a dosage form; the dosage form is a tablet or capsule; and the administration is oral.

[00218] Certain embodiments disclosed herein provide a method of treating breast cancer comprising an administration to a subject in need thereof a crystalline form of RAD1901-2HCl (e.g., a mixture of crystalline Form 1 and crystalline Form 1B as disclosed herein). In some embodiments, the breast cancer is ER+.

[00219] Certain embodiments disclosed herein provide a method of treating ovarian cancer comprising an administration to a subject in need thereof RAD1901-2HCl (Form 1 and Form 1B). In some embodiments, the ovarian cancer is ER+.

[00220] In some embodiments, provided herein is a method of treating ER+ breast cancer comprising an administration of a dosage form comprising one or more crystalline forms of RAD1901-2HCl as disclosed herein.

[00221] In some embodiments, the manufacture of a medicament useful for treating a subject in need with RAD1901-2HCl is provided herein, wherein the medicament comprises one or more crystalline and/or amorphous forms of RAD1901-2HCl as disclosed herein.

IV. Preparation of the Polymorphic Forms of RAD1901-2HCl

[00222] Provided herein are methods for preparing Forms 1, 2 and 3 of RAD1901-2HCl disclosed herein.

[00223] In certain embodiments, RAD1901-2HCl can be prepared by treating a RAD1901 solution in an organic solvent (e.g., EtOH, EtOAc, and mixtures thereof) with at least 2 eq. of HCl (e.g., in EtOH). In certain embodiments, a RAD1901-2HCl solution can be further concentrated, treated with an organic solvent (e.g., EtOAc), and filtered to provide RAD1901 as its bis-HCl salt, suitable for further processing according to the methods of form conversion provided in this disclosure.

[00224] In certain embodiments, Form 1 can be prepared by treating RAD1901-2HCl with an organic solvent substantially free of methanol (e.g., less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, or less than 0.5% of the organic solvent is methanol) with relatively low water content (e.g., less than 5% v/v). In certain embodiments, Form 1 can be prepared by treating RAD1901-2HCl with an organic solvent (e.g., EtOH, etc.) with relatively low water content (e.g., less than 5% v/v) and then with another organic solvent in which RAD1901-2HCl has a lower solubility (e.g., esters such as EtOAc, etc.). As used herein, unless otherwise specified, an organic solvent may be a single organic solvent or a mixture of multiple organic solvents.

[00225] Certain embodiments disclosed herein provide methods of preparing Form 1 of RAD1901-2HCl comprising precipitating from a solution comprising RAD1901-2HCl and a solvent, or slurring RAD1901-2HCl in a solvent, wherein the solvent comprises an organic solvent substantially free of methanol, and the content of water is at or below 5% v/v. In some embodiments, the organic solvent is selected from the group consisting of n-heptane, propyl acetate, ethyl acetate, isopropyl acetate, MIBK, MEK, 1-propanol, ethanol, TBME, 1,4-dioxane, toluene, 1,2-dimethoxyethane, tetrahydrofuran, dichloromethane, acetonitrile, nitromethane, and mixtures thereof.

[00226] In certain embodiments, Form 2, Form 3, or combinations thereof can be prepared by treating RAD1901-2HCl with an organic solvent containing water and/or methanol. In certain embodiments, Form 2, Form 3, or combinations thereof can be prepared by treating RAD1901-2HCl with an organic solvent containing water and/or methanol, and then with another organic solvent in which RAD1901-2HCl has a lower solubility (e.g., esters such as EtOAc, etc.). Form 3 can be preferably prepared via using solvents having a water content of 5% or higher. In certain embodiments, Form 2 can be prepared using MeOH with a water content of about 1 % to about 2%.

[00227] In certain embodiments, methods for preparing Form 1 of RAD1901-2HCl comprises heating a composition comprising Form 2, Form 3, or combinations thereof at a

temperature above 175 °C for a period of time sufficient for the conversion at a RH of about 90% or lower, about 85% or lower, about 80% or lower, about 75% or lower, about 70% or lower, about 65% or lower, about 60% or lower, about 55% or lower, about 50% or lower, about 45% or lower, or about 40% or lower.

[00228] In certain embodiments, methods of preparing Form 2 of RAD1901-2HCl comprises exposing a composition comprising Form 3 thereof to a RH of about 0% for a period of time sufficient for the conversion (e.g., 6 h at 0% RH).

[00229] In certain embodiments, methods of preparing Form 3 of RAD1901-2HCl comprises exposing a composition comprising Form 2, Form 3, or combinations thereof to a RH of about 40% or higher for a period of time sufficient for the conversion (e.g., about 2 weeks at RH 40%).

[00230] In certain embodiments, methods of preparing Form 3 of RAD1901-2HCl comprises exposing a composition comprising Form 1 to a RH of about 90% or higher for a period of time sufficient for the conversion (e.g., 1 week at 90% RH).

[00231] In some embodiments, Form 1B may be prepared by a method comprising treating RAD1901-2HCl with 2-ethoxyethanol. In certain embodiments, the method comprises:

- a) treating RAD1901-2HCl with 2-ethoxyethanol at about 25°C;
- b) heating the RAD1901-2HCl suspension of step a) to about 50 °C to about 60 °C, optionally cooling the heated RAD1901-2HCl suspension of step b) to 5 °C slowly, e.g., at about 0.25 °C/min, 0.1 °C/min, 0.2 °C/min, 0.3 °C/min, 0.4 °C/min, 0.5 °C/min, 0.05-0.5 °C/min, or 0.01 to 0.75 °C/min;
- c) subjecting the sample obtained from step b) to heat-cool cycles between about 50°C to 60 °C and about 25 °C for several days, e.g., 1 day to 1 week, 2 to 3 days, 1 to 4 days, 1 to 5 days, or 1 to 6 days, and the heat-cool cycles may be a 2-12 hour cycle, 3-11 hour cycle, 3-10 hour cycle, 4-9 hour cycle, 5-8 hour cycle, 6-11 hour cycle, 7-12 hour cycle, 4 hour cycle, 5 hour cycle, 6 hour cycle, 7 hour cycle, 8 hour cycle, 9 hour cycle, or 10 hour cycle; and
- d) filtering the resulting suspension and drying to obtain Form 1B of RAD1901-2HCl.

[00232] In some embodiments, Form 1B may be prepared by a method comprising treating RAD1901-2HCl with 2-ethoxyethanol in 50 volumes while stirring at 25 °C, 300-600 rpm (e.g., 400-600 rpm, or 500-600 rpm) for 10 minutes; heating the suspension to 50 °C; and subjecting the suspension to heat-cool cycles between 50 and 25 °C (8 hr/cycle) for 2-3 days; and filtering the suspension using a Buchner funnel and drying under suction for 30 min. to obtain Form 1B of RAD1901-2HCl. The resulting sample may be further dried under

vacuum for 4 hours at room temperature. Optionally, the suspension heated to 50 °C may be maintained at 50 °C for 10 mins and cooled the suspension to 5 °C at 0.25 °C/min before subjecting to the heat-cool cycles.

EXAMPLES

Instrument and methodology

[00233] A. X-Ray powder Diffraction (XRPD)

[00234] Two x-ray diffractometer instruments were used to collect X-ray diffraction patterns as described below.

[00235] A1. *Bruker AXS C2 GADDS*

[00236] X-Ray Powder Diffraction patterns were collected on a Bruker AXS C2 GADDS diffractometer using Cu K α radiation (40 kV, 40 mA), automated XYZ stage, laser video microscope for auto-sample positioning and a HiStar 2-dimensional area detector. X-ray optics consists of a single Göbel multilayer mirror coupled with a pinhole collimator of 0.3 mm. A weekly performance check was carried out using a certified standard NIST 1976 Corundum (flat plate).

[00237] The beam divergence, i.e. the effective size of the X-ray beam on the sample, was approximately 4 mm. A θ - θ continuous scan mode was employed with a sample - detector distance of 20 cm which gave an effective 2θ range of 3.2° – 29.7°. Typically, the sample was exposed to the X-ray beam for 120 seconds. The software used for data collection was GADDS for XP/2000 4.1.43 and the data were analyzed and presented using *Diffraction Plus* EVA v15.0.0.0.

[00238] A1-1) Ambient conditions

[00239] Samples run under ambient conditions were prepared as flat plate specimens using powder as received without grinding. A sample was lightly pressed on a glass slide to obtain a flat surface.

[00240] A1-2) Non-ambient conditions

[00241] Samples run under non-ambient conditions were mounted on a silicon wafer with a heat-conducting compound. The sample was then heated from ambient to the appropriate temperature at 20 °C/min and subsequently held isothermally for 1 minute before data

collection was initiated. The sample was observed to melt during the experiment and recrystallized upon continued heated above this temperature.

[00242] A2. Bruker AXS D8 Advance

[00243] X-Ray Powder Diffraction patterns were collected on a Bruker D8 diffractometer using Cu K α radiation (40 kV, 40 mA), θ - 2θ goniometer, and divergence of V4 and receiving slits, a Ge monochromator and a Lynxeye detector. The instrument was performance checked using a certified Corundum standard (NIST 1976). The software used for data collection was Diffrac *Plus* XRD Commander v2.6.1 and the data were analyzed and presented using Diffrac *Plus* EVA v15.0.0.0.

[00244] A2-1) Ambient conditions

[00245] Samples run under ambient conditions as flat plate specimens using powder as received. The sample was gently packed into a cavity, cut into polished, zero-background (510) silicon wafer. The sample was rotated in its own plane during analysis. The data were collected in an angular range of 2 to 42° 2θ , with a step size of 0.05° 2θ , and a collection time of 0.5 sec/step.

[00246] A2-2) Non-ambient conditions

[00247] Samples run under non-ambient conditions were prepared by gently packing into a cavity, cut into a silicon wafer to obtain a flat surface and mounted onto a humidity stage with an Ansyco controller and humidity sensor positioned directly next to the sample holder. The data were collected at 298.15 K with water temperature of 35.0 °C, in an angular range of 3 to 31° 2θ , with a step size of 0.025° 2θ , a collection time of 2.0 sec/step, and a collection time at each %RH was 41 min 28 sec.

[00248] X-Ray Powder Diffraction (XRPD) patterns were collected at variable humidity values from 0 to 95 % RH, based upon the humidity behavior of each compound observed during GVS experiments (described herein). For each Variable Humidity X-Ray Powder Diffraction (VH-XRPD) experiment performed, the % RH values selected are provided alongside the relevant experimental result. Full tables of detailing the % RH value at each collection point and the associated delay time at each value are provided in Tables 10-12.

[00249] Unless stated otherwise, listed 2θ values in this disclosure are +/- 0.2 degrees 2θ .

[00250] B. Nuclear Magnetic Resonance (NMR): ^1H NMR and ^{13}C NMR

[00251] NMR spectra were collected on a Bruker 400 MHz instrument equipped with an auto-sampler and controlled by a DRX400 console. Automated experiments were acquired using ICON-NMR v4.0.7 running with Topspin v1.3 using the standard Bruker loaded experiments. For non-routine spectroscopy, data were acquired through the use of Topspin alone. Samples were prepared in DMSO-*d*₆. Off-line analysis was carried out using ACD Spectrus Processor 2014.

[00252] C. Differential Scanning Calorimetry (DSC)

[00253] DSC data were collected on a TA Instruments Q2000 equipped with a 50 position autosampler. The calibration for thermal capacity was carried out using sapphire and the calibration for energy and temperature was carried out using certified indium. Each sample (e.g., 1 mg, 2 mg), in a pin-holed aluminum pan, was heated at 10 °C/min from 25 °C to 300 °C. A purge of dry nitrogen at 50 ml/min was maintained over the sample. Modulated temperature DSC was carried out using an underlying heating rate of 1 or 2 °C/min and temperature modulation parameters of ± 0.318 or 0.636 °C (amplitude) respectively, every 60 seconds (period).

[00254] The instrument control software was Advantage for Q Series v2.8.0.394 and Thermal Advantage v5.5.3 and the data were analyzed using Universal Analysis v4.5A.

[00255] Unless stated otherwise, listed DSC temperatures are $\pm 3^\circ\text{C}$.

[00256] D. Thermo-Gravimetric Analysis (TGA)

[00257] TGA data were collected on a TA Instruments Q500 TGA, equipped with a 16 position autosampler. The instrument was temperature calibrated using certified Alumel and Nickel. Each sample (e.g., 5 mg) was loaded onto a pre-tared aluminum DSC pan and heated at 10 °C/min from ambient temperature to 300 °C. A nitrogen purge at 60 ml/min was maintained over the sample.

[00258] The instrument control software was Advantage for Q Series v2.5.0.256 and Thermal Advantage v5.5.3 and the data were analyzed using Universal Analysis v4.5A.

[00259] E. Polarized Light Microscopy (PLM)

[00260] Samples were studied on a Nikon SMZ1500 polarized light microscope with a digital video camera connected to a DS Camera control unit DS-L2 for image capture. A small amount of each sample was placed on a glass slide, mounted in immersion oil, the individual

particles being separated as well as possible. The sample was viewed with appropriate magnification and partially polarized light, coupled to a λ false-color filter.

[00261] F. Scanning Electron Microscopy (SEM)

[00262] Data were collected on a Phenom Pro Scanning Electron Microscope. A small quantity of sample was mounted onto an aluminum stub using conducting double-sided adhesive tape. A thin layer of gold was applied using a sputter coater (20 mA, 120 s).

[00263] G. Water Determination by Karl Fischer Titration (KF)

[00264] The water content of each sample was measured on a Metrohm 874 Oven Sample Processor at 200 °C with 851 Titrano Coulometer using Hydranal Coulomat AG oven reagent and nitrogen purge. Weighed solid samples were introduced into a sealed sample vial. Approximately 10 mg of sample was used per titration and duplicate determinations were made. Data collection and analysis using Tiamo v2.2.

[00265] H. Chemical Purity Determination by HPLC

[00266] Purity analysis was performed on an Agilent HP1100 series system equipped with a diode array detector (255 nm with 90 nm bandwidth) and using ChemStation software vB.04.03. Samples were prepared as 0.4 - 0.6 mg/mL in acetonitrile: water 1:1 solution. HPLC analysis was performed on a Supelco Ascentic Express C18 reversed-phase column (100 x 4.6 mm, 2.7 μ m) with gradient elution shown in Table 1 at a flow rate of 2 mL/min. The column temperature was 25 °C; and each sample injection was 2 or 3 μ L.

Table 1. HPLC Gradient Elution

Time (min)	% Phase A (0.1% TFA in water)	% Phase B (0.085% TFA in acetonitrile)
0	95	5
6	5	95
6.2	95	5
8	95	5

[00267] I. Gravimetric Vapour Sorption (GVS)

[00268] Sorption isotherms were obtained using a SMS DVS Intrinsic moisture sorption analyzer, controlled by DVS Intrinsic Control software v1.0.1.2 (or v 1.0.1.3). The sample temperature was maintained at 25 °C by the instrument controls. The humidity was controlled by mixing streams of dry and wet nitrogen, with a total flow rate of 200 ml/min.

The relative humidity was measured by a calibrated Rotronic probe (dynamic range of 1.0 – 100 %RH), located near the sample. The weight change, (mass relaxation) of the sample as a function of %RH was constantly monitored by the microbalance (accuracy ± 0.005 mg).

[00269] A sample (e.g., 20 mg) was placed in a tared mesh stainless steel basket under ambient conditions. The sample was loaded and unloaded at 40% RH and 25 °C (typical room conditions). A moisture sorption isotherm was performed as outlined below (2 scans giving 1 complete cycle). Standard isotherms were performed at 25 °C at 10% RH intervals over a 0 – 90% RH range. Data analysis was carried out using Microsoft Excel using DVS Analysis Suite v6.2 (or 6.1 or 6.0).

[00270] In a cycle of 2 scans, the first scan was performed with adsorption of 40-90 %RH, followed by a second scan with desorption of 90-0 %RH and adsorption of 0-40 %RH, with intervals of 10 %RH, at 25 °C with stability dm/dt of 0.002 % °C/min. The sorption time was 6 hr time out.

[00271] The sample was recovered after completion of the isotherm and re-analyzed by XRPD. Custom moisture sorption methods were also performed at 25 °C at fixed % RH intervals over a 0 – 95% RH range, with the purpose to fully understand the sorption/desorption behavior of the compound under elevated conditions. The custom method performed for each GVS experiment was provided in Tables 2-4 below.

Table 2. Custom GVS method at high % RH (HighRH, Steps 1 and 2) and Single Cycle GVS method at high % RH (HighRH_Desorp_3, Steps 1, 2, 3, and 4)

Parameter	Steps			
	1	2	3	4
Adsorption/Desorption	40-80	90, 95	90-0	0-40
Intervals (% RH)	10	-	10	10
Sorption time	6 hr time out	Held at each RH for 800 mins	6 hr time out	6 hr time out
Stability dm/dt (% °C/min)	0.002	-	0.002	0.002

Table 3. Custom Double Cycle GVS method (HighRH_DoubleCycle_2)

Parameter	Steps					
	1	2	3	4	5	6
Adsorption/Desorption	40-80	90	95	90-0	0	0-40
Intervals (% RH)	10	-	-	10	-	10
Sorption time	6 hr time out	Held at each RH for 800 mins	Held for 1,600 mins	6 hr time out	Held for 800 mins	6 hr time out
Stability dm/dt (% °C/min)	0.002	-	-	0.002	-	0.002

Table 4. Custom Double Cycle GVS method (P2803-J06994_3)

Parameter	Steps				
	1	2	3	4	5
Adsorption/Desorption	40-80	90-95	90-0	0	0-40
Intervals (% RH)	10	-	10	-	10
Sorption time	6 hr time out	Held at each RH for 800 mins	6 hr time out	Held for 800 mins	6 hr time out
Stability dm/dt (% °C/min)	0.002	-	0.002	-	0.002

[00272] J. Ion Chromatography (IC)

[00273] Data were collected on a Metrohm 930 Compact IC Flex with 858 Professional autosampler and 800 Dosino dosage unit monitor, using IC MagicNet software v3.1. Accurately weighed samples were prepared as stock solutions in an appropriate dissolving solution and diluted appropriately prior to testing. Quantification was achieved by comparison with standard solutions of known concentration of the ion being analyzed. IC method for anion chromatography was performed on a Metrosep A Supp 5-150 IC column

(4.0 X 150 mm) at ambient temperature and a flow rate of 0.7 mL/min with injections of various μ L. The eluent used was 3.2 mM sodium carbonate, 1.0 mM sodium hydrogen carbonate in a 5% acetone aqueous solution. A conductivity detector was used for detection.

[00274] Example 1. Preparation and characterization of crystalline Forms 1, 2, and 3 of RAD1901-2HCl

[00275] RAD1901 in EtOH was added to EtOAc and the resultant mixture was heated until dissolution. The solution was cooled to approximately 20 °C and treated with 2.1 eq HCl in EtOH. The solution was concentrated and the resultant mixture was treated with EtOAc at approximately 20 °C and filtered to yield RAD1901 as its bis-HCl salt, suitable for further processing according to the methods of form conversion provided in this disclosure.

[00276] Two samples of RAD1901-2HCl, Samples 1 and 2, were prepared. Sample 1 was prepared by dissolving RAD1901-2HCl in a mixture of water and ethanol (1.5:19). The water content was reduced to <0.5% by azeotropic distillation and the concentrated solution was diluted with ethyl acetate. The mixture was stirred at ambient temperature for at least 2 hours and then the solid was collected by filtration. Sample 2 was prepared by dissolving RAD1901-2HCl in methanol. Ethyl acetate was added to the solution and the resulting mixture was stirred for at least 1 hour at ambient temperature. The solid was collected by filtration.

[00277] Form 1B was prepared via treatment of RAD1901-2HCl (Forms 2/3, 1.5 g) with 2-ethoxyethanol in 50 volumes (75 mL) while stirring at 25°C, 500 rpm. After 10 minutes, the suspension was heated to 50 °C, held for 10 mins, then cooled to 5 °C at 0.25 °C/min. The sample was then matured in heat-cool cycles between 50 and 25 °C (8 hr/cycle) for 3 days. The resulting suspension was filtered into a Buchner funnel and dried under suction for 30 min to afford Form 1B of RAD1901-2HCl. The white solid obtained was further dried under vacuum for 4 hours at RT. Optionally, the suspension may be heated to 50 °C and then directly subject to the heat-cool cycle without holding at 50 °C for 10 min and cooled to 5 °C at 0.25 °C/min.

[00278] Samples 1 and 2 were characterized by XRPD at various conditions. XRPD patterns were collected for the samples at ambient condition as the samples were provided; at variable temperature (VT-XRPD); at variable humidity (VH-XRPD); after the samples were exposed to 40 °C/75% RH for 1 week and 25 °C/97% RH for 1 week, respectively; and after a GVS measurement wherein the samples were exposed to 0-90% RH. Samples 1 and 2 were also

characterized by ^1H NMR, TGA, DSC, KF, IC, GVS (exposed to 0-90% RH), PLM, SEM, and HPLC (Table 5).

[00279] Characterizations of Sample 1 (majorly Form 1) and Sample 2 (mixture of Form 2 and Form 3) show that Form 1 was stable, had lower hygroscopicity and better thermal properties than Form 2. Additionally, Form 1 could be converted to the hydrate Form 3 at high RH (> 90%) (*e.g.*, for 7 days); Form 3 of RAD1901-2HCl could also be prepared by exposing Form 2 to >40% RH for 7 days; Sample 2 (mixture of Form 2 and Form 3) could be converted to Form 1 when heated at above 175 °C at <90% RH; and Form 2 may also be prepared by exposing Form 3 to < 40% RH for 8 hr. Thus, limiting the level of water/humidity in the preparation of RAD1901-2HCl may be beneficial to prepare Form 1 of RAD1901-2HCl. In certain embodiments, the percentage of water present in the preparation method was below 5%v/v and water content was determined by *e.g.* Karl Fischer titration (KF).

Table 5. Characterization of RAD1901-2HCl Samples 1 and 2

Characterization Method	Sample/Method	Sample 1	Sample 2
HPLC (Purity%, AUC)	N/A	99.2% AUC (Figure 2A)	99.2% AUC (Figure 3A)
^1H -NMR	N/A	Consistent with structure (Figure 2B)	Consistent with structure (Figure 3B)
XRPD	Ambient condition	Crystalline, Form 1 (Figure 4A)	Crystalline, mixture of Form 2 and 3 (Figure 5A)
XRPD	Storage at 40 °C/75% RH for 1 week	Form 1 (Figure 4B)	Form 3 (Figure 5B)
XRPD	Storage at 25 °C/97% RH for 1 week	Form 3 (Figures 4B and 5C)	Form 3 (Figures 5B and 5C)
VT-XRPD	N/A	N/A	Anhydrous Form 2 obtained on heating to 100°C.

Characterization Method	Sample/Method	Sample 1	Sample 2
			Sample melted ~160 °C and recrystallized as Form 1 above 175 °C (Figure 5D).
VH-XRPD	N/A	Form 1 converted to Form 3 over 24 hr at ~95% RH (Figure 4C)	Conversion to Form 3 at >90% RH (Figure 5E). Form 2 at 0% RH (Figure 5F)
XRPD post GVS	GVS (uptake 0-90% RH)	Form 1 (Figure 4D)	Mixture of form 2 and 3 (Figure 5G)
XRPD post GVS	GVS (HighRH method, HighRH_Desorp_3 method, Table 3)	Figure 4E	N/A
XRPD post GVS	GVS (HighRH_Desorp_3's 1 cycle and HighRH_Double_Cycle's 2 cycles, Tables 4 and 5)	Figure 4F	N/A
XRPD	0%RH	Figure 4G (Form 1), Figure 4H	Figure 5H (Form 2), Figure 4H
XRPD	92% RH	-	Figure 5I (Form 3), Figure 4H
GVS	Uptake 0-90% RH	1.8% wt. (reversible) (Figures 6A and 6B)	6.7% wt. from 0 – 40% RH; 2.0% wt. from 40 – 90% RH (Figures 7A and 7B)
GVS	HighRH method, Table 3	Figures 6C and 6D	N/A

Characterization Method	Sample/Method	Sample 1	Sample 2
GVS	HighRH_Desorp_3 method, Table 3	Figures 6E and 6F	N/A
GVS	HighRH_DoubleCycle_2 method, Tables 4 and 5	Figures 6G and 6H	N/A
TGA	N/A	0.4% weight loss between ambient and 100 °C (Figure 8, top)	6.1% weight loss between ambient and 200 °C (Figure 9, top)
DSC	N/A	Endotherm at 218 °C (onset) 150.0 J/g (melt) (Figure 8, bottom)	Endotherm at 157 °C (onset) 87 J/g (melt), exotherm at 187 °C (recryst.), endotherm at 207°C (onset) 33 J/g (melt as Form 1) (Figure 9, bottom)
KF	N/A	0.7 % water (conducted at 200 °C)	3.9 % water (conducted at 200 °C)
IC	N/A	2.0 eq (adjusted for TGA mass loss)	1.9 eq (adjusted for TGA mass loss)
PLM	N/A	Crystalline plates (Figure 10A)	Crystalline plates (Figure 11)
SEM	N/A	Stacked plates (Figures 12A-12C)	Stacked plates with cracks (evidence of desolvation) (Figures 13A-13C)

[00280] RP-HPLC analysis of Samples 1 and 2 showed 99.2% AUC collected at 255 nm (Figure 2A for Sample 1, and Figure 3A for Sample 2). ¹H-NMR of Samples 1 and 2 collected in d₆-DMSO are consistent with RAD1901-2HCl structure (Figure 2B for Sample 1, and Figure 3B for Sample 2).

[00281] Sample 1 was majorly Form 1 of RAD1901-2HCl having XRPD Pattern 1, Figures 4G at 0% RH, with peaks summarized in Table 7. Sample 1 showed XRPD pattern slightly different at ambient RH (Figure 4A, Table 6). Sample 2 was a mixture of Forms 2 and 3 of RAD1901-2HCl. Form 2 showed XRPD Pattern 2 (Figure 5H, sample 2 at 0% RH, peaks summarized in Table 8) and Form 3 showed XRPD Pattern 3 (Figure 5I, sample 2 at 92% RH, peaks summarized in Table 9).

[00282] Samples of Form 1 and Form 1B were characterized by XRPD and showed different patterns (Figure 22A: overlay of XRPD of Form 1 and Form 1B). Form 1 showed XRPD pattern of Figure 22B, peaks summarized in Table 7A. Form 1B showed XRPD pattern of Figure 22C, peaks summarized in Table 7B.

[00283] Forms 1 and 1B were further characterized by ¹³C Solid-State CPMAS NMR (Figure 23), ¹H Solid-State MAS NMR (Figure 24), FT-IR (Figures 25A-25C), and Raman (Figure 26).

[00284] The peak positions in the Form 1 and Form 1B ¹³C Solid-State NMR (SSNMR) spectra were similar; however, closer inspection indicated doubling of peaks in the Form 1 spectrum. This indicates that there were two molecules of RAD1901 in the crystallographic asymmetric unit of Form 1 giving rise to double the number of ¹³C environments and in Form 1B there was a single molecule of RAD1901 in the crystallographic asymmetric unit. This adds further weight to the distinct XRPD data and confirmed that Form 1 and Form 1B are two distinct polymorphic forms.

[00285] There were significantly more peaks present in the ¹H SSNMR spectrum of Form 1 compared to the ¹H SSNMR spectrum of Form 1B indicating that there were differences in the hydrogen environments, likely due to differences in the asymmetric unit and the hydrogen bonding networks within each polymorphic form.

Table 6. XRPD peaks of Sample 1 at ambient RH (Pattern 1)

Caption	Angle degrees, (2 θ)	Intensity (%)
7.1 °	7.1	93.1
7.8 °	7.8	6.9
8.1 °	8.1	4.1
8.6 °	8.6	7.2
9.1 °	9.1	5.6
11.0 °	11.0	20.8
11.1 °	11.1	9.2
11.4 °	11.4	9.1
12.0 °	12.0	30.3
12.1 °	12.1	16.5
12.7 °	12.7	5.9
13.8 °	13.8	39.6
14.2 °	14.2	100.0
14.8 °	14.8	4.3
15.6 °	15.6	3.7
16.1 °	16.1	24.3
17.3 °	17.3	5.2
17.8 °	17.8	12.7
18.4 °	18.4	58.5
18.9 °	18.9	29.9
19.7 °	19.7	16.5
20.2 °	20.2	12.9
21.1 °	21.1	10.3
22.1 °	22.1	13.3
23.0 °	23.0	21.9
23.2 °	23.2	13.7
23.6 °	23.6	16.1
24.0 °	24.0	18.0
24.6 °	24.6	10.4

Caption	Angle degrees, (2 θ)	Intensity (%)
25.1 °	25.1	43.9
25.7 °	25.7	6.7
26.5 °	26.5	23.3
27.1 °	27.1	30.4
27.3 °	27.3	12.8
27.8 °	27.8	10.4
28.4 °	28.4	14.6
28.7 °	28.7	9.6
29.1 °	29.1	14.9
29.9 °	29.9	24.6
30.3 °	30.3	15.3
30.5 °	30.5	10.3

Table 7. XRPD peaks of Sample 1 at 0% RH (Pattern 1)

Caption	Angle degrees (2 θ)	Intensity (%)
7.1 °	7.1	100.0
7.7 °	7.7	7.9
8.6 °	8.6	12.0
9.1 °	9.1	10.0
11.0 °	11.0	40.9
11.2 °	11.2	17.9
11.4 °	11.4	18.0
12.0 °	12.0	62.0
12.7 °	12.7	6.7
13.8 °	13.8	67.5
14.3 °	14.3	86.4
14.8 °	14.8	4.1

Caption	Angle degrees (2 θ)	Intensity (%)
15.5 °	15.5	4.8
16.2 °	16.2	36.3
16.8 °	16.8	7.8
17.3 °	17.3	7.9
17.8 °	17.8	20.1
18.3 °	18.3	83.5
18.9 °	18.9	47.3
19.7 °	19.7	20.5
20.2 °	20.2	19.8
20.9 °	20.9	7.6
21.2 °	21.2	13.6
22.0 °	22.0	24.7
23.1 °	23.1	30.7
23.6 °	23.6	25.3
24.0 °	24.0	27.5
24.5 °	24.6	15.3
25.1 °	25.1	58.4
25.8 °	25.8	9.8
26.5 °	26.5	31.1
27.2 °	27.2	43.4
27.5 °	27.5	12.3
27.8 °	27.8	12.7
28.5 °	28.5	17.6
28.7 °	28.7	11.6
29.1 °	29.1	21.1
30.0 °	30.0	25.8
30.3 °	30.3	23.8
30.5 °	30.5	16.1

Table 7A. XRPD Peaks of Form 1

RAD1901 2HCl Form 1	
Angle ($^{\circ}2\theta$)	d value ($\text{\AA}$)
7.14	12.37
7.76	11.38
8.63	10.24
9.09	9.72
10.99	8.05
11.15	7.93
11.40	7.76
12.02	7.36
12.69	6.97
13.78	6.42
14.24	6.22
16.13	5.49
16.74	5.29
17.79	4.98
18.35	4.83
18.88	4.70
19.70	4.50
20.21	4.39
21.16	4.20
22.08	4.02
22.94	3.87
23.63	3.76
24.02	3.70
24.53	3.63
25.08	3.55
25.75	3.46
26.05	3.42
26.43	3.37
27.13	3.28
27.83	3.20
28.41	3.14
29.07	3.07
29.38	3.04

Table 7B. XRPD Peaks of Form 1B (Pattern B)

RAD1901 2HCl Pattern B	
Angle ($^{\circ}2\theta$)	d value ($\text{\AA}$)
7.12	12.41
8.94	9.88
11.09	7.97
11.53	7.67
12.29	7.20
13.34	6.63
14.04	6.30
14.27	6.20
16.79	5.28
18.23	4.86
18.49	4.79
19.23	4.61
20.12	4.41
21.66	4.10
22.39	3.97
22.63	3.93
23.95	3.71
24.80	3.59
25.58	3.48
26.43	3.37
26.84	3.32
28.76	3.10

Table 8. XRPD peaks of Sample 2 at 0% RH (Pattern 2)

Caption	Angle degrees (2θ)	Intensity (%)
6.3 °	6.3	100.0
8.2 °	8.3	6.0
9.8 °	9.8	19.1
11.5 °	11.5	11.5
12.1 °	12.1	6.1
12.5 °	12.5	32.9
13.4 °	13.4	21.7
13.8 °	13.8	3.8
14.6 °	14.6	2.1
15.4 °	15.4	23.5
15.8 °	15.8	14.2
17.4 °	17.4	13.9
17.8 °	17.8	8.0
18.3 °	18.3	23.3
18.8 °	18.8	13.3
19.9 °	19.9	16.1
20.3 °	20.3	7.4
21.1 °	21.1	13.2
21.5 °	21.5	6.3
21.9 °	21.9	15.8
22.5 °	22.5	14.6
23.0 °	23.0	15.1
23.9 °	23.9	7.0
24.7 °	24.7	10.9
25.0 °	25.0	18.2
25.5 °	25.5	6.7
26.2 °	26.2	9.9
27.0 °	27.0	6.2
28.0 °	28.0	18.3
29.3 °	29.3	4.8

Caption	Angle degrees (2 θ)	Intensity (%)
29.9 °	29.9	20.4
30.3 °	30.3	6.4

Table 9. XRPD Peaks of Sample 2 at 92% RH (Pattern 3)

Caption	Angle degrees (2 θ)	Intensity (%)
5.8 °	5.8	100
8.1 °	8.1	10
9.5 °	9.5	35.2
11.5 °	11.5	33.6
12.4 °	12.4	29.5
12.6 °	12.7	22
13.1 °	13.1	34.5
13.6 °	13.6	13.1
15.1 °	15.1	34.8
16.1 °	16.1	16.4
16.9 °	16.9	6.7
17.4 °	17.4	19
18.0 °	18.0	17.5
18.4 °	18.4	9.7
18.9 °	18.9	19.1
19.9 °	19.9	11.4
21.3 °	21.3	50.1
21.7 °	21.7	27.5
22.4 °	22.4	19.3
22.8 °	22.8	29.9
23.3 °	23.3	40
24.2 °	24.2	22.2
24.8 °	24.8	41.8
25.4 °	25.4	18
26.2 °	26.2	19.5

Caption	Angle degrees (2 θ)	Intensity (%)
27.4 °	27.4	26.9
27.6 °	27.6	23.3
28.9 °	28.9	11.1
29.3 °	29.3	10.2
30.5 °	30.5	14.3

[00286] Form 1 was stable after storage at 40 °C/75% RH for 1 week and after exposure to 0-90% RH in a GVS, as confirmed by unchanged XRPD pattern (Pattern 1) of Form 1 sample pre- and post-GVS. However, Form 1 was converted to Form 3 after storage at 25 °C/97% RH for 1 week.

[00287] Form 1 was relatively non-hygroscopic between 0 and 90% RH as shown in GVS data (Figures 6A-6B). No changes were observed in the XRPD pattern pre- and post-GVS analysis (Figure 4D).

[00288] Form 1B showed similar XRPD pattern pre- and post-GVS analysis (Figure 21B).

[00289] Form 1 was stable to storage at 40 °C/75% RH for 7 days (from XRPD analysis), but storage at 25 °C/97% RH for 7 days resulted in conversion towards a hydrated state Form 3 (see Figure 4B).

[00290] An overlay of the new patterns obtained upon storage of Sample 1 and Sample 2 at elevated conditions is provided in Figure 5C, which are substantially consistent with Form 3. Importantly, this indicates that upon prolonged exposure to high RH, Sample 1 (Form 1) was converted to the hydrate Form 3.

[00291] To further explore the humidity behavior of Sample 1 (Form 1) upon exposure to high RH (>90%), custom GVS experiments were designed and carried out. Initially, the sample was treated by holding at 90 and then 95% RH for ~ 12 hours to see if hydrate formation could be observed (HighRH method of Steps 1 and 2 of Table 2, Figures 6C-6D).

[00292] Figures 6C-6D (HighRH method of Steps 1 and 2 of Table 2) shows Sample 1 (Form 1) took up 5-6%wt. when held at 95% RH for ~ 12 hours, indicating hydrate formation. XRPD analysis of the sample post-GVS experiment (HighRH, red in Figure 4E) showed significant changes compared to that of Form 1 (black in Figure 4E), with similarities to both

the hydrated state Form 3 and the anhydrous Form 1. Figure 4E suggested a mixture of states or incomplete conversion from Sample 1 to the hydrate form.

[00293] To test the stability of the hydrated state, GVS method HighRH_Desorp_3 was designed with a desorption step and subsequent adsorption (see Table 2 with steps 1-4, Figures 6E-6F).

[00294] The GVS data in Figures 6E-6F shows that the hydrated state (at 95% RH) was stable to desorption until near 0 % RH, and upon adsorption from 0 to 40 % RH, the sample did not convert back to anhydrous Form 1, but instead irreversibly converted to a new state (indicating a mixture of hydrate and anhydrous). Furthermore, the shape of the adsorption step from 0 to 40 % was observed to be highly similar to that of Form 2 (see Figure 7A). XRPD analysis of the sample post-GVS experiment ('HighRH_Desorp_3') confirmed that a mixture of Form 1 and Form 3 was present (see Figure 4E), as shown by starred peaks (indicating peaks present in either the XRPD pattern of the anhydrous or hydrated form). The XRPD patterns obtained for Sample 1 post GVS of HighRH_Desorp_3 is shown in green.

[00295] Finally, to ensure complete conversion to the anhydrous and hydrated forms, a GVS experiment was designed to increase both the length of the desorption step at 0 % RH, and the adsorption step at 95 % RH, respectively (Table 3). Based on the weight stabilization observed in the kinetic plots for Sample 1 in HighRH and HighRH_Desorp_3 methods discussed above (Figures 6D and 6F), a holding time of 800 mins at 0 % RH and 1600 mins at 95 % RH were chosen. A double cycle was also recorded for this experiment to observe whether the sample would return to Form 1 or form a mixed anhydrous/hydrated species (see Table 3, Figures 6G-6H).

[00296] The GVS data (Figures 6G-6H) show that after complete desorption at 0 % RH, and subsequent re-adsorption, the sample continued to uptake water and formed a mixed anhydrous/hydrated species. This species converted to the hydrate at 90 – 95 % RH (Form 3), which remained stable during desorption until 40%, below which the sample desorbed sharply. Subsequent adsorption from 0 to 40 % RH followed this step-wise transition, which can be clearly observed in the GVS Isotherm Plot of Sample 2 (see Figure 7A). This GVS data provides clear evidence that the Sample 1/Form 1 material irreversibly converted to a hydrate (Form 3) under exposure to high RH (> 90%), and upon desorption shifts into an equilibrium between the anhydrous state (Form 2) and the hydrated state (Form 3). XRPD analysis of the sample post-GVS experiment ('HighRH_DoubleCycle_2') confirmed the formation of the hydrate (Form 3), see Figure 4F.

[00297] To fully characterize the polymorphic behavior of Samples 1 and 2 at variable humidity, and to collect reference XRPD patterns for the 'pure' anhydrous Form 1 and Form 2 material, and 'pure' hydrated Form 3 material, Variable Humidity (VH) XRPD experiments were conducted on Samples 1 and 2. Initially, VH-XRPD experiments were conducted using Sample 1, and XRPD diffractograms were collected at selected humidity values, in line with those collected during GVS experiments (see Figures 6E-6F). XRPD diffractograms were collected initially at ambient RH, then collected over 24 hours at ~95 % RH and finally collected during desorption steps to 0 % RH and over 10 hours at 0 % RH (see Figure 4C). Full method details are provided in Table 10 below.

Table 10. Experimental conditions for collection of VH experiment on Sample 1
(sample: J06994_D8_VH, method: P2803-06NOV15)

Desired Humidity	Recorded humidity	Measured delay (hold) time (hrs)	Scan time (hrs)
Ambient	53.7	0	0.69*
94	96.1	2	0.69
94	95.3	2	0.69
94	94.9	2	0.69
94	94.7	2	0.69
94	94.5	2	0.69
94	94.5	2	0.69
94	94.4	2	0.69
94	94.3	2	0.69
94	94.3	2	0.69
94	94.2	2	0.69
80	82.4	1	0.69
70	72.8	1	0.69
60	63.6	1	0.69
50	51.7	1	0.69
40	40.3	1	0.69
30	29.3	1	0.69
20	17.3	1	0.69
10	5.9	1	0.69
0	0	1	0.69
0	0	4	0.69
0	0	4	0.69
10	5.8	2	0.69
20	17.2	2	0.69
30	29.1	2	0.69
40	40.0	2	0.69

*: each scan was 41 m 28 s (0.69 hrs)

[00298] The VH-XRPD experiment was unable to show a direct conversion from the starting material Sample 1 (Form 1) to the hydrated state (Form 3) over 24 hours at ~95 % RH (see Figure 4C). However, there were subtle changes in the diffractogram pattern observed at ~95 % RH, compared to that of the starting material at ambient RH and at 0 % RH (see starred peaks). These changes included a shoulder at 12 degrees 2 θ and an additional peak at 19 degrees 2 θ and indicated a slow conversion towards the hydrated state (see post 25/97' in Figure 4C). Thus, Form 1 may have converted to Form 3 (hydrate) over time, as supported by GVS data (Figures 6E-6F). One possible explanation for the slower kinetics in VH-XRPD is that VH-XRPD experiments relied on changes in the crystal structure of a sample at an exposed surface layer to varying humidity, whereas GVS experiments allowed all surfaces of the sample to be exposed as the sample was suspended in a wire basket.

[00299] Thermal analysis of the supplied materials showed that Sample 1 was anhydrous (by TGA and KF), and had no thermal events prior to melt or degradation. In comparison, Sample 2 had a complex thermal profile by DSC (see Figure 9B) and was found to be a hydrate (by TGA and KF). The DSC trace showed that Sample 2 desolvated upon heating from ambient to 150 °C, melted at ~157 °C and recrystallized at ~187 °C (see Figure 9B). TGA data showed that this desolvation event corresponded to a loss of 6.2 % weight, equivalent to 2 molecules of water.

[00300] Variable Temperature XRPD (VT-XRPD) experiments were therefore conducted to examine the thermal behavior of Sample 2 observed by DSC (see Figure 9B). VT-XRPD analysis shows that Sample 2 converted to the anhydrous state (Form 2, red) upon heating above 100 °C, then melted and recrystallized at ~175 °C (blue) as Form 1 material (Figure 5D).

[00301] This indicates that Sample 2 as a mixture of Forms 2 and 3 can be converted to Form 1 by recrystallization above 175 °C. However, it is clear that Form 1 material irreversibly converted to the hydrate Form 3 under exposure to high RH (> 90%).

[00302] VH-XRPD experiments were also conducted using Sample 2 and XRPD diffractograms were collected at selected humidity values of 0 % RH (Table 12) and 90 % RH (Table 11, to obtain reference XRPD patterns for the 'pure' anhydrous Form 2 and 'pure' hydrated Form 3 respectively. The GVS Kinetic Plot collected for Sample 2 (see Figure 7B) indicated relatively fast kinetics for conversion from anhydrous to hydrated form, therefore XRPD patterns were collected at time points of up to 10-14 hours (see Figures 5E-5F).

Table 11. Experimental conditions for collection of VH experiment on Sample 2 at high RH (sample: J06993_D8_VH_90, method: P2803-11NOV15)

Desired humidity	Recorded humidity	Measured delay (hold) time (hrs)	Scan time (hrs)
40	41.8	0	0.69
90	93.4	2	0.69
90	92.1	2	0.69
90	91.6	2	0.69
90	91.6	2	0.69

Table 12. Experimental conditions for collection of VH experiment on Sample 2 at 0 % RH (sample: J06993_D8_VH_0, method: P2803-12NOV15)

Desired humidity	Recorded humidity	Measured delay (hold) time (hrs)	Scan time (hrs)
0	0	2	0.69
0	0	2	0.69
0	0	2	0.69
0	0	2	0.69
0	0	0.69	0.69

[00303] As shown in Figure 5E, slight changes in the XRPD pattern of Sample 2 were observed between ambient (42% RH) and 92-93% RH (see starred peaks), showing conversion toward the hydrated state (as represented by the XRPD pattern post storage at 25 °C/ 97% RH). However, the kinetics remained relatively slow. Based on these observations, the XRPD pattern for anhydrous Sample 2 (at 0 % RH) was collected after drying a sample in a vacuum oven (RT, 8 hours) (see Figure 5F). The XRPD pattern collected at 0 % RH was consistent with a sample of anhydrous Sample 2 produced by heating to 100 °C on a VT-XRPD stage (see experimental section above and Figure 5D), and therefore provided a reference for the anhydrous Form 2.

[00304] Form 3 in Sample 2 was converted to Form 2 when Sample 2 was heated to 100 °C. Sample 2 started to melt around 160 °C and recrystallized as Form 1 at above 175 °C. The characterization data of Samples 1 and 2 are summarized in Table 5.

[00305] GVS experiments showed that Sample 2 was hygroscopic with a mass uptake of 6.7% wt. from 0% to 40% RH, plateauing above 40% RH (2.0% wt. from 40 – 90% RH) (see Figures 7A-7B). Thus, an equilibrium existed between the anhydrous and hydrated states for Sample 2 at near ambient RH (e.g., 40-65% RH).

[00306] The XRPD pattern collected for Sample 2 varied depending on the prevailing RH during measurement. For XRPD diffractograms pre- and post-GVS, see Figure 5G, which showed that a mixture of Form 2 and Form 3 existed in between 0% and 90% RH (post GVS).

[00307] Example 2. Solubility Assessment of Polymorphic Forms of RAD1901-2HCl

[00308] Solubility assessment was carried out on the Sample 1 of RAD1901-2HCl (majorly Form 1 shown by XRPD) in 24 solvent systems in HPLC vials (sample IDs: A1 to A24). RAD1901-2HCl (25 mg) was treated with increasing volumes of solvent until the material fully dissolved or until a maximum of 60 vol had been used (Table 13).

Table 13. Solubility assessment and polymorph screen on Form 1 of RAD1901-2HCl

Sample ID	Solvent	10 vol.	20 vol.	40 vol.	60 vol.	Cooled to 5 °C	After 50/RT maturation	Evaporation	XRPD	Figure No.
A1	n-Heptane	X	X	X	X	N/A	X	N/A	Form 1	14A
A2	Propyl acetate	X	X	X	X	N/A	X	N/A	Form 1	14A
A3	Ethyl acetate	X	X	X	X	N/A	X	N/A	Form 1	14A
A4	Isopropyl acetate	X	X	X	X	N/A	X	N/A	Form 1	14A
A5	MIBK	X	X	X	X	N/A	X	N/A	Form 1	14A
A6	2-propanol	X	X	X	X	N/A	X	N/A	Form 3*	14C
A7	MEK	X	X	X	X	N/A	X	N/A	Form	14A

Sample ID	Solvent	10 vol. l.	20 vol. l.	40 vol. l.	60 vol. l.	Cooled to 5 °C	After 50/RT maturation	Evaporation	XRP D	Figure No.
									1*	
A8	1-propanol	X	X	X	X	N/A	X	N/A	Form 1	14A
A9	Acetone	X	X	X	X	N/A	X	N/A	Form 3*	14C
A10	Ethanol	X	X	X	X	N/A	X	N/A	Form 1	14A
A11	Dimethyl sulfoxide	S				S	N/A	S	S	-
A12	Water	+/-	S			S	N/A	Solid	Form 3	14C
A13	TBME	X	X	X	X	N/A	X	N/A	Form 1	14B
A14	1,4-Dioxane	X	X	X	X	N/A	X	N/A	Form 1	14B
A15	Toluene	X	X	X	X	N/A	X	N/A	Form 1	14B
A16	1,2-dimethoxyethane	X	X	X	X	N/A	X	N/A	Form 1	14B
A17	Tetrahydrofuran	X	X	X	X	N/A	X	N/A	Form 1	14B (THF)
A18	Dichloromethane	X	X	X	X	N/A	X	N/A	Form 1	14B
A19	Acetonitrile	X	X	X	X	N/A	X	N/A	Form 1	14B (ACN)
A20	Methanol	+/-	S			Platel	N/A	N/A	Form	14C

Sample ID	Solvent	10 vol.	20 vol.	40 vol.	60 vol.	Cooled to 5 °C	After 50/RT maturation	Evaporation	XRPD	Figure No.
						et crystal			3	
A21	Nitromethane	X	X	X	X	N/A	S	Solids	Form 1	14B
A22	10% water/EtOH	+/-	S			Some crystal	N/A	N/A	Form 3*	14C
A23	10% water/IPA	X	X	+/-	S	S	N/A	Solids, green solution	Form 3	14C
A24	10% water/THF	X	X	+/-	S	S	N/A	Solids	Form 3	14C

Legend: X = suspension; S = solution; +/- = nearly dissolved; * = poorly crystalline; N/A = not applicable

[00309] After each addition of solvent, the system was stirred for 5 to 10 minutes at 25 °C, then shaken at 50 °C for 5 to 10 minutes, and observations made. Samples were allowed to stand at room temperature for 5 min before the addition of a new aliquot of solvent. After the assessment was completed, the suspensions obtained were matured (maturation) and the clear solutions were cooled (cooling) and slowly evaporated (evaporation) as described below. All solids recovered from maturation, cooling and evaporation experiments were analyzed by high resolution XRPD.

[00310] The suspensions obtained during the solubility assessment were matured by shaken in a maturation chamber between 50 °C and RT (8 hr per cycle) for up to 5 days. Then the mixture was allowed to stand at room temperature for 10 minutes. The resulting solids were filtered and air dried and analyzed by XRPD. The clear solutions obtained during maturation were evaporated in ambient conditions and the resulting residues were analyzed by XRPD.

[00311] The clear solutions obtained during the course of the solubility assessment were cooled on a Polar Bear device from 50 °C to 5 °C at 0.1 °C/min. Solids obtained upon

cooling were recovered from the vials, air dried and analyzed by XRPD. If no solid was obtained, the solutions were evaporated slowly through a needle inserted into the septum cap of the vial until a solid appeared at ambient conditions and the resulting solids were filtered, air dried and analyzed by XRPD.

[00312] The solubility assessment of the Sample 1 in different solvent systems showed that the compound had low solubility in alcohols, esters, and hydrocarbon solvents, but was highly soluble in water. XRPD analysis of solids recovered after maturation, cooling and evaporation (in the solvents listed in Table 13) found that either anhydrous Form 1 or hydrated Form 3 were produced (Figures 14A-43C). Consistent with the solid-state characterization of Sample 1 in Example 1, slurring in water or water/solvent systems produced the hydrated state, Form 3. Pattern 3 was also observed from slurring in 2-propanol, acetone and methanol, but it is likely that the hydrate resulted from residual water present in the solvent stock solutions (anhydrous solvents were not used in this screen).

[00313] During these screening experiments, it was observed that one sample (A20) produced crystals of plate morphology (see Figure 10B), and was submitted for Single Crystal analysis. However, these crystals were found to exist as stacks (as seen by SEM, see Figures 12A-12C), not single crystals and were therefore unsuitable for collection by SCXRD. Analysis of the crystals by XRPD found that the material was consistent with a hydrated state, and most closely resembled Pattern 3 (Figure 14C).

[00314] Example 3. Preparation and Characterization of Amorphous RAD1901-2HCl

[00315] A) Preparation and characterization of amorphous RAD1901-2HCl

[00316] As Sample 1 of RAD1901-2HCl showed high solubility in water and t-butanol/water (1:1), amorphous RAD1901-2HCl was prepared from each of these solvents by lyophilization. RAD1901-2HCl (100 mg) was placed into a scintillation vial and appropriate solvent systems tested for dissolution of the material. Water or t-butanol/water (1:1) (20-30 vol., 2-3 mL) was added to the sample at RT, and the mixture was vortexed until dissolution, and filtered to remove any remaining solid particles. The solution was frozen in a dry ice/acetone bath and the solvent removed by lyophilization. The resulting solids were analyzed for amorphous content by XRPD (Figure 15A), counterion identity by IC, purity by HPLC and NMR, and thermal properties by TGA and DSC (Table 14).

Table 14. Characterization data for amorphous RAD1901-2HCl produced by lyophilisation

Technique/Sample ID	Lyophilization in water	Lyophilization in t-Butanol/Water(1:1)
XRPD	Amorphous (Figure 15A)	Amorphous (Figure 15A)
¹ H-NMR	Consistent with starting material (Figure 16)	Consistent with starting material, 0.3 eq. residual t-butanol (Figure 16)
HPLC (Purity %)	99.3% AUC	99.2% AUC
DSC	Broad endotherm from 25 °C to 140 °C, endotherm at 149 °C (onset) (Figure 17A)	Broad endotherm from 25 °C to 140°C, endotherms at 103 °C (onset) and 147 °C (onset) (Figure 17A)
TGA	6.5 % wt. loss from RT to 190 °C (Figure 17B)	Two steps: 5.3 % wt. loss from RT to 120 °C and 1.8 % wt. loss from 120 °C to 190 °C (Figure 17B)
IC	Average = 1.79 (adjusted for TGA wt. loss = 1.93)	Average = 1.79 (adjusted for TGA wt. loss = 1.92)
mDSC	Broad endotherm 0-150 °C masks any Tg (Figure 16C)	Broad endotherm 0-100 °C masks any Tg
XRPD post storage at 25 °C/ 97% RH (10 days)	Consistent with Form 3 (Figure 15B)	Consistent with Form 3 (Figure 15B)
XRPD post storage at 40 °C/ 75% RH (10 days)	Consistent with Form 3 (Figure 15C)	Consistent with Form 3 (Figure 15C)

[00317] B) Scale-up preparation of amorphous RAD1901-2HCl

[00318] In a scale-up preparation of amorphous RAD1901-2HCl, RAD1901-2HCl (600 mg) was dissolved in water (20 vol., 12 mL) and filtered to remove any remaining solid particles. The solution was then aliquoted into 24 HPLC vials, frozen in a dry ice/acetone bath and the solvent removed by lyophilisation. Solids produced by lyophilization were used directly in solubility assessment and polymorph screens in Example 4.

[00319] Example 4. Solubility Assessment and Polymorph Screen of Amorphous RAD1901-2HCl

[00320] A) Solubility assessment and polymorph screen of amorphous RAD1901-2HCl

[00321] Amorphous RAD1901-2HCl prepared as described in Example 3B was used directly in solubility assessment and polymorph screens (Table 15). XRPD patterns were further obtained for amorphous RAD1901-2HCl prepared using other solvents.

Table 15. Solubility assessment and polymorph screen on amorphous RAD1901-2HCl

Samp le ID	Solvent	10 vo l.	After maturati on at 25 °C	PLM after maturati on at 25 °C	XRPD post 25 °C	After maturati on at 50 °C	XRPD post 50 °C/RT	Figu re No.
B1.	n-Heptane	X	X	No visible crystalsX	N/A	X	Amorph ous	18D
B2.	Propyl acetate	X	X	No visible crystalsX	N/A	X	Form 2/3	18B
B3.	Ethyl acetate	X	X	No visible crystalsX	N/A	X	Form 2/3	18B
B4.	Isopropyl acetate	X	X	No visible crystalsX	N/A	X	Form 2/3	18B
B5.	MIBK	X	X	No visible crystalsX	N/A	X	Form 3	18B
B6.	2-propanol	X	X	No visible crystalsX	N/A	X	Form 1 ⁺	18D
B7.	MEK	X	X	No visible	N/A	X	Form 1 ⁺	18D

Sample ID	Solvent	10 vol.	After maturation at 25 °C	PLM after maturation at 25 °C	XRPD post 25 °C	After maturation at 50 °C	XRPD post 50 °C/RT	Figure No.
				crystalsX				
B8.	1-propanol	X	X	No visible crystalsX	N/A	Crystalline material	Form 1	18A
B9.	Acetone	X	X	No visible crystalsX	N/A	X	Form 1*	18D
B10.	Ethanol	X	X	No visible crystalsX	N/A	Fine crystals	Form 1	18A
B11.	Dimethyl sulfoxide	S	S	S	N/A	S	S	-
B12.	Water	S	X	Fine needles	Form 3	Lath crystals	Form 3	18C
B13.	TBME	X	X	Birefringent solid	Amorphous	Some crystals	Poor crystalline	18D
B14.	1,4-Dioxane	X	X	No visible crystalsX	N/A	X	Poor crystalline	18D
B15.	Toluene	X	X	No visible crystalsX	N/A	Fine crystals	Form 3	18B
B16.	1,2-dimethoxyethane	X	X	No visible crystalsX	N/A	Crystalline material	Form 3*	18C
B17.	Tetrahydrofuran	X	X	No visible	N/A	Fine crystals	Form 1*	18A (TH

Sample ID	Solvent	10 vol.	After maturation at 25 °C	PLM after maturation at 25 °C	XRPD post 25 °C	After maturation at 50 °C	XRPD post 50 °C/RT	Figure No.
				crystalsX				F)
B18.	Dichloromethane	X	X	No visible crystalsX	N/A	Crystalline material	Form 3	18B
B19.	Methanol	X	Crystal	Cubic crystals	Form 3	Green solution	N/A	18C
B20.	Acetonitrile	X	X	No visible crystalsX	N/A	Crystalline material	Form 1	18A
B21.	Nitromethane	X	X	Cubic/needle crystals	Form 1	Needle crystals	Form 1	18A
B22.	10% water/EtOH	S	S	Needle/Lath crystals	Form 3	Green solution	N/A	18C
B23.	10% water/IPA	X	X	Fine crystals	Form 3	Fine crystals	Form 3	18C
B24.	10% water/THF	X	X	Fine crystals	Form 3	Fine crystals	Form 3	18C

Legend: X = suspension; S = solution; +/- = nearly dissolved; * = poorly crystalline; N/A = not applicable; +: Possibly some Form 3 present

[00322] In the polymorph screen of the amorphous RAD1901-2HCl prepared as described in Example 3B, an aliquot of each sample was examined for its morphology under the microscope, both after maturing at 25 °C, and after maturing at 50 °C/RT. If any crystalline material was observed at either maturation stage, the resulting solids were filtered, air dried and analyzed by high resolution XRPD. XRPD analysis of samples from the polymorph screen showed that only three distinct patterns could be observed: patterns for Forms 1, 2 and 3 previously observed (Figures 18A-18D). In some instances, the sample appeared to be a mixture of various polymorphic forms, e.g. Form 2 and Form 3 (Figures 18B-18C), similar

to the mixture of Forms 2 and 3 in Sample 2 having an equilibrium between the two solid forms, depending on the prevailing RH.

[00323] Similarly, samples prepared from 2-propanol and MEK may contain a mix of anhydrous Form 1 and hydrated Form 3 material (Figure 18D).

[00324] PLM images were obtained for crystals obtained during polymorph screens using amorphous RAD1901-2HCl prepared as described in Example 3B via cooling in methanol (Figure 19A), maturation in water (Figure 19B), or maturation in nitromethane (Figure 19C), respectively (Figure 19).

[00325] Despite collecting high resolution XRPD data, some samples were also poorly crystalline and their pattern could not be definitively assigned, but closely resembles that of Form 1 (Figure 18D). Therefore, no additional new patterns have been observed in these screens using amorphous RAD1901-2HCl.

[00326] B) Solubility assessment of amorphous RAD1901-2HCl in water/organic solvent system

[00327] Samples of amorphous RAD1901-2HCl were prepared in water/organic solvent mixtures containing varying ratios of water. The organic solvents chosen were anhydrous ethanol, methanol and ethyl acetate. The percentage of water in the water/organic solvent mixtures was varied between 0 and 10% (v/v) in order to place a limit on the level of water that can be present during production processes, and to retain formation of Form 1. Above this water activity limit, the hydrated Form 3 will be obtained, as shown by GVS experiments (see Figures 6G and 20A). It should be noted that samples prepared in ethyl acetate, were either slurried in anhydrous ethyl acetate, or in water saturated ethyl acetate.

[00328] The results from the water/organic solvent experiment are given in Table 16 and in Figures 20A-20C. The water activity values for each water/organic solvent mixture are provided in Table 16, and were calculated using the reference given in Bell, Halling, *Enzyme Microbiol. Technol.* **1997**, 20, 471, incorporated herein by reference.

Table 16 Solubility assessment and polymorph screen on amorphous RAD1901-2HCl

Sample ID	Solvent	Water activity	10 vol.	20 vol	30 vol	After stirring at 25 °C for 72 hours	XRPD	Figure No.
C1.	EtOH/H ₂ O (90:10)	0.58	S			X	Form 3	20A
C2.	EtOH/H ₂ O (95:5)	0.39	X			X	Form 1	20A
C3.	EtOH/H ₂ O (98:2)	0.20	X			X	Form 1	20A
C4.	EtOH/H ₂ O (99:1)	0.11	X			X	Form 1	20A
C5.	MeOH/H ₂ O (90:10)	0.33	S			S	S	
C6.	MeOH/H ₂ O (95:5)	0.19	S			Crystals	Form 3*	20B
C7.	MeOH/H ₂ O (98:2)	0.08	+/-			Crystals	Form 2	20B
C8.	MeOH/H ₂ O (99:1)	0.04	+/-			Crystals	Form 2	20B
C9.	Ethyl acetate (anhydrous)	0.00	X	X	X	X	Form 1*	20C
C10.	Water-saturated ethyl acetate	0.77	X	X	X	X	Form 3	20C

Legend: X = suspension; S = solution; +/- = nearly dissolved; * = poorly crystalline.

Table 17 Characterization of scaled-up Form 1B

Technique	Form 1	Pattern B (2 day dry)
XRPD	Crystalline	Crystalline, consistent with Pattern B obtained in 2-ethoxyethanol
¹ H-NMR	Consistent with structure	Consistent with as supplied, 0.03 eq. 2-ethoxyethanol
DSC	Endotherm at 218 °C (onset) 150.0 J/g (melt)	Small endotherm at 38.1 °C (onset), 2 J/g. Small endotherm at 210.3 °C (onset), 2 J/g. Melt endotherm at 227.8 °C (onset), 82 J/g.
TGA	0.4% weight loss between ambient and 100 °C	0.1% wt. loss from RT to 60 °C. No other events until degradation
GVS and XRPD post-GVS	Total mass change of 1.7% wt. from 0 and 90% RH, Sample is slightly hygroscopic, but exhibits reversible uptake and loss, and no hysteresis. XRPD post-GVS is consistent with Form 1.	Total change in mass of 1.4% wt. between 0 and 90% RH, with faster uptake at higher RH. Sample is slightly hygroscopic, but exhibits reversible uptake and loss, and no hysteresis. XRPD post-GVS is consistent with Pattern B.
VT-XRPD	N/A	No significant changes by XRPD on heating from 25 to 190 °C, and sample post-VT at 25 °C remained Pattern B.
IC (not adjusted for solvent)	2.0 eq. Cl	1.85 eq. Cl
KF	0.7% water	0.4% water
HPLC (purity %, AUC)	99.2%	99.5%
PLM	Crystalline plates	Very small plate-like particles, predominantly agglomerated. Soft agglomerates (up to 500 µm diameter) disperse in oil.
SEM	Stacked plates	Agglomerates of up to 300 µm diameter. Primary particles are stacked plates (1 to 20 µm diameter).
XRPD post-storage at 40 °C /75% RH and 25 °C /97% RH for 1 week	Remains as Form 1 at 40 °C /75% RH after 1 week Converts to Form 3 at 25 °C /97% RH after 1 week	Unchanged post storage at both conditions
IDR (SGF media)	Value cannot be determined due to rapid and complete disc disintegration	Value cannot be determined due to rapid and complete disc disintegration

[00329] The water/organic solvent experiments demonstrate a water activity limit above which the hydrated Form 3 was produced. Samples of amorphous RAD1901-2HCl obtained from Example 3b prepared in anhydrous ethanol crystallized as Form 1 material, consistent with the XRPD pattern obtained during polymorph screening of amorphous Sample 1 (see Table 15). It is also known that ethanol solvent is used in the production of Form 1 material of RAD1901-2HCl (Sample 1) during drug purification processes (along with ethyl acetate). Crystals produced from water/ethanol were Form 1 up to a ratio of 5% water/ethanol, above which the hydrate Form 3 resulted. This equates to a water activity limit of 0.39 (see Table 16), and indicates that at least on small-scale, up to 5% water can be present during drug production process to produce Form 1.

[00330] Amorphous RAD1901-2HCl in anhydrous methanol crystallized as Form 2 having XRPD Pattern 2. This is consistent with the supplied batch of sample 2, which was known to form during isolation of RAD1901-2HCl using methanol (and ethyl acetate) solvent. Crystals produced from water/methanol were Form 2 (anhydrous) up to a ratio of 2% water/methanol, above which the hydrate Form 3 having XRPD Pattern 3 was produced. This equates to a water activity limit of 0.08 (see Table 16), which is low, and may reflect the observations (by GVS, see Figure 7A) that at relatively low (ambient) RH, Form 2 material converts to the hydrate Form 3 or a mixture of Forms 2 and 3.

[00331] Slurrying of amorphous RAD1901-2HCl in anhydrous ethyl acetate produced crystals of Form 1 material, which supports the observation that Form 1 could be isolated using ethanol and ethyl acetate solvents in drug production processes, whereas Form 2 could be produced using methanol and ethyl acetate. The ratio of water/ethyl acetate was not varied, since the water-saturated ethyl acetate has above 2.7 % (v/v) water (e.g., 3.3% water at 20 °C), which equates to water activity of 0.77. Slurrying in water-saturated ethyl acetate produced the hydrate Form 3.

[00332] **Example 5.** A crystalline form of RAD1901-2HCl.

[00333] **Example 6.** A solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 7.1 degrees $2\theta \pm 0.2$ degree 2θ at about relative humidity 0%.

[00334] **Example 7.** A solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 7.1 degrees $2\theta \pm 0.2$ degree 2θ and/or 14.3 degrees $2\theta \pm 0.2$ degree 2θ at about relative humidity 0%.

[00335] Example 8. A solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising at least two peaks, in terms of 2-theta, selected from the group consisting of 7.1 degrees $2\theta \pm 0.2$ degree 2θ , 14.3 degrees $2\theta \pm 0.2$ degree 2θ and 18.3 degrees $2\theta \pm 0.2$ degree 2θ at about relative humidity 0%.

[00336] Example 9. A solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising at least three peaks, in terms of 2-theta, selected from the group consisting of 7.1 degrees $2\theta \pm 0.2$ degree 2θ , 14.3 degrees $2\theta \pm 0.2$ degree 2θ , 18.3 degrees $2\theta \pm 0.2$ degree 2θ , 13.8 degrees $2\theta \pm 0.2$ degree 2θ and 12.0 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00337] Example 10. A solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising at least four peaks, in terms of 2-theta, selected from the group consisting of 7.1 degrees $2\theta \pm 0.2$ degree 2θ , 14.3 degrees $2\theta \pm 0.2$ degree 2θ , 18.3 degrees $2\theta \pm 0.2$ degree 2θ , 13.8 degrees $2\theta \pm 0.2$ degree 2θ , 12.0 degrees $2\theta \pm 0.2$ degree 2θ , 25.1 degrees $2\theta \pm 0.2$ degree 2θ and 18.9 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00338] Example 11. A solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising at least five peaks, in terms of 2-theta, selected from the group consisting of 7.1 degrees $2\theta \pm 0.2$ degree 2θ , 14.3 degrees $2\theta \pm 0.2$ degree 2θ , 18.3 degrees $2\theta \pm 0.2$ degree 2θ , 13.8 degrees $2\theta \pm 0.2$ degree 2θ , 12.0 degrees $2\theta \pm 0.2$ degree 2θ , 25.1 degrees $2\theta \pm 0.2$ degree 2θ , 18.9 degrees $2\theta \pm 0.2$ degree 2θ , 27.2 degrees $2\theta \pm 0.2$ degree 2θ and 11.0 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00339] Example 12. A solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising at least five peaks, in terms of 2-theta, selected from the group consisting of 7.1 degrees $2\theta \pm 0.2$ degree 2θ , 14.3 degrees $2\theta \pm 0.2$ degree 2θ , 18.3 degrees $2\theta \pm 0.2$ degree 2θ , 13.8 degrees $2\theta \pm 0.2$ degree 2θ , 12.0 degrees $2\theta \pm 0.2$ degree 2θ , 25.1 degrees $2\theta \pm 0.2$ degree 2θ , 18.9 degrees $2\theta \pm 0.2$ degree 2θ , 27.2 degrees $2\theta \pm 0.2$ degree 2θ , 11.0 degrees $2\theta \pm 0.2$ degree 2θ and 16.2 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00340] Example 13. A solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising at least seven peaks, in terms of 2-theta, selected from the group consisting of 7.1 degrees $2\theta \pm 0.2$ degree 2θ , 14.3 degrees $2\theta \pm 0.2$ degree 2θ , 18.3 degrees $2\theta \pm 0.2$ degree 2θ , 13.8 degrees $2\theta \pm 0.2$ degree 2θ , 12.0 degrees $2\theta \pm 0.2$ degree 2θ , 25.1 degrees $2\theta \pm 0.2$ degree 2θ , 18.9 degrees $2\theta \pm 0.2$ degree 2θ , 27.2 degrees $2\theta \pm 0.2$ degree 2θ

2 θ , 11.0 degrees 2 θ $\pm$ 0.2 degree 2 θ and 16.2 degrees 2 θ $\pm$ 0.2 degree 2 θ , at about relative humidity 0%.

[00341] **Example 14.** A solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising at least eight peaks, in terms of 2-theta, selected from the group consisting of 7.1 degrees 2 θ $\pm$ 0.2 degree 2 θ , 14.3 degrees 2 θ $\pm$ 0.2 degree 2 θ , 18.3 degrees 2 θ $\pm$ 0.2 degree 2 θ , 13.8 degrees 2 θ $\pm$ 0.2 degree 2 θ , 12.0 degrees 2 θ $\pm$ 0.2 degree 2 θ , 25.1 degrees 2 θ $\pm$ 0.2 degree 2 θ , 18.9 degrees 2 θ $\pm$ 0.2 degree 2 θ , 27.2 degrees 2 θ $\pm$ 0.2 degree 2 θ , 11.0 degrees 2 θ $\pm$ 0.2 degree 2 θ and 16.2 degrees 2 θ $\pm$ 0.2 degree 2 θ , at about relative humidity 0%.

[00342] **Example 15.** A solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising at least nine peaks, in terms of 2-theta, selected from the group consisting of 7.1 degrees 2 θ $\pm$ 0.2 degree 2 θ , 14.3 degrees 2 θ $\pm$ 0.2 degree 2 θ , 18.3 degrees 2 θ $\pm$ 0.2 degree 2 θ , 13.8 degrees 2 θ $\pm$ 0.2 degree 2 θ , 12.0 degrees 2 θ $\pm$ 0.2 degree 2 θ , 25.1 degrees 2 θ $\pm$ 0.2 degree 2 θ , 18.9 degrees 2 θ $\pm$ 0.2 degree 2 θ , 27.2 degrees 2 θ $\pm$ 0.2 degree 2 θ , 11.0 degrees 2 θ $\pm$ 0.2 degree 2 θ and 16.2 degrees 2 θ $\pm$ 0.2 degree 2 θ , at about relative humidity 0%.

[00343] **Example 16.** A solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising the peaks, in terms of 2-theta, of 7.1 degrees 2 θ $\pm$ 0.2 degree 2 θ , 14.3 degrees 2 θ $\pm$ 0.2 degree 2 θ , 18.3 degrees 2 θ $\pm$ 0.2 degree 2 θ , 13.8 degrees 2 θ $\pm$ 0.2 degree 2 θ , 12.0 degrees 2 θ $\pm$ 0.2 degree 2 θ , 25.1 degrees 2 θ $\pm$ 0.2 degree 2 θ , 18.9 degrees 2 θ $\pm$ 0.2 degree 2 θ , 27.2 degrees 2 θ $\pm$ 0.2 degree 2 θ , 11.0 degrees 2 θ $\pm$ 0.2 degree 2 θ and 16.2 degrees 2 θ $\pm$ 0.2 degree 2 θ , at about relative humidity 0%.

[00344] **Example 17.** A solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern substantially as shown in Figure 4G at about relative humidity 0%.

[00345] **Example 18.** A solid form of RAD1901-2HCl, having a differential scanning calorimetry (DSC) thermogram comprising a melting onset at 218.2 °C and an endothermic peak at 232.1 °C.

[00346] **Example 19.** The solid form of Example 18, having a differential scanning calorimetry (DSC) thermogram substantially as shown in the bottom figure of Figure 8.

[00347] **Example 20.** A solid form of RAD1901-2HCl, having a thermogravimetric analysis (TGA) substantially as shown in the top graph of Figure 8.

[00348] **Example 21.** A composition comprising RAD1901 wherein at least 5% w/w of the total amount of RAD1901 is a solid form of any one of previous examples.

[00349] **Example 22.** A composition comprising RAD1901 wherein at least 25% w/w of the total amount of RAD1901 is a solid form of any one of previous examples.

[00350] **Example 23.** A composition comprising RAD1901 wherein at least 50% w/w of the total amount of RAD1901 is a solid form of any one of previous examples.

[00351] **Example 24.** A composition comprising RAD1901 wherein at least 90% w/w of the total amount of RAD1901 is a solid form of any one of previous examples.

[00352] **Example 25.** A composition comprising RAD1901 wherein at least 95% w/w of the total amount of RAD1901 is a solid form of any one of previous examples.

[00353] **Example 26.** A composition comprising RAD1901 wherein at least 98% w/w of the total amount of RAD1901 is a solid form of any one of previous examples.

[00354] **Example 27.** A pharmaceutical composition comprising the solid form of any of Examples 5-26 and one or more pharmaceutically acceptable excipients.

[00355] **Example 28.** A process for preparing a solid form of any of Examples 5-27 comprising precipitating from a solution comprising RAD1901-2HCl and a solvent, or slurring RAD1901-2HCl in a solvent, wherein the solvent comprises an organic solvent substantially free of methanol, and the content of water is at or below 5% v/v.

[00356] **Example 29.** The process according to Example 28 wherein the solvent is selected from the group consisting of n-heptane, propyl acetate, ethyl acetate, isopropyl acetate, methyl isobutyl ketone (MIBK), methyl ethyl ketone (MEK), 1-propanol, ethanol, t-butyl methyl ether (TBME), 1,4-dioxane, toluene, 1,2-dimethoxyethane, tetrahydrofuran, dichloromethane, acetonitrile, nitromethane, and mixtures thereof.

[00357] **Example 30.** A method of treating breast cancer comprising an administration to a subject in need thereof a solid form of any of Examples 5-26.

[00358] **Example 31.** The method of Example 30 wherein said breast cancer is ER+.

[00359] **Example 32.** A method of treating ovarian cancer comprising an administration to a subject in need thereof a solid form of RAD1901-2HCl according to any of Examples 5-26.

[00360] **Example 33.** A solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 6.3 degrees $2\theta \pm 0.2$ degree 2θ at about relative humidity 0%.

[00361] Example 34. A solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 6.3 degrees $2\theta \pm 0.2$ degree 2θ and/or 12.5 degrees $2\theta \pm 0.2$ degree 2θ at about relative humidity 0%.

[00362] Example 35. A solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising at least two peaks, in terms of 2-theta, selected from the group consisting of 6.3 degrees $2\theta \pm 0.2$ degree 2θ , 12.5 degrees $2\theta \pm 0.2$ degree 2θ and 15.4 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00363] Example 36. A solid form of RAD1901-2HCl, having an X-ray powder diffraction pattern comprising at least three peaks, in terms of 2-theta, selected from the group consisting of 6.3 degrees $2\theta \pm 0.2$ degree 2θ , 12.5 degrees $2\theta \pm 0.2$ degree 2θ , 15.4 degrees $2\theta \pm 0.2$ degree 2θ , 18.3 degrees $2\theta \pm 0.2$ degree 2θ and 13.4 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

[00364] Example 37. A solid form of RAD1901-2HCl having an X-ray powder diffraction pattern substantially as shown in Figure 5H at about relative humidity 0%.

[00365] Example 38. A pharmaceutical composition comprising a solid form according to any one of Examples 32-37 and one or more pharmaceutically acceptable excipients.

[00366] Example 39. A solid form of RAD1901-2HCl that is a hydrate.

[00367] Example 40. The solid form of RAD1901-2HCl of Example 39 that is a dehydrate.

[00368] Example 41. The solid form of Examples 39 or 40 having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 5.8 degrees $2\theta \pm 0.2$ degree 2θ at about relative humidity 92%.

[00369] Example 42. The solid form of any of Examples 39-41 having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 5.8 degrees $2\theta \pm 0.2$ degree 2θ and/or 21.3 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 92%.

[00370] Example 43. The solid form of any of Examples 39-41 having an X-ray powder diffraction pattern comprising at least two peaks, in terms of 2-theta, selected from the group consisting of 5.8 degrees $2\theta \pm 0.2$ degree 2θ , 21.3 degrees $2\theta \pm 0.2$ degree 2θ and 24.8 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 92%.

[00371] Example 44. The solid form of any of Examples 39-41 having an X-ray powder diffraction pattern comprising at least three peaks, in terms of 2-theta, selected from the

group consisting of 5.8 degrees $2\theta \pm 0.2$ degree 2θ , 21.3 degrees $2\theta \pm 0.2$ degree 2θ , 24.8 degrees $2\theta \pm 0.2$ degree 2θ , 23.3 degrees $2\theta \pm 0.2$ degree 2θ and 9.5 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 92%.

[00372] **Example 45.** The solid form of any of Examples 39-41 having an X-ray diffraction pattern comprising at least four peaks, in terms of 2-theta, selected from the group consisting of 5.8 degrees $2\theta \pm 0.2$ degree 2θ , 21.3 degrees $2\theta \pm 0.2$ degree 2θ , 24.8 degrees $2\theta \pm 0.2$ degree 2θ , 23.3 degrees $2\theta \pm 0.2$ degree 2θ , 12.1 degrees $2\theta \pm 0.2$ degree 2θ and 9.5 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 92%.

[00373] **Example 46.** A solid form of RAD1901-2HCl that is amorphous.

[00374] **Example 47.** A form of RAD1901-2HCl as an amorphous material in a dispersion matrix.

[00375] **Example 48.** A tablet comprising 400 mg amorphous RAD1901-2HCl dispersed into a matrix.

[00376] Although specific embodiments of the present invention are herein illustrated and described in detail, the invention is not limited thereto. The above detailed descriptions are provided as exemplary of the present invention and should not be construed as constituting any limitation of the invention. Modifications will be obvious to those skilled in the art, and all modifications that do not depart from the spirit of the invention are intended to be included with the scope of the appended claims.

Claims

1. A solid form of RAD1901-2HCl having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 11.53 degrees $2\theta \pm 0.2$ degree 2θ at about relative humidity 0%.
2. The solid form of claim 1, having an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at 11.53 degrees $2\theta \pm 0.2$ degree 2θ and 22.63 degrees $2\theta \pm 0.2$ degree 2θ at about relative humidity 0%.
3. The solid form of claim 1, having an X-ray powder diffraction pattern further comprising at least one peak, in terms of 2-theta, selected from the group consisting of 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , and 19.23 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.
4. The solid form of claim 1, having an X-ray powder diffraction pattern further comprising at least two peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , 19.23 degrees $2\theta \pm 0.2$ degree 2θ , and 26.84 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.
5. The solid form of claim 1, having an X-ray powder diffraction pattern further comprising at least three peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , 19.23 degrees $2\theta \pm 0.2$ degree 2θ , 26.84 degrees $2\theta \pm 0.2$ degree 2θ , and 8.94 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.
6. The solid form of claim 1, having an X-ray powder diffraction pattern further comprising at least four peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , 19.23 degrees $2\theta \pm 0.2$ degree 2θ , 26.84 degrees $2\theta \pm 0.2$ degree 2θ , 8.94 degrees $2\theta \pm 0.2$ degree 2θ , and 22.39 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.
7. The solid form of claim 1, having an X-ray powder diffraction pattern further comprising at least five peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , 19.23 degrees $2\theta \pm 0.2$ degree 2θ , 26.84 degrees $2\theta \pm 0.2$ degree 2θ , 8.94 degrees $2\theta \pm 0.2$ degree 2θ , 22.39 degrees $2\theta \pm 0.2$ degree 2θ , and 24.80 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.

8. The solid form of claim 1, having an X-ray powder diffraction pattern further comprising at least five peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , 19.23 degrees $2\theta \pm 0.2$ degree 2θ , 26.84 degrees $2\theta \pm 0.2$ degree 2θ , 8.94 degrees $2\theta \pm 0.2$ degree 2θ , 22.39 degrees $2\theta \pm 0.2$ degree 2θ , 24.80 degrees $2\theta \pm 0.2$ degree 2θ , and 25.58 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.
9. The solid form of claim 1, having an X-ray powder diffraction pattern further comprising at least six peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , 19.23 degrees $2\theta \pm 0.2$ degree 2θ , 26.84 degrees $2\theta \pm 0.2$ degree 2θ , 8.94 degrees $2\theta \pm 0.2$ degree 2θ , 22.39 degrees $2\theta \pm 0.2$ degree 2θ , 24.80 degrees $2\theta \pm 0.2$ degree 2θ , 25.58 degrees $2\theta \pm 0.2$ degree 2θ , and 21.66 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.
10. The solid form of claim 1, having an X-ray powder diffraction pattern further comprising at least seven peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , 19.23 degrees $2\theta \pm 0.2$ degree 2θ , 26.84 degrees $2\theta \pm 0.2$ degree 2θ , 8.94 degrees $2\theta \pm 0.2$ degree 2θ , 22.39 degrees $2\theta \pm 0.2$ degree 2θ , 24.80 degrees $2\theta \pm 0.2$ degree 2θ , 25.58 degrees $2\theta \pm 0.2$ degree 2θ , 21.66 degrees $2\theta \pm 0.2$ degree 2θ , and 28.76 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.
11. The solid form of claim 1, having an X-ray powder diffraction pattern comprising the peaks, in terms of 2-theta, of 8.94 degrees $2\theta \pm 0.2$ degree 2θ , 11.53 degrees $2\theta \pm 0.2$ degree 2θ , 14.04 degrees $2\theta \pm 0.2$ degree 2θ , 19.23 degrees $2\theta \pm 0.2$ degree 2θ , 21.66 degrees $2\theta \pm 0.2$ degree 2θ , 22.39 degrees $2\theta \pm 0.2$ degree 2θ , 22.63 degrees $2\theta \pm 0.2$ degree 2θ , 24.80 degrees $2\theta \pm 0.2$ degree 2θ , 25.58 degrees $2\theta \pm 0.2$ degree 2θ , 26.84 degrees $2\theta \pm 0.2$ degree 2θ , and 28.76 degrees $2\theta \pm 0.2$ degree 2θ , at about relative humidity 0%.
12. The solid form of claim 1, having an X-ray powder diffraction pattern as shown in Figure 22C at about relative humidity 0%.
13. A solid form of RAD1901-2HCl, having a differential scanning calorimetry (DSC) thermogram comprising a melting onset at 210.3 °C and an endothermic peak at 233.8 °C.
14. The solid form of claim 13, having a differential scanning calorimetry (DSC) thermogram as shown in the bottom of Figure 21A.

15. A solid form of RAD1901-2HCl, having a thermogravimetric analysis (TGA) thermogram as shown in the top of Figure 21A.
16. A pharmaceutical composition comprising the solid form of claim 1 and one or more pharmaceutically acceptable excipients.
17. A process for preparing the solid form of claim 1 comprising precipitating from a solution comprising RAD1901-2HCl and a solvent, or slurring RAD1901-2HCl in a solvent, wherein the solvent comprises an organic solvent excluding methanol, and the content of water is at or below 5% v/v.
18. The process according to claim 17, wherein the organic solvent is selected from the group consisting of 2-ethoxyethanol, 1,2-dichloroethane, and ethyl acetate.
19. The process according to claim 18, wherein the organic solvent is 2-ethoxyethanol.
20. The process according to claim 18, wherein the organic solvent is 1,2-dichloroethane.
21. The process according to claim 18, wherein the organic solvent is ethyl acetate.
22. A method of treating ER⁺ cancer comprising the administration of RAD1901-2HCl containing Form 1B.
23. A solid form of RAD1901-2HCl, having a ¹³C solid-state CPMAS NMR pattern as shown for Pattern B in Figure 22.
24. A solid form of RAD1901-2HCl having a ¹H solid-state MAS NMR pattern as shown for Pattern B in Figure 24.
25. A solid form of RAD1901-2HCl having an FT-IR pattern as shown in Figure 25C.
26. A solid form of RAD1901-2HCl having a Raman Spectroscopy pattern as shown for Pattern B in Figure 26.
27. A method of treating breast cancer comprising an administration to a subject in need thereof the solid form of RAD1901-2HCl as described in any one of the claims 1-16.
28. The method of claim 27 wherein said breast cancer is ER⁺.
29. A method of treating ovarian cancer comprising an administration to a subject in need thereof the solid form of RAD1901-2HCl as described in any one of the claims 1-16.