

CLAIMS

1. An amorphous solid dispersion comprising an *N*-(3-(2-(2-hydroxyethoxy)-6-morpholinopyridin-4-yl)-4-methylphenyl)-2-(trifluoromethyl)isonicotinamide, or a pharmaceutically acceptable salt thereof, and one or more stabilizing polymers, wherein the weight ratio of Compound A, or a pharmaceutically acceptable salt thereof, to one or more stabilizing polymers is between about 5:95 to about 90:10, about 40:60, about 80:20; preferably about 60:40.
2. The amorphous solid dispersion according to claim 1, wherein the amorphous solid dispersion is made by spray drying, co-grinding, hot-melt extrusion, freeze drying, rotary evaporation, solvent evaporation, co-precipitation, lyophilization, or any suitable solvent removal process, preferably, hot-melt extrusion.
3. The amorphous solid dispersion according to claim 2, wherein the amorphous solid dispersion is prepared from *N*-(3-(2-(2-hydroxyethoxy)-6-morpholinopyridin-4-yl)-4-methylphenyl)-2-(trifluoromethyl)isonicotinamide in an amorphous form, in a crystalline form, or in a mixture thereof.
4. The amorphous solid dispersion according to claim 3, wherein *N*-(3-(2-(2-hydroxyethoxy)-6-morpholinopyridin-4-yl)-4-methylphenyl)-2-(trifluoromethyl)isonicotinamide is in the crystalline Monohydrate Form H_A characterized by having an X-ray powder diffraction pattern with at least one, two, three, four or five peaks having an angle of refraction 2 theta (θ) values selected from 7.3, 10.7, 16.3, 16.7, 17.4, 23.0, 24.3, 25.3, 28.3, 32.0 when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.
5. The amorphous solid dispersion according to any one of claims 1 to 4, wherein the one or more stabilizing polymers is selected from the group consisting of polyvinyl pyrrolidone (povidone or PVP), polyvinylpyrrolidone (crospovidone or PVP-XL), hydroxypropyl cellulose (HPC), low-substituted hydroxypropyl cellulose (L-HPC), hypromellose (HPMC), hypromellose acetate succinate (HPMC-AS), hypromellose phthalate (HPMC-P), carboxymethyl cellulose, croscarmellose sodium (NaCMC), methyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethyl cellulose, carboxymethylhydroxyethyl cellulose, polyethylene glycol (PEG), polyvinylalcohol, polyvinylpyrrolidone–vinyl acetate copolymer (copovidone or PVP/VA), polyvinyl alcohol–polyethylene glycol co-polymer, polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer, polyacrylates, polymethacrylates, or a mixture thereof.
6. The amorphous solid dispersion according to claim 5, wherein the stabilizing polymer is HPMC, preferably HPMC 2910.

7. The amorphous solid dispersion according to any one of claims 1 to 6, further comprising a glidant selected from the group consisting of silicon dioxide, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and the like and mixtures thereof, preferably silicon dioxide, more preferably colloidal silicon dioxide.
8. The amorphous solid dispersion according to any one of claims 1 to 7, further comprising a solubilizer selected from the group consisting of polyoxyethylene alkylaryl ethers, polyethylene glycol fatty acid esters, D- α -tocopheryl polyethylene glycol succinate, polyoxyethylene sorbitan fatty acid ester, alkyl sulfates or sulfonates, lecithin, polyethoxylated castor oils and the like and mixtures thereof.
9. The amorphous solid dispersion according to any one of claims 1 to 8, wherein *N*-(3-(2-(2-hydroxyethoxy)-6-morpholinopyridin-4-yl)-4-methylphenyl)-2-(trifluoromethyl)isonicotinamide, or a pharmaceutically acceptable salt thereof, is from about 1% to about 90% (w/w), from about 10% (w/w) to about 85% (w/w), preferably from about 15% (w/w) to about 80% (w/w), from about 20% (w/w) to about 75% (w/w), or from about 30% (w/w) to about 60% (w/w) of the dispersion.
10. The pharmaceutical composition comprising an amorphous solid dispersion according to any one of claims 1 to 9 and optionally one or more pharmaceutically acceptable excipient(s) selected from solubilizers, diluents, binders, disintegrants, fillers, lubricants, glidants, surfactants, stabilizing agents, antioxidants, alkaline stabilizers, colors, flavors, preservatives, and combinations thereof.
11. The pharmaceutical composition according to claim 10 wherein the pharmaceutical composition comprises from about 10 mg to about 300 mg of *N*-(3-(2-(2-hydroxyethoxy)-6-morpholinopyridin-4-yl)-4-methylphenyl)-2-(trifluoromethyl)isonicotinamide, or a pharmaceutically acceptable salt thereof, preferably 50 mg, 100 mg, 200 mg, or 300 mg of *N*-(3-(2-(2-hydroxyethoxy)-6-morpholinopyridin-4-yl)-4-methylphenyl)-2-(trifluoromethyl)isonicotinamide, or a pharmaceutically acceptable salt thereof.
12. The pharmaceutical composition according to any one of claims 10 to 11, wherein the pharmaceutical composition is in the form of a tablet, a capsule, a caplet, beads, granules, oral suspension, oral solution, or microemulsion.
13. A pharmaceutical composition according to any one of claims 10 to 12, wherein the pharmaceutical composition is in the form of a tablet or a capsule comprising: (a) an amorphous solid dispersion of Compound A in the form of granules, (b) at least one intra-granular excipient, (c) at least one extra-granular excipient, and (d) optionally, a coating.

14. The pharmaceutical composition according to claim 13, wherein the extra-granular excipients are selected from solublizers, diluents, binders, disintegrants, fillers, lubricants, glidants, surfactants, stabilizing agents, antioxidants, alkaline stabilizers, colors, flavors, preservatives, and combinations thereof.
15. The pharmaceutical composition according to claim 14, wherein the extra-granular excipients comprise diluents selected from the group consisting of microcrystalline cellulose, calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose powdered, dextrans, dextrans, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners and combinations thereof, preferably lactose, microcrystalline cellulose, or lactose and microcrystalline cellulose.
16. The pharmaceutical composition according to claim 14, wherein the extra-granular excipients comprise disintegrants selected from the group consisting of croscarmellose sodium, low-substituted hydroxypropyl cellulose (L-HPC), polyvinylpyrrolidone (crospovidone), sodium bicarbonate, sodium starch glycolate, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, starch, crystalline cellulose, hydroxypropyl starch, pregelatinized starch, and mixtures thereof, preferably sodium bicarbonate and crospovidone, more preferably croscarmellose sodium.
17. A method for preparing an amorphous solid dispersion according to any one of claims 1 to 9 or a pharmaceutical composition according to any one of claims 10 to 16, which comprises preparing a mixture of *N*-(3-(2-(2-hydroxyethoxy)-6-morpholinopyridin-4-yl)-4-methylphenyl)-2-(trifluoromethyl)isonicotinamide, or a pharmaceutically acceptable salt thereof, one or more stabilizing polymers, and optionally one or more pharmaceutically acceptable excipients; heating the mixture to form a molten mass; extruding the molten mass; cooling the molten mass to form an amorphous solid dispersion; and optionally the granulating the amorphous solid dispersion and/or compacting granules of the amorphous solid dispersion for further processing with optionally one or more pharmaceutically acceptable excipients to form a composition suitable for use in dosage forms, preferably a tablets or a capsule.
18. The pharmaceutical composition according to any one of claims 10 to 16 for use as a medicament.
19. The pharmaceutical composition according to any one of claims 10 to 16 for use in the treatment of cancer.

20. The pharmaceutical composition according any one of claims 10 to 16 for use in the treatment of cancer, in particular in the treatment of cancers harboring MAPK pathway alterations such as KRAS-mutant NSCLC (non-small cell lung cancer), KRAS-mutant pancreatic cancer (e.g., KRAS-mutant pancreatic ductal adenocarcinoma (PDAC)), KRAS-mutant CRC (colorectal cancer), and NRAS-mutant melanoma.
21. Use of the pharmaceutical composition according to any one of claims 10 to 16 in the manufacture of a medicament for treating cancer.
22. The use of claim 21, wherein the cancer is harboring MAPK pathway alterations such as KRAS-mutant NSCLC (non-small cell lung cancer), KRAS-mutant pancreatic cancer (e.g., KRAS-mutant pancreatic ductal adenocarcinoma (PDAC)), KRAS-mutant CRC (colorectal cancer), and NRAS-mutant melanoma.