

PHARMACEUTICAL COMPOSITIONS COMPRISING A PKC INHIBITOR**RELATED APPLICATION**

This application claims priority to U.S. Provisional Application No. 63/520,857 filed on August 21, 2023. The content of this application is hereby incorporated by reference in its entirety.

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BACKGROUND

Uveal melanoma (UM) is the most common primary intraocular malignant tumor in adults. UM is a type of eye cancer in the uvea of the eye and is traditionally classed as originating in the iris, choroid, and ciliary body, but can also be divided into class I (low metastatic risk) and class II (high metastatic risk). Because there are no lymphatic channels to the uveal tract, metastasis occurs through local extension and/or blood-borne dissemination. The most common site of metastasis for uveal melanoma is the liver; the liver is the first site of metastasis for 80%-90% of ocular melanoma patients. Other common sites of metastasis include the lung, bones, and just beneath the skin (subcutaneous). Approximately 50 percent of patients will develop metastases within 15 years after treatment of the primary tumor, and the liver will be involved 90% of the time.

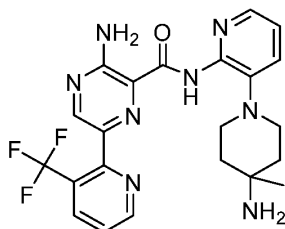
International application no. PCT/IB2015/055951 (WO 2016/020864) discloses a number of potent and selective PKC inhibitors including 3-amino-N-(3-(4-amino-4-methylpiperidin-1-yl)pyridin-2-yl)-6-(3-(trifluoromethyl)pyridin-2-yl)pyrazine-2-carboxamide. This compound is useful in the treatment of certain cancers, including uveal melanoma.

Provided herein are improved pharmaceutical compositions comprising 3-amino-N-(3-(4-amino-4-methylpiperidin-1-yl)pyridin-2-yl)-6-(3-(trifluoromethyl)pyridin-2-yl)pyrazine-2-carboxamide.

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SUMMARY

There exists a need for improved pharmaceutical compositions of 3-amino-N-(3-(4-amino-4-methylpiperidin-1-yl)pyridin-2-yl)-6-(3-(trifluoromethyl)pyridin-2-yl)pyrazine-2-carboxamide ("Compound 1") having the following structure:



Thus, in an aspect, provided herein are pharmaceutical compositions comprising a superdisintegrant, a binder, a lubricant, a filler, and Compound 1, or a pharmaceutically acceptable salt thereof. Also provided herein is a method of treating cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of the present disclosure. In some embodiments, the cancer is uveal melanoma. In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer harbors GNAQ mutations. In some embodiments, cancer harbors GNA11 mutations.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an XRPD diffractogram of a crystalline form of Compound 1.

Figure 2 shows a DSC thermogram of a crystalline form of Compound 1.

Figure 3 shows a manufacturing process for tablets comprising Compound 1.

DETAILED DESCRIPTION

Provided herein is a pharmaceutical composition comprising a PKC inhibitor, or a pharmaceutically acceptable salt thereof. This composition is useful for the treatment of cancer, for example, uveal melanoma, including metastatic uveal melanoma.

Definitions

Listed below are definitions of various terms used herein. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, and peptide chemistry are those well-known and commonly employed in the art.

As used herein, the articles “a” and “an” refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element. Furthermore, use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting.

As used herein, the term “about” will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. As used herein when referring to a measurable value such as an amount, a temporal duration, and the like, the term “about” is meant to encompass variations of $\pm 10\%$, including $\pm 5\%$, $\pm 1\%$, and $\pm 0.1\%$ from the specified value, as such variations are

appropriate to perform the disclosed methods. For example, a dose of about 300 mg may be understood to mean that the dose may vary between 270 mg and 330 mg.

As used in the specification and in the claims, the term “comprising” may include the embodiments “consisting of” and “consisting essentially of.” The terms “comprise(s),”

5 “include(s),” “having,” “has,” “may,” “contain(s),” and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or words that require the presence of the named ingredients/steps and permit the presence of other ingredients/steps. However, such description should be construed as also describing compositions or processes as “consisting of” and “consisting essentially of” the enumerated compounds, which allows the
10 presence of only the named compounds, along with any pharmaceutically acceptable carriers, and excludes other compounds.

It should be noted that ratios, concentrations, amounts, and other numerical data may be expressed herein in a range format. It is to be understood that such a range format is used for convenience and brevity, and thus, should be interpreted in a flexible manner to
15 include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. To illustrate, a dose range of “200 mg to about 600 mg” should be interpreted to include not only the explicitly recited concentration of about 200 mg to about 600 mg, but also include individual dosage (e.g.,
20 250 mg, 400 mg, 550 mg) and the sub-ranges (e.g., 250 mg to 450 mg) within the indicated range. To further illustrate, a tumor size reduction of “30%-50%” should be interpreted to include not only the explicitly recited concentration of about 30% to about 50%, but also include individual percentages (e.g., 35%, 40%, 50%) and the sub-ranges (e.g., 35%-45%) within the indicated range. The term “about” can include $\pm 1\%$, $\pm 2\%$, $\pm 3\%$, $\pm 4\%$, $\pm 5\%$, $\pm 6\%$,
25 $\pm 7\%$, $\pm 8\%$, $\pm 9\%$, or $\pm 10\%$, of the numerical value(s) being modified. In addition, the phrase “about ‘x’ to ‘y’” includes “about ‘x’ to about ‘y’”.

As used herein, “metastasis” or “metastatic” means the spread of cancer from its primary site to other places in the body. Cancer cells can break away from a primary tumor, penetrate into lymphatic and blood vessels, circulate through the bloodstream, and grow in a
30 distant focus (metastasize) in normal tissues elsewhere in the body. Metastasis can be local or distant. Metastasis is a sequential process, contingent on tumor cells breaking off from the primary tumor, traveling through the bloodstream, and stopping at a distant site. At the new site, the cells establish a blood supply and can grow to form a life-threatening mass. Both stimulatory and inhibitory molecular pathways within the tumor cell regulate this behavior,
35 and interactions between the tumor cell and host cells in the distant site are also significant.

As used herein, the term “treating” or “treatment” refers to inhibiting a disease; for example, inhibiting a disease, condition, or disorder in an individual who is experiencing or

displaying the pathology or symptomology of the disease, condition, or disorder (*i.e.*, arresting further development of the pathology and/or symptomology) or ameliorating the disease; for example, ameliorating a disease, condition, or disorder in an individual who is experiencing or displaying the pathology or symptomology of the disease, condition, or disorder (*i.e.*, reversing the pathology and/or symptomology) such as decreasing the severity of the disease.

As used herein, the term “prevent” or “prevention” means no disorder or disease development if none had occurred, or no further disorder or disease development if there had already been development of the disorder or disease. Also considered is the ability of one to prevent some or all of the symptoms associated with the disorder or disease.

As used herein, the term “patient,” “individual,” or “subject” refers to a human or a non-human mammal. Non-human mammals include, for example, livestock and pets, such as ovine, bovine, porcine, canine, feline and marine mammals. Preferably, the patient, subject, or individual is human.

As used herein, the terms “effective amount,” “pharmaceutically effective amount,” and “therapeutically effective amount” refer to a nontoxic but sufficient amount of an agent to provide the desired biological result. That result may be reduction or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. An appropriate therapeutic amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation. The agent is administered to a subject, either alone or as part of a pharmaceutical composition and either in a single dose or as part of a series of doses.

As used herein, the term “pharmaceutically acceptable” refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively non-toxic, *i.e.*, the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

As used herein, the term “pharmaceutically acceptable salt” refers to derivatives of the disclosed compounds wherein a parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts described herein include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts discussed herein can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these

compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used. The phrase "pharmaceutically acceptable salt" is not limited to a mono, or 1:1, salt. For example, "pharmaceutically acceptable salt" also includes bis-salts, such as a bis-hydrochloride salt. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and Journal of Pharmaceutical Science, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

As used herein, the term "composition" or "pharmaceutical composition" refers to a mixture of at least one compound or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers. The pharmaceutical composition facilitates administration of the composition to a patient or subject. Multiple techniques of administering a compound exist in the art including, but not limited to, intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

As used herein, the term "pharmaceutically acceptable carrier" means a pharmaceutically acceptable material, composition or carrier, such as a liquid or solid filler, stabilizer, dispersing agent, suspending agent, diluent, excipient, thickening agent, solvent or encapsulating material, involved in carrying or transporting a compound useful to the patient such that it may perform its intended function. Typically, such constructs are carried or transported from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation, including the compound disclosed herein, and not injurious to the patient. Some examples of materials that may serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; surface active agents; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

As used herein, "pharmaceutically acceptable carrier" also includes any and all coatings, antibacterial and antifungal agents, and absorption delaying agents, and the like that are compatible with the activity of a compound disclosed herein, and are physiologically acceptable to the patient. Supplementary active compounds may also be incorporated into

the compositions. The “pharmaceutically acceptable carrier” may further include a pharmaceutically acceptable salt of the compound(s) disclosed herein. Other additional ingredients that may be included in the pharmaceutical compositions are known in the art and described, for example, in Remington’s Pharmaceutical Sciences (Genaro, Ed., Mack

5 Publishing Co., 1985, Easton, PA), which is incorporated herein by reference.

As used herein, the term “superdisintegrant” refers to substances that facilitate disintegration and decrease the disintegration time. Non limiting examples include cross-linked polyvinyl pyrrolidone (crospovidone), xanthan gum, chitin, gellan gum, sodium starch glycolate, croscarmellose sodium, and microcrystalline cellulose. In an embodiment, the

10 superdisintegrant is crospovidone.

As used herein, the term “binder” refers to chemical compounds that have an adhesive property to promote cohesiveness. Binders are typically polymeric materials that are included into pharmaceutical compositions to allow for an increase in surviving bond formation when exposed to high forces resulting in compacts with adequate mechanical strength, e.g., in a tablet. Non limiting examples include hydroxypropylcellulose, methylcellulose [MC], povidone [PVP], starch, gelatin, resins, and hydroxypropyl cellulose. In an embodiment, the binder is hydroxypropyl cellulose of super low viscosity.

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The term “lubricant,” is used herein to refer to an additive that reduces friction to prevent cracking or breakage of a tablet. Non limiting examples include magnesium stearate, calcium stearate, stearic acid, talc, sodium stearyl fumarate, carrageenan, glyceryl behenate, and sodium lauryl sulfate. In an embodiment, the lubricant is magnesium stearate.

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The term “filler,” as used herein, refers to an inactive substance used to make an active pharmaceutical ingredient, such as Compound 1, easier to measure. Non limiting examples include microcrystalline cellulose, lactose, mannitol, pre-gelatinized starch, titanium dioxide, glycerin, and dextrin. In an embodiment, the filler is microcrystalline cellulose.

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The term “friability of a tablet,” as used herein, refers to the tendency of a tablet to lose component particles due to abrasion, friction, or mechanical shock.

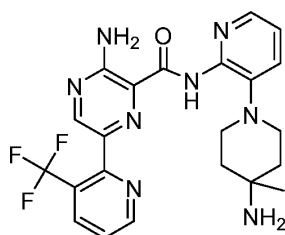
The dose amounts (for Compound 1) are expressed as free base equivalent amounts, unless indicated otherwise.

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Pharmaceutical Compositions

In an aspect, provided herein is a pharmaceutical composition comprising: a superdisintegrant; a binder; a lubricant; a filler;

35 and Compound 1:



(1)

or a pharmaceutically acceptable salt thereof.

In an embodiment, the pharmaceutical composition comprises about 1 – 5 % w/w
 5 superdisintegrant. In another embodiment, the pharmaceutical composition comprises about
 3 – 7 % w/w binder. In yet another embodiment, the pharmaceutical composition comprises
 about 0.25 – 3 % w/w lubricant. In yet another embodiment, the pharmaceutical composition
 comprises about 0.05 – 3 % w/w lubricant. In still another embodiment, the pharmaceutical
 composition comprises about 15 – 35 % w/w filler. In an embodiment, the pharmaceutical
 10 composition comprises about 45 – 85 % w/w of Compound 1, or a pharmaceutically
 acceptable salt thereof.

In another embodiment, the pharmaceutical composition comprises:

about 2 – 4 % w/w superdisintegrant;

about 4 – 6 % w/w binder;

15 about 20 – 30 % w/w filler;

about 0.5 – 3 % w/w lubricant; and

about 50 – 80 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In another embodiment, the pharmaceutical composition comprises:

about 2 – 4 % w/w superdisintegrant;

20 about 4 – 6 % w/w binder;

about 20 – 30 % w/w filler;

about 0.25 – 2 % w/w lubricant; and

about 50 – 80 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In another embodiment, the pharmaceutical composition comprises:

25 2 – 4 % w/w superdisintegrant;

4 – 6 % w/w binder;

20 – 30 % w/w filler;

0.5 – 3 % w/w lubricant; and

50 – 80 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

30 In yet another embodiment, the pharmaceutical composition comprises:

about 3 % w/w superdisintegrant;

about 5 % w/w binder;

about 24 % w/w filler;
about 1 % w/w lubricant; and
about 67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the pharmaceutical composition comprises:

5 3 % w/w superdisintegrant;
5 % w/w binder;
24 % w/w filler;
1 % w/w lubricant; and
67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

10 In yet another embodiment, the pharmaceutical composition comprises:

about 3 % w/w superdisintegrant;
about 5 % w/w binder;
about 25 % w/w filler;
about 0.50 % w/w lubricant; and

15 about 67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the pharmaceutical composition comprises:

about 3 % w/w superdisintegrant;
about 5 % w/w binder;
about 24.33 % w/w filler;
about 1 % w/w lubricant; and

about 66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the pharmaceutical composition comprises:

about 3 % w/w superdisintegrant;
about 5 % w/w binder;
about 24.83 % w/w filler;
about 0.50 % w/w lubricant; and

about 66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the pharmaceutical composition comprises:

3 % w/w superdisintegrant;
5 % w/w binder;
24.83 % w/w filler;
0.50 % w/w lubricant; and

66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the pharmaceutical composition comprises:

35 3 % w/w superdisintegrant;
5 % w/w binder;
24.83 % w/w filler;

0.50 % w/w lubricant; and
66.67 % w/w of Compound 1.

In yet another embodiment, the pharmaceutical composition comprises:

3 % w/w superdisintegrant;
5 5 % w/w binder;
24.33 % w/w filler;
1 % w/w lubricant; and
66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In an embodiment, the superdisintegrant is crospovidone. In another embodiment,
10 the binder is hydroxypropyl cellulose. In yet another embodiment, the lubricant is magnesium stearate. In still another embodiment, the filler is microcrystalline cellulose.

In an embodiment, the pharmaceutical composition comprises
crospovidone;
hydroxypropyl cellulose;
15 microcrystalline cellulose;
magnesium stearate; and
Compound 1, or a pharmaceutically acceptable salt thereof.

In an embodiment, the pharmaceutical composition comprises
crospovidone;
20 hydroxypropyl cellulose;
microcrystalline cellulose;
magnesium stearate; and
Compound 1.

In still another embodiment, the pharmaceutical composition comprises
25 about 2 – 4 % w/w crospovidone;
about 4 – 6 % w/w hydroxypropyl cellulose;
about 20 – 30 % w/w microcrystalline cellulose;
about 0.5 – 3 % w/w magnesium stearate; and
about 50 – 80 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In still another embodiment, the pharmaceutical composition comprises
30 2 – 4 % w/w crospovidone;
4 – 6 % w/w hydroxypropyl cellulose;
20 – 30 % w/w microcrystalline cellulose;
0.5 – 3 % w/w magnesium stearate; and
35 50 – 80 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.
In another embodiment, the pharmaceutical composition comprises
about 3 % w/w crospovidone;

about 5 % w/w hydroxypropyl cellulose;
about 24 % w/w microcrystalline cellulose;
about 1 % w/w magnesium stearate; and
about 67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

5 In another embodiment, the pharmaceutical composition comprises

3 % w/w crospovidone;
5 % w/w hydroxypropyl cellulose;
24 % w/w microcrystalline cellulose;
1 % w/w magnesium stearate; and

10 67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In another embodiment, the pharmaceutical composition comprises

about 3 % w/w crospovidone;
about 5 % w/w hydroxypropyl cellulose;
about 24.33 % w/w microcrystalline cellulose;
about 1 % w/w magnesium stearate; and

15 about 66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In another embodiment, the pharmaceutical composition comprises

3 % w/w crospovidone;
5 % w/w hydroxypropyl cellulose;
20 24.33 % w/w microcrystalline cellulose;
1 % w/w magnesium stearate; and

66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In still another embodiment, the pharmaceutical composition comprises

about 2 – 4 % w/w crospovidone;

25 about 4 – 6 % w/w hydroxypropyl cellulose super low viscosity;

about 20 – 30 % w/w microcrystalline cellulose;

about 0.5 – 3 % w/w magnesium stearate; and

about 50 – 80 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the pharmaceutical composition comprises:

30 about 2 – 4 % w/w crospovidone;

about 4 – 6 % w/w hydroxypropyl cellulose super low viscosity;

about 20 – 30 % w/w microcrystalline cellulose;

about 0.25 – 2 % w/w magnesium stearate; and

about 50 – 80 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

35 In still another embodiment, the pharmaceutical composition comprises

2 – 4 % w/w crospovidone;

4 – 6 % w/w hydroxypropyl cellulose super low viscosity;

20 – 30 % w/w microcrystalline cellulose;
0.5 – 3 % w/w magnesium stearate; and
50 – 80 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In another embodiment, the pharmaceutical composition comprises
5 about 3 % w/w crospovidone;
about 5 % w/w hydroxypropyl cellulose super low viscosity;
about 24 % w/w microcrystalline cellulose;
about 1 % w/w magnesium stearate; and
about 67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

10 In another embodiment, the pharmaceutical composition comprises:
about 3 % w/w crospovidone;
about 5 % w/w hydroxypropyl cellulose super low viscosity;
about 25 % w/w microcrystalline cellulose;
about 0.50 % w/w magnesium stearate; and
15 about 67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In another embodiment, the pharmaceutical composition comprises
3 % w/w crospovidone;
5 % w/w hydroxypropyl cellulose super low viscosity;
24 % w/w microcrystalline cellulose;
20 1 % w/w magnesium stearate; and
67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.
In another embodiment, the pharmaceutical composition comprises:
about 3 % w/w crospovidone;
about 5 % w/w hydroxypropyl cellulose super low viscosity;
25 about 24.83 % w/w microcrystalline cellulose;
about 0.50 % w/w magnesium stearate; and
about 66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In another embodiment, the pharmaceutical composition comprises:
3 % w/w crospovidone;
30 5 % w/w hydroxypropyl cellulose super low viscosity;
24.83 % w/w microcrystalline cellulose;
0.50 % w/w magnesium stearate; and
66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In another embodiment, the pharmaceutical composition comprises:
35 about 3 % w/w crospovidone;
about 5 % w/w hydroxypropyl cellulose;
about 24.83 % w/w microcrystalline cellulose;

about 0.50 % w/w magnesium stearate; and
about 66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In another embodiment, the pharmaceutical composition comprises:

3 % w/w crospovidone;

5 5 % w/w hydroxypropyl cellulose;

24.83 % w/w microcrystalline cellulose;

0.50 % w/w magnesium stearate; and

66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In another embodiment, the pharmaceutical composition comprises:

10 about 3 % w/w crospovidone;

about 5 % w/w hydroxypropyl cellulose;

about 24.83 % w/w microcrystalline cellulose;

about 0.50 % w/w magnesium stearate; and

66.67 % w/w of Compound 1.

15 In another embodiment, the pharmaceutical composition comprises:

3 % w/w crospovidone;

5 % w/w hydroxypropyl cellulose;

24.83 % w/w microcrystalline cellulose;

0.50 % w/w magnesium stearate; and

20 66.67 % w/w of Compound 1.

In another embodiment, the pharmaceutical composition comprises:

about 3 % w/w crospovidone;

about 5 % w/w hydroxypropyl cellulose super low viscosity;

about 24.83 % w/w microcrystalline cellulose;

25 about 0.50 % w/w magnesium stearate; and

about 66.67 % w/w of Compound 1.

In another embodiment, the pharmaceutical composition comprises:

3 % w/w crospovidone;

5 % w/w hydroxypropyl cellulose super low viscosity;

30 24.83 % w/w microcrystalline cellulose;

0.50 % w/w magnesium stearate; and

66.67 % w/w of Compound 1.

In another embodiment, the pharmaceutical composition comprises

about 3 % w/w crospovidone;

35 about 5 % w/w hydroxypropyl cellulose super low viscosity;

about 24.33 % w/w microcrystalline cellulose;

about 1 % w/w magnesium stearate; and

about 66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In another embodiment, the pharmaceutical composition comprises

3 % w/w crospovidone;

5 % w/w hydroxypropyl cellulose super low viscosity;

5 24.33 % w/w microcrystalline cellulose;

1 % w/w magnesium stearate; and

66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the pharmaceutical composition comprises Compound 1.

In still another embodiment, wherein the pharmaceutical composition is in tablet form.

10 In still another embodiment, wherein the tablet is an immediate release form. In an embodiment the tablets are coated with a film. In an embodiment the film is Opadry® Yellow.

In an embodiment, the pharmaceutical composition comprising Compound 1 or a pharmaceutically acceptable salt thereof, is a capsule form. In an embodiment, the capsule is a hard gelatin capsule. In an embodiment, the capsule is an immediate release form.

15 In an embodiment, the pharmaceutical composition comprising Compound 1 or a pharmaceutically acceptable salt thereof, is a capsule form, wherein the capsule comprises gelatin. In an embodiment, the pharmaceutical composition comprising Compound 1 or a pharmaceutically acceptable salt thereof, is a capsule form, wherein the capsule comprises titanium dioxide (E171). In an embodiment, the pharmaceutical composition comprises

20 Compound 1 or a pharmaceutically acceptable salt thereof, is a capsule form, wherein the capsule comprises gelatin and titanium dioxide (E171). In an embodiment, the capsule is a hard gelatin capsule having size 0 capsule shell comprising gelatin and titanium oxide. In an embodiment, the capsule is a hard gelatin capsule having size 1 capsule shell comprising gelatin and titanium oxide. In an embodiment, the capsule is a hard gelatin capsule having
25 size 2 capsule shell comprising gelatin and titanium oxide.

In an embodiment, the pharmaceutical composition comprises about 25 mg to 400 mg free base equivalent of Compound 1. In another embodiment, the pharmaceutical composition comprises 25 mg free base equivalent of Compound 1. In another embodiment, the pharmaceutical composition comprises 100 mg free base equivalent of Compound 1. In
30 yet another embodiment, the pharmaceutical composition comprises 200 mg free base equivalent of Compound 1. In still another embodiment, the pharmaceutical composition comprises 300 mg free base equivalent of Compound 1.

In an embodiment, a Compound 1, 100 mg IR (immediate release) Tablet, is a round shaped coated tablet. In an embodiment, the Compound 1, 300 mg IR Tablet is a yellow
35 colored, oval shaped coated tablet. In an embodiment, a Compound 1, 100 mg IR Tablet has debossing on one side. In an embodiment, a Compound 1, 300 mg IR Tablet has debossing on one side. In an embodiment, a Compound 1, 100 mg IR Tablet is coated with Opadry®

Yellow (20A120007). In an embodiment, a Compound 1, 300 mg IR Tablet is coated with Opadry® Yellow (20A120007).

In an embodiment, the pharmaceutical composition is administered orally, i.e., it is formulated for oral administration to a subject.

5 In an embodiment, the pharmaceutical composition comprises 1-5%, 2-4%, or 3% w/w of a coating, such as Opadry® Yellow. In an embodiment, the w/w is outside the total percentage of the non-coating components of the pharmaceutical composition.

In an embodiment, the pharmaceutical composition comprises Compound 1 in crystalline form.

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Characterization of Crystalline Forms

In certain embodiments, the crystalline forms described herein are identifiable on the basis of characteristic peaks in an X-ray powder diffraction (XRPD) analysis. X-ray powder diffraction is a scientific technique using X-ray, neutron, or electron diffraction on powder, microcrystalline, or other solid materials for structural characterization of solid materials. A description of the methods used to obtain certain XRPD diffractograms in connection with the crystalline forms provided herein can be found in the Examples below. In an embodiment, the X-ray powder diffraction data provided herein is obtained by a method utilizing Cu, k-Alpha 1 radiation.

20 In an aspect, provided herein is a crystalline form of 3-amino-N-[3-(4-amino-4-methylpiperidin-1-yl)pyridin-2-yl]-6-[3-(trifluoromethyl)pyridin-2-yl]pyrazine-2-carboxamide (Compound 1), wherein the crystalline form is characterized by an XRPD diffractogram having peaks expressed in degrees-2-theta at angles (± 0.2 degrees) of 8.3, 15.0, and 16.6.

In an embodiment, the crystalline form of Compound 1 is characterized by an XRPD diffractogram having peaks expressed in degrees-2-theta at angles (± 0.2 degrees) of 8.3, 15.0, 16.6, and 25.0.

In an embodiment, the crystalline form of Compound 1 is characterized by an XRPD diffractogram having peaks expressed in degrees-2-theta at angles (± 0.2 degrees) of 8.3, 15.0, 16.6, 25.0, and 23.1.

30 In an embodiment, the crystalline form of Compound 1 is characterized by an XRPD diffractogram having peaks expressed in degrees-2-theta at angles (± 0.2 degrees) of 8.3, 15.0, 16.6, and 11.8.

In another embodiment, the crystalline form of Compound 1 is characterized by an XRPD diffractogram having peaks expressed in degrees-2-theta at angles (± 0.2 degrees) of 8.3, 15.0, 16.6, 25.0, 23.1, 11.8, and 22.4.

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In yet another embodiment, the crystalline form of Compound 1 is characterized by an XRPD diffractogram having peaks expressed in degrees-2-theta at angles (± 0.2 degrees) of 8.3, 15.0, 16.6, 25.0, 23.1, 11.8, 22.4, and 23.7.

In yet another embodiment, the crystalline form of Compound 1 is characterized by an XRPD diffractogram having peaks expressed in degrees-2-theta at angles (± 0.2 degrees) of 8.3, 15.0, 16.6, 25.0, 23.1, 11.8, 22.4, 23.7, and 24.8.

In yet another embodiment, the crystalline form of Compound 1 is characterized by an XRPD diffractogram having peaks expressed in degrees-2-theta at angles (± 0.2 degrees) of 8.3, 15.0, 16.6, 25.0, 23.1, 11.8, 22.4, and 23.7.

In yet another embodiment, the crystalline form of Compound 1 is characterized by an XRPD diffractogram comprising at least three or at least four peaks expressed in degrees-2-theta at angles (± 0.2 degrees) of 8.3, 15.0, 16.6, 25.0, 23.1, 11.8, 22.4, and 23.7.

In still another embodiment, the crystalline form of Compound 1 is characterized by an XRPD diffractogram depicted in Figure 1.

In another embodiment, the crystalline form of Compound 1 is characterized by an XRPD diffractogram having peaks expressed in degrees-2-theta at angles listed in Table 19.

Table 19.

Angle	Angle	Angle	Angle
8.3	18.8	25.7	32.4
9.7	19.2	26.3	33.0
10.5	19.5	26.5	33.4
10.9	19.9	26.8	33.9
11.8	20.2	27.6	34.4
13.0	20.7	28.3	35.0
15.0	21.0	28.8	35.3
15.8	21.9	29.3	35.8
16.0	22.4	29.7	37.2
16.6	23.1	30.5	37.7
16.8	23.7	30.9	38.8
17.3	24.0	31.4	
18.4	24.9	31.8	

In an embodiment, the crystalline form of Compound 1 has a DSC thermogram characterized by an endotherm with an onset temperature of about 245.5 °C.

Methods of Treatment

In an aspect, provided herein is a method of treating cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of the present disclosure.

5 In an embodiment, the cancer is melanoma. In an embodiment, the cancer is uveal melanoma. In another embodiment, the cancer is a solid tumor. In another embodiment, the cancer is metastatic uveal melanoma. In an embodiment, the cancer is cutaneous melanoma. In an embodiment, the cancer is mucosal melanoma. In another embodiment, the subject has an intraocular tumor. In another embodiment, the intraocular tumor is
10 malignant. In another embodiment, the intraocular tumor is not malignant. In yet another embodiment, the cancer harbors GNAQ mutations. In still another embodiment, the cancer harbors GNA11 mutations.

In still another embodiment, the uveal melanoma is a solid tumor harboring GNAQ or GNA11 mutations. In an embodiment, the patient has an additional non-ocular tumor. In an
15 embodiment, the non-ocular tumor is metastatic.

In another embodiment, the cancer is selected from the group consisting of melanoma, uveal melanoma, lymphoma, diffuse large B-cell lymphoma (DLBCL), ibrutinib resistant cancers, papillary cancer, thyroid cancer, ovarian cancer, colon cancer, pancreatic cancer, non-small cell lung cancer (NSCLC), hematological cancers, chronic myelogenous
20 leukemia (CML), acute lymphoblastic leukemia (ALL), and acute myeloid leukemia.

In another aspect, provided herein is a method for treating uveal melanoma, including uveal melanoma harboring GNAQ or GNA11 mutations, in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition of the present disclosure to reduce or prevent tumor growth in
25 the subject.

In yet another aspect, provided herein is a method for treating lymphoma, including diffuse large B-cell lymphoma (DLBCL), in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition of the present disclosure.

30 Exemplary lengths of time associated with the course of the treatment methods is about five years, about 4 years, about 3 years, about 2 years, about 1 years, about 11 months, about 10 months, about 9 months, about 8 months, about 7 months, about 6 months, about 5 months, about 4 months, about 3 months, about 2 months, or about 1 month.

35 Exemplary lengths of time associated with the course of the treatment methods is about five years and so on; or any days, weeks, months, or years in between; for example, a

treatment cycle can include 5 months and additional weeks and/or days, or one year and additional months, weeks, and/or days, and the like.

In some embodiments, Compound 1, or a pharmaceutically acceptable salt thereof, is administered continuously (i.e., a continuous treatment until termination).

5 The UM to be treated can include one or more of a number of mutations, including a substitution mutation, an insertion mutation, and/or a deletion in GNAQ or GNA11 mutation. In some aspects, the GNAQ or GNA11 mutation is a gain of function mutation. In some aspects, the GNAQ or GNA11 mutation activates the PKC signaling pathway. In various aspects, the GNAQ or GNA11 mutation can be the substitution of glutamine in codon 209
10 (Q209) and/or a substitution of arginine in codon 183 (R183). The GNAQ or GNA11 mutation can be a substitution other than glutamine in codon 209 (Q209), other than a substitution of arginine in codon 183 (R183), or other than both. In some aspects, the GNAQ mutation is one of Q209P, Q209L, Q209H, Q209K, or Q209Y, or the GNA11 mutation is one of Q209P, Q209L, Q209K or Q209H. In further aspects, the GNAQ mutation can be R183Q, or the
15 GNA11 mutation can be R183C or R183H. In yet further examples, the GNAQ or GNA11 mutation is at one or more of R256, L279, R166, A168, R210, R213, R166, A231, A342, D333, G171, R147, R73, T47, E191, E221, R149, T175, T379, T85, A86, E163, D195, E319, E191, E280, E49, P293, R300, R338, R60, D155, D205, D321, I226, R37, or V240. In further examples, the UM can comprise one or more of a Q209P, Q209L, Q209H, Q209K,
20 Q209Y, or R183Q mutation in GNAQ, or the UM can comprise one or more of a Q209P, Q209L, Q209H, or Q209K mutation in GNA11. Additional examples of mutations in GNAQ or GNA11 are described in WO 2020/146355, which is incorporated by reference herewith in its entirety.

 Exemplary lengths of time associated with the course of the treatment methods
25 disclosed herein include: about one week; about two weeks; about three weeks; about four weeks; about five weeks; about six weeks; about seven weeks; about eight weeks; about nine weeks; about ten weeks; about eleven weeks; about twelve weeks; about thirteen weeks; about fourteen weeks; about fifteen weeks; about sixteen weeks; about seventeen weeks; about eighteen weeks; about nineteen weeks; about twenty weeks; about twenty-one
30 weeks; about twenty-two weeks; about twenty-three weeks; about twenty four weeks; about 4 months; about seven months; about eight months; about nine months; about ten months; about eleven months; about twelve months; about thirteen months; about fourteen months; about fifteen months; about sixteen months; about seventeen months; about eighteen months; about nineteen months; about twenty months; about twenty one months; about
35 twenty-two months; about twenty-three months; about twenty-four months; about thirty months; about three years; about four years and about five years and so on; or any days, weeks, months, or years in between; for example a treatment cycle can include 5 months

and additional weeks and/or days, or one year and additional months, weeks, and/or days, and the like.

In an embodiment of the methods, the method involves the administration of a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, to a subject (including, but not limited to a human or animal) in need of treatment (including a subject identified as in need).

Administration / Dosage / Formulations

Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

In particular, the selected dosage level will depend upon a variety of factors including the activity of the particular compound employed, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds or materials used in combination with the compound, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A medical doctor, e.g., physician or veterinarian, having ordinary skill in the art may readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could begin administration of the pharmaceutical composition to dose the disclosed compound at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In particular embodiments, it is especially advantageous to formulate the compound in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the patients to be treated; each unit containing a predetermined quantity of the disclosed compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The dosage unit forms are dictated by and directly dependent on (a) the unique characteristics of the disclosed compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding/formulating such a disclosed compound for the treatment of pain, a depressive disorder, or drug addiction in a patient.

In one embodiment, the compounds provided herein are formulated using one or more pharmaceutically acceptable excipients or carriers. In one embodiment, the

pharmaceutical compositions provided herein comprise a therapeutically effective amount of a disclosed compound and a pharmaceutically acceptable carrier.

The optimum ratios, individual and combined dosages, and concentrations of the drug compounds that yield efficacy without toxicity are based on the kinetics of the active ingredients' availability to target sites, and are determined using methods known to those of skill in the art.

In an embodiment is a method of treating cancer in a subject in need thereof comprising administering to the subject the pharmaceutical composition disclosed herein at a dose of about 50 mg BID to about 400 mg BID of Compound 1 (measured as free base) for at least 1 week, 2 weeks, 3 weeks, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, 44 weeks, 48 weeks, or 52 weeks. In an embodiment of the methods, the pharmaceutical composition is administered at a dose of about 100 mg BID, about 200 mg BID, or about 300 mg BID of Compound 1 (measured as free base) for at least 1 week, 2 weeks, 3 weeks, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, 44 weeks, 48 weeks, or 52 weeks.

Routes of administration of any of the compositions discussed herein include oral, nasal, rectal, intravaginal, parenteral, buccal, sublingual or topical. The compounds may be formulated for administration by any suitable route, such as for oral or parenteral, for example, transdermal, transmucosal (e.g., sublingual, lingual, (trans)buccal, (trans)urethral, vaginal (e.g., trans- and perivaginally), (intra)nasal and (trans)rectal), intravesical, intrapulmonary, intraduodenal, intragastrical, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, and topical administration. In one embodiment, the preferred route of administration is oral.

Suitable compositions and dosage forms include, for example, tablets, capsules, caplets, pills, gel caps, troches, dispersions, suspensions, solutions, syrups, granules, beads, transdermal patches, gels, powders, pellets, magmas, lozenges, creams, pastes, plasters, lotions, discs, suppositories, liquid sprays for nasal or oral administration, dry powder or aerosolized formulations for inhalation, compositions and formulations for intravesical administration and the like. It should be understood that the formulations and compositions are not limited to the particular formulations and compositions that are described herein.

For oral application, particularly suitable are tablets, dragees, liquids, drops, suppositories, or capsules, caplets and gel caps. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically excipients that are suitable for the manufacture of tablets. Such excipients

include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay the release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent.

For parenteral administration, the disclosed compounds may be formulated for injection or infusion, for example, intravenous, intramuscular or subcutaneous injection or infusion, or for administration in a bolus dose or continuous infusion. Suspensions, solutions or emulsions in an oily or aqueous vehicle, optionally containing other formulatory agents such as suspending, stabilizing or dispersing agents may be used.

Kits

In an aspect, the present disclosure provides a kit for treating uveal melanoma, comprising a pharmaceutical composition of the present disclosure. In some embodiments, the kit further comprises packaging and instructions. In yet another embodiment, the uveal melanoma is metastatic uveal melanoma. In yet another embodiment, the metastatic uveal melanoma is a solid tumor harboring GNAQ or GNA11 mutations.

In certain embodiments, the kit comprises a pharmaceutical product comprising a pharmaceutical composition of the present disclosure.

In additional embodiments, pharmaceutical kits are provided. The kit includes a sealed container approved for the storage of pharmaceutical compositions, the container containing one of the above-described pharmaceutical compositions. In some embodiments, the sealed container minimizes the contact of air with the ingredients, e.g. an airless bottle. In other embodiments, the sealed container is a sealed tube. An instruction for the use of the composition and the information about the composition are to be included in the kit.

The kits provided herein comprise prescribing information, for example, to a patient or health care provider, or as a label in a packaged pharmaceutical formulation. Prescribing information may include for example efficacy, dosage and administration, contraindication and adverse reaction information pertaining to the pharmaceutical formulation.

A kit provided herein can be designed for conditions necessary to properly maintain the components housed therein (e.g., refrigeration or freezing). A kit can contain a label or packaging insert including identifying information for the components therein and instructions for their use (e.g., dosing parameters, clinical pharmacology of the active ingredient(s), including mechanism(s) of action, pharmacokinetics and pharmacodynamics, adverse effects, contraindications, etc.).

Each component of the kit can be enclosed within an individual container, and all of the various containers can be within a single package. Labels or inserts can include manufacturer information such as lot numbers and expiration dates. The label or packaging insert can be, e.g., integrated into the physical structure housing the components, contained
5 separately within the physical structure, or affixed to a component of the kit (e.g., an ampule, syringe or vial).

Non-Limiting Exemplary Embodiments:

In further embodiments 1 to 78 below, the present disclosure includes:

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1. In Embodiment 1 is a pharmaceutical composition comprising a superdisintegrant; a binder; a lubricant; a filler; and Compound 1, or a pharmaceutically acceptable salt thereof.

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2. In Embodiment 2 is the pharmaceutical composition of embodiment 1, wherein the pharmaceutical composition comprises about 1 – 5 % w/w superdisintegrant.

3. In Embodiment 3 is the pharmaceutical composition of embodiment 1 or 2, wherein the pharmaceutical composition comprises about 3 – 7 % w/w binder.

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4. In Embodiment 4 is the pharmaceutical composition of any one of embodiments 1 to 3, wherein the pharmaceutical composition comprises about 0.25 – 3 % w/w lubricant.

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5. In Embodiment 4 is the pharmaceutical composition of any one of embodiments 1 to 3, wherein the pharmaceutical composition comprises about 0.05 – 3 % w/w lubricant.

6. In Embodiment 6 is the pharmaceutical composition of any one of embodiments 1 to 5, wherein the pharmaceutical composition comprises about 15 – 35 % w/w filler.

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7. In Embodiment 6 is the pharmaceutical composition of any one of embodiments 1 to 6, wherein the pharmaceutical composition comprises about 45 – 85 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

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7A. In Embodiment 7A is the pharmaceutical composition of any one of embodiments 1 to 7, comprising:

about 2 – 4 % w/w superdisintegrant;

about 4 – 6 % w/w binder;

about 20 – 30 % w/w filler;

about 0.5 – 3 % w/w lubricant; and

about 50 – 80 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

8. In Embodiment 8 is the pharmaceutical composition of any one of embodiments 1 to 5 7, comprising:

about 2 – 4 % w/w superdisintegrant;

about 4 – 6 % w/w binder;

about 20 – 30 % w/w filler;

about 0.25 – 2 % w/w lubricant; and

- 10 about 50 – 80 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

9. In Embodiment 9 is the pharmaceutical composition of any one of embodiments 1 to 7, comprising:

2 – 4 % w/w superdisintegrant;

- 15 4 – 6 % w/w binder;

20 – 30 % w/w filler;

0.5 – 3 % w/w lubricant; and

50 – 80 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

- 20 10. In Embodiment 10 is the pharmaceutical composition of any one of embodiments 1 to 9, comprising:

2 – 4 % w/w superdisintegrant;

4 – 6 % w/w binder;

20 – 30 % w/w filler;

- 25 0.25 – 2 % w/w lubricant; and

50 – 80 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

11. In Embodiment 11 is the pharmaceutical composition of any one of embodiments 1 to 10, comprising:

- 30 about 3 % w/w superdisintegrant;

about 5 % w/w binder;

about 24 % w/w filler;

about 1 % w/w lubricant; and

about 67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

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12. In Embodiment 12 is the pharmaceutical composition of any one of embodiments 1 to 10, comprising:

- about 3 % w/w superdisintegrant;
about 5 % w/w binder;
about 25 % w/w filler;
about 0.50 % w/w lubricant; and
5 about 67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.
13. In Embodiment 13 is the pharmaceutical composition of any one of embodiments 1 to 10, comprising:
about 3 % w/w superdisintegrant;
10 about 5 % w/w binder;
about 24.33 % w/w filler;
about 1 % w/w lubricant; and
about 66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.
- 15 14. In Embodiment 14 is the pharmaceutical composition of any one of embodiments 1 to 10, comprising:
about 3 % w/w superdisintegrant;
about 5 % w/w binder;
about 24.83 % w/w filler;
20 about 0.50 % w/w lubricant; and
about 66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.
- 15 15. In Embodiment 15 is the pharmaceutical composition of any one of embodiments 1 to 10, and 13, comprising:
25 3 % w/w superdisintegrant;
5 % w/w binder;
24.33 % w/w filler;
1 % w/w lubricant; and
66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.
30
16. In Embodiment 16 is the pharmaceutical composition of any one of embodiments 1 to 10, 12, and 14, comprising:
3 % w/w superdisintegrant;
5 % w/w binder;
35 24.83 % w/w filler;
0.50 % w/w lubricant; and
66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

17. In Embodiment 17 is the pharmaceutical composition of any one of embodiments 1 to 16, wherein the superdisintegrant is crospovidone.

5 18. In Embodiment 18 is the pharmaceutical composition of any one of embodiments 1 to 17, wherein the binder is hydroxypropyl cellulose.

19. In Embodiment 19 is the pharmaceutical composition of embodiment 18, wherein the hydroxypropyl cellulose is hydroxypropyl cellulose of super low viscosity.

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20. In Embodiment 20 is the pharmaceutical composition of any one of embodiments 1 to 19, wherein the filler is microcrystalline cellulose.

15 21. In Embodiment 21 is the pharmaceutical composition of any one of embodiments 1 to 20, wherein the lubricant is magnesium stearate.

22. In Embodiment 22 is the pharmaceutical composition of any one of embodiments 1 to 10 and 17 to 21, comprising:

20 about 2 – 4 % w/w crospovidone;
 about 4 – 6 % w/w hydroxypropyl cellulose super low viscosity;
 about 20 – 30 % w/w microcrystalline cellulose;
 about 0.5 – 3 % w/w magnesium stearate; and
 about 50 – 80 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

25 23. In Embodiment 23 is the pharmaceutical composition of any one of embodiments 1 to 10 and 17 to 22, comprising:

30 about 2 – 4 % w/w crospovidone;
 about 4 – 6 % w/w hydroxypropyl cellulose super low viscosity;
 about 20 – 30 % w/w microcrystalline cellulose;
 about 0.25 – 2 % w/w magnesium stearate; and
 about 50 – 80 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

24. In Embodiment 24 is the pharmaceutical composition of any one of embodiments 1 to 10 and 17 to 23, comprising:

35 about 3 % w/w crospovidone;
 about 5 % w/w hydroxypropyl cellulose super low viscosity;
 about 24 % w/w microcrystalline cellulose;

about 1 % w/w magnesium stearate; and
about 67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

25. In Embodiment 25 is the pharmaceutical composition of any one of embodiments 1 to
5 10 and 17 to 24, comprising:
3 % w/w crospovidone;
5 % w/w hydroxypropyl cellulose super low viscosity;
24 % w/w microcrystalline cellulose;
1 % w/w magnesium stearate; and
10 67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

26. In Embodiment 26 is the pharmaceutical composition of any one of embodiments 1 to
10, and 17 to 23, comprising:
about 3 % w/w crospovidone;
15 about 5 % w/w hydroxypropyl cellulose super low viscosity;
about 24.33 % w/w microcrystalline cellulose;
about 1 % w/w magnesium stearate; and
about 66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

- 20 27. In Embodiment 27 is the pharmaceutical composition of any one of embodiments 1 to
10, and 17 to 23, and 26, comprising:
3 % w/w crospovidone;
5 % w/w hydroxypropyl cellulose super low viscosity;
24.33 % w/w microcrystalline cellulose;
25 1 % w/w magnesium stearate; and
66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

28. In Embodiment 28 is the pharmaceutical composition of any one of embodiments 1 to
10, 12, and 17 to 23, comprising:
30 about 3 % w/w crospovidone;
about 5 % w/w hydroxypropyl cellulose super low viscosity;
about 25 % w/w microcrystalline cellulose;
about 0.50 % w/w magnesium stearate; and
about 67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

- 35 29. In Embodiment 29 is the pharmaceutical composition of any one of embodiments 1 to
10, 12, 17 to 23, and 28 comprising:

- 3 % w/w crospovidone;
5 % w/w hydroxypropyl cellulose super low viscosity;
25 % w/w microcrystalline cellulose;
0.50 % w/w magnesium stearate; and
5 67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.
30. In Embodiment 30 is the pharmaceutical composition of any one of embodiments 1 to 10, 14, 17 to 23, and 28 comprising:
about 3 % w/w crospovidone;
10 about 5 % w/w hydroxypropyl cellulose super low viscosity;
about 24.83 % w/w microcrystalline cellulose;
about 0.50 % w/w magnesium stearate; and
about 66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.
- 15 31. In Embodiment 31 is the pharmaceutical composition of any one of embodiments 1 to 10, 14, and 16 to 23, and 30, comprising:
3 % w/w crospovidone;
5 % w/w hydroxypropyl cellulose super low viscosity;
24.83 % w/w microcrystalline cellulose;
20 0.50 % w/w magnesium stearate; and
66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.
32. In Embodiment 32 is the pharmaceutical composition of any one of embodiments 1 to 25 31, wherein the pharmaceutical composition comprises Compound 1.
33. In Embodiment 33 is the pharmaceutical composition of any one of embodiments 1 to 32, wherein Compound 1 is in a crystalline form.
34. In Embodiment 34 is the pharmaceutical composition of any one of embodiments 1 to 30 33, wherein the pharmaceutical composition is in tablet form.
35. In Embodiment 35 is the pharmaceutical composition of embodiment 34, wherein the tablet is an immediate release form.
- 35 36. In Embodiment 36 is the pharmaceutical composition of Embodiment 34 or 35, wherein the tablet is coated with a film.

37. In Embodiment 37 is the pharmaceutical composition of Embodiment 36, wherein the film is Opadry® Yellow.
38. In Embodiment 38 is the pharmaceutical composition of Embodiment 36, wherein the film is Opadry® AMB.
39. In Embodiment 39 the pharmaceutical composition of any one of Embodiments 1 to 38, wherein the disintegration time of the tablet is less than 10 minutes.
40. In Embodiment 40 the pharmaceutical composition of any one of Embodiments 1 to 39, wherein the friability of the tablet is less than 0.5% w/w.
41. In Embodiment 41 is the pharmaceutical composition of any one of Embodiments 1 to 39, wherein the friability of the tablet is 0.5% w/w.
42. In Embodiment 42 is the pharmaceutical composition of any one of Embodiments 1 to 39, wherein the friability of the tablet is less than or equal to 1.0 % w/w.
43. In Embodiment 43 is the pharmaceutical composition of any one of Embodiments 1 to 42, wherein the dissolution of the tablet is greater than 80% at 15 minutes.
44. In Embodiment 44 is the pharmaceutical composition of any one of Embodiments 1 to 43, wherein the dissolution of the tablet is greater than 85% at 15 minutes.
45. In Embodiment 45 is the pharmaceutical composition of any one of Embodiments 1 to 44, wherein the dissolution of the tablet is greater than 90% at 15 minutes.
46. In Embodiment 46 is the pharmaceutical composition of any one of Embodiments 1 to 45, wherein the dissolution of the tablet is greater than 95% at 15 minutes.
47. In Embodiment 47 is the pharmaceutical composition of any one of embodiments 1 to 46, wherein the pharmaceutical composition comprises about 25 mg to 400 mg free base equivalent of Compound 1.
48. In Embodiment 48 is the pharmaceutical composition of any one of embodiments 1 to 47, wherein the pharmaceutical composition comprises 100 mg free base equivalent of Compound 1.

49. In Embodiment 49 is the pharmaceutical composition of any one of embodiments 1 to 47, wherein the pharmaceutical composition comprises 200 mg free base equivalent of Compound 1.

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50. In Embodiment 50 is the pharmaceutical composition of any one of embodiments 1 to 47, wherein the pharmaceutical composition comprises 300 mg free base equivalent of Compound 1.

10 51. In Embodiment 51 is the pharmaceutical composition of any one of embodiments 1 to 50, wherein the pharmaceutical composition is administered orally.

52. In Embodiment 52 is the pharmaceutical composition of any one of embodiments 1 to 51, wherein the Compound 1 is in a crystalline form characterized by an XRPD diffractogram
15 having peaks expressed in degrees-2-theta at angles (± 0.2 degrees) of 8.3, 15.0, and 16.6.

53. In Embodiment 53 is the pharmaceutical composition of any one of embodiments 1 to 52, wherein the Compound 1 is in a crystalline form characterized by an XRPD diffractogram having peaks expressed in degrees-2-theta at angles (± 0.2 degrees) of 8.3, 15.0, 16.6,
20 25.0, and 23.1.

54. In Embodiment 54 is the pharmaceutical composition of any one of embodiments 1 to 53, wherein the Compound 1 is in a crystalline form characterized by an XRPD diffractogram having peaks expressed in degrees-2-theta at angles (± 0.2 degrees) of 8.3, 15.0, 16.6,
25 25.0, 23.1, 11.8, and 22.4.

55. In Embodiment 55 is the pharmaceutical composition of any one of embodiments 1 to 54, wherein the Compound 1 is in a crystalline form characterized by an XRPD diffractogram having peaks expressed in degrees-2-theta at angles (± 0.2 degrees) of 8.3, 15.0, 16.6,
30 25.0, 23.1, 11.8, 22.4, and 23.7.

56. In Embodiment 56 is the pharmaceutical composition of any one of embodiments 1 to 51, wherein the Compound 1 is in a crystalline form characterized by an XRPD diffractogram comprising at least three or at least four peaks expressed in degrees-2-theta at angles (± 0.2 degrees) selected from the group consisting of about 8.3, 15.0, 16.6, 25.0, 23.1, 11.8, 22.4, and 23.7.

57. In Embodiment 57 is the pharmaceutical composition of any one of embodiments 1 to 56, wherein the Compound 1 is in a crystalline form characterized by an XRPD diffractogram depicted in Figure 1.

5 58. In Embodiment 58 is the pharmaceutical composition of any one of embodiments 1 to 57, wherein the Compound 1 is in a crystalline form characterized by a DSC thermogram having an endotherm with an onset temperature of about 245.5 °C.

59. In Embodiment 59 is a method of treating cancer in a subject in need thereof
10 comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of any one of embodiments 1 to 58.

60. In Embodiment 60 is the method of embodiment 59, wherein the cancer is uveal melanoma.

15

61. In Embodiment 61 is the method of embodiment 59 or 60, wherein the cancer is a solid tumor.

62. In Embodiment 62 is the method of any one of embodiments 59 to 61, wherein the
20 cancer is metastatic uveal melanoma.

63. In Embodiment 63 is the method of any one of embodiments 59 to 62, wherein the subject has an intraocular tumor.

25 64. In Embodiment 64 is the method of embodiment 63, wherein the intraocular tumor is not malignant.

65. In Embodiment 65 is the method of embodiment 63, wherein the intraocular tumor is malignant.

30

66. In Embodiment 66 is the method of embodiment 59, wherein the cancer is cutaneous melanoma.

67. In Embodiment 67 is the method of embodiment 59, wherein the cancer is mucosal
35 melanoma.

68. In Embodiment 68 is the method of any one of embodiments 59 to 67, wherein the cancer harbors GNAQ mutations.

69. In Embodiment 69 is the method of any one of embodiments 59 to 68, wherein the
5 cancer harbors GNA11 mutations.

70. In Embodiment 70 is the method of any one of embodiments 1 to 69, wherein the pharmaceutical composition is administered at a dose of about 50 mg BID to about 400 mg BID of Compound 1 (measured as free base) for at least 1 week, 2 weeks, 3 weeks, 4
10 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, 44 weeks, 48 weeks, or 52 weeks.

71. In Embodiment 71 is the method of any one of embodiments 1 to 70, wherein the pharmaceutical composition is administered at a dose of about 100 mg BID, about 200 mg
15 BID, or about 300 mg BID of Compound 1 (measured as free base) for at least 1 week, 2 weeks, 3 weeks, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, 44 weeks, 48 weeks, or 52 weeks.

72. In Embodiment 72 is the pharmaceutical composition of any one of embodiments 1 to
20 58 for use in a therapy.

73. In Embodiment 73 is the pharmaceutical composition of any one of embodiments 1 to 58 for use in treating cancer.

25 74. In Embodiment 74 is the use according to embodiment 73, wherein the cancer is melanoma.

75. In Embodiment 75 is the use according to embodiment 73, wherein the cancer is
30 uveal melanoma.

76. In Embodiment 76 is the use according to embodiment 73, wherein the cancer is metastatic uveal melanoma.

77. In Embodiment 77 is the use according to embodiment 73, wherein the cancer is
35 cutaneous melanoma.

78. In Embodiment 78 is the use according to embodiment 73, wherein the cancer is mucosal melanoma.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures, embodiments,
5 claims, and examples described herein. Such equivalents were considered to be within the scope of this disclosure and covered by the claims appended hereto. For example, it should be understood, that modifications in reaction conditions, including but not limited to reaction times, reaction size/volume, and experimental reagents, such as solvents, catalysts,
10 pressures, atmospheric conditions, *e.g.*, nitrogen atmosphere, and reducing/oxidizing agents, with art-recognized alternatives and using no more than routine experimentation, are within the scope of the present application.

It is to be understood that wherever values and ranges are provided herein, all values and ranges encompassed by these values and ranges, are meant to be encompassed within the scope of the present disclosure. Moreover, all values that fall within these ranges, as well
15 as the upper or lower limits of a range of values, are also contemplated by the present application.

The following examples further illustrate aspects of the present disclosure. However, they are in no way a limitation of the teachings of the present disclosure as set forth.

20

EXAMPLES

The pharmaceutical compositions disclosed herein are further illustrated by the following examples, which should not be construed as further limiting. The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of organic synthesis and pharmaceutical formulations, which are within the skill of the art.

25

Processes for preparing Compound 1, Compound 1 crystalline form, and the biological activity of Compound 1 can be found, at least, in WO 2016/020864, the content of which is incorporated in its entirety. Compound 1 is referred to as Example 9 in WO 2016/020864 and is shown to have IC₅₀ values of 1.9 nM and 0.4 nM against PKC α and PKC θ , respectively (Table 2).

30

The Compound 1 crystal form was determined using a Bruker D8 advance X-Ray Diffractometer or equivalent.

Example 1. Pharmaceutical Composition Development

In one aspect, the pharmaceutical composition comprising Compound 1 is an
35 Immediate Release (IR) tablet for oral administration containing Compound 1 provided for in two dosage strengths, 100 mg and 300 mg, referred to herein as:

- Compound 1, 100 mg IR Tablets
- Compound 1, 300 mg IR Tablets

The Compound 1, 100 mg IR Tablets are yellow colored, round shaped uncoated tablets and the Compound 1, 300 mg IR Tablets are yellow colored, oval shaped uncoated tablets. In an embodiment, Compound 1, 100 mg IR Tablets, are round shaped coated tablets. In an embodiment, Compound 1, 300 mg IR Tablets the tablets are yellow colored, oval shaped coated tablets. In an embodiment, Compound 1, 100 mg IR Tablets have debossing on one side. In an embodiment, Compound 1, 300 mg IR Tablets have debossing on one side. In an embodiment, Compound 1, 100 mg IR Tablets are coated with Opadry® Yellow (20A120007). In an embodiment, Compound 1, 300 mg IR Tablets are coated with Opadry® Yellow (20A120007). The Compound 1 crystalline form is used in the compositions described below.

Composition of Compound 1 IR Tablets

The quantitative compositions of the Compound 1 IR Tablets are presented in Table 1. Compound 1, 100 mg IR Tablets and Compound 1, 300 mg IR Tablets are dose proportional.

Table 1: Quantitative Compositions of Compound 1 IR Tablets

Component	Function	100 mg		300 mg	
		mg per tablet	(%w/w)	mg per tablet	(%w/w)
Compound 1 ¹	Drug substance	100.00	66.67	300.00	66.67
Hydroxypropyl Cellulose	Granulation Binder	7.50	5.00	22.50	5.00
Microcrystalline cellulose	Filler	36.50	24.33	109.50	24.33
Crospovidone	Disintegrant	4.50	3.00	13.50	3.00
Magnesium stearate ²	Lubricant	1.50	1.00	4.50	1.00
Total Tablet		150.00	100.00	450.00	100.00
^{1.} No overages are included in the formulation.					
^{2.} Magnesium stearate is of vegetable source.					

In an embodiment, the quantitative compositions of the Compound 1 IR Tablets are according to Table 1A. Compound 1, 100 mg IR Tablets and Compound 1, 300 mg IR Tablets are dose proportional.

Table 1A: Quantitative Compositions of Compound 1 IR Tablets

Component	Function	100 mg		300 mg	
		mg per tablet	(%w/w)	mg per tablet	(%w/w)
Compound 1 ¹	Drug substance	100.00	66.67	300.00	66.67
Hydroxypropyl Cellulose	Granulation Binder	7.50	5.00	22.50	5.00
Microcrystalline cellulose	Filler	37.25	24.83	111.75	24.83
Crospovidone	Disintegrant	4.50	3.00	13.50	3.00
Magnesium stearate ²	Lubricant	0.75	0.50	2.25	0.50
Total Tablet		150.00	100.00	450.00	100.00
^{1.} No overages are included in the formulation. ^{2.} Magnesium stearate is of vegetable source.					

A screening of superdisintegrants demonstrated that Crospovidone was a better disintegrant than Croscarmellose sodium (CCNa). Tablets composed of Croscarmellose sodium showed a marked increase in disintegration time during storage; whereas tablets composed of Crospovidone did not show any change in disintegration time during storage. Additional feasibility batches were conducted to assess the impact of various binders at different levels on disintegration time. Hydroxypropyl cellulose extra fine particle size grade (HPC EXF), Hydroxypropyl Methyl Cellulose low viscosity grade (Methocel E5 Premium LV) and Hydroxypropyl cellulose super low viscosity (HPC-SL) (see AAPS PharmSciTech 2013 Mar;14(1):151-9) were evaluated. On the basis of disintegration time and processability, HPC-SL was selected as the binder of choice for the Compound 1 IR Tablets.

Additional feasibility batches were conducted to assess the impact of various surfactants like Sodium lauryl sulfate (SLS) and Poloxamer (Kolliphor P 407) on Compound 1 drug release and found no obvious difference in dissolution between tablets with and without surfactants. Hence It was determined that a surfactant is not needed as a wetting agent in Compound 1 Tablets.

Additional feasibility batches were conducted to assess the impact of granulation fluid level, Compound 1 particle size and compression force on tablet dissolution.

Based on the feasibility batches, it was determined that Compound 1 with smaller particle size leads to better tablet properties and a more robust manufacturing process.

Example 2. Manufacturing of Compound 1 Tablets 100 mg and 300 mg

In order to develop a manufacturing process for the Compound 1 IR Tablets, a high shear wet granulation was selected. This selection was made based on the projected efficacious high dose necessitating the development of a high drug load formulation.

Formulation development focused on selecting the most appropriate super-disintegrant, binder and to determine if a wetting agent was required.

Manufacturing Formula for Initial Feasibility Development, CCNa with HPC EXF as Binder

- 5 The first feasibility batch was conducted using the super-disintegrant (CCNa) and binder (HPC EXF), the drug load was fixed at about 67% and SLS was included as a wetting agent.

Table 2. Manufacturing formula of Compound 1 Tablets 300 mg initial feasibility batch, CCNa and HPC EXF

Major Composition	CCNa and HPC EXF		
Material	mg/unit	% w/w	g/batch
Intra granular			
Compound 1	300.00	66.67	135.01
Croscarmellose Sodium (CCNa)	9.68	2.15	4.35
Hydroxypropyl cellulose (Klucel HPC EXF)	9.68	2.15	4.35
Sodium lauryl sulfate, SLS Fine	3.24	0.72	1.46
Granulating Fluid			
Purified Water	N/A	20.00*	29.03
Extra granular			
Microcrystalline Cellulose PH102	113.90	25.31	51.25
Croscarmellose Sodium	9.00	2.00	4.05
Magnesium stearate	4.50	1.00	2.03
Total	450.00	100.00	202.50

- 10 * Granulating fluid (%) to dry-mix weight

Manufacturing Procedure for Initial Feasibility Development, CCNa with HPC EXF as Binder

- Granulation:** Compound 1, Croscarmellose Sodium, Hydroxypropyl cellulose (EXF), and Sodium lauryl sulfate (SLS) were co-sifted through 20 mesh screen. Sifted materials were loaded into 1 L RMG bowl and dry mixing was performed for 05 minutes. Purified water was added into the mixture by using peristaltic pump at a fixed speed and granulation was performed with the below listed parameters in Table 3.

- Drying and Sizing:** Wet granules were charged into Tray Dryer with an inlet temperature of 60°C for 30 minutes. Semi-dried granules were milled through comil FZB-150 using 1.2 mm screen. Semi-dried granules were dried further until the desired LOD was attained. Drying parameters are listed in Table 4.

Table 3: Wet granulation parameters of initial feasibility batch, CCNa and HPC EXF

Stage	Stage	Impeller speed (rpm)	Chopper speed (rpm)	Time (min'sec")
	Dry mixing	150	Off	5'00"

Granulation (1L RMG bowl)	Water Addition	400	1000	10'00"
	Kneading	600	2000	1'00"
	Granulating fluid quantity: 120.0 g; percent of granulating fluid to dry-mix weight: 20.0%.			
Drying (Tray Dryer)	Stage	Set temp (°C)	Drying time (min)	LOD % (w/w) at 105°C
	Semi drying*	60	30	5.06
	Final drying	60	15	0.19
	*Semi-dried granules were milled using 1.2 mm screen with impeller speed of 1000 rpm.			

Blending: Microcrystalline Cellulose PH102 and Croscarmellose Sodium were co-sifted through a 30 mesh sieve and blended with dried granules for 10 minutes at 15 rpm using 1 L bin.

- 5 **Lubrication:** Magnesium stearate was sifted through a 60 mesh sieve, added to the above blend and mixed for 03 minutes at 15 rpm.

Table 4: Powder flow characteristics and sieve analysis details of initial feasibility batch, CCNa and HPC EXF

	Compound 1	Lubricated Blend
Bulk Density (g/ml)	0.521	0.541
Tapped Density (g/ml)	0.806	0.665
Compressibility Index (%)	35.36	18.76
Hausner's Ratio	1.547	1.231
Sieve#	PSD (%), sized granules	
20	0.33	
30	3.67	
40	6.33	
60	30.67	
80	21.00	
100	11.33	
120	13.33	
140	3.67	
200	6.33	
Pan	3.00	
#60 retained	41.00	
#60 passed	58.67	

- 10 **Compression:** The lubricated blend was compressed into tablets to a target weight of 450 mg using 15.6×7.4 mm oval shaped punches.

Table 5: Compression parameter of Compound 1 tablets 300 mg, initial feasibility batch, CCNa and HPC EXF

	Compound 1 Tablets 300 mg	
Main composition	CCNa and HPC EXF	
Description	Yellow colored, oval shaped uncoated tablets, plain on both	
Main Compression (kN)	13.70	
Thickness Scale (mm)	8.0	
Individual Weight (mg)	451 to 457	
Thickness (mm)	4.87 to 4.91	
Hardness (N)	122 to 133	
Disintegration Time (min' sec'')	2'49" to 3'46"	
Friability (% w/w)	0.19	
Remarks	Compression parameters were found satisfactory.	
Disintegration time impact on ambient storage for 12 days*		
Period (Day)	DT (min' sec'')	Hardness(N)
Initial (Day 0)	2'49" to 3'46"	122 to 133
Storage for 12 days	11'12" to 15'06"	125 to 130

*: Disintegration time was found satisfactory at initial stage. But tablets stored at ambient storage for 12 days showed an increased disintegration time, however hardness was not altered.

Observation: A wet granulation feasibility batch with intra and extra granular

- 5 Croscarmellose sodium was performed. Storage at ambient conditions resulted in a significant increase in disintegration time. This increase in disintegration time was assigned to a molecular interaction between the drug substance and CCNa. Hence, the use of Croscarmellose sodium was discontinued, and further formulation development work focused on the evaluation of Crospovidone and Sodium starch glycolate as suitable
- 10 disintegrants.

Evaluation of Crospovidone and Sodium starch glycolate (SSG)

- Two feasibility trial batches were executed with alternative superdisintegrants i.e., Crospovidone (Polyplasdone XL) and Sodium starch glycolate (Explotab). The disintegration
- 15 time of these two batches were measured immediately after manufacturing and after storage in ambient conditions.

Table 6: Manufacturing formula of Compound 1 Tablets 300 mg (Crospovidone vs SSG)

Disintegrant	Crospovidone			SSG		
Material	mg/unit	% w/w	g/batch	mg/unit	% w/w	g/batch
Intra granular						
Compound 1	300.00	66.67	30.00	300.00	66.67	30.00

Crospovidone (Polyplasdone XL)	9.68	2.15	0.97	N/A	N/A	N/A
Sodium starch glycolate Type A (Explotab) (SSG)	N/A	N/A	N/A	9.68	2.15	0.97
Hydroxypropyl cellulose (Klucel HPC EXF)	9.68	2.15	0.97	9.68	2.15	0.97
Sodium lauryl sulfate SLS Fine	3.24	0.72	0.32	3.24	0.72	0.32
Granulating Fluid						
Purified Water	N/A	16.60*	5.36	N/A	16.50*	5.32
Extra granular						
Microcrystalline Cellulose PH102	113.90	25.31	11.39	113.90	25.31	11.39
Crospovidone (Polyplasdone XL)	9.00	2.00	0.90	N/A	N/A	N/A
Sodium starch glycolate Type A (Explotab) (SSG)	N/A	N/A	N/A	9.00	2.00	0.90
Magnesium stearate	4.50	1.00	0.45	4.50	1.00	0.45
Total	450.00	100.00	45.00	450.00	100.00	45.00

* Granulating fluid (%) to dry-mix weight

Granulation: Compound 1, Hydroxypropyl cellulose (EXF), Sodium lauryl sulfate (SLS), and Crospovidone (Polyplasdone XL) / Sodium starch glycolate Type A (Explotab) were co-sifted through a 20 mesh screen. Sifted materials were loaded into a 200 mL Turbula and dry mixing was performed for 15 minutes. As the batch size was low, wet granulation was performed manually with an adequate quantity of water to produce desired granules.

Blending: Microcrystalline Cellulose PH102 and Crospovidone (Polyplasdone XL) / Sodium starch glycolate Type A (Explotab) were co-sifted through a 30 mesh screen. Sifted materials were loaded along with sized granules into the 0.2 L Turbula bin and blended for 10 minutes at 46 rpm.

Lubrication: Magnesium stearate was sifted through a 60 mesh sieve, added to the above blend and mixed for 05 minutes at 46 rpm.

Compression: The lubricated blend was compressed into tablets to a target weight of 450 mg using 16×6.5 mm, capsule shaped punches.

Table 7: Compression parameter of Compound 1 tablets 300 mg, disintegrant type selection, Crospovidone vs SSG

Disintegrant	Crospovidone	SSG
Description	Yellow colored, capsule shaped uncoated tablets, plain on both sides	Yellow colored, capsule shaped uncoated tablets, plain on both sides
Individual Weight (mg)	443 to 455	440 to 461
Thickness (mm)	4.66 to 4.77	4.50 to 4.67
Hardness (N)	107 to 114	101 to 124
Disintegration Time (min' sec")	2'01" to 2'20"	1'47" to 3'03"
Remarks	Compression parameters were found satisfactory	Compression parameters were found satisfactory

Table 8: Disintegration time of batch with Crospovidone and batch with SSG during the storage period

Batch	Period (Day)	Initial (Day 0)	Storage period (Ambient storage)			
Crospovidone*	DT (min' sec")	2'01" to 2'20"	3'05" (Day 1)	2'20" (Day 3)	3'25" (Day 4)	2'57" (Day 11)
	Hardness (N)	107 to 114	N/A			
SSG*	DT (min' sec")	1'47" to 3'03"	2'26" (Day 1)	2'53" (Day 3)	2'53" (Day 4)	2'28" (Day 11)
	Hardness (N)	101 to 124	N/A			

*: No change in disintegration time was observed after 11 days ambient storage for Crospovidone and Sodium starch glycolate prototypes.

Drug Release Profile, Disintegrant Type Selection, CCNa vs Crospovidone vs SSG

Table 9: Dissolution profile of Compound 1 Tablets 300 mg, disintegrant type selection batches, CCNa vs Crospovidone vs SSG

Medium	Drug release in 0.01M HCl (pH 2.0)								
Test conditions	Apparatus: USP-II	RPM: 50 RPM			Volume: 900 mL				
	Compound 1 % Release (300 mg)								
	Time (min)	5	10	15	20	30	45	60	250rpm/15min
Disintegrant: CCNa	1	13.5	22.1	28.7	N/A	58.4	68.8	73.8	105.2
	2	27.0	42.4	48.7	N/A	70.4	81.6	85.4	104.7
	3	16.1	26.8	38.0	N/A	69.9	76.7	80.9	104.1
	Mean	18.9	30.4	38.5	N/A	66.2	75.7	80.0	104.7
	RSD (%)	38.2	35.0	26.1	N/A	10.3	8.5	7.3	0.5
	1	52.0	65.9	74.0	80.7	85.3	88.5	90.3	100.8

Disintegrant: Crospovidone	2	65.9	77.1	83.8	87.4	90.9	92.9	94.5	101.9
	3	58.4	68.1	73.9	78.2	82.7	85.8	87.4	97.0
	Mean	58.8	70.4	77.2	82.1	86.3	89.1	90.7	99.9
	RSD (%)	11.9	8.4	7.4	5.8	4.8	4.1	3.9	2.6
Disintegrant: SSG	1	64.5	78.9	84.3	87.3	89.2	90.1	90.8	96.0
	2	55.6	75.6	84.4	88.8	92.1	93.5	94.1	98.0
	3	59.8	74.1	80.7	84.6	87.6	89.1	89.9	94.7
	Mean	60.0	76.2	83.2	86.9	89.6	90.9	91.6	96.2
	RSD (%)	7.5	3.2	2.5	2.5	2.5	2.6	2.4	1.7
Medium	Drug release in pH 6.8 Phosphate Buffer								
Test conditions	Apparatus: USP-II			RPM: 50 RPM		Volume: 900 mL			
	Compound 1 % Release (300 mg)								
	Time (min)	5	10	15	20	30	45	60	250rpm/15min
Disintegrant: CCNa	1	58.8	86.2	94.0	97.3	99.8	100.5	101.0	102.4
	2	46.6	65.9	79.0	83.6	86.7	88.0	88.8	102.1
	3	67.0	87.3	91.7	93.9	94.9	95.8	95.7	103.1
	Mean	57.5	79.8	88.2	91.6	93.8	94.8	95.1	102.5
	RSD (%)	17.9	15.1	9.2	7.8	7.1	6.6	6.4	0.5
Disintegrant: Crospovidone	1	36.3	47.9	55.2	60.8	67.4	73.1	75.8	87.7
	2	40.3	52.8	61.4	66.6	73.9	79.0	81.9	100.6
	3	35.6	47.7	53.8	58.3	64.5	70.2	73.7	98.7
	Mean	37.4	49.5	56.8	61.9	68.6	74.1	77.1	95.7
	RSD (%)	6.7	5.9	7.1	6.9	7.0	6.1	5.5	7.2
Disintegrant: SSG	1	53.1	69.0	76.2	79.9	82.7	83.6	84.3	94.0
	2	47.6	65.2	72.9	77.3	80.4	81.4	81.9	87.2
	3	55.7	75.6	83.1	87.0	89.6	90.5	90.7	93.1
	Mean	52.1	69.9	77.4	81.4	84.2	85.2	85.6	91.4
	RSD (%)	8.0	7.5	6.7	6.2	5.7	5.6	5.3	4.0

Conclusion:

Crospovidone: Granulation and compression parameters were found to be satisfactory.

- 5 Rapid disintegration was observed. Drug release in pH 6.8 phosphate buffer was slightly slower compared to drug release in 0.01 M HCl.

Sodium starch glycolate: Granulation and compression parameters were found to be satisfactory. Rapid disintegration was observed. Drug release in pH 6.8 phosphate buffer was similar compared to drug release in 0.01 M HCl.

Both disintegrants exhibited satisfactory disintegration efficiency compared to croscarmellose sodium prototypes. No change in disintegration was observed upon storage for tablets containing Crospovidone or SSG.

5 *Disintegrant Level Optimization Studies, Crospovidone vs Sodium starch glycolate (SSG)*

In order to optimize the level of super-disintegrant in the Compound 1 Tablets, batches with 2% intra granular and 2% extra granular disintegrant were produced. The dissolution of tablets was relatively slower than the 200 mg Powder in Capsule (PIC) for Compound 1 (i.e., 88% drug release in 5 minutes & 98% drug release in 10 minutes). Hence
10 feasibility batches were executed with 4% w/w intra and 2% w/w extra granular disintegrant to attain a rapid drug release profile.

Table 10: Manufacturing formula of Compound 1 Tablets 300 mg (disintegrant level optimization, Crospovidone vs SSG)

Disintegrant	Crospovidone			Sodium starch glycolate		
Material	mg/unit	% w/w	g/batch	mg/unit	% w/w	g/batch
Intra granular						
Compound 1	300.00	66.67	150.00	300.00	66.67	150.00
Crospovidone (Polyplasdone XL)	18.00	4.00	9.00	N/A	N/A	N/A
Sodium starch glycolate Type A (Explotab) (SSG)	N/A	N/A	N/A	18.00	4.00	9.00
Hydroxypropyl cellulose (Klucel HPC EXF)	9.68	2.15	4.84	9.68	2.15	4.84
Sodium lauryl sulfate SLS Fine	3.24	0.72	1.62	3.24	0.72	1.62
Granulating Fluid						
Purified Water	N/A	12.00*	19.86	N/A	12.00*	19.86
Extra granular						
Microcrystalline Cellulose PH102	105.58	23.46	52.79	105.58	23.46	52.79
Crospovidone (Polyplasdone XL)	9.00	2.00	4.50	N/A	N/A	N/A
Sodium starch glycolate Type A (Explotab) (SSG)	N/A	N/A	N/A	9.00	2.00	4.50
Magnesium stearate	4.50	1.00	2.25	4.50	1.00	2.25
Total	450.00	100.00	225.00	450.00	100.00	225.00

* Granulating fluid (%) to dry-mix weight

Manufacturing Procedure, Disintegrant Level Optimization Batches, Crospovidone vs SSG

Granulation: Compound 1, Hydroxypropyl cellulose (EXF), Sodium lauryl sulfate (SLS), and Crospovidone (Polyplasdone XL) / Sodium starch glycolate Type A (Explotab) were co-sifted through a 20 mesh screen. Sifted materials were loaded into 1 L RMG bowl and dry mixing was performed for 5 minutes. Purified water was added into the mixture by using peristaltic pump at a fixed speed and granulation was performed with the below listed parameters in Table 11.

Drying and Sizing: Wet granules were charged into a Tray Dryer with an inlet temperature of 60°C for 15 minutes. Semi-dried granules were milled through Comil FZB-150 using 1.2 mm screen. Semi-dried granules were dried further until the LOD reached less than 0.5% w/w at 105°C. Drying parameters are listed in Table 11.

Table 11: Wet granulation parameters of disintegrant level optimization batches, Crospovidone vs SSG

Wet granulation parameters of disintegrant level optimization batches, Crospovidone batch				
Stage	Stage	Impeller speed (rpm)	Chopper speed (rpm)	Time (min'sec")
Granulation (1L RMG bowl)	Dry mixing	220	Off	5'00"
	Water Addition	580	1550	6'15"
	Kneading	870	2200	1'00"
	Granulating fluid quantity: 19.85 g; percent of granulating fluid to dry-mix weight: 12.0%.			
Drying (Tray Dryer)	Stage	Set temp (°C)	Drying time (min)	LOD % (w/w) at 105°C
	Initial wet mass	--	--	9.93
	Semi drying*	60	15	0.71
	Final drying	60	15	0.35
*Semi-dried granules were milled using 1.2 mm screen with impeller speed of 1000 rpm.				
Wet granulation parameters of disintegrant level optimization batches, SSG batch				
Stage	Stage	Impeller speed (rpm)	Chopper speed (rpm)	Time (min'sec")
Granulation (1L RMG bowl)	Dry mixing	220	Off	5
	Water Addition	580	1550	7'28"
	Kneading	870	2200	1'00"
	Granulating fluid quantity: 19.85 g; percent of granulating fluid to dry-mix weight: 12.0%.			
Drying (Tray Dryer)	Stage	Set temp (°C)	Drying time (min)	LOD % (w/w) at 105°C
	Initial wet	--	--	12.35

	Semi	60	15	2.41
	Final drying	60	15	0.39
*Semi-dried granules were milled using 1.2 mm screen with impeller speed of 1000 rpm.				

Blending: Microcrystalline Cellulose PH102 and Crospovidone (Polyplasdone XL) / Sodium starch glycolate Type A (Explotab) (SSG) were co-sifted through a 30 mesh screen. Sifted materials were loaded along with sized granules into the 0.2 L Turbula bin and blended for 10 minutes at 46 rpm.

Lubrication: Magnesium stearate was sifted through a 60 mesh sieve, added to the above blend and mixed for 03 minutes at 46 rpm.

Compression: The lubricated blend was compressed into tablets to a target weight of 450 mg using 17×6.7 mm, capsule shaped punches.

10 **Table 12: Dissolution profile of Compound 1 Tablets 300 mg disintegrant level optimization, Crospovidone vs SSG**

Medium	Drug release in 0.01M HCl (pH 2.0)								
Test conditions	Apparatus: USP-II		RPM: 50 RPM			Volume: 900 mL			
	Compound 1 % Release (300 mg)								
	Time (min)	5	10	15	20	30	45	60	250rpm /15min
4% Intra + 2% Extra Crospovidone	1	62.0	76.0	82.0	85.0	87.4	89.0	89.9	98.6
	2	79.5	86.8	89.6	91.5	93.0	94.0	94.7	100.0
	3	74.1	83.0	86.6	88.6	91.2	92.9	94.0	100.0
	Mean	71.9	81.9	86.1	88.3	90.5	91.9	92.9	99.5
	RSD (%)	12.5	6.7	4.4	3.7	3.1	2.9	2.8	0.8
4% Intra + 2% Extra SSG	1	66.6	93.6	97.7	98.6	99.2	99.8	100.2	102.1
	2	59.6	87.1	90.6	92.4	94.0	94.8	95.3	99.7
	3	54.9	89.3	97.6	99.1	99.9	100.3	100.5	101.9
	Mean	60.4	90.0	95.3	96.7	97.7	98.3	98.7	101.2
	RSD (%)	9.7	3.7	4.3	3.9	3.3	3.1	3.0	1.3%
Medium	Drug release in pH 6.8 Phosphate					Buffer			
Test conditions	Apparatus: USP-II		RPM: 50 RPM			Volume: 900 mL			
	Compound 1 % Release (300 mg)								
	Time (min)	5	10	15	20	30	45	60	250rpm /15min
4% Intra + 2% Extra Crospovidone	1	53.4	66.7	75.3	81.9	88.0	90.8	93.0	100.1
	2	52.0	72.7	84.4	88.6	90.9	91.7	92.4	99.6
	3	66.2	75.4	80.3	83.6	86.3	88.4	89.6	97.7
	Mean	57.2	71.6	80.0	84.7	88.4	90.3	91.7	99.1
	RSD (%)	13.6	6.2	5.7	4.1	2.6	1.9	2.0	1.3
4% Intra + 2% Extra SS)	1	69.4	86.0	91.0	93.2	94.1	94.8	94.9	100.4
	2	63.7	79.9	85.7	88.1	90.6	90.9	91.5	97.4

	3	66.1	80.8	86.3	89.8	93.6	94.2	94.9	100.6
	Mean	66.4	82.2	87.7	90.4	92.8	93.3	93.8	99.4
	RSD (%)	4.3	4.0	3.3	2.9	2.1	2.3	2.1	1.8

Conclusion: Prototypes of disintegrant level optimizations (i.e., 4% intra and 2% extra granular Crospovidone/SSG) resulted in a satisfactory granulation and tablet properties. No significant difference in drug release was observed between 2% and 4% intra-granular disintegrant for SSG prototypes. Improved drug release profile was observed for 4% intra-granular Crospovidone prototypes than the 2% intra-granular Crospovidone batches in pH 6.8 phosphate buffer. However, drug release profiles were similar for both 2% and 4% intra-granular disintegrant prototypes in 0.01M HCl (pH 2.0).

It was observed that the disintegration time of tablets composed of 4% intra and 2% extra granular SSG increased from its initial disintegration time of 1'54"~2'36" minutes to 8'14" minutes after 20 days of room temperature storage. While the change in disintegration time upon storage did not have an impact on dissolution time, it is suspected that the change in disintegration time of the SSG prototypes would lead to a significant change in dissolution time with longer storage times. Therefore, SSG-containing prototypes were abandoned.

Drug release profiles of feasibility batches with different granulation vehicle levels i.e., 18%, 20%, and 23% w/w water showed that tablet hardness is directly impacting tablet drug release and disintegration time. Low hardness tablets produced using different granulation fluid levels resulted in a very rapid drug release profile (>90% drug released within 10 minutes). Optimum hardness tablets produced using different granulation fluid levels resulted also in a rapid drug release (>90% drug released within 20 minutes). High hardness tablets produced using different granulation fluid levels resulted in a relatively slower drug release profile than for other tablets at lower hardness levels (>90% drug release could be reached only at 60 minutes). However, optimum hardness tablets produced at different granulation fluid levels resulted in a similar drug release. This confirmed that tablet hardness has a higher impact on drug release than the granulation fluid level. Hence, it was critical to identify suitable hardness range before manufacturing.

Feasibility Batch Manufacturing with Hydroxypropyl Cellulose SL (HPC-SL) as a Binder

A feasibility batch was executed with HPC-SL as a binder and different concentrations of crospovidone were evaluated mainly to identify an optimum disintegrant concentration (2% vs 3% Crospovidone) that would lead to satisfactory drug release results. Fine grade Compound 1 (Particle size details: $D_{10}=24.3\ \mu$, $D_{50}=83.1\ \mu$, $D_{90}=211\ \mu$) was utilized in these feasibility batches, and tablets were compressed at different compression

forces to generate tablets with different hardness values (Low, Optimum, and High). Drug release profiles were generated for tablets compressed at different compression forces.

Table 13: Manufacturing formula of Compound 1 Tablets 300 mg, HPC-SL as a binder and fine grade Compound 1 (2% vs 3% Crospovidone)

Disintegrant + Binder	2% Crospovidone + 5%HPC-SL			3% Crospovidone + 5%HPC-SL		
Material	mg/unit	% w/w	g/batch	mg/unit	% w/w	g/batch
Intra granular						
Compound 1	300.00	66.67	150.00	300.00	66.67	150.00
Microcrystalline Cellulose PH102	114.00	25.33	57.00	109.50	24.33	54.75
Crospovidone (Polyplasdone XL)	9.00	2.00	4.50	13.50	3.00	6.75
Hydroxypropyl Cellulose SL	22.50	5.00	11.25	22.50	5.00	11.25
Granulating Fluid						
Purified Water	N/A	25.00*	55.69	N/A	25.00*	55.69
Extra granular						
Magnesium stearate	4.50	1.00	2.25	4.50	1.00	2.25
Total	450.00	100.00	225.00	450.00	100.00	225.00

5 * Granulating fluid (%) to dry-mix weight

Manufacturing Procedure for Feasibility batch with HPC-SL as a Binder and Fine Grade Compound 1 (2% vs 3% Crospovidone)

- Granulation:** Compound 1, Microcrystalline Cellulose PH102, Crospovidone (Polyplasdone XL) and Hydroxypropyl Cellulose SL were co-sifted through a 30 mesh screen. Sifted materials were loaded into a 4 L RMG bowl and dry mixing was performed for 10 minutes.
- Drying and Sizing:** Wet granules were charged into a Tray Dryer with an inlet temperature of 60°C for 20 minutes. Semi-dried granules were milled through a comil 193 using 1.143 mm screen. Semi-dried granules were dried further until the LOD reached less than 2.0% w/w at 105°C.
- 15

Table 14: Wet granulation parameters of feasibility batch with HPC-SL as a binder and fine grade Compound 1 (2% vs 3% Crospovidone)

Wet granulation parameters of feasibility batch with HPC-SL as a binder (2% Crospovidone)				
Stage	Stage	Impeller speed	Chopper speed (rpm)	Time (min'sec")
Granulation	Dry mixing	220	0	10'00"
	Water Addition	580	1550	7'28"
	Kneading	870	2200	1'00"

	Granulating fluid quantity: 55.70 g; percent of granulating fluid to dry-mix weight: 25.0%.			
Drying	Stage	Set temp (°C)	Drying time (min)	LOD % (w/w) at 105°C
	Dry mix	--	--	1.51
	Initial wet	--	--	21.65
	Semi	60	20	6.23
	Final drying	60	20	1.23
	*Semi-dried granules were milled using 1.143 mm screen with impeller speed of 1000 rpm.			
Wet granulation parameters of feasibility batch with HPC-SL as a binder (3% Crospovidone)				
Stage	Stage	Impeller speed	Chopper speed (rpm)	Time (min'sec'')
Granulation (1L RMG bowl)	Dry mixing	220	0	10'00"
	Water Addition	580	1550	7'20"
	Kneading	870	2200	1'00"
	Granulating fluid quantity: 55.73 g; percent of granulating fluid to dry-mix weight: 25.0%.			
Drying (Tray Dryer)	Stage	Set temp (°C)	Drying time (min)	LOD % (w/w) at 105°C
	Dry mix	--	--	1.48
	Initial wet mass	--	--	19.95
	Semi drying*	60	20	10.73
	Final drying	60	20	1.74
	*Semi-dried granules were milled using 1.143 mm screen with impeller speed of 1000 rpm.			

Lubrication: Magnesium stearate was sifted through a 60 mesh sieve and loaded along with sized granules into the 0.2 L Turbula bin and blended for 03 minutes at 46 rpm.

Compression: The lubricated granules were compressed into tablets with different hardness level to a target weight of 450 mg using 14×6.5 mm, oval shaped punches.

Observation and Conclusion: For feasibility batch with 2% Crospovidone, a higher disintegration time was observed for high hardness tablets and hardness changes had a great impact on tablet disintegration time. Drug release profile of optimum hardness tablets was slower and complete drug release was observed only at 45 minutes.

For feasibility batch with 3% Crospovidone, the disintegration time was satisfactory for tablets compressed at different hardness levels. The drug release profile of optimum hardness tablets was similar to that of high hardness tablets. Based on the disintegration time and drug release results, it can be concluded that tablet hardness had a minimal impact on drug release for feasibility batches with 3% Crospovidone. Hence 5% HPC-SL and 3% Crospovidone was selected for further studies.

Table 15: Manufacturing Compound 1 Tablet 100 mg & 300 mg, scale up batch (HPC-SL)

Material Name	Common Granules		100 mg Tablet	300 mg
Material	% w/w	g/batch	mg/Tab	mg/Tab
Intra granular				
Compound 1	66.67	1140.00	100.00	300.00
Microcrystalline Cellulose PH102	24.33	416.10	4.50	13.50
Crospovidone (Polyplasdone XL)	3.00	51.30	7.50	22.50
Hydroxypropyl Cellulose SL	5.00	85.50	36.50	109.50
Granulating Fluid				
Purified Water	23.00% w/w for dry mix			
Extra granular				
Magnesium stearate	1.00	17.10	1.50	4.50
Total	100.00	1710.00	150.00	450.00

Dry mixing: Compound 1, Microcrystalline Cellulose PH102, Crospovidone (Polyplasdone

- 5 XL) and Hydroxypropyl Cellulose SL were co-sifted through a 30 mesh screen. Sifted materials were loaded into a 6 L RMG bowl and dry mixing was performed for 10 minutes. Purified water was added into the mixture by using a peristaltic pump at a fixed speed, and granulation was performed.

Drying: Wet granules were loaded into a Fluid Bed Dryer (GPCG 2) with an inlet

- 10 temperature of 60°C. Drying was continued until the LOD reached less than 2.0% w/w at 105°C.

Lubrication: Magnesium stearate were sifted through a 60 mesh sieve and loaded along with sized granules into the 5 L bin blender and blended for 03 minutes at 15 rpm.

Compression:

- 15 100 mg Tablets: The lubricated granules were compressed into tablets with different hardness level to a target tablet weight of 150 mg using 7 mm, round shaped punches. Description of compressed tablets: Yellow colored, round shaped uncoated tablets, plain on both sides.

- 20 300 mg Tablets: The lubricated granules were compressed into tablets with different hardness level to a target tablet weight of 450 mg using 14×6.5 mm, oval shaped punches. Description of compressed tablets: Yellow colored, oval shaped uncoated tablets, GP letter on one side, plain on the other side.

Table 16: Dissolution profile of Compound 1 Tablets 100 mg and 300 mg

Medium	Drug release in 0.01M HCl (pH 2.0)								
Test conditions	Apparatus:	RPM: 60 RPM			Volume: 900 mL				
	Compound 1 % Release, 100 mg Tablets								
	Time (min)	5	10	15	20	30	45	60	250rpm /15min
Strength: 100 mg									
46 to 58 N Hardness 24 to 27min DT Highest Hardness	1	15.5	34.4	51.9	64.7	80.9	94.4	99.7	102.0
	2	15.8	32.8	47.3	59.9	80.4	93.1	100.1	103.5
	3	15.4	34.1	49.4	61.6	84.6	91.4	94.8	103.1
	Mean	15.6	33.8	49.6	62.1	82.0	93.0	98.2	102.9
	RSD (%)	1.6	2.6	4.6	3.9	2.8	1.6	3.0	0.7
48 - 55 N Hardness 12- 16 min DT High Hardness	1	23.6	39.9	55.0	69.5	96.0	100.6	100.8	102.1
	2	12.2	29.0	51.1	66.4	96.4	100.2	100.8	100.6
	3	17.4	39.6	53.8	70.5	96.6	99.8	99.4	99.9
	Mean	17.7	36.2	53.3	68.8	96.3	100.2	100.3	100.9
	RSD (%)	32.0	17.1	3.7	3.1	0.3	0.4	0.8	1.1
45 - 64 N Hardness 6 - 8 min DT Optimum Hardness	1	57.9	89.8	95.4	96.8	98.6	99.8	98.2	98.1
	2	39.4	74.3	94.2	99.0	101.5	102.0	102.2	101.3
	3	61.6	89.1	96.0	97.1	95.0	98.6	97.8	97.5
	Mean	52.9	84.4	95.2	97.6	98.4	100.1	99.4	99.0
	RSD (%)	22.5	10.4	1.0	1.2	3.3	1.7	2.4	2.1
37 - 44 N Hard 2 to 3 min DT Low Hardness	1	86.0	97.9	101.1	102.4	102.5	102.8	102.4	102.8
	2	87.3	100.4	101.2	101.8	100.4	100.7	101.0	101.0
	3	84.4	97.3	101.1	100.9	101.1	100.3	101.1	101.9
	Mean	85.9	98.5	101.1	101.7	101.3	101.3	101.5	101.9
	RSD (%)	1.7	1.7	0.0	0.7	1.1	1.3	0.8	0.9
18 - 26 N Hard	1	82.9	97.6	100.5	102.1	102.5	103.0	102.9	102.8
	2	86.4	99.3	102.6	103.5	103.5	103.4	103.4	103.6

Medium	Drug release in 0.01M HCl (pH 2.0)								
Test conditions 1 to 2 min DT Lowest Hardness	Apparatus:	RPM: 60 RPM			Volume: 900 mL				
	Compound 1 % Release, 100 mg Tablets								
	Time (min)	5	10	15	20	30	45	60	250rpm /15min
	3	88.2	100.1	102.6	103.6	104.0	103.9	104.0	103.9
	Mean	85.8	99.0	101.9	103.1	103.3	103.4	103.4	103.4
	RSD (%)	3.2	1.3	1.2	0.8	0.7	0.4	0.5	0.6
Strength: 300 mg									
168 - 186 N Hard 16 - 20 min DT Highest Hardness	1	31.7	59.5	82.1	93.3	97.3	97.6	98.3	99.6
	2	19.5	46.7	73.5	92.2	98.3	99.4	100.5	101.4
	3	22.6	47.5	70.7	89.3	97.7	100.3	101.0	102.6
	Mean	24.6	51.3	75.4	91.6	97.8	99.1	99.9	101.2
	RSD (%)	25.6	14.0	7.9	2.2	0.5	1.4	1.5	1.5
147 - 172 N Hard	1	33.6	59.0	82.4	93.8	97.7	97.9	98.0	99.3
	2	28.5	54.4	76.3	90.2	95.4	97.2	97.5	99.6

14 - 16 min DT High Hardness	3	28.4	58.2	83.0	93.7	97.3	97.8	98.2	99.1
	Mean	30.2	57.2	80.6	92.6	96.8	97.6	97.9	99.3
	RSD (%)	9.7	4.3	4.6	2.2	1.2	0.4	0.4	0.3
133 - 146 N Hard 07 - 09 min DT Optimum Hardness	1	60.4	91.9	97.4	97.9	97.9	99.2	99.2	99.4
	2	42.2	87.0	96.5	97.8	98.7	100.3	100.4	100.7
	3	46.4	90.7	99.6	99.9	100.5	101.2	101.1	101.2
	Mean	49.7	89.9	97.8	98.6	99.0	100.2	100.3	100.4
	RSD (%)	19.2	2.8	1.6	1.2	1.3	1.0	0.9	0.9
112 - 132 N Hard 3 - 5 min DT Low Hardness	1	74.9	94.0	97.8	98.6	99.2	98.7	98.9	99.4
	2	70.6	95.1	98.2	99.0	99.2	99.1	99.5	99.4
	3	79.9	94.0	96.3	96.8	97.0	97.4	97.7	97.5
	Mean	75.1	94.3	97.4	98.1	98.5	98.4	98.7	98.7
	RSD (%)	6.2	0.7	1.0	1.2	1.3	0.9	1.0	1.1
94 - 109 N Hard 1 - 2 min DT Lowest Hardness	1	84.7	97.3	100.3	101.6	102.4	102.9	103.0	103.3
	2	86.4	96.0	99.5	101.0	102.0	102.1	102.8	102.9
	3	87.9	98.7	100.8	101.2	101.8	102.0	101.8	102.0
	Mean	86.3	97.3	100.2	101.3	102.1	102.4	102.5	102.8
	RSD (%)	1.9	1.4	0.6	0.3	0.3	0.4	0.6	0.6

Physical observation during dissolution testing: 100 mg and 300 mg tablets

dissolution test using 60 rpm: Mild sticking at initial time point for all units and cone formation

were observed for later time points. 100 mg and 300 mg tablets using 75 rpm: Very mild

5 sticking at initial time point for all units but no cone formation were observed.

Table 17: Dissolution profile of Compound 1 Tablets 100 mg and 300 mg, 062G comil screen batch

Medium	Drug release in 0.01M HCl (pH 2.0)								
Test Conditions	Apparatus: USP-II			RPM: 60 RPM			Volume: 900 mL		
	Compound 1 % Release								
	Time (min)	5	10	15	20	30	45	60	250rpm /15min
100 mg Tablets	1	47.5	93.2	103.2	104.4	104.4	104.0	104.2	104.3
	2	48.3	93.1	100.5	101.3	101.0	100.7	101.1	100.8
	3	58.0	97.9	102.2	102.9	102.5	102.4	102.9	102.5
	Mean	51.3	94.7	102.0	102.9	102.6	102.4	102.7	102.5
	RSD (%)	11.3	2.9	1.3	1.5	1.7	1.6	1.5	1.7
300 mg Tablets	1	59.1	93.1	99.2	100.4	101.0	101.4	101.4	101.8
	2	55.2	92.0	98.3	100.3	101.3	101.1	101.4	101.3
	3	66.1	97.5	100.8	100.9	101.3	101.6	101.6	101.6
	Mean	60.1	94.2	99.4	100.5	101.2	101.4	101.5	101.6
	RSD (%)	9.2	3.0	1.3	0.3	0.2	0.2	0.1	0.2

Observation: During granulation, 27% w/w water was utilized to attain a desired granulation

10 end point. Kneading was performed for 60 seconds and granular mass was found optimum.

Wet masses were dried in a Retsch dryer (Fluidized dryer). After complete drying (LOD Below 2%), granules were divided into two equal portions and the two portions were co-milled through a 062R screen and a 062G screen, respectively. Compressibility index and Particle size distribution of sized granules were found to be similar for batches milled with the 062R screen or the 062G screen. Hence, dry milling can be performed with either the 062G screen or 062R screen. Compression parameters of 100 mg strength and 300 mg strength were found satisfactory. Hardness and DT matched with Lead prototype, scale up batches. No sticking tendency was observed during compression of the Compound 1 100 and 300 mg Tablets.

10

Conclusion and Summary

From the study results the following critical parameters were identified and summarized below:

Compound 1 particle size: A smaller Compound 1 particle size resulted in satisfactory granulation and compression properties in comparison with a large Compound 1 particle size. Granulation and compression were reproducible using a smaller Compound 1 particle size.

Disintegrant: Feasibility batches with Croscarmellose sodium and Sodium starch glycolate resulted in a significant increase in disintegration time upon storage at ambient conditions. Tablets composed of crospovidone did not show any change in disintegration time upon storage at ambient conditions and at accelerated conditions for up to six months. Therefore, crospovidone was selected as the binder of choice for the production of Compound 1 IR Tablets. The optimum level of crospovidone appears to be at least 3%. A 3% disintegrant level was identified to use in the production of Compound 1 IR Tablets.

Binder: Several binders were studied. Feasibility studies included prototypes composed of HPC EXF, povidone, HPMC E5 and HPC-SL. Tablets composed of povidone had good dissolution properties but high friability values. Tablets composed of HPMC E5 had good tablet hardness and friability but variable dissolution values at different hardness values. Tablets composed of HPC-SL had optimum hardness and friability values and dissolution values were fairly consistent. A study of the impact of compression force and Compound 1 particle size on tablet dissolution profiles showed that formulations composed of HPC-SL and 3% crospovidone have a sufficiently broad processing window to enable production at large scale.

Wetting agent: A few feasibility batches were conducted to assess if a wetting agent was required to facilitate granulation and dissolution. Results from these feasibility batches produced with SLS or without SLS and poloxamer showed that wetting agents are not required.

Granulation Fluid level: A granulation fluid level of approx. 25% w/w and using a small particle size Compound 1 resulted in a satisfactory granulation and compression properties. In an embodiment, the granulation fluid level is 20-30% w/w .

Compression:

5 100 mg Tablets:

Target weight =150.0 mg

Punch = 7 mm, round shaped punches, plain on both sides.

Target DT = ~Less than 8 minutes (Limit: <15 minutes)

300 mg Tablets:

10 Target weight = 450.0 mg

Punch: 14×6.5 mm, oval shaped punches, plain on both sides

Target DT = Less than 8 minutes (Limit: <15 minutes)

Dissolution method:

Medium: 0.01M HCl, Apparatus: USP Type II (Paddle), Rotational speed: 75 rpm, Volume:

15 900 mL.

In an embodiment, the quantitative compositions of the Compound 1 IR Tablets are according to Table 18.

Table 18: Unit formula for Compound 1 Tablets 100 mg and 300 mg

Strength	100 mg Tablets		300 mg Tablets	
Ingredient Name	Quantity (mg)	% w/w	Quantity (mg)	% w/w
Intra granular				
Compound 1	100.00	66.67	300.00	66.67
Crospovidone (Polyplasdone XL)	4.50	3.00	13.5	3.00
Hydroxypropyl Cellulose HPC-SL	7.50	5.00	22.50	5.00
Microcrystalline Cellulose PH-102	36.50	24.33	109.50	24.33
Granulation Fluid				
Purified water	--	20.00%*	--	20.00%*
Lubrication				
Magnesium Stearate (LIGAMED MF-2-V)	1.50	1.00	4.50	1.00
Total	150.00	100.00	450.00	100.00

20 * 20% w/w purified water will be added as a standard initial quantity for granulation and final quantity of purified water shall be finalized based on granulation end point.

Compositions in Table 18A show improved tablet properties such as reducing the sensitivity of the tablet properties, for example, hardness and disintegration and thus dissolution due to

over lubrication. In an embodiment, the quantitative compositions of the Compound 1 IR Tablets are according to Table 18A.

Table 18A: Unit formula for Compound 1 Tablets 100 mg and 300 mg

Strength	100 mg Tablets		300 mg Tablets	
Ingredient Name	Quantity (mg)	% w/w	Quantity (mg)	% w/w
Intra granular				
Compound 1	100.00	66.67	300.00	66.67
Crospovidone XL	4.50	3.00	13.50	3.00
Hydroxypropyl Cellulose HPC-SL	7.50	5.00	22.50	5.00
Microcrystalline Cellulose PH-101	37.25	24.83	111.75	24.83
Magnesium Stearate	0.75	0.50	2.25	0.50
Total	150.00	100.00	450.00	100.00

- 5 In an embodiment, the quantitative compositions of the Compound 1 IR Tablets are according to Table 18B.

Table 18B: Unit formula for Compound 1 Tablets 100 mg and 300 mg with Coating

Strength	100 mg Tablets		300 mg Tablets	
Ingredient Name	Quantity (mg)	% w/w	Quantity (mg)	% w/w
Intra granular				
Compound 1	100.00	66.67	300.00	66.67
Crospovidone XL	4.50	3.00	13.50	3.00
Hydroxypropyl Cellulose HPC-SL	7.50	5.00	22.50	5.00
Microcrystalline Cellulose PH-101	37.25	24.83	111.75	24.83
Magnesium Stearate	0.75	0.50	2.25	0.50
Total Core	150.00	100.00	450.00	100.00
Opadry® Yellow	4.5	3.0	13.5	3.0
Total Coated Tablet	154.50	103.00	463.50	103.00

Clinical Batch Manufacturing Procedure and Process Flow Chart

- 10 **Compound 1 Milling (Applicable only if higher particle size Compound 1 used for granulation)**

- The comil U5 with 024R screen for 1 cycle was used to the Compound 1, then the resulting material was further milled using by 006R screen for 1 cycle (determined further milling required based on milled Compound 1 PSD).

Dry mixing

- Compound 1, Microcrystalline Cellulose PH102, Crospovidone (Polyplasdone XL) and Hydroxypropyl Cellulose SL were co-sifted through a 30 mesh screen.
 - The sifted materials were loaded into high shear granulator and underwent dry mixing
- 5 for 10 minutes with a slow Impeller speed and chopper off.

Binder Addition and Kneading

- Purified water was added into the mixture by using peristaltic pump with a target addition time of ~8 minutes with slow Impeller and chopper speeds.
- Kneading was performed for 1 minute with fast Impeller and chopper speeds.

10 Drying

- The wet granules were loaded into Fluid Bed Dryer and underwent drying with an inlet temperature of 60°C. The wet granules were then dried until the LOD reached less than 2.0% w/w.

Dry Milling

- 15 • The dried granules were milled through Co-mill U5 using 062G/062R screen.

Lubrication

- Magnesium stearate was sifted through a 60 mesh screen to the granules and the resulting materials were lubricated for 5 minutes. *Note: lubrication time was changed to 3 minutes from 5 minutes based on the observations (lubrication stage) from GMP*
- 20 *Clinical batch.*

Powder Flow Characteristics

- Bulk density & tapped density tests and sieve analysis were performed.

Compression100 mg Tablets:

- 25 • Target weight: 150 mg
- Punch: 7 mm, round shaped punches, plain on both sides.
 - Average tablet weight (n=10): $1500 \pm 5\%$ (1425 to 1575 mg)
 - Individual tablet weight: $150 \pm 7.5\%$ (139 to 161 mg)
 - Hardness: Target ~40N
- 30 • Disintegration time: NMT 8 minutes for compression set up; NMT 12 minutes for in-process.
- Friability: NMT 0.5% w/w for compression set up; NMT 1.0% w/w for in-process test.

300 mg Tablets:

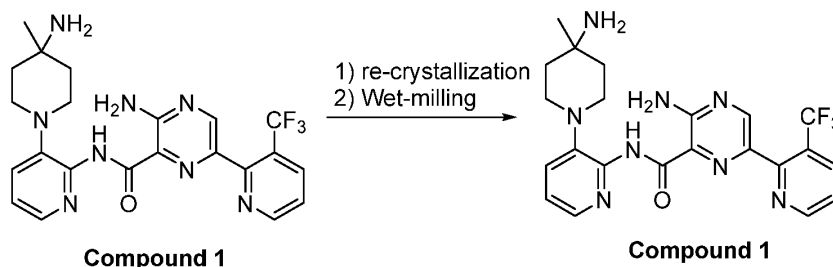
- 35 • Target weight: 450 mg
- Punch: 14×6.5 mm, oval shaped punches, plain on both sides.
 - Average tablet weight (n=10): $4500 \pm 5\%$ (4275 to 4725 mg)

- Individual tablet weight: $450 \pm 7.5\%$ (417 to 483 mg)
 - Hardness: Target ~100N
 - Disintegration time: NMT 8 minutes for compression set up; NMT 12 minutes for in-process.
- 5 • Friability: NMT 0.5% w/w for compression set up; NMT 1.0% w/w for in-process test.

Manufacturing process flow chart is shown in figure 3.

In an embodiment, USP/NF is the quality reference for hydroxypropyl cellulose, microcrystalline cellulose, croscopovidone, and magnesium stearate. "USP" refers to the United States Pharmacopeia. "NF" refers to National Formulary. In an embodiment, Ph. Eur. is the quality reference for hydroxypropyl cellulose, microcrystalline cellulose, croscopovidone, and magnesium stearate. "Ph. Eur." refers to the European Pharmacopoeia.

Example 3. Alternative procedure to prepare Compound 1 crystalline form



15 Ethanol (714 g), 3-amino-N-(3-(4-amino-4-methylpiperidin-1-yl)pyridin-2-yl)-6-(3-(trifluoromethyl)pyridin-2-yl)pyrazine-2-carboxamide (Compound 1) (210 g, 1.00 equiv) and water (861 g) were added to a Reactor (R1). The slurry was heated to 55°C for 1 h to obtain a clear solution, which was filtered to Reactor 2 (R2). A mixture of ethanol and water (107 g, 0.23:0.28 wt ratio of EtOH/water) was used to rinse R1 and then filtered into R2. The temperature of the solution in R2 was adjusted to 45°C, then cooled to 35°C over 1 h and then 3-amino-N-(3-(4-amino-4-methylpiperidin-1-yl)pyridin-2-yl)-6-(3-(trifluoromethyl)pyridin-2-yl)pyrazine-2-carboxamide (Compound 1, 1.1 g) seed crystals were added to R2. The resulting slurry in R2 was stirred at 35°C for 5 h, before adding water (1680 g) over 8 h at 35°C. The contents of R2 was cooled to 5°C over 5 h, and then stirred at 5°C for 3 h. The slurry was then wet-milled until the particle size distribution target was met (d50 range = 30-65 µm). The slurry was filtered, the resulting solid was washed with water (420 g) and the solid was then dried under vacuum at 55°C for 20 h to yield 3-amino-N-(3-(4-amino-4-methylpiperidin-1-yl)pyridin-2-yl)-6-(3-(trifluoromethyl)pyridin-2-yl)pyrazine-2-carboxamide (Compound 1) (190.7 g, 99.9% purity, 99.8 wt% assay, 90.6% yield) as a pale yellow solid. MS (ESI, *m/z*): 473.2024 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.60 (s, 1H), 8.96 (dd,

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$J = 4.7, 1.0 \text{ Hz, } 1\text{H}$), $8.75 \text{ (s, } 1\text{H)}$, $8.40 \text{ (dd, } J = 8.1, 1.3 \text{ Hz, } 1\text{H)}$, $8.10 \text{ (dd, } J = 4.8, 1.6 \text{ Hz, } 1\text{H)}$, $8.05 \text{ (br. s, } 2\text{H)}$, $7.72 \text{ (dd, } J = 7.9, 4.8 \text{ Hz, } 1\text{H)}$, $7.55 \text{ (dd, } J = 7.9, 1.6 \text{ Hz, } 1\text{H)}$, $7.14 \text{ (dd, } J = 7.8, 4.8 \text{ Hz, } 1\text{H)}$, $2.90 - 2.84 \text{ (m, } 2\text{H)}$, $2.67 - 2.63 \text{ (m, } 2\text{H)}$, $1.24 - 1.12 \text{ (m, } 6\text{H)}$, $0.60 \text{ (s, } 3\text{H)}$.

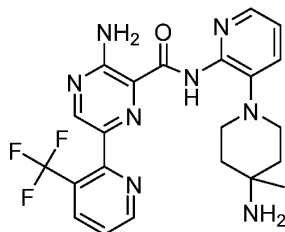
XRPD: Figure 1 (using Cu-K α radiation). DSC: Figure 2.

5 Particular embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Upon reading the foregoing, description, variations of the disclosed embodiments may become apparent to individuals working in the art, and it is expected that those skilled artisans may employ such variations as appropriate. Accordingly, it is intended that the invention be practiced otherwise than as
10 specifically described herein, and that the invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

15 All patent applications, patents, and printed publications cited herein are incorporated herein by reference in the entireties, except for any definitions, subject matter disclaimers or disavowals, and except to the extent that the incorporated material is inconsistent with the express disclosure herein, in which case the language in this disclosure controls.

CLAIMS

1. A pharmaceutical composition comprising:
a superdisintegrant;
a binder;
5 a lubricant;
a filler;
and Compound 1:

**(1)**

- 10 or a pharmaceutically acceptable salt thereof.
2. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises about 1 – 5 % w/w superdisintegrant.
- 15 3. The pharmaceutical composition of any one of claims 1 or 2, wherein the pharmaceutical composition comprises about 3 – 7 % w/w binder.
4. The pharmaceutical composition of any one of claims 1 to 3, wherein the pharmaceutical composition comprises about 0.25 – 3 % w/w lubricant.
- 20 5. The pharmaceutical composition of any one of claims 1 to 4, wherein the pharmaceutical composition comprises about 15 – 35 % w/w filler.
6. The pharmaceutical composition of any one of claims 1 to 5, wherein the pharmaceutical composition comprises about 45 – 85 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.
- 25 7. The pharmaceutical composition of any one of claims 1 to 6, comprising:
about 2 – 4 % w/w superdisintegrant;
30 about 4 – 6 % w/w binder;
about 20 – 30 % w/w filler;
about 0.25 – 2 % w/w lubricant; and

about 50 – 80 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

8. The pharmaceutical composition of any one of claims 1 to 7, comprising:
about 3 % w/w superdisintegrant;
5 about 5 % w/w binder;
about 25 % w/w filler;
about 0.50 % w/w lubricant; and
about 67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.
- 10 9. The pharmaceutical composition of any one of claims 1 to 7, comprising:
3 % w/w superdisintegrant;
5 % w/w binder;
24.83 % w/w filler;
0.50 % w/w lubricant; and
15 66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.
10. The pharmaceutical composition of any one of claims 1 to 9, wherein the superdisintegrant is crospovidone.
- 20 11. The pharmaceutical composition of any one of claims 1 to 10, wherein the binder is hydroxypropyl cellulose.
12. The pharmaceutical composition of claim 11, wherein the hydroxypropyl cellulose is hydroxypropyl cellulose of super low viscosity.
- 25 13. The pharmaceutical composition of any one of claims 1 to 12, wherein the filler is microcrystalline cellulose.
14. The pharmaceutical composition of any one of claims 1 to 13, wherein the lubricant is
30 magnesium stearate.
15. The pharmaceutical composition of any one of claims 1 to 7 and 10 to 13, comprising:
about 2 – 4 % w/w crospovidone;
35 about 4 – 6 % w/w hydroxypropyl cellulose super low viscosity;
about 20 – 30 % w/w microcrystalline cellulose;
about 0.25 – 2 % w/w magnesium stearate; and

about 50 – 80 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

16. The pharmaceutical composition of any one of claims 1 to 8 and 10 to 15, comprising:

- 5 about 3 % w/w crospovidone;
 about 5 % w/w hydroxypropyl cellulose super low viscosity;
 about 25 % w/w microcrystalline cellulose;
 about 0.50 % w/w magnesium stearate; and
 about 67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

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17. The pharmaceutical composition of any one of claims 1 to 7 and 9 to 14, comprising:

- 3 % w/w crospovidone;
 5 % w/w hydroxypropyl cellulose super low viscosity;
 24.83 % w/w microcrystalline cellulose;
15 0.50 % w/w magnesium stearate; and
 66.67 % w/w of Compound 1, or a pharmaceutically acceptable salt thereof.

18. The pharmaceutical composition of any one of claims 1 to 17, wherein the pharmaceutical composition comprises Compound 1.

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19. The pharmaceutical composition of any one of claims 1 to 18, wherein the Compound 1 is in a crystalline form.

20. The pharmaceutical composition of claim 19, wherein the Compound 1 is in a
25 crystalline form characterized by an XRPD diffractogram comprising at least three or at least
four peaks expressed in degrees-2-theta at angles ($\pm$ 0.2 degrees) selected from the group
consisting of about 8.3, 15.0, 16.6, 25.0, 23.1, 11.8, 22.4, and 23.7.

21. The pharmaceutical composition of claim 19, wherein the Compound 1 is in a
30 crystalline form characterized by an XRPD diffractogram depicted in Figure 1.

22. The pharmaceutical composition of any one of claims 1 to 21, wherein the pharmaceutical composition is in tablet form.

35 23. The pharmaceutical composition of any one of claims 1 to 22, wherein the tablet is an immediate release form.

24. The pharmaceutical composition of claim 22 or 23, wherein the tablet is coated with a film.
25. The pharmaceutical composition of any one claims 22 to 24, wherein the disintegration
5 time of the tablet is less than 10 minutes.
26. The pharmaceutical composition of any one of claims 22 to 25, wherein the friability of the tablet is less than 0.5% w/w.
- 10 27. The pharmaceutical composition of any one of claims 22 to 26, wherein the dissolution of the tablet is greater than 80% at 15 minutes.
28. The pharmaceutical composition of any one of claims 1 to 27, wherein the pharmaceutical composition comprises about 25 mg to 400 mg free base equivalent of
15 Compound 1.
29. The pharmaceutical composition of any one of claims 1 to 28, wherein the pharmaceutical composition comprises 100 mg free base equivalent of Compound 1.
- 20
30. The pharmaceutical composition of any one of claims 1 to 28, wherein the pharmaceutical composition comprises 300 mg free base equivalent of Compound 1.
31. The pharmaceutical composition of any one of claims 1 to 30, wherein the
25 pharmaceutical composition is administered orally.
32. A method of treating cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of any one of claims 1 to 31.
- 30
33. The method of claim 32, wherein the cancer is uveal melanoma.
34. The method of claim 32 or 33, wherein the cancer is metastatic uveal melanoma.
- 35 35. The method of any one of claims 32 to 34, wherein the cancer harbors GNAQ mutations.

36. The method of any one of claims 32 to 35, wherein the cancer harbors GNA11 mutations.