diesease ameliorated by modulation of premature translation termination or nonsense-mediated mRNA decay. The present invention provides such novel crystalline forms, for example, crystalline forms of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid.

[005] Citation of any reference in Section 2 of this application is not to be construed as an admission that such reference is prior art to the present application.

3. SUMMARY

[005a] In one aspect, the present disclosure refers to a process for preparing Form A crystals of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid **characterized by**:

an X-ray powder diffraction pattern comprising at least three peak positions (º2θ±0.2), when measured using Cu Kα radiation, selected from the group consisting of 4.96, 6.39, 10.10, 11.54, 12.62, 12.81, 13.92, 14.16, 14.55, 14.88, 15.07, 15.58, 16.27, 16.61, 18.74, 18.94, 19.28, 19.94, 20.27, 20.74, 20.97, 21.22, 21.93, 22.58, 22.80, 23.00, 23.79, 24.14, 24.46, 25.44, 25.64, 26.07, 26.34, 26.74, 27.06, 27.79, 28.42, 29.09, 30.48.

wherein the process comprises:

(1) exposing a Form B crystal to a relative humidity of 79% at 60 °C; or

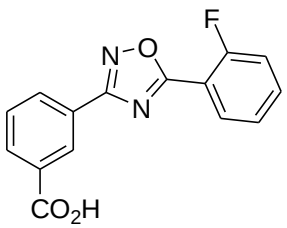
(2) milling a Form B crystal at ambient or sub-ambient temperature; or

(3) slurrying a Form B crystal in methyl isobutyl ketone, or a 1:1 mixture of dioxane and water; or

(4) subliming or heating a Form B crystal;

wherein the Form B crystal of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid has a representative X-ray powder diffraction pattern as provided in FIG. 5.

[006] The present disclosure provides novel crystalline forms of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid, which has the following chemical structure (I):



[007]

[008] (I)

[009] In particular, crystalline forms of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid are useful for the treatment, prevention or management of diseases ameliorated by modulation of premature translation termination or nonsense-mediated mRNA decay, as described in U.S. Patent No. 6,992,096 B2, issued January 31, 2006, which is incorporated herein by reference in its entirety. In addition, the present provides a crystalline form of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid which is substantially pure, i.e., its purity greater than about 90%.

[010] Certain examples of the present disclosure provide pharmaceutical dosage forms and compositions comprising a crystalline form of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid and a pharmaceutically-acceptable diluent, excipient or carrier. The present disclosure further provides methods of their use for the treatment, prevention or management of diseases ameliorated by modulation of premature translation termination or nonsense-mediated mRNA decay. In certain examples, the present disclosure provides methods of making, isolating and/or characterizing the crystalline forms of the present disclosure. The crystalline forms of the present disclosure are useful as active pharmaceutical ingredients for the preparation of formulations for use in animals or humans. Thus, the present disclosure

encompasses the use of these crystalline forms as a final drug product. The crystalline forms and final drug products of the present disclosure are useful, for example, for the treatment, prevent or management of the diseases described herein.

4. DETAILED DESCRIPTION OF THE INVENTION

4.1 Brief Description of the Drawings

[011] **FIG. 1** provides an X-ray powder diffraction (XRPD) pattern of a sample comprising Form A of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid.

[012] **FIG. 2** provides differential scanning calorimetry (DSC) and thermogravimentric analysis (TGA) thermograms of a sample comprising Form A of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid.

[013] **FIG. 3** provides a dynamic vapor sorption (DVS) isotherm of a sample comprising Form A of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid.

[014] **FIG. 4** provides a solid-state ^{13}C NMR spectrum of a sample comprising Form A of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid.

[015] **FIG. 5** provides a XRPD pattern of a sample comprising Form B of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid.

[016] **FIG. 6** provides DSC and TGA thermograms of a sample comprising Form B of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid.

[017] **FIG. 7** provides a DVS isotherm of a sample comprising Form B of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid.

[018] **FIG. 8** provides an overlay of experimental XRPD patterns showing a characteristic peak set of Form A (Top) with respect to several samples comprising Form B (second from top to bottom) of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid, illustrating peak shift among certain Form B samples.

[019] **FIG. 9** provides crystal packing diagram of Form A of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid, viewed down the crystallographic *b* axis and showing an outline of the unit cell.

[020] **FIG. 10** provides a XRPD pattern of Form A of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid simulated from a single-crystal X-ray diffraction crystal structure obtained from a representative single crystal of Form A.

What is claimed is:

1. A process for preparing Form A crystals of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid **characterized by**:

an X-ray powder diffraction pattern comprising at least three peak positions (º2θ±0.2), when measured using Cu Kα radiation, selected from the group consisting of 4.96, 6.39, 10.10, 11.54, 12.62, 12.81, 13.92, 14.16, 14.55, 14.88, 15.07, 15.58, 16.27, 16.61, 18.74, 18.94, 19.28, 19.94, 20.27, 20.74, 20.97, 21.22, 21.93, 22.58, 22.80, 23.00, 23.79, 24.14, 24.46, 25.44, 25.64, 26.07, 26.34, 26.74, 27.06, 27.79, 28.42, 29.09, 30.48.

wherein the process comprises:

(1) exposing a Form B crystal to a relative humidity of 79% at 60 °C; or
(2) milling a Form B crystal at ambient or sub-ambient temperature; or
(3) slurrying a Form B crystal in methyl isobutyl ketone, or a 1:1 mixture of dioxane and water; or
(4) subliming or heating a Form B crystal;

wherein the Form B crystal of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid has a representative X-ray powder diffraction pattern as provided in FIG. 5.

2. The process of claim 1, wherein the Form B crystal of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid is **characterized by** an X-ray powder diffraction pattern comprising at least three peak positions (º2θ±0.2), when measured using Cu Kα radiation, selected from the group consisting of 6.14, 6.39, 6.96, 7.92, 10.78, 12.44, 12.61, 12.88, 13.52, 13.78, 13.97, 14.30, 15.46, 15.68, 15.89, 16.33, 16.76, 17.03, 20.10, 21.03, 23.34, 23.86, 24.18, 24.42, 24.64, 26.62, 26.96, 27.29, 27.64, 27.96, 28.81, 31.05, 32.38, 32.58, 36.23, 37.81, 38.28, 38.44, 39.16; or

wherein the Form B crystal of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid is **characterized by** an X-ray powder diffraction pattern comprising at least three peak positions (shifted 1) (º2θ±0.2), when measured using Cu Kα radiation: 6.42, 7.00, 7.89, 10.85, 12.61, 12.92, 13.47, 13.97,

15.81, 16.45, 17.12, 20.05, 21.05, 23.92, 24.28, 27.00, 27.39, 27.84, 28.04, 28.94, 31.10, 32.58, 36.11, 37.71, 38.15, 38.61; or

wherein the Form B crystal of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid is **characterized by** an X-ray powder diffraction pattern comprising at least three peak positions (shifted 2) (º2θ±0.2), when measured using Cu Kα radiation: 6.10, 6.38, 6.54, 7.10, 8.02, 10.91, 12.71, 13.50, 13.62, 13.86, 14.10, 15.56, 15.70, 15.91, 16.55, 16.96, 17.22, 17.50, 19.82, 20.08, 20.34, 21.15, 23.78, 23.93, 24.38, 24.56, 26.88, 27.16, 27.48, 27.88, 28.04, 28.78, 29.02, 32.71, 36.01, 38.10, 38.56, 39.38; or

wherein the Form B crystal of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid is **characterized by** an X-ray powder diffraction pattern comprising at least three peak positions (shifted 3) (º2θ±0.2), when measured using Cu Kα radiation: 1.79, 2.30, 2.57, 2.78, 3.29, 3.59, 3.89, 4.07, 4.34, 4.49, 4.76, 5.06, 6.47, 6.91, 7.96, 10.89, 12.87, 13.58, 13.99, 15.97, 16.48, 17.10, 20.00, 20.36, 21.04, 23.40, 24.29, 24.89, 26.87, 27.49, 27.80, 28.07, 29.08, 38.61; or

wherein the Form B crystal of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid is **characterized by** an X-ray powder diffraction pattern comprising at least three peak positions (º2θ±0.2), when measured using Cu Kα radiation: 6.22, 6.51, 7.13, 8.17, 10.91, 12.87, 13.80, 14.12, 14.28, 15.78, 16.23, 16.54, 17.15, 20.33, 21.22, 21.36, 23.94, 24.30, 27.30, 27.58, 28.00, 28.74, 28.96, 32.70, 36.74, 38.18, 38.38, 38.52, 39.31; or

wherein the Form B crystal of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid is **characterized by** an X-ray powder diffraction pattern comprising at least three peak positions shifted (º2θ±0.2), when measured using Cu Kα radiation: 6.04, 6.49, 7.91, 10.92, 12.61, 12.92, 13.10, 13.42, 13.82, 13.99, 15.40, 15.76, 16.51, 17.15, 19.92, 20.04, 21.01, 23.92, 24.28, 24.48, 26.77, 27.14, 27.40, 27.74, 28.09, 28.82, 28.99, 31.03, 32.58, 35.64, 35.85, 37.48, 37.66, 38.62.

3. The process of claim 1 or 2, wherein the Form B crystal of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid has a purity of greater than 90%.

4. The process of claim 1 or 2, wherein the Form B crystal of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid has a maximum combined molar equivalent of solvent per mole of Form B of less than 6, less than 5, less than 4, less than 3, less than 2, less than 1.5, less than 1, less than 0.75, less than 0.5, or less than 0.25.

5. The process of claim 1 or 2, wherein said Form A crystals of 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid are further **characterized by** at least one of the following:

(a) unit cell parameters when measured at 150 K: a=24.2240 Å; b=3.74640 Å; c=27.4678 Å; α=90°; β=92.9938°; γ=90°; *V*=2489.38(17) Å^3; Z=8; calculated density (d_{calc}, g cm^{-3}) is 1.517 g cm^{-3}; and the space group is $P2_1/n$ (no. 14);

(b) a thermogravimetric analysis thermogram which has a mass loss of less than 1% of the total mass of the sample upon heating from 33 °C to 205 °C;

(c) a differential scanning calorimetry thermogram which has an endothermic event with a peak temperature at 244 °C; and

(d) fractional atomic coordinates equal to the following coordinates:

Átom	x	y	z	U(Å ^{2})
F(122)	0.43198(12)	0.7655(8)	-0.17546(10)	0.0487(10)
F(222)	-0.20343(15)	0.7129(10)	0.06378(14)	0.0781(14)
O(13)	0.42977(13)	0.4875(8)	-0.08927(11)	0.0324(10)
O(23)	-0.12941(13)	0.4507(9)	0.12653(12)	0.0402(10)
O(151)	0.25519(13)	0.4795(9)	0.10765(12)	0.0382(10)
O(152)	0.29215(13)	0.2155(9)	0.17515(12)	0.0403(10)
O(251)	0.16226(13)	0.4813(9)	0.15012(12)	0.0385(10)
O(252)	0.19645(13)	0.1939(9)	0.21659(12)	0.0393(10)
N(11)	0.35817(15)	0.5856(9)	-0.04386(14)	0.0279(10)
N(14)	0.44373(16)	0.3409(10)	-0.04263(14)	0.0327(12)
N(21)	-0.04134(16)	0.5165(9)	0.11065(14)	0.0305(12)
N(24)	-0.09772(17)	0.3201(11)	0.16787(15)	0.0388(14)
C(12)	0.37827(18)	0.6256(11)	-0.08637(17)	0.0266(14)
C(15)	0.40019(19)	0.4091(11)	-0.01823(17)	0.0261(14)
C(22)	-0.0926(2)	0.5601(12)	0.09502(18)	0.0319(15)
C(25)	-0.0471(2)	0.3690(11)	0.15580(17)	0.0302(15)
C(121)	0.35225(19)	0.7961(11)	-0.12930(17)	0.0291(14)
C(122)	0.3784(2)	0.8567(12)	-0.17244(18)	0.0345(15)
C(123)	0.3519(2)	1.0117(12)	-0.21257(19)	0.0407(17)
C(124)	0.2973(2)	1.1101(13)	-0.21014(19)	0.0416(17)
C(125)	0.2694(2)	1.0543(12)	-0.1677(2)	0.0409(17)
C(126)	0.2966(2)	0.8996(12)	-0.12784(18)	0.0349(15)
C(151)	0.39702(19)	0.3013(11)	0.03319(16)	0.0260(14)
C(152)	0.34897(19)	0.3623(11)	0.05704(16)	0.0261(15)

Átom	x	y	z	U(Å ^{2})
C(153)	0.34631(18)	0.2594(11)	0.10554(16)	0.0253(14)
C(154)	0.39150(19)	0.0970(11)	0.13029(17)	0.0279(14)
C(155)	0.43977(19)	0.0412(11)	0.10614(17)	0.0291(15)
C(156)	0.44250(19)	0.1421(11)	0.05765(17)	0.0292(15)
C(157)	0.2955(2)	0.3188(12)	0.13209(18)	0.0312(15)
C(221)	-0.1109(2)	0.7083(12)	0.04727(19)	0.0388(17)
C(222)	-0.1643(3)	0.7823(15)	0.0331(2)	0.053(2)
C(223)	-0.1825(3)	0.9272(15)	-0.0122(3)	0.064(2)
C(224)	-0.1415(4)	0.9930(16)	-0.0433(3)	0.068(3)
C(225)	-0.0870(3)	0.9202(15)	-0.0316(2)	0.066(2)
C(226)	-0.0678(3)	0.7766(12)	0.01365(17)	0.0543(19)
C(251)	0.00110(19)	0.2695(11)	0.18877(17)	0.0300(15)
C(252)	0.05426(19)	0.3352(11)	0.17481(17)	0.0289(15)
C(253)	0.09949(19)	0.2449(11)	0.20524(17)	0.0277(15)
C(254)	0.0919(2)	0.0940(11)	0.25087(17)	0.0296(15)
C(255)	0.0389(2)	0.0335(11)	0.26491(17)	0.0300(15)
C(256)	-0.0064(2)	0.1185(12)	0.23430(17)	0.0322(15)
C(257)	0.1559(2)	0.3165(12)	0.18902(17)	0.0305(15)
H(123)	0.371	1.050	-0.241	0.048
H(124)	0.278	1.217	-0.238	0.050
H(125)	0.232	1.123	-0.166	0.049
H(126)	0.278	0.862	-0.099	0.042
H(151)	0.227	0.491	0.125	0.057
H(152)	0.318	0.473	0.041	0.031
H(154)	0.389	0.025	0.163	0.033
H(155)	0.471	-0.066	0.123	0.035
H(156)	0.475	0.103	0.041	0.035
H(223)	-0.220	0.975	-0.020	0.077
H(224)	-0.151	1.094	-0.074	0.082
H(225)	-0.061	0.969	-0.055	0.080
H(226)	-0.030	0.729	0.021	0.065
H(252)	0.226	0.213	0.202	0.059
H(254)	0.123	0.034	0.272	0.035
H(255)	0.033	-0.068	0.296	0.036
H(256)	-0.043	0.074	0.244	0.039
H(25A)	0.060	0.443	0.144	0.035