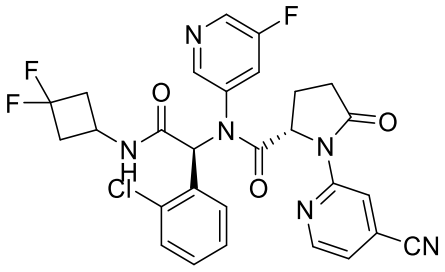


(I).

or a hydrate or solvate thereof. In one embodiment Form E is a solvated form. In another embodiment Form E is an isopropyl acetate solvate of a compound of Formula I.

[0013a] In one aspect, there is provided a solid state form E of a methyl isobutyl ketone (MIBK) solvate of a compound of formula (I), (ivosidenib) characterized by an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 5.5 ± 0.2 °2θ, 6.1 ± 0.2 °2θ, 6.3 ± 0.2 °2θ, 7.6 ± 0.2 °2θ, 9.3 ± 0.2 °2θ, 9.4 ± 0.2 °2θ, 9.8 ± 0.2 °2θ, 11.2 ± 0.2 °2θ, 11.5 ± 0.2 °2θ, 11.6 ± 0.2 °2θ, 12.0 ± 0.2 °2θ, 13.2 ± 0.2 °2θ, 13.9 ± 0.2 °2θ, 14.3 ± 0.2 °2θ, 14.4 ± 0.2 °2θ, 15.0 ± 0.2 °2θ, 15.3 ± 0.2 °2θ, 15.7 ± 0.2 °2θ, 16.8 ± 0.2 °2θ, 17.1 ± 0.2 °2θ, 17.8 ± 0.2 °2θ, 17.9 ± 0.2 °2θ, 18.3 ± 0.2 °2θ, 18.8 ± 0.2 °2θ, 19.1 ± 0.2 °2θ, 19.3 ± 0.2 °2θ, 19.6 ± 0.2 °2θ, 19.9 ± 0.2 °2θ, 20.1 ± 0.2 °2θ, 20.2 ± 0.2 °2θ, 20.9 ± 0.2 °2θ, 21.0 ± 0.2 °2θ, 22.0 ± 0.2 °2θ, 22.5 ± 0.2 °2θ, 23.0 ± 0.2 °2θ, 23.6 ± 0.2 °2θ, 24.2 ± 0.2 °2θ, 24.5 ± 0.2 °2θ, 25.0 ± 0.2 °2θ, 25.3 ± 0.2 °2θ, 26.2 ± 0.2 °2θ, 27.6 ± 0.2 °2θ, 27.9 ± 0.2 °2θ, 28.3 ± 0.2 °2θ, 29.2 ± 0.2 °2θ, 29.8 ± 0.2 °2θ, 30.3 ± 0.2 °2θ, 30.8 ± 0.2 °2θ, 31.5 ± 0.2 °2θ, 32.5 ± 0.2 °2θ, 33.0 ± 0.2 °2θ, 34.1 ± 0.2 °2θ, 34.5 ± 0.2 °2θ and 34.8 ± 0.2 °2θ (Form E).

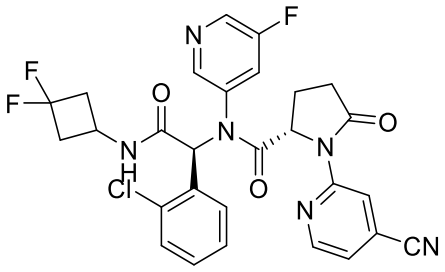
[0014] One embodiment of the present disclosure is Form G of a compound of formula (I):



(I).

or a hydrate or solvate thereof. In another embodiment Form G is a solvated or hydrated form of the compound of Formula I.

[0015] One embodiment of the present disclosure is Form M of a compound of formula (I):



(I).

or a hydrate or solvate thereof. In another embodiment Form M is an anhydrous form of the compound of Formula I.

[0015a] In another aspect, there is provided an anhydrous solid state form of a compound of formula (I) (ivosidenib) characterized by an x-ray powder diffraction pattern comprising one or two or three or four or five or six or seven or eight or nine peaks chosen from 9.2 ± 0.2 °2θ, 10.1 ± 0.2 °2θ, 10.6 ± 0.2 °2θ, 11.4 ± 0.2 °2θ, 11.9 ± 0.2 °2θ, 12.5 ± 0.2 °2θ, 13.1 ± 0.2 °2θ, 13.4 ± 0.2 °2θ, 14.4 ± 0.2 °2θ, 15.3 ± 0.2 °2θ, 15.8 ± 0.2 °2θ, 17.2 ± 0.2 °2θ, 17.7 ± 0.2 °2θ, 17.8 ± 0.2 °2θ, 18.5 ± 0.2 °2θ, 19.5 ± 0.2 °2θ, 19.7 ± 0.2 °2θ, 19.9 ± 0.2 °2θ, 20.4 ± 0.2 °2θ, 20.9 ± 0.2 °2θ, 21.4 ± 0.2 °2θ, 22.0 ± 0.2 °2θ, 22.2 ± 0.2 °2θ, 22.9 ± 0.2 °2θ, 23.2 ± 0.2 °2θ, 24.6 ± 0.2 °2θ, 24.7 ± 0.2 °2θ, 25.0 ± 0.2 °2θ, 25.8 ± 0.2 °2θ, 26.2 ± 0.2 °2θ, 26.6 ± 0.2 °2θ, 27.0 ± 0.2 °2θ, 27.3 ± 0.2 °2θ, 27.8 ± 0.2 °2θ, 29.1 ± 0.2 °2θ, 29.7 ± 0.2 °2θ, 30.3 ± 0.2 °2θ, 31.3 ± 0.2 °2θ, 31.9 ± 0.2 °2θ, 33.1 ± 0.2 °2θ, 33.6 ± 0.2 °2θ, 33.8 ± 0.2 °2θ and 34.6 ± 0.2 °2θ (Form M).

[0016] One embodiment of the present disclosure is a Form N of a compound of formula (I)

embodiment, the partially crystalline form is at least 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%, or 99.9% crystalline form I. In another embodiment, the partially crystalline form is at least 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%, or 99.9% crystalline form K.

[0020] In another aspect, the present disclosure provides a process for making Form L of ivosidenib comprising making one or more meta-stable forms of ivosidenib in an anhydrous, hydrated, or solvated form, and allowing such one or more meta-stable form of ivosidenib to convert to Form L. One aspect provides a process where the one or more meta-stable form is selected from forms C, D, E, F, H, J, M, or N, each individually in an anhydrous, hydrated, or solvated form.

[0020a] In another aspect, there is provided a process for making Form L of ivosidenib comprising making one or more meta-stable form of ivosidenib in anhydrous, hydrated, or solvated form, and allowing such one or more meta-stable form of ivosidenib to convert to Form L, wherein the meta-stable forms are selected from: (a) a solid state form of ivosidenib characterized by an x-ray powder diffraction pattern substantially corresponding with the XRPD pattern shown in Fig. 12 and a DSC and TGA profile substantially corresponding to those shown in Fig. 13 (Form A); (b) a solid state form of ivosidenib characterized an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 3.8 ± 0.2 °2θ, 7.3 ± 0.2 °2θ, 8.0 ± 0.2 °2θ, 9.3 ± 0.2 °2θ, 11.3 ± 0.2 °2θ, 11.9 ± 0.2 °2θ, 12.2 ± 0.2 °2θ, 13.5 ± 0.2 °2θ, 15.8 ± 0.2 °2θ, 17.7 ± 0.2 °2θ, 18.6 ± 0.2 °2θ, 20.7 ± 0.2 °2θ, 21.6 ± 0.2 °2θ, 22.5 ± 0.2 °2θ, 23.1 ± 0.2 °2θ, 25.4 ± 0.2 °2θ and 27.6 ± 0.2 °2θ (Form C); (c) a solid state form of ivosidenib characterized by an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 7.3 ± 0.2 °2θ, 8.4 ± 0.2 °2θ, 10.2 ± 0.2 °2θ, 10.3 ± 0.2 °2θ, 11.1 ± 0.2 °2θ, 12.7 ± 0.2 °2θ, 13.4 ± 0.2 °2θ, 14.6 ± 0.2 °2θ, 16.3 ± 0.2 °2θ, 17.0 ± 0.2 °2θ, 17.9 ± 0.2 °2θ, 19.4 ± 0.2 °2θ, 20.4 ± 0.2 °2θ, 21.3 ± 0.2 °2θ, 21.8 ± 0.2 °2θ, 23.4 ± 0.2 °2θ, 24.6 ± 0.2 °2θ, 25.2 ± 0.2 °2θ, 25.6 ± 0.2 °2θ, 26.1 ± 0.2 °2θ, 26.6 ± 0.2 °2θ, 28.1 ± 0.2 °2θ and 28.8 ± 0.2 °2θ (Form D); (d) a solid state form of ivosidenib as a methyl isobutyl ketone (MIBK) solvate characterized by an x-ray powder diffraction pattern comprising a peak at 6.3± 0.2 °2θ and one or more of the following peaks 11.6± 0.2 °2θ, 12.0 ± 0.2 °2θ , 17.1 ± 0.2 °2θ, and 21.0 ± 0.2 °2θ (Form E); (e) a solid state form of ivosidenib characterized by an x-ray powder diffraction pattern comprising one or two or three or

four or five peaks chosen from 6.5 ± 0.2 °2θ, 7.2 ± 0.2 °2θ, 9.1 ± 0.2 °2θ, 11.7 ± 0.2 °2θ, 12.8 ± 0.2 °2θ, 13.3 ± 0.2 °2θ, 13.7 ± 0.2 °2θ, 14.4 ± 0.2 °2θ, 15.2 ± 0.2 °2θ, 16.1 ± 0.2 °2θ, 17.4 ± 0.2 °2θ, 18.2 ± 0.2 °2θ, 18.8 ± 0.2 °2θ, 19.5 ± 0.2 °2θ, 20.0 ± 0.2 °2θ, 20.6 ± 0.2 °2θ, 21.6 ± 0.2 °2θ, 22.6 ± 0.2 °2θ, 23.3 ± 0.2 °2θ, 23.8 ± 0.2 °2θ, 24.3 ± 0.2 °2θ, 25.4 ± 0.2 °2θ, 26.3 ± 0.2 °2θ, 26.8 ± 0.2 °2θ, 28.0 ± 0.2 °2θ, 28.4 ± 0.2 °2θ, 29.0 ± 0.2 °2θ, 30.5 ± 0.2 °2θ, 31.6 ± 0.2 °2θ, 32.2 ± 0.2 °2θ, 34.0 ± 0.2 °2θ, 34.9 ± 0.2 °2θ, 35.3 ± 0.2 °2θ, 36.1 ± 0.2 °2θ and 38.3 ± 0.2 °2θ (Form F); (f) a solid state form of ivosidenib characterized by an x-ray powder diffraction pattern substantially corresponding with the XRPD pattern shown in Fig. 25 and a DSC and TGA profile substantially corresponding to those shown in Fig. 26 (Form G); (g) a solid state form of ivosidenib characterized by an x-ray powder diffraction pattern substantially corresponding with the XRPD pattern shown in Fig. 27 and a DSC and TGA profile substantially corresponding to those shown in Fig. 28 (Form H); (h) a solid state form of ivosidenib characterized by an x-ray powder diffraction pattern substantially corresponding with the XRPD pattern shown in Fig. 29 and a DSC and TGA profile substantially corresponding to those shown in Fig. 30 (Form I); (i) a solid state form of ivosidenib characterized by an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 6.4 ± 0.2 °2θ, 8.2 ± 0.2 °2θ, 9.4 ± 0.2 °2θ, 10.3 ± 0.2 °2θ, 11.9 ± 0.2 °2θ, 13.2 ± 0.2 °2θ, 16.1 ± 0.2 °2θ, 16.8 ± 0.2 °2θ, 17.6 ± 0.2 °2θ, 18.6 ± 0.2 °2θ, 19.7 ± 0.2 °2θ, 21.4 ± 0.2 °2θ, 22.5 ± 0.2 °2θ, 23.2 ± 0.2 °2θ, 25.0 ± 0.2 °2θ, 26.0 ± 0.2 °2θ, 27.1 ± 0.2 °2θ, 29.6 ± 0.2 °2θ and 35.5 ± 0.2 °2θ (Form J); (j) an anhydrous solid state form of ivosidenib characterized by an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 11.4 ± 0.2 °2θ, 17.7 ± 0.2 °2θ, 17.8 ± 0.2 °2θ, 19.7 ± 0.2 °2θ, and 21.4 ± 0.2 °2θ. (Form M); (k) a solid state form of ivosidenib characterized by an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 8.6 ± 0.2 °2θ, 14.4 ± 0.2 °2θ, 18.6 ± 0.2 °2θ, 20.3 ± 0.2 °2θ and 22.9 ± 0.2 °2θ. (Form N); and wherein Form L of ivosidenib is characterized by an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 8.7 ± 0.2 °2θ, 13.2 ± 0.2 °2θ, 15.7 ± 0.2 °2θ, 18.5 ± 0.2 °2θ, 18.5 ± 0.2 °2θ, 19.6 ± 0.2 °2θ, 20.7 ± 0.2 °2θ, 21.5 ± 0.2 °2θ, 26.4 ± 0.2 °2θ and 27.3 ± 0.2 °2θ.

[0021] In another aspect, the present disclosure provides a pharmaceutical composition comprising ivosidenib in a mixture of two or more solid state forms chosen from Form L, Form B, Form A, Form C, Form D, Form E, Form F, Form G,

Form H, Form I, Form J, Form K, Form M, and Form N, each individually in an anhydrous, hydrated, or solvated form. In one aspect, the pharmaceutical composition comprises no more than 0.15% (area% by HPLC) of a compound selected from: (i) 2-((2*S*)-2-((1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)(5-fluoropyridin-3-yl)carbamoyl)-5-oxopyrrolidin-1-yl)isonicotinamide; (ii) (*S*)-*N*-((*S*)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-5-oxo-*N*-(pyridin-3-yl)pyrrolidine-2-carboxamide; (iii) (*S*)-*N*-((*R*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide; (iv) (*R*)-*N*-((*S*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide; and (v) (*R*)-*N*-((*R*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide. In one aspect, the pharmaceutical composition comprises Form L together with one or more of Form B, Form A, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, Form K, Form M, and Form N, each individually in an anhydrous, hydrated, or solvated form. In another aspect, the pharmaceutical composition may optionally contain amorphous ivosidenib. In yet another aspect, the pharmaceutical composition comprises one or more forms of ivosidenib that are chosen from Form B, Form A, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, Form K, Form

Form	Identity	Melting point (DSC, °C)	Weight loss (TGA, %)
Form M	Anhydrate	170	< 1%
Form N	Anhydrate	214	< 1%
Pattern 3	Solvate		

[00129] The forms were characterized by x-ray powder diffraction (XRPD), which are overlaid together in Figure 1. The forms were further characterized by differential scanning calorimetry (DSC), and by thermogravimetric analysis (TGA).

[00130] Certain of the polymorphs of ivosidenib as disclosed herein are interconvertible~~, as is shown in Figure 2~~. For instance, the anhydrate Form L can be converted to anhydrate Form N by treating with an isopropyl acetate (iPrOAc):heptane mixture, containing at most 25% iPrOAc at 70 ºC.

Form L

[00131] Form L is an anhydrous form of ivosidenib having a melting point as determined by differential scanning calorimetry (DSC) of 150 C, and a weight loss in thermogravimetric analysis (TGA) of 0.44%.

[00132] In one embodiment, to synthesize Form L of ivosidenib, a mixture of ivosidenib (3.5 kg, 7.28 mol) in 1,4-dioxane (35 L) is degassed by N_2 bubbling for a maximum of 20 min. 2-chloro-4-cyanopyridine (1.21 kg, 8.73 mol), tris(dibenzylideneacetone)-dipalladium(0) (167 g, 0.18 mol), and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos) (211 g, 0.36 mol) are added and the reaction mixture is degassed by N_2 bubbling for a maximum of 10 min. $K2CO_3$ (1.21 kg, 8.73 mol) is added and the reaction mixture is degassed by N_2 bubbling for a maximum of 30 min. The reaction mixture is heated at 90-100°C for 4 to 24 hours until the reaction is complete. The reaction mixture is then cooled to 15-25°C and filtered through Celite and is washed with ethyl acetate, and the combined filtrate and wash are concentrated.

[00133] The 1,4-dioxane is removed, and the residual solid is dissolved in ethyl acetate (77.5 L). The ethyl acetate solution is washed successively with a 5% aqueous solution of $NaHSO_3$, a 2% aqueous solution of EDTA disodium, and a 1% aqueous solution of EDTA disodium salt. The organic phase is treated with activated carbon at 55-65°C for a maximum of 2 h, and is purified by silica gel chromatography. After chromatography, the resulting product is purified by two recrystallizations: first compound 1 is dissolved in ethyl acetate and heated to 60-70°C and heptane is added. The reaction mixture is cooled to 15-25°C and stirred

for 1-3 h. The product is filtered and is dissolved in dichloromethane, then is filtered and is precipitated with heptane, is filtered and dried to produce Form L.

[00134] In one embodiment, a single crystalline form, Form L, of ivosidenib is characterized by the X-ray powder diffraction (XRPD) pattern shown in Figure 1, and data shown in Table 2, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from Figure 1, and as shown in Table 2. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 2.

Table 2: Peaks of Form L by XRPD

Angle (2-Theta°)	Intensity (%)
8.7	90.3
13.2	60.0
15.7	85.5
18.5	72.5
19.6	31.5
20.7	71.6
21.5	100.0
26.4	64.2
27.3	45.6

[00135] In another embodiment, Form L can be characterized by the peaks identified at 2θ angles of 8.7, 15.7, 18.5, 20.7, 21.5, and 26.4°. In another embodiment, Form L can be characterized by the peaks identified at 2θ angles of 8.7, 15.7, 18.5, and 21.5°.

[00136] In another embodiment, Form L can be characterized by the differential scanning calorimetry profile (DSC) shown in Figure ~~3~~2. The DSC graph plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C /min. The profile is characterized by an endothermic transition with an onset temperature of about 140.1°C with a melt at about 149.9°C.

[00137] In another embodiment, Form L can be characterized by thermal gravimetric analysis (TGA) shown in Figure ~~4~~3. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss represents a loss of about 0.44% of

25.0	8.9
31.4	22.0

[00143] In another embodiment, Form B can be characterized by the peaks identified at 2θ angles of 9.9, 11.7, 19.6, 22.5, 23.0, and 31.4°. In another embodiment, Form B can be characterized by the peaks identified at 2θ angles of 9.9, 11.7, 19.6, and 23.0°.

[00144] In another embodiment, Form B can be characterized by the differential scanning calorimetry profile (DSC) shown in Figure ~~5~~4. The DSC graph plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C /min. The profile is characterized by an endothermic transition with an onset temperature of about 62.7°C with a melt at about 72.5°C, and an endothermic transition with an onset temperature of about 145.6°C with a melt at about 153.6°C.

[00145] In another embodiment, Form B can be characterized by thermal gravimetric analysis (TGA) shown in Figure ~~6~~5. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss represents a loss of about 0.57 % of the weight of the sample as the temperature is changed from about 29.3°C to 170.3°C.

Form M and Form N

[00146] Forms M and N of ivosidenib are anhydrous forms obtained at high heptane concentrations. Form N is obtained at a high heptane concentration of between 75-95% at 70°C, and Form M is obtained at very high heptane concentrations (95%) at 40°C.

[00147] To determine the most stable anhydrous form, competitive slurries using Form L, Form M, and Form N were carried out in dichloromethane, heptane, tBME and acetone. These experiments indicated that Form N was a stable anhydrous form under the conditions assessed, correlating with the thermal data obtained which indicated a significantly higher melting temperature of *ca*. 215°C and melting enthalpy of *ca.* 53 mJ/mg for Form N compared with the melting temperature (*ca*. 170°C) and enthalpy (*ca.* 33 mJ/mg) of Form M . To determine the likelihood of obtaining these forms during the crystallization, slurry conversion experiments were carried out, employing a crystallization procedure involving mixing 141.6 g of Form B ivosidenib and 432 mL iPrOAc in a 1 L vessel and stirring at 50°C and 210 rpm. The temperature was increased to 70°C to dissolve material. Anti-solvent addition (60 mL

	Form L + Form M		900	500	42.5	114
	Form N + Form M		1200	500	20.5	68.5
Acetone	Form L + Form N	50	100	175	20.5	68.5
	Form L + Form M		100	125	20.5	68.5
	Form N + Form M		100	175	20.5	68.5

Characterization of Form N

[00151] A sample of Form N was poorly soluble in 5:95 v/v iPrOAc:heptane and remained a thick slurry throughout the experiment. XRPD analysis of both the centrifuged sample (taken after 15 h at 70°C) and the dried product was consistent with Form N and there was excellent agreement between the diffractograms of the scale-up material and the sample isolated from the solid form mapping experiments.

[00152] Both the slurry and the dried material were birefringent by PLM analysis, with a needle-like morphology. TG analysis of the dried material showed essentially no weight loss, consistent with the Form N anhydrous form (see Figure ~~7~~6). DTA showed an endothermic event at onset *ca*. 212.0°C (peak at *ca*. 215.8°C), likely due to melting of the material as shown in Figure ~~7~~6.

[00153] DSC analysis of the small sample removed after 15 h and dried for *ca*. 2 h under vacuum showed an endothermic event at onset *ca*. 212.7°C (peak at *ca.* 214.8°C, enthalpy of 53.0 mJ/mg), likely due to melting of the material, as shown in Figure ~~8~~7. DSC analysis of the bulk dried material showed an endothermic event at onset *ca*. 212.6°C (peak at *ca.* 215.4°C, enthalpy of 52.7 mJ/mg), likely due to melting of the material, as shown in Figure ~~8~~7.

[00154] HPLC analysis was carried out on the filtrate (< 1 min filtration time, 80 mm diameter Buchner funnel, 101 mL mother liquor isolated), giving a mother liquor purity of 91.4%. The isolated yield was 4.66 g, 93%. The purity of the isolated solid was found to be 99.9% by HPLC analysis. See Figure ~~9~~8.

[00155] GC analysis of the material indicated that both iPrOAc and heptane content was < LOQ (LOQ solutions of iPrOAc (100 ppm) and heptane (200 ppm) run).

[00156] The solubility of Form N in methanol was found to be 113 mg/ml.

[00157] The peaks by XRPD of Form N of ivosidenib are defined as follows. Form N may be be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 5.

39.00	33.5	30.06	167.90	2.68	170.18	4.58
40.00	34.0	19.88	175.52	2.64	98.49	2.65
41.00	34.4	28.21	181.73	2.61	139.72	3.76

Characterization of Form M

[00158] Form M material was poorly soluble in 5:95 v/v iPrOAc:heptane and remained a thick slurry throughout experiment. XRPD analysis of both the centrifuged sample (taken after 13 h at 40°C) and the dried product was consistent with Pattern 5 and there was excellent agreement between the diffractograms of the scale-up material and the sample isolated from the solid form mapping experiments. (See Figure 1.)

[00159] Both the slurry and the dried material were very slightly birefringent by PLM analysis, with no clearly defined morphology.

[00160] TG analysis of the dried material showed essentially no weight loss, consistent with the Pattern 5 anhydrous form. (See Figure ~~10~~9.) DTA showed a broad endothermic event at onset *ca*. 160.4°C (peak at *ca*. 172.4°C), likely due to melting of the material, as can be seen in Figure ~~10~~9.

[00161] DSC analysis of the small sample removed after 13 h and dried for *ca*. 1.5 h under vacuum showed an endothermic event at onset *ca*. 161.7°C (peak at *ca.* 170.0°C, enthalpy of 32.0 mJ/mg), likely due to melting of the material. DSC analysis of the bulk dried material showed an endothermic event at onset *ca*. 161.5°C (peak at *ca.* 170.5°C, enthalpy of 33.9 mJ/mg), likely due to melting of the material, which is shown in Figure ~~11~~10.

[00162] HPLC analysis was carried out on the filtrate (< 1 min filtration time, 80 mm diameter Buchner funnel, 110 mL mother liquor isolated), giving a mother liquor purity of 91.8%. The isolated yield was 4.63 g, 92%. The purity of the isolated solid was found to be 99.9% by HPLC analysis. (See Figure ~~12~~11.)

[00163] GC analysis of the Pattern 5 material indicated that the iPrOAc content was *ca*. 299 ppm, while the heptane content was *ca*. 339 ppm. (LOQ solutions of iPrOAc (100 ppm) and heptane (200 ppm) run).

[00164] The solubility of Form M in methanol was found to be 109 mg/ml.

[00165] The peaks by XRPD of Form M of ivosidenib are defined as follows. Form M may be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 6.

41.00	33.6	21.01	200.37	2.67	166.53	6.79
42.00	33.8	14.99	214.98	2.65	98.97	4.04
43.00	34.6	58.60	235.18	2.60	290.23	11.83

Form A

[00166] From a sample of ivosidenib, which was partially crystalline as evidenced by the XRPD pattern shown in Figure ~~13~~12, the crystalline form was named as freebase Form A. DSC and TGA data are displayed in Figure ~~14~~13. The DSC curve exhibits an endothermic peak at 30.8 °C (onset). About 1.6% of weight loss was observed below ~150.0 ºC in the TGA data shown in Figure ~~14~~13.

Screening to discover additional polymorphs

[00167] Different crystallization or solid transition methods were applied to discover the various crystalline forms of freebase of ivosidenib, with part of experiments intended to identify a stable form. The methods utilized in the present study are summarized in Table 7, which include slow evaporation, slurry conversion at RT, anti-solvent addition and slow cooling (from 50 °C to 5 °C).

Table 7: Experiment types for polymorph screening

Method	Number of Experiments	Crystalline Forms identified
Slurry conversion at RT	10	freebase Form C, D, E, F, G, H, I
Anti-solvent addition	8	freebase Form B, K
Slow cooling (50 ˚C -5 ˚C)	15	freebase Form B, C, E, G, J
Slow evaporation	15	freebase Form B, C

[00168] Approximate solubility of ivosidenib freebase was determined in 20 solvent systems at RT. In the experiment, ~2 mg of ivosidenib was added into a 3-mL glass vial, followed by the addition of corresponding solvent. The solvent was added by 100 µL step wise until the solution was visually clear or a total volume of 2 mL was reached. The results are listed in Table 8. This solubility information was used to select solvents for the polymorph screening.

Table 8: Solubility of ivosidenib

Solvent	Solubility (mg/mL)
MeOH	>47.6

MIBK	freebase Form E
2-MeTHF	freebase Form J
MEK	freebase Form B
MTBE	amorphous
CH_2Cl_2	oil
Dioxane/Heaptane,9:1	oil
Acetone/Heptane,2:1	oil
THF/H_2O,4:1	oil

Slow Evaporation

[00173] Slow evaporation experiments were performed in 15 solvents by dissolving ~10 mg of ivosidenib freebase in 0.2-0.4 mL of solvent in a 3 mL glass vial. The resulting visually clear solutions were covered with caps and subjected to slow evaporation to induce precipitation. The solids were isolated for XRPD analysis and the results summarized in Table 12 indicate that freebase Type B and Type C were generated.

Table 12: polymorph screening by slow evaporation

Solvent, v/v	Solid Form
MeOH	amorphous
EtOH	amorphous
IPA	freebase Form C
ACN	amorphous
Acetone	amorphous
EtOAc	oil
IPAC	amorphous
MTBE	oil
THF	oil
$CHCl_3$	amorphous
1,4-Dioxane	amorphous
Acetic acid	amorphous
MeOH/H_2O, 9:1	freebase Form B
ACN/H_2O, 4:1	amorphous
Acetone/Heptane, 9:1	amorphous

Characterization of Form C

[00174] The XRPD pattern of ivosidenib freebase Form C sample shown in Figure ~~15~~ 14 indicates that it is a crystalline form. The DSC and TGA overlay of ivosidenib freebase Form C is displayed in Figure ~~16~~15. The TGA data shows ~8.3 wt% weight loss before 192.2 °C. Three endothermic peaks were observed at 52.7 °C, 99.3 °C and 133.7 °C (onset) in DSC curve due to the evaporation of remaining solvent. The H^1 NMR spectrum (Figure ~~17~~16) shows that IPA is the main solvent contained in freebase Form C. The NMR results indicate that the IPA content is 8.0% which

conforms to 8.3 wt% weight loss in TGA curve. The results suggest freebase Form C is an IPA solvate.

Table 13: XRPD peaks of Form C of ivosidenib

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.8	46.300740	0.401472	23.46889	11.71
7.3	241.140300	0.133824	12.13444	60.99
8.0	395.400100	0.050184	11.02412	100.00
9.3	113.455600	0.100368	9.51782	28.69
11.3	374.029900	0.083640	7.81079	94.60
11.9	219.648500	0.066912	7.45421	55.55
12.2	104.524200	0.100368	7.27595	26.44
13.5	86.832810	0.200736	6.56156	21.96
15.8	182.680700	0.100368	5.61815	46.20
17.7	101.392400	0.267648	5.02136	25.64
18.6	117.819400	0.535296	4.76330	29.80
20.7	156.030500	0.200736	4.28895	39.46
21.6	217.857800	0.100368	4.10828	55.10
22.5	151.701700	0.133824	3.95953	38.37
23.1	150.989000	0.401472	3.85292	38.19
25.4	121.780700	0.200736	3.50233	30.80
27.6	172.247100	0.133824	3.23157	43.56

Peaks were searched in X'Pert HighScore Plus (version 3.0) with the following parameters: minimum significance = 2.0, minimum tip width = 0.01 degree 2 theta, maximum tip width = 1.00 degree 2 theta, peak base width = 2.00 degrees 2 theta, method = minimum 2nd derivative.

Form D

[00175] The XRPD pattern of ivosidenib freebase Form D sample shown in Figure ~~18~~ 17 indicates that it is a crystalline form which differs from that of ivosidenib freebase Form A. The DSC and TGA overlay of Form D is displayed in Figure ~~19~~18. The TGA data shows ~8.1 wt% weight loss before 127.3 °C. An endotherm was observed at 90.6 °C in DSC curve due to the evaporation of remaining solvent. The ^{1}H NMR result displayed in Figure ~~20~~ 19 shows ^{1}H peaks of methyl of acetonitrile (ACN) is at

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
28.8	40.294450	0.200736	3.10021	4.51

Peaks were searched in X'Pert HighScore Plus (version 3.0) with the following parameters: minimum significance = 2.0, minimum tip width = 0.01 degree 2 theta, maximum tip width = 1.00 degree 2 theta, peak base width = 2.00 degrees 2 theta, method = minimum 2nd derivative.

Form E

[00176] The XRPD pattern of ivosidenib freebase Type E sample shown in Figure ~~21~~ 20 indicates that it is a crystalline form which differs from that of Form A. The DSC and TGA overlay of ivosidenib freebase Form E is displayed in Figure ~~22~~21. The TGA data shows ~9.5 wt% weight loss before 145.0 °C. An endotherm was observed at 93.1 °C in DSC curve due to the evaporation of remaining solvent. The TGA and DSC results suggest freebase Form E is a solvate. The ^{1}H NMR result displayed in Figure ~~23~~ 22 shows ^{1}H NMR peaks representing the two methyl of isobutyl from methyl isobutyl ketone (MIBK) at 0.92 ppm, and one peak representing ivosidenib at 8.73 ppm. According to the area ratio, the mole equivalent of (2*S*)-*N*-{(1*S*)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)amino]-2-oxoethyl}-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide and MIBK is about 1:0.7, which conforms to the weight loss of TGA, suggesting freebase Type E is a MIBK solvate~~, specifically an isopropyl acetate solvate~~.

[00177] The peaks by XRPD of Form E of ivosidenib are defined as follows. Form E may be be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 15.

TABLE 15: XRPD peaks of Form E of ivosidenib

No.	Pos. [°2θ]	Area [cts*°2θ]	Backgr.[cts]	d-spacing [Å]	Height [cts]	Rel. Int. [%]
1.00	5.5	8.39	348.16	15.96	110.75	2.42
2.00	6.1	18.79	343.01	14.42	496.34	10.83
3.00	6.3	231.40	341.81	14.10	4584.42	100.00
4.00	7.6	12.88	330.34	11.65	85.05	1.86
5.00	9.3	15.38	315.88	9.56	304.67	6.65
6.00	9.4	20.30	314.97	9.46	321.69	7.02
7.00	9.8	11.61	310.83	9.00	306.69	6.69
8.00	11.2	22.11	334.83	7.89	219.06	4.78
9.00	11.5	30.45	340.40	7.69	804.38	17.55

53.00	34.1	16.46	290.71	2.63	163.02	3.56
54.00	34.5	8.94	311.74	2.60	143.32	3.13
55.00	34.8	19.09	325.52	2.58	378.13	8.25

Form F

[00178] The XRPD pattern of ivosidenib freebase Form F sample shown in Figure ~~24~~ 23 indicates that it is a crystalline form which differs from that of Form A. The DSC and TGA overlay of ivosidenib freebase Form F is displayed in Figure ~~25~~24. The TGA data shows ~11.5 wt% weight loss before 152.8 °C. An endotherm was observed at 105.6 °C in DSC curve. The TGA and DSC results suggest freebase Form F is likely a solvate or hydrate.

Table 16: XRPD peaks of Form F of ivosidenib

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
6.5	1086.979000	0.117096	13.68154	52.77
7.2	1151.151000	0.100368	12.31814	55.88
9.1	244.587100	0.066912	9.72595	11.87
11.7	664.987100	0.133824	7.58351	32.28
12.8	650.677100	0.133824	6.89427	31.59
13.3	1130.126000	0.133824	6.63824	54.86
13.7	284.674700	0.133824	6.45331	13.82
14.4	381.854100	0.150552	6.14904	18.54
15.2	287.244300	0.133824	5.84115	13.94
16.1	1772.357000	0.117096	5.50364	86.04
17.4	1200.352000	0.167280	5.09533	58.27
18.2	241.634000	0.133824	4.86657	11.73
18.8	2059.915000	0.133824	4.70864	100.00
19.5	819.051400	0.133824	4.55089	39.76
20.0	870.585800	0.133824	4.44427	42.26
20.6	1626.584000	0.117096	4.31448	78.96
21.6	818.280300	0.133824	4.10662	39.72
22.6	660.516600	0.133824	3.93602	32.07
23.3	471.948900	0.100368	3.81792	22.91
23.8	320.357400	0.133824	3.74633	15.55

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
24.3	392.720700	0.133824	3.65617	19.06
25.4	897.012000	0.117096	3.50659	43.55
26.3	407.102800	0.117096	3.38897	19.76
26.8	687.800600	0.133824	3.32176	33.39
28.0	263.638700	0.167280	3.18905	12.80
28.4	249.314700	0.100368	3.14472	12.10
29.0	237.219700	0.133824	3.08287	11.52
30.5	168.470800	0.167280	2.92873	8.18
31.6	153.652800	0.133824	2.83369	7.46
32.2	155.988900	0.167280	2.78108	7.57
34.0	220.356200	0.200736	2.63550	10.70
34.9	93.962200	0.200736	2.57241	4.56
35.3	136.162100	0.200736	2.54045	6.61
36.1	135.162000	0.167280	2.48978	6.56
38.3	120.879200	0.100368	2.34932	5.87

Peaks were searched in X'Pert HighScore Plus (version 3.0) with the following parameters: minimum significance = 2.0, minimum tip width = 0.01 degree 2 theta, maximum tip width = 1.00 degree 2 theta, peak base width = 2.00 degrees 2 theta, method = minimum 2nd derivative.

Form G

[00179] The XRPD pattern of ivosidenib freebase Form G sample shown in Figure ~~26~~ 25 indicates that it is a crystalline form, which differs from that of Form A. The DSC and TGA overlay of ivosidenib freebase Form G is displayed in Figure ~~27~~26. The TGA data shows ~5.1 wt% weight loss before 147.9 °C. Three endothermic peaks were observed at 42.5 °C, 113.5 °C and 135.5 °C (onset) in DSC curve. The TGA and DSC results suggest freebase Form G is likely a solvate or hydrate.

Form H

[00180] The XRPD pattern of ivosidenib freebase Form H sample shown in Figure ~~28~~ 27 indicates that it is a crystalline form which differs from that of Form A. The DSC and TGA overlay of ivosidenib freebase Form H is displayed in Figure ~~29~~28. The TGA data shows ~3.7 wt% weight loss before 171.4 °C. Two endothermic peaks were

observed at 69.0 °C and 153.7 °C (onset) in DSC curve. The TGA and DSC results suggest freebase Form H is likely a solvate or hydrate.

Form I

[00181] The XRPD pattern of ivosidenib freebase Form I shown in Figure ~~30~~ 29 indicates that it is a partially crystalline form. The DSC and TGA overlay of ivosidenib freebase Form I is displayed in Figure ~~31~~30. The TGA data shows ~1.1 wt% weight loss before 200.6 °C which is probably due to the existence of residual solvent. Two endothermic peaks were observed at 63.9 °C and 133.8 °C (onset) in DSC curve. The H^1 NMR spectrum (Figure ~~32~~31) shows that EtOH is the main solvent contained in freebase Form I. The peak at 1.0 ppm represents the methyl group from EtOH, and the peak at 7.5 ppm is from (2*S*)-*N*-{(1*S*)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)amino]-2-oxoethyl}-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide. According to the area ratio, the mole equivalent of (2*S*)-*N*-{(1*S*)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)amino]-2-oxoethyl}-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide and EtOH is 1:0.34.

[00182] A characteristic XRPD peak by which Form I may be identified occurs at about 8.1º.

[00183] Form I of ivosidenib is an anhydrate/solvate form.

Form J

[00184] The XRPD pattern of ivosidenib freebase Form J shown in Figure ~~33~~ 32 indicates that it is a crystalline form, which is different from freebase Form A. The DSC and TGA overlay of ivosidenib freebase Type J is displayed in Figure ~~34~~33. The TGA data shows ~15.3 wt% weight loss before 132.0 °C which is probably due to the existence of residual solvent. An endotherm was observed at 79.7 °C (onset) in DSC curve demonstrating that freebase Form J is a solvate or hydrate.

Table 17: XRPD peaks of Form J of ivosidenib

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
6.4	35.574370	0.802944	13.82161	7.21
8.2	181.636100	0.133824	10.76889	36.81
9.4	176.789900	0.100368	9.36099	35.83
10.3	123.932900	0.100368	8.60983	25.12
11.9	172.761300	0.100368	7.44210	35.01
13.2	79.875150	0.200736	6.72240	16.19

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
16.1	286.665700	0.100368	5.49963	58.10
16.8	137.992300	0.133824	5.29035	27.97
17.6	493.415200	0.083640	5.04965	100.00
18.6	114.006700	0.200736	4.76137	23.11
19.7	219.114300	0.200736	4.51583	44.41
21.4	219.063600	0.117096	4.15665	44.40
22.5	277.427700	0.200736	3.95958	56.23
23.2	192.926300	0.133824	3.82946	39.10
25.0	218.797700	0.133824	3.56786	44.34
26.0	115.162400	0.267648	3.42523	23.34
27.1	64.280120	0.200736	3.29216	13.03
29.6	38.778450	0.334560	3.01888	7.86
35.5	21.745430	0.401472	2.52854	4.41

Peaks were searched in X'Pert HighScore Plus (version 3.0) with the following parameters: minimum significance = 2.0, minimum tip width = 0.01 degree 2 theta, maximum tip width = 1.00 degree 2 theta, peak base width = 2.00 degrees 2 theta, method = minimum 2nd derivative.

Form K

[00185] The XRPD pattern of ivosidenib freebase Form K is shown in Figure ~~35~~ 34 and indicates that it is a partially crystalline form.

Pattern 3

[00186] A solvate form of ivosidenib referred to as Pattern 3 is observed when a slurry of any of the anhydrous forms (that is, one or more of Form L, Form M, and Form N) in DCM convert to Pattern 3. However, upon drying under vacuum, Pattern 3 converts to Form L.

Interconversion of Forms of Ivosidenib

[00187] The polymorphs of ivosidenib can interconvert under certain conditions. For example, Figure ~~36~~ 35 shows an overlay of DSC curves of Form L, Form M, and Form N as described herein.

[00188] Mixtures of 1:1 anhydrate Forms L, M, and N were mixed with dichloromethane, and all studies resulted in the formation of the Form E solvate. This solvate when dried, produces Form L.

[00189] Form L, suspended and rotated in methanol at room temperature, converts to Form B as shown in Figure ~~37~~36. Form M and Form N when slurried in methanol also produce Form B. The solubility of Form M and N are ~ 110 mg/mL, well above the concentration of AG-120 in the SDI spray solution (~ 70 mg/mL).

[00190] Form B is a thermodynamically stable hydrate form. All other forms (such as Form A, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, Form K, and Form L can be converted to Form B when subjected to the conditions described above, namely, under the conditions listed under the heading "Form B." Form L is a thermodynamically stable form of ivosidenib when isolated from DCM, or a mixed solvent containing DCM and a hydrocarbon solvent. All other forms (that is, any of Form A, Form B, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, and Form K) may be made by crystallization in such a solution. Form L may also be obtained by drying Pattern 3. The present disclosure, therefore, includes a method of synthesis of Form B and of Form L via any one or more of the other identified forms of ivosidenib. As such, Form A, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, Form K, and Form L could be considered a synthetic intermediate of Form B, in that one or more of these forms may be used to convert to Form B. Similarly, Form A, Form B, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, and Form K could be considered a synthetic intermediate of Form L.

Crystallinity Experiments

[00191] Ivosidenib tablets may be manufactured using a spray-dried dispersion (50:50) intermediate of ivosidenib drug substance and at least one other additive, such as HPMCAS. The ivosidenib and HPMCAS may be dissolved completely in methanol before spray-drying. The ivosidenib spray-dried intermediate (SDI) may be consistently produced as an amorphous material, and may be used to manufacture final drug products, such as those used in clinical efficacy trials and registration stability tests.

[00192] In order to assess the impact of crystalline polymorphic forms on dissolution profiles, variant tablets were manufactured with SDI spiked with drug substance of two different crystalline polymorphs: Form B, and Form L, which forms are as described above. As used herein, the term "spiked" or "spiking" is used

additional minute at about 25 rpm. Microcrystalline cellulose PH-103 can then be added to the blend, and mixed for about 85 revolutions. The resulting pre-blend may be screened such as by using a Quadro comi 197S equipped with an 093R screen at about 1800 ± 100 rpm. The screened pre-blend can then be blended with croscarmellose sodium, sodium lauryl sulfate NF and colloidal silicon dioxide for about 22 minutes and 50 seconds ± 10 seconds at about 25 rpm. The blend can be lubricated withe magnesium stearate for about 4 minutes at about 25 rpm.

[00196] The pre-blend can then be roller compacted and milled, such as by using a 1 mm screen. For example, one roller can be a smooth roller, and the other roller can be a knurled roller, with a roll compaction force of about 5.0 kilonewton per centimeter (kN/cm) with a roll gap of about 2.0 mm and a roll speed of about 2 rpm.

[00197] The compacted milled granules may be blended with extragranular excipients microcrystalline cellulose PH 103, colloidal silicon dioxide, and croscarmellose sodium for about 22 minutes followed by lubrication with magnesium stearate for 4 minutes at a speed of about 25 rpm to produce the final blend. The final blends can then be compressed in tablet form, such as to a tablet hardness of about 18 ± 2 kilopascal (kP), or about 27 ± 4 kP, or about 37 ± 2 kP. The tablets may be optionally film coated to a target coating weight gain, such as a weight gain of about 5.0% w/w.

[00198] Dissolution profiles of tablets formulated as described above are presented in Figure ~~38~~37. Table 19 describes the dissolution of 250 mg tablets spiked with Form L ivosidenib in twelve individual vessels containing a solution at pH 6.8 and containing 0.6% SDS, referred to as Medium A; Table 20 lists the results of a similar trial for tablets spiked with Form B.

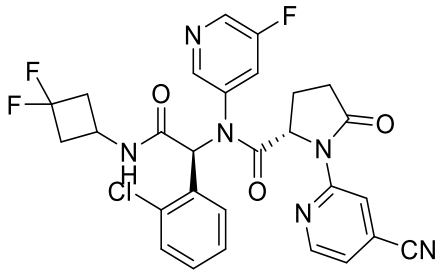
Table 19: Dissolution profile for ivosidenib tablets, 250 mg manufactured using polymorph Form L drug substance [pH 6.8 + 0.6%SDS]

Vessel	% Dissolution					
	10 min	20 min	30 min	45 min	60 min	90 min
1	24	57	80	92	97	100
2	13	45	69	86	94	100
3	26	69	86	95	98	100
4	28	67	84	93	96	97
5	20	55	80	93	98	101
6	24	60	81	93	97	100
7	19	54	78	92	97	99

CLAIMS

What is claimed is:

1. A ~~Solid~~ solid state ~~Form~~ form E of a methyl isobutyl ketone (MIBK) solvate of a compound of formula (I):



(I).

(ivosidenib) characterized by an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 5.5 ± 0.2 °2θ, 6.1 ± 0.2 °2θ, 6.3 ± 0.2 °2θ, 7.6 ± 0.2 °2θ, 9.3 ± 0.2 °2θ, 9.4 ± 0.2 °2θ, 9.8 ± 0.2 °2θ, 11.2 ± 0.2 °2θ, 11.5 ± 0.2 °2θ, 11.6 ± 0.2 °2θ, 12.0 ± 0.2 °2θ, 13.2 ± 0.2 °2θ, 13.9 ± 0.2 °2θ, 14.3 ± 0.2 °2θ, 14.4 ± 0.2 °2θ, 15.0 ± 0.2 °2θ, 15.3 ± 0.2 °2θ, 15.7 ± 0.2 °2θ, 16.8 ± 0.2 °2θ, 17.1 ± 0.2 °2θ, 17.8 ± 0.2 °2θ, 17.9 ± 0.2 °2θ, 18.3 ± 0.2 °2θ, 18.8 ± 0.2 °2θ, 19.1 ± 0.2 °2θ, 19.3 ± 0.2 °2θ, 19.6 ± 0.2 °2θ, 19.9 ± 0.2 °2θ, 20.1 ± 0.2 °2θ, 20.2 ± 0.2 °2θ, 20.9 ± 0.2 °2θ, 21.0 ± 0.2 °2θ, 22.0 ± 0.2 °2θ, 22.5 ± 0.2 °2θ, 23.0 ± 0.2 °2θ, 23.6 ± 0.2 °2θ, 24.2 ± 0.2 °2θ, 24.5 ± 0.2 °2θ, 25.0 ± 0.2 °2θ, 25.3 ± 0.2 °2θ, 26.2 ± 0.2 °2θ, 27.6 ± 0.2 °2θ, 27.9 ± 0.2 °2θ, 28.3 ± 0.2 °2θ, 29.2 ± 0.2 °2θ, 29.8 ± 0.2 °2θ, 30.3 ± 0.2 °2θ, 30.8 ± 0.2 °2θ, 31.5 ± 0.2 °2θ, 32.5 ± 0.2 °2θ, 33.0 ± 0.2 °2θ, 34.1 ± 0.2 °2θ, 34.5 ± 0.2 °2θ and 34.8 ± 0.2 °2θ (Form E)~~or a hydrate or solvate thereof~~.

2. The solid state form E ~~compound~~ of claim 1, wherein the solid state is characterized by an x-ray powder diffraction pattern comprising a peak at 6.3± 0.2 °2θ and one or more of the following peaks: 11.6± 0.2 °2θ, 12.0 ± 0.2 °2θ , 17.1 ± 0.2 °2θ, and 21.0 ± 0.2 °2θ~~the Form E is a solvated form~~.

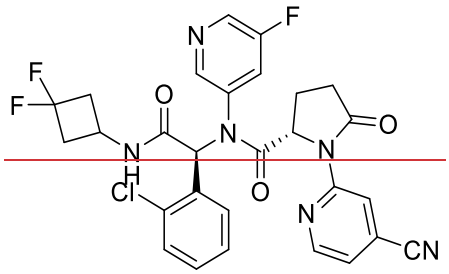
3. The ~~compound of~~ solid state form E of claim ~~2~~1, wherein the solid state is characterized by two or more of the following: ~~the compound is Form E isopropyl acetate solvate.~~

(a) an x-ray powder diffraction pattern substantially corresponding to the pattern shown in Fig. 20;

(b) a TGA and DSC profile substantially corresponding to those depicted in Fig. 21;

(c) a ^{1}H NMR pattern substantially corresponding to the pattern shown in Fig. 22.

~~4. Solid state Form G of a compound of formula (I):~~

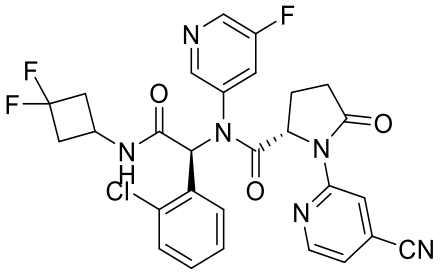


(I).

~~or a hydrate or solvate thereof.~~

~~5. The compound of claim 4, wherein the Form G is a solvated or hydrated form.~~

~~6.~~4. An anhydrous ~~Solid~~ solid state ~~Form~~ form ~~M~~ of a compound of formula (I):

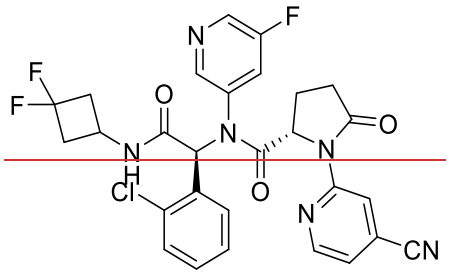


(I).

~~or a hydrate or solvate thereof~~ (ivosidenib) characterized by an x-ray powder diffraction pattern comprising one or two or three or four or five or six or seven or eight or nine peaks chosen from 9.2 ± 0.2 °2θ, 10.1 ± 0.2 °2θ, 10.6 ± 0.2 °2θ, 11.4 ± 0.2 °2θ, 11.9 ± 0.2 °2θ, 12.5 ± 0.2 °2θ, 13.1 ± 0.2 °2θ, 13.4 ± 0.2 °2θ, 14.4 ± 0.2 °2θ, 15.3 ± 0.2 °2θ, 15.8 ± 0.2 °2θ, 17.2 ± 0.2 °2θ, 17.7 ± 0.2 °2θ, 17.8 ± 0.2 °2θ, 18.5 ± 0.2 °2θ, 19.5 ± 0.2 °2θ, 19.7 ± 0.2 °2θ, 19.9 ± 0.2 °2θ, 20.4 ± 0.2 °2θ, 20.9 ± 0.2 °2θ, 21.4 ± 0.2 °2θ, 22.0 ± 0.2 °2θ, 22.2 ± 0.2 °2θ, 22.9 ± 0.2 °2θ, 23.2 ± 0.2 °2θ, 24.6 ± 0.2 °2θ, 24.7 ± 0.2 °2θ, 25.0 ± 0.2 °2θ, 25.8 ± 0.2 °2θ, 26.2 ± 0.2 °2θ, 26.6 ± 0.2 °2θ, 27.0 ± 0.2 °2θ, 27.3 ± 0.2 °2θ, 27.8 ± 0.2 °2θ, 29.1 ± 0.2 °2θ, 29.7 ± 0.2 °2θ, 30.3 ± 0.2 °2θ, 31.3 ± 0.2 °2θ, 31.9 ± 0.2 °2θ, 33.1 ± 0.2 °2θ, 33.6 ± 0.2 °2θ, 33.8 ± 0.2 °2θ and 34.6 ± 0.2 °2θ (Form M).

~~7.~~5. The ~~compound of~~solid state form M of claim ~~6~~4, wherein ~~the Form M is anhydrous~~ the solid state is characterized by an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 11.4 ± 0.2 °2θ, 17.7 ± 0.2 °2θ, 17.8 ± 0.2 °2θ, 19.7 ± 0.2 °2θ, and 21.4 ± 0.2 °2θ.

~~8. Solid state Form N of a compound of formula (I):~~



(I).

or a hydrate or solvate thereof.

9.6. The compound solid state form M of claim 84, wherein the solid state is characterized by one or more of the following:Form N is anhydrous

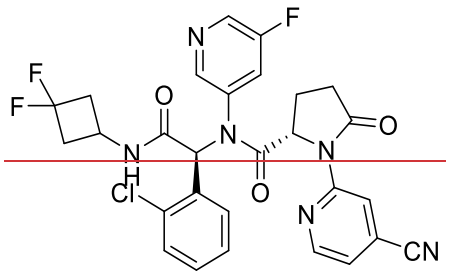
(a) an x-ray powder diffraction pattern substantially corresponding to the pattern shown in Fig. 1 for Form M;

(b) a TGA/DTA profile substantially corresponding to those depicted in Fig. 9;

(c) a DSC profile substantially corresponding to that shown in Fig. 10.

10. A pharmaceutical composition comprising one or more compounds of any one of claims 1 – 9.

11. A solid state form of the compound of Formula I



(I).

or a hydrate or solvate thereof that is chosen from A, C, D, E, F, G, H, I, J, K, M, or N.

12. The solid state form of claim 11, wherein the form is partially crystalline.

13. The solid state form of claim 12, selected from Form A.

14. The solid state form of claim 12, selected from Form I.

15. The solid state form of claim 12, selected from Form K.

16. The solid state form of claim 11, or a hydrate or solvate thereof, selected from Form A.

17. The solid state form of claim 11, or a hydrate or solvate thereof, selected from Form I.

18. The solid state form of claim 11, or a hydrate or solvate thereof, selected from Form K.

~~19. The solid state form of claim 11, wherein the form includes 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%, or 99.9% crystalline form B.~~

~~20. The solid state form of claim 11, wherein the form includes 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%, or 99.9% crystalline form L.~~

~~21.~~7. A process for making Form L of ivosidenib comprising making one or more meta-stable form of ivosidenib in anhydrous, hydrated, or solvated form, and allowing such one or more meta-stable form of ivosidenib to convert to Form L, wherein the meta-stable forms are selected from:

(a) a solid state form of ivosidenib characterized by an x-ray powder diffraction pattern substantially corresponding with the XRPD pattern shown in Fig. 12 and a DSC and TGA profile substantially corresponding to those shown in Fig. 13 (Form A);

(b) a solid state form of ivosidenib characterized an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 3.8 ± 0.2 °2θ, 7.3 ± 0.2 °2θ, 8.0 ± 0.2 °2θ, 9.3 ± 0.2 °2θ, 11.3 ± 0.2 °2θ, 11.9 ± 0.2 °2θ, 12.2 ± 0.2 °2θ, 13.5 ± 0.2 °2θ, 15.8 ± 0.2 °2θ, 17.7 ± 0.2 °2θ, 18.6 ± 0.2 °2θ, 20.7 ± 0.2 °2θ, 21.6 ± 0.2 °2θ, 22.5 ± 0.2 °2θ, 23.1 ± 0.2 °2θ, 25.4 ± 0.2 °2θ and 27.6 ± 0.2 °2θ (Form C);

(c) a solid state form of ivosidenib characterized by an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 7.3 ± 0.2 °2θ, 8.4 ± 0.2 °2θ, 10.2 ± 0.2 °2θ, 10.3 ± 0.2 °2θ, 11.1 ± 0.2 °2θ, 12.7 ± 0.2 °2θ, 13.4 ± 0.2 °2θ, 14.6 ± 0.2 °2θ, 16.3 ± 0.2 °2θ, 17.0 ± 0.2 °2θ, 17.9 ± 0.2 °2θ, 19.4 ± 0.2 °2θ, 20.4 ± 0.2 °2θ, 21.3 ± 0.2 °2θ, 21.8 ± 0.2 °2θ, 23.4 ± 0.2 °2θ, 24.6 ± 0.2 °2θ, 25.2 ± 0.2 °2θ, 25.6 ± 0.2 °2θ, 26.1 ± 0.2 °2θ, 26.6 ± 0.2 °2θ, 28.1 ± 0.2 °2θ and 28.8 ± 0.2 °2θ (Form D);

(d) a solid state form of ivosidenib as a methyl isobutyl ketone (MIBK) solvate characterized by an x-ray powder diffraction pattern comprising a peak at 6.3± 0.2 °2θ and one or more of the following peaks 11.6± 0.2 °2θ, 12.0 ± 0.2 °2θ , 17.1 ± 0.2 °2θ, and 21.0 ± 0.2 °2θ (Form E);

(e) a solid state form of ivosidenib characterized by an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 6.5 ± 0.2 °2θ, 7.2 ± 0.2 °2θ, 9.1 ± 0.2 °2θ, 11.7 ± 0.2 °2θ, 12.8 ± 0.2 °2θ, 13.3 ± 0.2 °2θ, 13.7 ± 0.2 °2θ, 14.4 ± 0.2 °2θ, 15.2 ± 0.2 °2θ, 16.1 ± 0.2 °2θ, 17.4

± 0.2 °2θ, 18.2 ± 0.2 °2θ, 18.8 ± 0.2 °2θ, 19.5 ± 0.2 °2θ, 20.0 ± 0.2 °2θ, 20.6 ± 0.2 °2θ, 21.6 ± 0.2 °2θ, 22.6 ± 0.2 °2θ, 23.3 ± 0.2 °2θ, 23.8 ± 0.2 °2θ, 24.3 ± 0.2 °2θ, 25.4 ± 0.2 °2θ, 26.3 ± 0.2 °2θ, 26.8 ± 0.2 °2θ, 28.0 ± 0.2 °2θ, 28.4 ± 0.2 °2θ, 29.0 ± 0.2 °2θ, 30.5 ± 0.2 °2θ, 31.6 ± 0.2 °2θ, 32.2 ± 0.2 °2θ, 34.0 ± 0.2 °2θ, 34.9 ± 0.2 °2θ, 35.3 ± 0.2 °2θ, 36.1 ± 0.2 °2θ and 38.3 ± 0.2 °2θ (Form F);

(f) a solid state form of ivosidenib characterized by an x-ray powder diffraction pattern substantially corresponding with the XRPD pattern shown in Fig. 25 and a DSC and TGA profile substantially corresponding to those shown in Fig. 26 (Form G);

(g) a solid state form of ivosidenib characterized by an x-ray powder diffraction pattern substantially corresponding with the XRPD pattern shown in Fig. 27 and a DSC and TGA profile substantially corresponding to those shown in Fig. 28 (Form H);

(h) a solid state form of ivosidenib characterized by an x-ray powder diffraction pattern substantially corresponding with the XRPD pattern shown in Fig. 29 and a DSC and TGA profile substantially corresponding to those shown in Fig. 30 (Form I);

(i) a solid state form of ivosidenib characterized by an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 6.4 ± 0.2 °2θ, 8.2 ± 0.2 °2θ, 9.4 ± 0.2 °2θ, 10.3 ± 0.2 °2θ, 11.9 ± 0.2 °2θ, 13.2 ± 0.2 °2θ, 16.1 ± 0.2 °2θ, 16.8 ± 0.2 °2θ, 17.6 ± 0.2 °2θ, 18.6 ± 0.2 °2θ, 19.7 ± 0.2 °2θ, 21.4 ± 0.2 °2θ, 22.5 ± 0.2 °2θ, 23.2 ± 0.2 °2θ, 25.0 ± 0.2 °2θ, 26.0 ± 0.2 °2θ, 27.1 ± 0.2 °2θ, 29.6 ± 0.2 °2θ and 35.5 ± 0.2 °2θ (Form J);

(j) an anhydrous solid state form of ivosidenib characterized by an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 11.4 ± 0.2 °2θ, 17.7 ± 0.2 °2θ, 17.8 ± 0.2 °2θ, 19.7 ± 0.2 °2θ, and 21.4 ± 0.2 °2θ. (Form M);

(k) a solid state form of ivosidenib characterized by an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 8.6 ± 0.2 °2θ, 14.4 ± 0.2 °2θ, 18.6 ± 0.2 °2θ, 20.3 ± 0.2 °2θ and 22.9 ± 0.2 °2θ. (Form N); and

wherein Form L of ivosidenib is characterized by an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 8.7 ± 0.2 °2θ, 13.2 ± 0.2 °2θ, 15.7 ± 0.2 °2θ, 18.5 ± 0.2 °2θ, 18.5 ± 0.2 °2θ, 19.6 ± 0.2 °2θ, 20.7 ± 0.2 °2θ, 21.5 ± 0.2 °2θ, 26.4 ± 0.2 °2θ and 27.3 ± 0.2 °2θ.

~~22.~~8. The process of claim ~~21~~7, wherein the one or meta-stable form is selected from C, D, E, F, H, J, M, or N~~, each individually in anhydrous, hydrated, or solvated form~~.

9. The process of claim 7, wherein the meta-stable form is Form C.

10. The process of claim 7, wherein the meta-stable form is Form D.

11. The process of claim 7, wherein the meta-stable form is Form E.

12. The process of claim 7, wherein the meta-stable form is Form F.

13. The process of claim 7, wherein the meta-stable form is Form H.

14. The process of claim 7, wherein the meta-stable form is Form J.

15. The process of claim 7, wherein the meta-stable form is Form M.

16. The process of claim 7, wherein the meta-stable form is Form N.

~~23. A pharmaceutical composition comprising ivosidenib in a mixture of two or more of Form L, Form B, Form A, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, Form K, Form M, and Form N, each individually in anhydrous, hydrated, or solvated form.~~

~~24. The pharmaceutical composition of claim 23, further comprising no more than 0.15% (area% by HPLC) of a compound selected from:~~
~~2-((2*S*)-2-((1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)(5-fluoropyridin-3-yl)carbamoyl)-5-oxopyrrolidin-1-yl)isonicotinamide;~~
~~(*S*)-*N*-((*S*)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-5-oxo-*N*-(pyridin-3-yl)pyrrolidine-2-carboxamide;~~
~~(*S*)-*N*-((*R*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide;~~
~~(*R*)-*N*-((*S*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide; and~~
~~(*R*)-*N*-((*R*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide.~~

~~25. The pharmaceutical composition of claim 23, comprising at least one of Form A, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, Form K, Form M, and Form N; and about 10% or less of Form B.~~

~~26. The pharmaceutical composition of claim 23, comprising at least one of Form A, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, Form K, Form M, and Form N; and about 10% or less of Form L.~~

~~27. The pharmaceutical composition of claim 23, further comprising an amorphous form of the compound of Formula I.~~

28. The pharmaceutical composition of claim 23, wherein the mixture comprises Form L and one or more of Form B, Form A, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, Form K, Form M, and Form N, each individually in anhydrous, hydrated, or solvated form.

29. The pharmaceutical composition of claim 28, where the Form B, Form A, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, Form K, Form M, or Form N, each individually in anhydrous, hydrated, or solvated form converts to Form L.

30. A solid dosage form comprising a substantially amorphous drug product intermediate and further comprising any one or more of Form A, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, Form K, Form M, or Form N, each individually in an anhydrous, hydrated, or solvated form.

31. A solid dosage form comprising ivosidenib in a substantially amorphous form and further comprising any one or more of crystalline Form L, Form B, Form A, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, Form K, Form M, or Form N, each individually in anhydrous, hydrated, or solvated form, and one or more pharmaceutically acceptable excipients.

32. The solid dosage form of claim 31, further comprising no more than 0.15% (area% by HPLC) of a compound selected from:

2-((2*S*)-2-((1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)(5-fluoropyridin-3-yl)carbamoyl)-5-oxopyrrolidin-1-yl)isonicotinamide;

(*S*)-*N*-((*S*)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-5-oxo-*N*-(pyridin-3-yl)pyrrolidine-2-carboxamide;

(*S*)-*N*-((*R*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide;

(*R*)-*N*-((*S*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide; and

(*R*)-*N*-((*R*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide.

33. The solid dosage form of claim 31, further comprising a polymer chosen from hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose phthalate (HPMCP), hydroxypropylmethylcellulose acetate succinate (HPMCAS), hydroxypropylcellulose (HPC), ethylcellulose, or cellulose acetate phthalate; polyvinylpyrrolidones (PVP); polyethylene glycols (PEG); polyvinyl alcohols (PVA), Polyvinyl Acetate Phthalate (PVAP); acrylates, polyvinylpyrollidone-vinyl

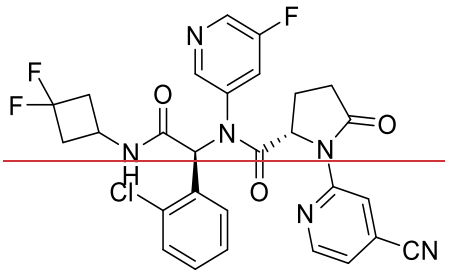
acetate (PVP-VA), polyvinyl caprolactam-polyvinyl, and acetate-polyethyleneglycol copolymer, Methylacrylate/methacrylic acid copolymer; Soluplus; Copovidone; and mixtures thereof.

34. The solid dosage form of claim 33, wherein the polymer is chosen from HPMC, HPMCP, HPMCAS, PVAP and copovidone

35. A pharmaceutical composition comprising Form L drug product, where the Form L drug product is created via any one or more of Form B, Form A, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, Form K, Form M, or Form N each individually in anhydrous, hydrated, or solvated form.

36. The pharmaceutical composition of claim 35, wherein the Form L drug product contains Form L and one or more of Form B, Form A, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, Form K, Form M, or Form N each individually in anhydrous, hydrated, or solvated form.

37. A compound selected from one of forms E, G, M, or N, of a compound of formula (I)



(I).

each individually in anhydrous, hydrated, or solvated form that is substantially free of any other solid state forms of the compound of formula (I).

38. A solid form of ivosidenib having an x-ray powder diffraction pattern comprising a peak at 6.3± 0.2 °2θ and one or more of the following peaks 11.6± 0.2 °2θ, 12.0 ± 0.2 °2θ , 17.1 ± 0.2 °2θ, and 21.0 ± 0.2 °2θ. (Form E).

39. A solid form of ivosidenib having an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 11.4 ± 0.2 °2θ, 17.7 ± 0.2 °2θ, 17.8 ± 0.2 °2θ, 19.7 ± 0.2 °2θ, and 21.4 ± 0.2 °2θ. (Form M).

40. A solid form of ivosidenib having an x-ray powder diffraction pattern comprising one or two or three or four or five peaks chosen from 8.6 ± 0.2 °2θ, 14.4 ± 0.2 °2θ, 18.6 ± 0.2 °2θ, 20.3 ± 0.2 °2θ and 22.9± 0.2 °2θ. (Form N).

41. A pharmaceutical composition comprising ivosidenib and one or more pharmaceutically acceptable excipients wherein the composition contains no more than 0.15% (area% by HPLC) of a compound selected from:
2-((2*S*)-2-((1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)(5-fluoropyridin-3-yl)carbamoyl)-5-oxopyrrolidin-1-yl)isonicotinamide;
(*S*)-*N*-((*S*)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-5-oxo-*N*-(pyridin-3-yl)pyrrolidine-2-carboxamide;
(*S*)-*N*-((*R*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide;
(*R*)-*N*-((*S*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide; and
(*R*)-*N*-((*R*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide.

42. A pharmaceutical composition comprising ivosidenib and one or more pharmaceutically acceptable excipients, wherein the composition contains no more than 0.10% (area % by HPLC) of one or more of:
3-amino-5-fluoropyridine;
2-chloro-4-cyanopyridine;
(*S*)-*N*-((*S*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide;
2-(2-Chlorophenyl)-*N*-(3,3-difluorocyclobutyl)-2-((5-fluoropyridin-3-yl)amino)acetamide;
(*S*)-5-(((*S*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)(5-fluoropyridin-3-yl)amino)-4-((4-cyanopyridin-2-yl)amino)-5-oxopentanoic acid;
(*S*)-4-(bis(4-cyanopyridin-2-yl)amino)-5-(((*S*)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)(5-fluoropyridin-3-yl)amino)-5-oxopentanoic acid;
(*S*)-2-(2-Chlorophenyl)-2-((5-((4-cyanopyridin-2-yl)amino)-2-oxo-3,4-dihydro-2*H*-pyran-6-yl)(5-fluoropyridin-3-yl)amino)-*N*-(3,3-difluorocyclobutyl)acetamide;
(2*S*)-*N*-((1*S*)-2-((2-chloro-3,3-difluorocyclobutyl)amino)-1-(2-chlorophenyl)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide;
(*S*)-1-(4-Cyanopyridin-2-yl)-*N*-((S)-1-(2,4-dichlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide;

~~(*S*)-1-(4-Cyanopyridin-2-yl)-*N*-((*S*)-1-(2,3-dichlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide;~~

~~(*S*)-*N*-((*S*)-1-(4-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide;~~

~~3-((2*S*)-1-(4-carbamoylpyridin-2-yl)-*N*-(1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-5-oxopyrrolidine-2-carboxamido)-5-fluoropyridine 1-oxide;~~

~~4-carbamoyl-2-((2*S*)-2-((1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)(5-fluoropyridin-3-yl)carbamoyl)-5-oxopyrrolidin-1-yl)pyridine 1-oxide; and~~

~~(*S*)-1-(4-Cyanopyridin-2-yl)-*N*-((*S*)-1-(3,3-difluorocyclobutyl)-2-oxoindolin-3-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide, or salts, hydrates, or solvates thereof.~~

~~43. A pharmaceutical composition comprising ivosidenib and one or more pharmaceutically acceptable excipients, wherein the composition contains no more than 2 ppm of one or more of benzaldehyde, benzyl chloride, 2-chlorobenzyl chloride, 1-chloro-2-(chloromethyl)benzene, 1-chloro-2-(dichloromethyl)benzene, phenol, and benzene.~~

~~44. A pharmaceutical composition comprising ivosidenib and one or more pharmaceutically acceptable excipients, wherein the composition contains no more than 10 ppm of palladium.~~

~~45. A pharmaceutical composition comprising ivosidenib and one or more pharmaceutically acceptable excipients, wherein the composition contains no more than 300 ppm of molybdenum.~~

~~46. A pharmaceutical composition comprising ivosidenib and one or more pharmaceutically acceptable excipients, wherein the composition contains no more than:~~

~~5000 ppm of isopropyl acetate;~~

~~600 ppm *n*-heptane;~~

~~600 ppm dichloromethane; or~~

~~2 ppm benzene.~~

~~47. A method for testing the suitability of an ivosidenib composition for use in therapy wherein the composition comprises less than a total of 2% of process contaminants, heavy metal impurities, and residual solvents.~~

48. The method of claim 47, wherein the process contaminant is one or more of: 2-((2*S*)-2-((1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)(5-fluoropyridin-3-yl)carbamoyl)-5-oxopyrrolidin-1-yl)isonicotinamide; (*S*)-*N*-((*S*)-1-(2-chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-5-oxo-*N*-(pyridin-3-yl)pyrrolidine-2-carboxamide; (*S*)-*N*-((*R*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide; (*R*)-*N*-((*S*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide; and (*R*)-*N*-((*R*)-1-(2-Chlorophenyl)-2-((3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide.

49. The method of claim 47, wherein the residual solvent is one or more of: benzaldehyde, benzyl chloride, 2-chlorobenzyl chloride, 1-chloro-2-(chloromethyl)benzene, 1-chloro-2-(dichloromethyl)benzene, phenol, or benzene.

50. The method of claim 47, wherein the heavy metal impurity is one or more of palladium and molybdenum.