

## METHODS OF TREATING ESTROGEN RECEPTOR-MEDIATED DISORDERS

### RELATED APPLICATIONS

[0001] This application claims priority to and benefit of U.S. Application No. 63/413,475, filed October 5, 2022, the entire contents of which are hereby incorporated by reference.

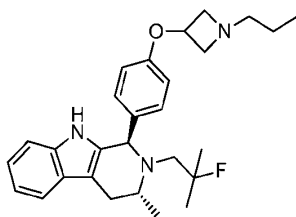
### BACKGROUND

[0002] Breast cancer is the most frequently diagnosed cancer in women. Around 5 to 10% of cases are metastatic at diagnosis, and close to 30% of patients with early stage disease will go on to relapse and develop metastatic disease. Reinert, T., & Barrios, C. H., *Therapeutic Advances in Medical Oncology*, 7(6), 304–320 (2015); Sini, V., Cinieri, S., Conte, P., Laurentiis, M. D., Leo, A. D., Tondini, C., & Marchetti, P., *Critical Reviews in Oncology/Hematology*, 100, 57–68 (2016). Endocrine therapy is the first line of treatment for advanced stage estrogen receptor positive cancer. Most patients develop resistance to endocrine therapy over time, however. Alternative treatments, such as fulvestrant, a selective estrogen receptor degrader, exist but have limited potential due to poor bioavailability.

### SUMMARY

[0003] The present disclosure provides, among other things, methods of treating, stabilizing, or lessening the severity or progression of estrogen receptor-mediated diseases, disorders, and conditions via administration of an orally bioavailable estrogen receptor antagonist and an orally bioavailable CDK4/6 inhibitor.

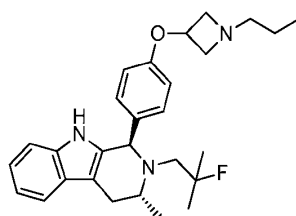
[0004] In some embodiments, the present disclosure provides a method of treating an estrogen receptor-mediated disease in a subject comprising administering to the subject a composition comprising Compound 1



**Compound 1**

or a pharmaceutically acceptable salt thereof, in combination with a composition comprising ribociclib, or a pharmaceutically acceptable salt thereof.

[0005] In some embodiments, the present disclosure provides a kit comprising a composition comprising Compound 1



**Compound 1**

or a pharmaceutically acceptable salt thereof, and a composition comprising ribociclib, or a pharmaceutically acceptable salt thereof, optionally wherein the kit comprises a label indicating that Compound 1 and ribociclib are useful for the treatment of estrogen receptor mediated-diseases, disorders, and conditions.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0006] **FIG. 1A** is a plot illustrating mean (SD) Compound 1 plasma concentration-time profiles following a single oral dose of 30 mg Compound 1 as monotherapy and in combination with 600 mg ribociclib.

[0007] **FIG. 1B** is a plot illustrating mean (SD) Compound 1 plasma concentration-time profiles following a single oral dose of 60 mg Compound 1 as monotherapy and in combination with 600 mg ribociclib.

[0008] **FIG. 1C** is a plot illustrating mean (SD) Compound 1 plasma concentration-time profiles following a single oral dose of 120 mg Compound 1 as monotherapy and in combination with 600 mg ribociclib.

[0009] **FIG. 2A** is a plot illustrating steady state Compound 1 plasma concentration-time profiles for 30 mg Compound 1 in combination with 600 mg ribociclib and mean (SD) Compound 1 steady state plasma concentration-time profiles for 30 mg Compound 1 as monotherapy.

[0010] **FIG. 2B** is a plot illustrating steady state Compound 1 plasma concentration-time profiles for 60 mg Compound 1 in combination with 600 mg ribociclib and mean (SD) Compound 1 steady state plasma concentration-time profiles for 60 mg Compound 1 as monotherapy.

[0011] FIG. 3 is a plot illustrating geometric mean (SD) ribociclib plasma pharmacokinetic parameters following a single oral dose for 600 mg ribociclib as a monotherapy and in combination with 3 different doses of Compound 1.

[0012] FIG. 4 is a plot illustrating steady state geometric mean (SD) ribociclib plasma dose-normalized pharmacokinetic parameters for 600 mg ribociclib as a monotherapy and in combination with 2 different doses of Compound 1.

### DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0013] The present disclosure provides, among other things, methods of treating estrogen receptor-mediated diseases in a subject comprising administering a composition comprising Compound 1 or a pharmaceutically acceptable salt thereof, in combination with a composition comprising ribociclib or a pharmaceutically acceptable salt thereof. In particular, the present disclosure encompasses an insight that certain synergies may be achieved when combining Compound 1 and ribociclib when treating an estrogen receptor-mediated disease relative to administration of Compound 1 or ribociclib administered in isolation.

#### Definitions

[0014] **About:** As used herein, the term “about” refers to a value that is similar, in context to the referenced value. In general, those skilled in the art, familiar with the context, will appreciate the relevant degree of variance encompassed by “about” in that context. For example, in some embodiments, the term “about” may encompass a range of values that are within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less of the referred value. In some embodiments, “about” refers to  $\pm 10\%$ ,  $\pm 9\%$ ,  $\pm 8\%$ ,  $\pm 7\%$ ,  $\pm 6\%$ ,  $\pm 5\%$ ,  $\pm 4\%$ ,  $\pm 3\%$ ,  $\pm 2\%$ ,  $\pm 1\%$  of a referenced value.

[0015] **Administration:** As used herein, the term “administration” typically refers to the administration of a composition to a subject or system, for example to achieve delivery of an agent that is, or is included in or otherwise delivered by, the composition.

[0016] **Agent:** As used herein, the term “agent” refers to an entity (e.g., for example, a lipid, metal, nucleic acid, polypeptide, polysaccharide, small molecule, etc., or complex, combination, mixture or system [e.g., cell, tissue, organism] thereof), or phenomenon (e.g., heat, electric current or field, magnetic force or field, etc.).

[0017] **Antagonist:** As used herein, the term “antagonist” may refer to an agent, or condition whose presence, level, degree, type, or form is associated with a decreased level or activity of a target. An antagonist may include an agent of any chemical class including, for example, small molecules, polypeptides, nucleic acids, carbohydrates, lipids, metals, and/or any other entity that shows the relevant inhibitory activity. In some embodiments, an antagonist may be a “direct antagonist” in that it binds directly to its target; in some embodiments, an antagonist may be an “indirect antagonist” in that it exerts its influence by means other than binding directly to its target; e.g., by interacting with a regulator of the target, so that the level or activity of the target is altered). In some embodiments, an “antagonist” may be referred to as an “inhibitor”.

[0018] **Associated:** Two events or entities are “associated” with one another, as that term is used herein, if the presence, level, degree, type and/or form of one is correlated with that of the other. For example, a particular entity (e.g., polypeptide, genetic signature, metabolite, microbe, etc.) is considered to be associated with a particular disease, disorder, or condition, if its presence, level and/or form correlates with incidence of and/or susceptibility to the disease, disorder, or condition (e.g., across a relevant population). In some embodiments, two or more entities are physically “associated” with one another if they interact, directly or indirectly, so that they are and/or remain in physical proximity with one another. In some embodiments, two or more entities that are physically associated with one another are covalently linked to one another; in some embodiments, two or more entities that are physically associated with one another are not covalently linked to one another but are non-covalently associated, for example by means of hydrogen bonds, van der Waals interaction, hydrophobic interactions, magnetism, and combinations thereof.

[0019] **Biological Sample:** As used herein, the term “biological sample” typically refers to a sample obtained or derived from a biological source (e.g., a tissue or organism or cell culture) of interest, as described herein. In some embodiments, a source of interest comprises an organism, such as an animal or human. In some embodiments, a biological sample is or comprises biological tissue or fluid. In some embodiments, a biological sample may be or comprise bone marrow; blood; blood cells; ascites; tissue or fine needle biopsy samples; cell-containing body fluids; free floating nucleic acids; sputum; saliva; urine; cerebrospinal fluid, peritoneal fluid; pleural fluid; feces; lymph; gynecological fluids; skin swabs; vaginal swabs; oral swabs; nasal swabs; washings or lavages such as a ductal lavages or bronchoalveolar lavages; aspirates; scrapings; bone marrow

specimens; tissue biopsy specimens; surgical specimens; feces, other body fluids, secretions, and/or excretions; and/or cells therefrom, etc. In some embodiments, a biological sample is or comprises cells obtained from an individual. In some embodiments, obtained cells are or include cells from an individual from whom the sample is obtained. In some embodiments, a sample is a “primary sample” obtained directly from a source of interest by any appropriate means. For example, in some embodiments, a primary biological sample is obtained by methods selected from the group consisting of biopsy (e.g., fine needle aspiration or tissue biopsy), surgery, collection of body fluid (e.g., blood, lymph, feces etc.), etc. In some embodiments, as will be clear from context, the term “sample” refers to a preparation that is obtained by processing (e.g., by removing one or more components of and/or by adding one or more agents to) a primary sample. For example, filtering using a semi-permeable membrane. Such a “processed sample” may comprise, for example nucleic acids or proteins extracted from a sample or obtained by subjecting a primary sample to techniques such as amplification or reverse transcription of mRNA, isolation and/or purification of certain components, etc.

**[0020]     *Biomarker*:** The term “biomarker” is used herein, consistent with its use in the art, to refer to an entity (or form thereof) whose presence, or level, correlates with a particular biological event or state of interest, so that it is considered to be a “marker” of that event or state. To give but a few examples, in some embodiments, a biomarker may be or comprise a marker for a particular disease state, or for likelihood that a particular disease, disorder or condition may develop, occur, or reoccur. In some embodiments, a biomarker may be or comprise a marker for a particular disease or therapeutic outcome, or likelihood thereof. Thus, in some embodiments, a biomarker is predictive, in some embodiments, a biomarker is prognostic, in some embodiments, a biomarker is diagnostic, of the relevant biological event or state of interest.

**[0021]     *Combination therapy*:** As used herein, the term “combination therapy” refers to those situations in which a subject is concomitantly exposed to two or more therapeutic regimens (e.g., two or more therapeutic agents). In some embodiments, the two or more regimens may be administered concomitantly; in some embodiments, such regimens may be administered sequentially (e.g., all “doses” of a first regimen are administered prior to administration of any doses of a second regimen); in some embodiments, such agents are administered in overlapping dosing regimens. In some embodiments, “administration” of combination therapy may involve administration of one or more agent(s) or modality(ies) to a subject receiving the other agent(s) or

modality(ies) in the combination. For clarity, combination therapy does not require that individual agents be administered together in a single composition (or even necessarily at the same time), although in some embodiments, two or more agents, or active moieties thereof, may be administered together in a combination composition, or even in a combination compound (e.g., as part of a single chemical complex or covalent entity).

**[0022]     *Comparable:*** As used herein, the term “comparable” refers to two or more agents, entities, situations, sets of conditions, etc., that may not be identical to one another but that are sufficiently similar to permit comparison there between so that one skilled in the art will appreciate that conclusions may reasonably be drawn based on differences or similarities observed. In some embodiments, comparable sets of conditions, circumstances, individuals, or populations are characterized by a plurality of substantially identical features and one or a small number of varied features. Those of ordinary skill in the art will understand, in context, what degree of identity is required in any given circumstance for two or more such agents, entities, situations, sets of conditions, etc. to be considered comparable. For example, those of ordinary skill in the art will appreciate that sets of circumstances, individuals, or populations are comparable to one another when characterized by a sufficient number and type of substantially identical features to warrant a reasonable conclusion that differences in results obtained or phenomena observed under or with different sets of circumstances, individuals, or populations are caused by or indicative of the variation in those features that are varied.

**[0023]     *Corresponding to:*** As used herein, the phrase “corresponding to” refers to a relationship between two entities, events, or phenomena that share sufficient features to be reasonably comparable such that “corresponding” attributes are apparent. For example, in some embodiments, the term may be used in reference to a compound or composition, to designate the position and/or identity of a structural element in the compound or composition through comparison with an appropriate reference compound or composition. For example, in some embodiments, a monomeric residue in a polymer (e.g., an amino acid residue in a polypeptide or a nucleic acid residue in a polynucleotide) may be identified as “corresponding to” a residue in an appropriate reference polymer. For example, those of ordinary skill will appreciate that, for purposes of simplicity, residues in a polypeptide are often designated using a canonical numbering system based on a reference related polypeptide, so that an amino acid “corresponding to” a residue at position 190, for example, need not actually be the 190<sup>th</sup> amino acid in a particular amino acid

chain but rather corresponds to the residue found at 190 in the reference polypeptide; those of ordinary skill in the art readily appreciate how to identify "corresponding" amino acids. For example, those skilled in the art will be aware of various sequence alignment strategies, including software programs such as, for example, BLAST, CS-BLAST, CUSASW++, DIAMOND, FASTA, GGSEARCH/GLSEARCH, Genoogle, HMMER, HHpred/HHsearch, IDF, Infernal, KLAST, USEARCH, parasail, PSI-BLAST, PSI-Search, ScalaBLAST, Sequilab, SAM, SSEARCH, SWAPHI, SWAPHI-LS, SWIMM, or SWIPE that can be utilized, for example, to identify "corresponding" residues in polypeptides and/or nucleic acids in accordance with the present disclosure.

**[0024]     *Dosage form or unit dosage form:*** Those skilled in the art will appreciate that the term "dosage form" may be used to refer to a physically discrete unit of an active agent (e.g., a therapeutic or diagnostic agent) for administration to a subject. Typically, each such unit contains a predetermined quantity of active agent. In some embodiments, such quantity is a unit dosage amount (or a whole fraction thereof) appropriate for administration in accordance with a dosing regimen that has been determined to correlate with a desired or beneficial outcome when administered to a relevant population (i.e., with a therapeutic dosing regimen). Those of ordinary skill in the art appreciate that the total amount of a therapeutic composition or agent administered to a particular subject is determined by one or more attending physicians and may involve administration of multiple dosage forms.

**[0025]     *Dosing regimen or therapeutic regimen:*** Those skilled in the art will appreciate that the terms "dosing regimen" and "therapeutic regimen" may be used to refer to a set of unit doses (typically more than one) that are administered individually to a subject, typically separated by periods of time. In some embodiments, a given therapeutic agent has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which is separated in time from other doses. In some embodiments, individual doses are separated from one another by a time period of the same length; in some embodiments, a dosing regimen comprises a plurality of doses and at least two different time periods separating individual doses. In some embodiments, all doses within a dosing regimen are of the same unit dose amount. In some embodiments, different doses within a dosing regimen are of different amounts. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount different from

the first dose amount. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount same as the first dose amount. In some embodiments, a dosing regimen is correlated with a desired or beneficial outcome when administered across a relevant population (i.e., is a therapeutic dosing regimen).

**[0026]     *Excipient:*** As used herein, the term “excipient” refers to a non-therapeutic agent that may be included in a pharmaceutical composition, for example, to provide or contribute to a desired consistency or stabilizing effect. Suitable pharmaceutical excipients include, for example, starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like.

**[0027]     *Improved, increased or reduced:*** As used herein, the terms “improved,” “increased,” or “reduced,” or grammatically comparable comparative terms thereof, indicate values that are relative to a comparable reference measurement. For example, in some embodiments, an assessed value achieved with an agent of interest may be “improved” relative to that obtained with a comparable reference agent. Alternatively or additionally, in some embodiments, an assessed value achieved in a subject or system of interest may be “improved” relative to that obtained in the same subject or system under different conditions (e.g., prior to or after an event such as administration of an agent of interest), or in a different, comparable subject (e.g., in a comparable subject or system that differs from the subject or system of interest in presence of one or more indicators of a particular disease, disorder or condition of interest, or in prior exposure to a condition or agent, etc.).

**[0028]     *Oral:*** The phrases “oral administration” and “administered orally” as used herein have their art-understood meaning referring to administration by mouth of a compound or composition.

**[0029]     *Parenteral:*** The phrases “parenteral administration” and “administered parenterally” as used herein have their art-understood meaning referring to modes of administration other than enteral and topical administration, usually by injection, and include, without limitation, intravenous, intramuscular, intra-arterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, and intrasternal injection and infusion.

**[0030]     *Patient or subject:*** As used herein, the term “patient” or “subject” refers to any organism to which a provided composition is or may be administered, e.g., for experimental,

diagnostic, prophylactic, cosmetic, and/or therapeutic purposes. Typical patients or subjects include animals (e.g., mammals such as mice, rats, rabbits, non-human primates, and/or humans). In some embodiments, a patient is a human. In some embodiments, a patient or a subject is suffering from or susceptible to one or more disorders or conditions. In some embodiments, a patient or subject displays one or more symptoms of a disorder or condition. In some embodiments, a patient or subject has been diagnosed with one or more disorders or conditions. In some embodiments, a patient or a subject is receiving or has received certain therapy to diagnose and/or to treat a disease, disorder, or condition.

**[0031]     *Pharmaceutical composition:*** As used herein, the term “pharmaceutical composition” refers to an active agent, formulated together with one or more pharmaceutically acceptable carriers. In some embodiments, the active agent is present in unit dose amounts appropriate for administration in a therapeutic regimen to a relevant subject (e.g., in amounts that have been demonstrated to show a statistically significant probability of achieving a predetermined therapeutic effect when administered), or in a different, comparable subject (e.g., in a comparable subject or system that differs from the subject or system of interest in presence of one or more indicators of a particular disease, disorder or condition of interest, or in prior exposure to a condition or agent, etc.). In some embodiments, comparative terms refer to statistically relevant differences (e.g., that are of a prevalence and/or magnitude sufficient to achieve statistical relevance). Those skilled in the art will be aware, or will readily be able to determine, in a given context, a degree and/or prevalence of difference that is required or sufficient to achieve such statistical significance.

**[0032]     *Pharmaceutically acceptable:*** As used herein, the phrase “pharmaceutically acceptable” refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

**[0033]     *Pharmaceutically acceptable carrier:*** As used herein, the term “pharmaceutically acceptable carrier” means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting the subject compound 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 and not injurious to the patient. Some examples of materials which can 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; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; pH buffered solutions; polyesters, polycarbonates and/or polyanhydrides; and other non-toxic compatible substances employed in pharmaceutical formulations.

**[0034] Pharmaceutically acceptable salt:** The term "pharmaceutically acceptable salt", as used herein, refers to salts of such compounds that are appropriate for use in pharmaceutical contexts, i.e., salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). In some embodiments, pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts, which are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. In some embodiments, pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the

like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. In some embodiments, pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

**[0035] *Prevent or prevention:*** As used herein, the terms “prevent” or “prevention”, when used in connection with the occurrence of a disease, disorder, and/or condition, refer to reducing the risk of developing the disease, disorder and/or condition and/or to delaying onset of one or more characteristics or symptoms of the disease, disorder or condition. Prevention may be considered complete when onset of a disease, disorder or condition has been delayed for a predefined period of time.

**[0036] *Reference:*** As used herein, the term “reference” describes a standard or control relative to which a comparison is performed. For example, in some embodiments, an agent, animal, individual, population, sample, sequence or value of interest is compared with a reference or control agent, animal, individual, population, sample, sequence or value. In some embodiments, a reference or control is tested and/or determined substantially simultaneously with the testing or determination of interest. In some embodiments, a reference or control is a historical reference or control, optionally embodied in a tangible medium. Typically, as would be understood by those skilled in the art, a reference or control is determined or characterized under comparable conditions or circumstances to those under assessment. Those skilled in the art will appreciate when sufficient similarities are present to justify reliance on and/or comparison to a particular possible reference or control.

**[0037] *Small molecule:*** As used herein, the term “small molecule” means a low molecular weight organic and/or inorganic compound. In general, a “small molecule” is a molecule that is less than about 5 kilodaltons (kD) in size. In some embodiments, a small molecule is less than about 4 kD, 3 kD, about 2 kD, or about 1 kD. In some embodiments, the small molecule is less than about 800 daltons (D), about 600 D, about 500 D, about 400 D, about 300 D, about 200 D, or about 100 D. In some embodiments, a small molecule is less than about 2000 g/mol, less than about 1500 g/mol, less than about 1000 g/mol, less than about 800 g/mol, or less than about 500 g/mol. In some embodiments, a small molecule is not a polymer.

**[0038]** In some embodiments, a small molecule does not include a polymeric moiety. In some embodiments, a small molecule is not and/or does not comprise a protein or polypeptide (e.g., is not an oligopeptide or peptide). In some embodiments, a small molecule is not and/or does not comprise a polynucleotide (e.g., is not an oligonucleotide). In some embodiments, a small molecule is not and/or does not comprise a polysaccharide; for example, in some embodiments, a small molecule is not a glycoprotein, proteoglycan, glycolipid, etc.). In some embodiments, a small molecule is not a lipid.

**[0039]** In some embodiments, a small molecule is a modulating agent (e.g., is an inhibiting agent or an activating agent). In some embodiments, a small molecule is biologically active. In some embodiments, a small molecule is detectable (e.g., comprises at least one detectable moiety). In some embodiments, a small molecule is a therapeutic agent.

**[0040]** Those of ordinary skill in the art, reading the present disclosure, will appreciate that certain small molecule compounds described herein may be provided and/or utilized in any of a variety of forms such as, for example, crystal forms (e.g., polymorphs, solvates, etc), salt forms, protected forms, pro-drug forms, ester forms, isomeric forms (e.g., optical and/or structural isomers), isotopic forms, etc.

**[0041]** Those of ordinary skill in the art will appreciate that certain small molecule compounds have structures that can exist in one or more stereoisomeric forms. In some embodiments, such a small molecule may be utilized in accordance with the present disclosure in the form of an individual enantiomer, diastereomer or geometric isomer, or may be in the form of a mixture of stereoisomers; in some embodiments, such a small molecule may be utilized in accordance with the present disclosure in a racemic mixture form.

**[0042]** Those of skill in the art will appreciate that certain small molecule compounds have structures that can exist in one or more tautomeric forms. In some embodiments, such a small molecule may be utilized in accordance with the present disclosure in the form of an individual tautomer, or in a form that interconverts between tautomeric forms.

**[0043]** Those of skill in the art will appreciate that certain small molecule compounds have structures that permit isotopic substitution (e.g.,  $^2\text{H}$  or  $^3\text{H}$  for  $\text{H}$ ;  $^{11}\text{C}$ ,  $^{13}\text{C}$  or  $^{14}\text{C}$  for  $^{12}\text{C}$ ;  $^{13}\text{N}$  or  $^{15}\text{N}$  for  $^{14}\text{N}$ ;  $^{17}\text{O}$  or  $^{18}\text{O}$  for  $^{16}\text{O}$ ;  $^{36}\text{Cl}$  for  $^{35/37}\text{Cl}$ ;  $^{18}\text{F}$  for  $^{19}\text{F}$ ;  $^{131}\text{I}$  for  $^{127}\text{I}$ ; etc). In some embodiments, such a small molecule may be utilized in accordance with the present disclosure in one or more isotopically modified forms, or mixtures thereof.

[0044] In some embodiments, reference to a particular small molecule compound may relate to a specific form of that compound. In some embodiments, a particular small molecule compound may be provided and/or utilized in a salt form (e.g., in an acid-addition or base-addition salt form, depending on the compound); in some such embodiments, the salt form may be a pharmaceutically acceptable salt form.

[0045] In some embodiments, where a small molecule compound is one that exists or is found in nature, that compound may be provided and/or utilized in accordance in the present disclosure in a form different from that in which it exists or is found in nature. Those of ordinary skill in the art will appreciate that, in some embodiments, a preparation of a particular small molecule compound that contains an absolute or relative amount of the compound, or of a particular form thereof, that is different from the absolute or relative (with respect to another component of the preparation including, for example, another form of the compound) amount of the compound or form that is present in a reference preparation of interest (e.g., in a primary sample from a source of interest such as a biological or environmental source) is distinct from the compound as it exists in the reference preparation or source. Thus, in some embodiments, for example, a preparation of a single stereoisomer of a small molecule compound may be considered to be a different form of the compound than a racemic mixture of the compound; a particular salt of a small molecule compound may be considered to be a different form from another salt form of the compound; a preparation that contains only a form of the compound that contains one conformational isomer ((Z) or (E)) of a double bond may be considered to be a different form of the compound from one that contains the other conformational isomer ((E) or (Z)) of the double bond; a preparation in which one or more atoms is a different isotope than is present in a reference preparation may be considered to be a different form; etc.

[0046] ***Therapeutic agent:*** As used herein, the phrase “therapeutic agent” in general refers to any agent that elicits a desired pharmacological effect when administered to an organism. In some embodiments, an agent is considered to be a therapeutic agent if it demonstrates a statistically significant effect across an appropriate population. In some embodiments, the appropriate population may be a population of model organisms. In some embodiments, an appropriate population may be defined by various criteria, such as a certain age group, gender, genetic background, preexisting clinical conditions, etc. In some embodiments, a therapeutic agent is a substance that can be used to alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce

severity of, and/or reduce incidence of one or more symptoms or features of a disease, disorder, and/or condition. In some embodiments, a “therapeutic agent” is an agent that has been or is required to be approved by a government agency before it can be marketed for administration to humans. In some embodiments, a “therapeutic agent” is an agent for which a medical prescription is required for administration to humans.

**[0047]** *Treat:* As used herein, the terms “treat,” “treatment,” or “treating” refer to any method used to partially or completely alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of, and/or reduce incidence of one or more symptoms or features of a disease, disorder, and/or condition. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition. In some embodiments, treatment may be administered to a subject who exhibits only early signs of the disease, disorder, and/or condition, for example, for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

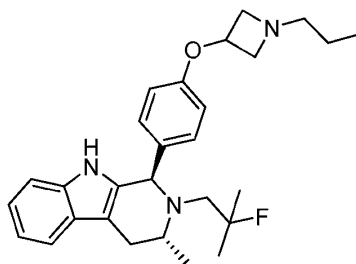
**[0048]** *Therapeutically effective amount:* As used herein, the term “therapeutically effective amount” refers to an amount of a substance (e.g., a therapeutic agent, composition, and/or formulation) that elicits a desired biological response when administered as part of a therapeutic regimen. In some embodiments, a therapeutically effective amount of a substance is an amount that is sufficient, when administered to a subject suffering from or susceptible to a disease, disorder, and/or condition, to treat, diagnose, prevent, and/or delay the onset of the disease, disorder, and/or condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a substance may vary depending on such factors as the desired biological endpoint, the substance to be delivered, the target cell or tissue, etc. For example, the effective amount of compound in a formulation to treat a disease, disorder, and/or condition is the amount that alleviates, ameliorates, relieves, inhibits, prevents, delays onset of, reduces severity of and/or reduces incidence of one or more symptoms or features of the disease, disorder and/or condition. In some embodiments, a therapeutically effective amount is administered in a single dose; in some embodiments, multiple unit doses are required to deliver a therapeutically effective amount.

**[0049]** It is understood by one skilled in the art that compounds referred to herein may be enriched at any or all atoms above naturally occurring isotopic ratios with one or more isotopes such as, but not limited to, deuterium ( $^2\text{H}$  or D).

[0050] The compounds of the invention, or their pharmaceutically acceptable salts, may contain chiral centers, which, unless specified otherwise, may be either of the (R) or (S) configuration, or which may comprise a mixture thereof. Accordingly, the present application includes stereoisomers of the compounds described herein, where applicable, either individually or admixed in any proportions. Stereoisomers may include, but are not limited to, enantiomers, diastereomers, racemic mixtures, and combinations thereof. Such stereoisomers can be prepared and separated using conventional techniques, either by reacting enantiomeric starting materials, or by separating isomers of compounds of the present application.

#### Methods of Treating Estrogen Receptor Mediated Diseases

[0051] The present disclosure provides, among other things, a method of treating estrogen receptor-mediated diseases, disorders, and conditions comprising administering to a patient in need thereof, Compound 1



**Compound 1**

or a pharmaceutically acceptable salt thereof, and ribociclib, or a pharmaceutically acceptable salt thereof. In some embodiments, Compound 1 and ribociclib are administered to a patient as separate compositions, each comprising one or more suitable pharmaceutically acceptable excipients.

[0052] The present disclosure encompasses an insight that particular synergies may be achieved when administering Compound 1 and ribociclib together to a patient suffering from an estrogen receptor-mediated disease, disorder, or condition. The presently claimed methods may exhibit benefits over currently available methods of treatment such as fulvestrant, as both Compound 1 and ribociclib are orally bioavailable, and can be administered to a patient in any suitable form, including as a capsule or tablet or the like.

[0053] The estrogen receptor (“ER”) is involved in a variety of biological processes, relating, for example, to development of the female reproductive system, maintenance of bone mass, protection of cardiovascular and/or central nervous system components, etc. (see, for example, Pearce & Jordan *Crit. Rev. Onc/Hem* 50:3, 2004; Heldring *Phys. Rev.* 87:905, 2007). The ER has been implicated in a variety of cancers. In many tumors that express the estrogen receptor (i.e., ER<sup>+</sup> tumors, also referred to herein as hormone positive or HR<sup>+</sup> tumors), active ER $\alpha$  signaling has been demonstrated to drive cell proliferation (although ER $\beta$  signaling has been reported to be able to achieve tumor suppressor effects; see, for example, Nilsson & Gustafson *Clin. Pharmacol. Ther.* 89:44, 2011). Typically, tumors (e.g., breast tumors) with as few as 1% of cells staining positive for ER are classified as “ER<sup>+</sup>”. Therapies targeting the ER are standard of care for many patients with ER<sup>+</sup> tumors (see, for example, Cardoso et al *Annals Onc.* <https://doi.org/10.1093/annonc/mdmx036>, 2017; Rugo et al. *J. Clin. Oncol.* 34:3069, 2016; Senkus et al. *Annals Onc.* 26:v8, 2015; Sareddy & Vadlamudi *Clin. J Nat. Med.* 13:801, 2015). For early stage breast cancer patients, for example, recommended therapy typically involves tumor resection, followed by ER-targeted therapy (e.g., as discussed below). For advanced breast cancer, including metastatic breast cancer, ER-targeted therapy is the mainstay.

[0054] Among other things, presence or development of certain ER mutations has been reported to impact effectiveness of various ER-targeted therapies (see, for example, Jeselsohn et al. *Nature Rev. Clin. Onc.* 12, 573, 2015; Gelsomino et al. *Breast Cancer Res. Treat* 157:253, 2016; Toy et al. 2013). Some particularly problematic mutations are those that “activate” one or more aspects of ER expression and/or function; some activating mutations have been reported that can render the ER ligand-independent (i.e., constitutively active). For example, particular mutations in the ER ligand binding domain, including D538G and Y537S, have been demonstrated to constitutively activate the ER; other mutations including deletions and/or fusions that remove the ligand binding domain, can have similar effects (see, for example, Li et al. *Cell Repts* 4:1116, 2013; Veeraraghavan et al. *Breast Cancer Research and Treatment* 158, 219–232, 2016; Veeraraghavan, et al. *Nature Comms* 5:4577, 2014). Some reports have indicated that as many as 50% of women with metastatic breast cancer may have activating ER mutations detectable in circulating tumor DNA.

[0055] Nevertheless, regardless of mechanism of action of a particular agent, clinical experience thus far has revealed that incomplete effects (e.g., within an individual patient and/or across patient populations) and/or development of resistance remain a problem.

[0056] In some embodiments described herein an estrogen receptor-mediated disease is a cancer. In some embodiments, a cancer is breast cancer. In some embodiments, a cancer (e.g., a breast cancer) has metastasized to another organ (e.g., the brain, bones, lungs, and/or liver). In some embodiments, an organ having metastases is the brain of the subject. In some embodiments, an organ having metastases is a bone of the subject. In some embodiments, an organ having metastases is a lung of the subject. In some embodiments, an organ having metastases is the liver of the subject.

[0057] In some embodiments, a subject is suffering from HR+/HER2- metastatic breast cancer. In some embodiments, a subject is suffering from cancer that has metastasized to another organ (e.g., brain, lung, liver, and/or bone). In some embodiments, a subject is suffering from histologically or cytologically confirmed advanced or metastatic breast cancer (e.g., for which standard curative measures do not exist).

[0058] In some embodiments, a subject suffering from a disease described herein has previously been administered an endocrine therapy. In some embodiments, a subject has received at least 6 months of a prior continuous endocrine therapy for locally advanced or metastatic breast cancer. In some embodiments, a subject has received no more than 2 prior hormonal regimens for advanced or metastatic disease.

[0059] In some embodiments, a subject suffering from a disease described herein has previously been administered chemotherapy (e.g., chemotherapy for locally advanced or metastatic disease). In some embodiments, a subject has previously been administered no more than one chemotherapy regimen for locally advanced or metastatic breast cancer.

[0060] In some embodiments, a subject has previously received at least one of a CDK4/6 inhibitor, an aromatase inhibitor, chemotherapy, fulvestrant, or a combination thereof.

### **Compound 1**

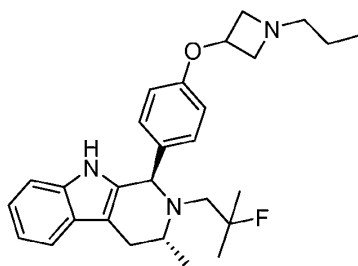
[0061] In some embodiments, the present disclosure appreciates a particular usefulness of Compound 1, which is a complete estrogen receptor antagonist. In some embodiments, a

“complete estrogen receptor antagonist,” as that term is used herein, is characterized by complete antagonism of the estrogen receptor with no or minimal residual estrogen receptor agonist activity. For example, it is understood that a complete estrogen antagonist is an agent (e.g., a small molecule compound) that shows ER antagonism and no ER agonism in one or more of ER $\alpha$  protein level assays, MCF-7 cell line assays, Ishikawa cell line assays (measuring wild type ER and certain mutants including mutants lacking AF1 and/or AF2 domains), and rodent uterine weight gain assays. *See, generally*, WO 2017/059139. Alternatively or additionally, in some embodiments, a complete estrogen receptor antagonist has three characteristics: it (1) inhibits *both* activating function 1 (AF1) and activating function 2 (AF2), as *complete* anti-estrogen activity requires inactivation of both AF1 and AF2; (2) promotes ER degradation; and (3) lacks the partial ER agonist activity observed with certain other agents. Without being bound by theory, it is understood that complete inhibition of both AF1 and AF2 is required for complete estrogen receptor activity, as activating mutations in the gene that codes for estrogen receptor 1 allows for activation of both AF1 and AF2 even in the absence of estrogen.

[0062] Given the importance of ER signaling in many cancers, as well as in certain cardiovascular, inflammatory, and neurodegenerative diseases, significant effort has been invested in developing therapeutic agents and modalities that target the ER. There is some fluidity/flexibility in terminology that has been used to describe ER-targeting agents, but a variety of agents, with different mechanisms, have been developed and/or studied.

[0063] Currently, fulvestrant is the only approved therapy that has each characteristic of a complete estrogen receptor antagonist described above. But fulvestrant suffers from numerous shortcomings, including poor oral bioavailability, and an inability to cross the blood brain barrier.

[0064] Compound 1



Compound 1

overcomes the shortcomings of fulvestrant, and is an orally bioavailable Complete Estrogen Receptor ANtagonist (“CERAN”). Compound 1 is described in WO 2017/059139, as Compound B, otherwise referred to as (1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole. The synthesis and certain attributes of Compound 1 are reported in WO 2017/059139.

**[0065]** Compound 1 potently competes with the endogenous activating estrogenic ligand 17-beta estradiol for binding in the ligand binding pocket. Compound 1 blocks estrogen-driven transcriptional activity, inhibits estrogen-driven breast cancer cell growth, and induces degradation of the ER. Compound 1, as a CERAN, both completely inactivates ER and degrades ER, as well as completely inactivating ER by inactivating both the activation function 1 (AF1) and activation function 2 (AF2) transcriptional activation functions. Compound 1 robustly degrades the estrogen receptor in ER+ cell lines. *In vivo* studies demonstrated that Compound 1 has no agonist activity in the immature ovariectomized mouse uterus and blocks estrogen-driven uterine weight increase. Previous therapies, such as traditional selective estrogen receptor degraders (SERDs), which only degrade ER, or selective estrogen receptor modulators (SERMs) which have mixed agonist and antagonist effects, fail to achieve the complete estrogen receptor antagonism achieved by Compound 1.

**[0066]** Unless otherwise indicated, as used herein “Compound 1” refers to Compound 1 in any available form, such as, e.g., a salt form and/or solid form. It will be understood, therefore, that reference to an amount (e.g., in mg) of Compound 1 means the amount of Compound 1 in free base form. Accordingly, Compound 1 may be provided and/or utilized as, e.g., a salt form of Compound 1 such that the amount of the salt (or other form) is an amount that corresponds to the “free base equivalent” of Compound 1.

**[0067]** In some embodiments, a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, further comprises one or more pharmaceutically acceptable carriers or excipients. For example, pharmaceutically acceptable compositions described herein may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricants and other tableting aids such as a magnesium stearate and microcrystalline cellulose.

When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

**[0068]** Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and/or i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents. The active compounds can also be in micro-encapsulated form with one or more excipients as noted above.

**[0069]** Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings (i.e. buffering agents) and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

**[0070]** In some embodiments, Compound 1 is administered to the subject in an amount that is from about 15 mg to about 360 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is from about 30 mg to about 360 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is from about 30 mg to about 300 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is from about 30 mg to about 120 mg. In some embodiments, Compound 1 is administered to the subject

in an amount that is from about 60 mg to about 120 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is from about 15 mg to about 100 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is about 120 mg, about 150 mg, about 210 mg, or about 300 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is about 30 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is about 60 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is about 90 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is about 120 mg.

**[0071]** In some embodiments, Compound 1 is administered to the subject in an amount that is about 15 mg to about 360 mg per day (QD). In some embodiments, Compound 1 is administered to the subject in an amount that is about 30 mg to about 360 mg per day (QD). In some embodiments, Compound 1 is administered to the subject in an amount that is about 30 mg to about 300 mg per day (QD). In some embodiments, Compound 1 is administered to the subject in an amount that is about 30 mg to about 120 mg per day (QD). In some embodiments, Compound 1 is administered to the subject in an amount that is about 60 mg to about 120 mg per day (QD). In some embodiments, Compound 1 is administered to the subject in an amount that is from about 15 mg to about 100 mg QD. In some embodiments, Compound 1 is administered to the subject in an amount that is about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg QD. In some embodiments, Compound 1 is administered to the subject in an amount that is about 120 mg, about 150 mg, about 210 mg, or about 300 mg QD. In some embodiments, Compound 1 is administered to the subject in an amount that is about 30 mg QD. In some embodiments, Compound 1 is administered to the subject in an amount that is about 60 mg QD. In some embodiments, Compound 1 is administered to the subject in an amount that is about 90 mg QD. In some embodiments, Compound 1 is administered to the subject in an amount that is about 120 mg QD.

**[0072]** In some embodiments, Compound 1 is administered to the subject in a unit dosage form. In some embodiments, a unit dosage form is a capsule or tablet. In some embodiments, a unit dosage form comprises about 15 mg to about 120 mg of Compound 1. In some embodiments,

a unit dosage form comprises about 15 mg to about 100 mg of Compound 1. In some embodiments, a unit dosage form comprises about 60 mg to about 120 mg of Compound 1. In some embodiments, a unit dosage form comprises about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg of Compound 1. In some embodiments, a unit dosage form comprises about 15 mg of Compound 1. In some embodiments, a unit dosage form comprises about 30 mg of Compound 1. In some embodiments, a unit dosage form comprises about 60 mg of Compound 1. In some embodiments, a unit dosage form comprises about 90 mg of Compound 1. In some embodiments, a unit dosage form comprises about 120 mg of Compound 1. In some embodiments, a unit dosage form is a capsule. In some embodiments, a unit dosage form is a tablet.

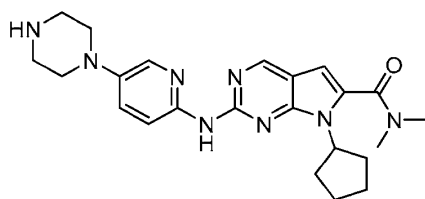
**[0073]** In some embodiments, a total daily dose of Compound 1 administered to the subject is in an amount that is about 15 mg to about 360 mg per day (QD). In some embodiments, a total daily dose of Compound 1 administered to the subject is about 30 mg to about 360 mg. In some embodiments, a total daily dose of Compound 1 administered to the subject is about 30 mg to about 300 mg. In some embodiments, a total daily dose of Compound 1 administered to the subject is about 30 mg to about 120 mg. In some embodiments, a total daily dose of Compound 1 administered to the subject is about 60 mg to about 120 mg. In some embodiments, a total daily dose of Compound 1 administered to the subject is in an amount that is from about 15 mg to about 100 mg QD. In some embodiments, a total daily dose of Compound 1 administered to the subject is in an amount that is about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg QD. In some embodiments, a total daily dose of Compound 1 administered to the subject is about 120 mg, about 150 mg, about 210 mg, or about 300 mg. In some embodiments, a total daily dose of Compound 1 administered to the subject is in an amount that is about 30 mg. In some embodiments, a total daily dose of Compound 1 administered to the subject is about 60 mg. In some embodiments, a total daily dose of Compound 1 administered to the subject is about 90 mg. In some embodiments, a total daily dose of Compound 1 administered to the subject is about 120 mg.

**[0074]** In some embodiments, Compound 1 is administered to the subject once daily for a 28-day cycle. In some embodiments, Compound 1 is administered to the subject once daily for two 28-day cycles. In some embodiments, Compound 1 is administered to the subject once daily for three, four, five, or more 28-day cycles. In some embodiments, Compound 1 is administered to

the subject once daily for six, seven, eight, nine, ten, eleven, twelve, or more 28-day cycles. In some embodiments, Compound 1 is administered to the subject once daily until symptoms of disease are no longer measureable. In some embodiments, Compound 1 is administered for the duration of the subject's life. In some embodiments, Compound 1 is administered once daily for one or more 28-day cycles, followed by a dose holiday. A "dose holiday" as used herein refers to a period of time wherein an agent (e.g., Compound 1) is not administered to the subject. In some embodiments, a dose holiday is one day, one week, or one 28-day cycle. In some embodiments, Compound 1 is administered once daily for one or more 28-day cycles, followed by a dose holiday, and then resumption of administration of Compound 1 once daily at the same dose level prior to the dose holiday.

### Ribociclib

**[0075]** Ribociclib is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Ribociclib has the following structure:



Ribociclib is also known by the following name: 7-cyclopentyl-*N,N*-dimethyl-2-[[5-(piperazin-1-yl)pyridin-2-yl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide. Ribociclib is approved for treatment of hormone receptor positive (e.g., HR+ or ER+), human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with: (i) an aromatase inhibitor as initial endocrine-based therapy; or (ii) fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men. The complete prescribing information for ribociclib is found in the label for KISQALI<sup>®</sup>, located at [www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/209092s0081bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209092s0081bl.pdf), which is incorporated herein by reference in its entirety.

**[0076]** Ribociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play a crucial role in signaling pathways which lead to cell cycle progression and cellular proliferation. The cyclin D-CDK4/6 complex regulates cell

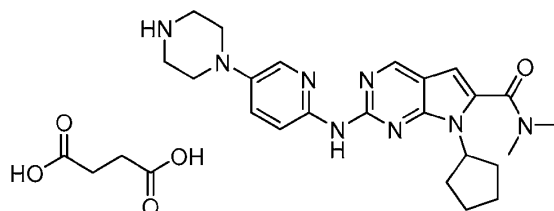
cycle progression through phosphorylation of the retinoblastoma protein (pRb). *In vitro*, ribociclib decreased pRb phosphorylation leading to arrest in the G1 phase of the cell cycle and reduced cell proliferation in breast cancer cell lines. *In vivo*, treatment with single agent ribociclib in a rat xenograft model with human tumor cells led to decreased tumor volumes, which correlated with inhibition of pRb phosphorylation. In studies using patient-derived estrogen receptor positive breast cancer xenograft models, combination of ribociclib and antiestrogen (e.g., letrozole) resulted in increased tumor growth inhibition compared to each drug alone. Additionally, the combination of ribociclib and fulvestrant resulted in tumor growth inhibition in an estrogen receptor positive breast cancer xenograft model.

**[0077]** In some embodiments, a composition comprising ribociclib, or a pharmaceutically acceptable salt thereof, is provided and/or utilized in any suitable pharmaceutical composition or dosage form. In some embodiments, a composition comprising ribociclib, or a pharmaceutically acceptable salt thereof, further comprises one or more pharmaceutically acceptable carriers or excipients. For example, pharmaceutically acceptable compositions described herein may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions.

**[0078]** In some embodiments, ribociclib or a pharmaceutically acceptable salt thereof is provided and/or utilized in a film-coated tablet for oral use. In some embodiments, a tablet comprising ribociclib or a pharmaceutically acceptable salt thereof also comprises one or more of colloidal silicon dioxide, croscopovidone, hydroxypropylcellulose, magnesium stearate, or microcrystalline cellulose. In some embodiments, a tablet comprising ribociclib or a pharmaceutically acceptable salt thereof is coated with a film-coating that comprises one or more of iron oxide black, iron oxide red, lecithin (soya), polyvinyl alcohol (partially hydrolysed), talc, titanium dioxide, and xanthan gum.

**[0079]** Unless otherwise indicated, as used herein “ribociclib” refers to ribociclib in any available form, such as, e.g., a salt form and/or solid form. It will be understood, therefore, that reference to an amount (e.g., in mg) of ribociclib means the amount of ribociclib in free base form. Accordingly, ribociclib may be provided and/or utilized as, e.g., a salt form of ribociclib such that the amount of the salt (or other form) is an amount that corresponds to the “free base equivalent” of ribociclib.

[0080] In some embodiments, ribociclib is provided and/or utilized in a salt form. For example, in some embodiments, ribociclib is provided and/or utilized as ribociclib succinate:



Ribociclib succinate is also known by the following name: Butanedioic acid—7-cyclopentyl-*N,N*-dimethyl-2-[[5-(piperazin-1-yl)pyridin-2-yl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (1/1).

[0081] In some embodiments, ribociclib is administered to the subject in an amount that is from about 200 mg to about 800 mg. In some embodiments, ribociclib is administered to the subject in an amount that is from about 500 mg to about 700 mg. In some embodiments, ribociclib is administered to the subject in an amount that is about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, or about 800 mg. In some embodiments, ribociclib is administered to the subject in an amount that is about 600 mg. In some embodiments, ribociclib is administered to the subject in an amount that is about 400 mg. In some embodiments, ribociclib is administered to the subject in an amount that is about 200 mg.

[0082] In some embodiments, ribociclib is administered to the subject in an amount that is about 200 mg to about 800 mg once per day (QD). In some embodiments, ribociclib is administered to the subject in an amount that is about 500 mg to about 700 mg once per day (QD). In some embodiments, ribociclib is administered to the subject in an amount that is about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, or about 800 mg once per day (QD). In some embodiments, ribociclib is administered to the subject in an amount that is about 600 mg QD. In some embodiments, ribociclib is administered to the subject in an amount that is about 400 mg QD. In some embodiments, ribociclib is administered to the subject in an amount that is about 200 mg QD.

[0083] In some embodiments, ribociclib is administered to the subject in a unit dosage form. In some embodiments, a unit dosage form is a capsule or tablet. In some embodiments, a unit

dosage form comprises about 150 mg to about 250 mg of ribociclib. In some embodiments, a unit dosage form comprises about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, or about 800 mg of ribociclib. In some embodiments, a unit dosage form comprises about 200 mg of ribociclib. In some embodiments, a unit dosage form comprises about 254.4 mg of ribociclib succinate. In some embodiments, a unit dosage form is a capsule. In some embodiments, a unit dosage form is a tablet.

**[0084]** In some embodiments, a total daily dose of ribociclib administered to the subject is in an amount that is about 200 mg to about 800 mg. In some embodiments, a total daily dose of ribociclib administered to the subject is about 500 mg to about 700 mg. In some embodiments, a total daily dose of ribociclib administered to the subject is in an amount that is about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, or about 800 mg. In some embodiments, a total daily dose of ribociclib administered to the subject is about 600 mg. In some embodiments, a total daily dose of ribociclib administered to the subject is about 400 mg. In some embodiments, a total daily dose of ribociclib administered to the subject is about 200 mg.

**[0085]** In some embodiments, ribociclib is administered to the subject once daily for 21 days of a 28-day cycle (i.e., once daily for 21-days followed by a 7-day dose holiday).

### **Combination Therapies**

**[0086]** The present disclosure encompasses the recognition that combination of certain agents can beneficially be used to completely antagonize the estrogen receptor. Accordingly, in some embodiments, the present disclosure provides a method of treating a subject suffering from an ER-associated disorder (e.g., a cancer or breast cancer) comprising administering Compound 1, or a pharmaceutically acceptable salt thereof in combination with ribociclib, or pharmaceutically acceptable salts thereof.

**[0087]** In some embodiments, the present disclosure provides combination therapy comprising administration of Compound 1 and ribociclib. In some embodiments, the present disclosure encompasses an insight that certain synergies may be achieved when combining Compound 1 and ribociclib when treating an estrogen receptor-mediated disease relative to administration of Compound 1 or ribociclib administered in isolation.

**[0088]** In some embodiments, the present disclosure provides a method of treating a disease, disorder, or condition comprising administering once daily to a subject about 15 mg to about 360 mg Compound 1, or a pharmaceutically acceptable salt thereof, in combination with about 200 mg to about 800 mg of ribociclib, or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure provides a method of treating a disease, disorder, or condition comprising administering once daily to a subject about 30 mg to about 120 mg Compound 1, or a pharmaceutically acceptable salt thereof, in combination with about 600 mg ribociclib, or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure provides a method of treating a disease, disorder, or condition comprising administering once daily to a subject about 30 mg Compound 1, or a pharmaceutically acceptable salt thereof, in combination with about 600 mg ribociclib, or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure provides a method of treating a disease, disorder, or condition comprising administering once daily to a subject about 60 mg Compound 1, or a pharmaceutically acceptable salt thereof, in combination with about 600 mg of ribociclib, or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure provides a method of treating a disease, disorder, or condition comprising administering once daily to a subject about 90 mg Compound 1, or a pharmaceutically acceptable salt thereof, in combination with about 600 mg of ribociclib, or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure provides a method of treating a disease, disorder, or condition comprising administering once daily to a subject about 120 mg Compound 1, or a pharmaceutically acceptable salt thereof, in combination with about 600 mg of ribociclib, or a pharmaceutically acceptable salt thereof.

**[0089]** In some embodiments, Compound 1 is administered daily for a 28 day cycle, and ribociclib is administered daily for 21 days of the 28-day cycle (i.e., the same 28 day cycle). In some embodiments, Compound 1 and ribociclib are administered for one, two, three, four, five, or more 28-day cycles.

**[0090]** It is understood that administration of Compound 1 and ribociclib can be administered concomitantly or separately. For example, in some embodiments, Compound 1 and ribociclib are administered concomitantly. In some embodiments, Compound 1 and ribociclib are administered at approximately the same time each day (e.g., for the first 21 days of a 28-day cycle). In some embodiments, ribociclib is administered prior to administration of Compound 1. In some embodiments, ribociclib is administered after administration of Compound 1.

**[0091]** In some embodiments, the present disclosure provides a method comprising administering Compound 1 or a pharmaceutically acceptable salt thereof to a subject who has received or is receiving ribociclib (e.g., according to a regimen provided herein). In some embodiments, the present disclosure provides a method comprising administering ribociclib to a subject who has received or is receiving Compound 1 (e.g., according to a regimen provided herein).

**[0092]** In some embodiments, the present disclosure provides an improvement in a method of treating a disease, disorder, or condition comprising administering Compound 1, or a pharmaceutically acceptable salt thereof, and ribociclib in combination, the improvement comprises administering from about 30 mg to about 120 mg Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the improvement further comprises administering about 600 mg of ribociclib, or a pharmaceutically acceptable salt thereof. In some embodiments, an improvement comprises administering 30 mg Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, an improvement comprises administering 60 mg Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, an improvement comprises administering 90 mg Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, an improvement comprises administering 120 mg Compound 1, or a pharmaceutically acceptable salt thereof.

**[0093]** In some embodiments, a method described herein further comprises administering letrozole, or a pharmaceutically acceptable salt thereof. In some embodiments, a method described herein further comprises administering about 2.5 mg of letrozole or a pharmaceutically acceptable salt thereof.

### **Kits**

**[0094]** In some embodiments, the present disclosure provides a kit comprising one or more compositions comprising Compound 1, or a pharmaceutically acceptable salt thereof, and one or more compositions comprising ribociclib, or a pharmaceutically acceptable salt thereof. In some embodiments, a kit comprises a composition that comprises about 30 mg to about 360 mg of Compound 1 or a pharmaceutically acceptable salt thereof, and a composition that comprises about 200 mg to about 800 mg of ribociclib, or a pharmaceutically acceptable salt thereof. In some embodiments, a kit comprises a composition that comprises about 30 mg of Compound 1 or a

pharmaceutically acceptable salt thereof, and a composition that comprises about 600 mg of ribociclib, or a pharmaceutically acceptable salt thereof. In some embodiments, a kit comprises a composition that comprises about 60 mg of Compound 1 or a pharmaceutically acceptable salt thereof, and a composition that comprises about 600 mg of ribociclib, or a pharmaceutically acceptable salt thereof. In some embodiments, a kit comprises a composition that comprises about 90 mg of Compound 1 or a pharmaceutically acceptable salt thereof, and a composition that comprises about 600 mg of ribociclib, or a pharmaceutically acceptable salt thereof. In some embodiments, a kit comprises a composition that comprises about 120 mg of Compound 1 or a pharmaceutically acceptable salt thereof, and a composition that comprises about 600 mg of ribociclib, or a pharmaceutically acceptable salt thereof. In some embodiments, a kit further comprises packaging material that comprises a label which indicates that Compound 1 and ribociclib can be used for treating an estrogen-receptor mediated disease, disorder, or condition.

### EXAMPLES

#### **Example 1. A Phase 1b Open-Label Multicenter Study of Compound 1 in Combination with the CDK4/6 Inhibitor Ribociclib in Adult Subjects with Advanced and/or Metastatic HR Positive, HER2 Negative Breast Cancer**

[0095] The present example provides a Phase 1b open-label, 2-part study of Compound 1 in combination with ribociclib.

[0096] The study was designed to determine the dose-limiting toxicity (DLT), maximum tolerated dose (MTD), and/or recommended Phase 2 dose (RP2D); and to characterize the safety and pharmacokinetic (PK) profile of Compound 1 in combination with ribociclib in adult subjects with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (MBC). Subjects will receive treatment and will be evaluated in 28-day cycles.

[0097] The present example comprises two parts:

[0098] Part 1 (Dose Escalation): This part will evaluate the safety and pharmacokinetics of a range of doses of Compound 1 administered orally (PO) once daily (QD) to subjects in combination with 600 mg of ribociclib administered PO QD (and to determine the RP2D. The dose escalation study design will include cohorts of 3 to 6 evaluable subjects who are sequentially enrolled and monitored for DLTs during the first cycle of study treatment. At the cohort safety

review, PK and safety events will be reviewed and the DLT observation may be extended to 2 cycles.

**[0099]** Part 2 (Dose Expansion): This part of the study will further evaluate the safety and pharmacology of Compound 1 at the RP2D in combination with ribociclib and provide an exploratory estimate of anti-tumor activity of the combinations.

**[0100]** The objectives for Part 1 (Dose Escalation) of the study are as described below:

*Primary Objectives*

- To identify the dose-limiting toxicity (DLT), maximum tolerated dose (MTD), and/or RP2D of Compound 1 when administered in combination with ribociclib.
- To assess the safety and tolerability of Compound 1 when administered in combination with ribociclib.
- To assess the PK of Compound 1 and ribociclib when administered in each combination.

*Secondary Objectives*

- To preliminarily assess the anti-tumor activity (ORR, defined as confirmed complete response [CR] + confirmed partial response [PR]) of Compound 1 when administered in combination with ribociclib, as assessed by the investigator using the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1).
- To estimate the CBR (CR + PR + SD  $\geq$  24 weeks) of Compound 1 when administered in combination with ribociclib.
- To estimate the duration of response (DoR) of Compound 1 in subjects with HR+/HER2-metastatic or locally advanced breast cancer with no evidence of CNS metastases who have progressed after receiving at least 1 hormonal treatment regimen in the metastatic or locally advanced setting.

*Exploratory Objectives*

- To evaluate the pharmacodynamics effects of treatment with Compound 1 on biomarkers in plasma and ctDNA.
- To correlate biomarkers of ER $\alpha$  and PR expression with clinical activity of Compound 1.

**[0101]** The objectives for Part 2 (Dose Expansion) of the study are as described below:

*Primary Objectives*

- To characterize the safety and tolerability of Compound 1 at the RP2D when administered in combination with ribociclib.

- To characterize the PK of Compound 1 at the RP2D and ribociclib.

#### *Secondary Objectives*

- To preliminarily assess the anti-tumor activity (ORR, defined as confirmed complete response [CR] + confirmed partial response [PR]) of Compound 1 when administered in combination with ribociclib, as assessed by the investigator using RECIST v1.1.
- To estimate the CBR of Compound 1 in subjects with HR+/HER2- metastatic or locally advanced breast cancer with no evidence of CNS metastases who have progressed after receiving at least 1 hormonal treatment regimen in the metastatic or locally advanced setting.
- To estimate the duration of response (DoR) of Compound 1 in subjects with HR+/HER2- metastatic or locally advanced breast cancer with no evidence of CNS metastases who have progressed after receiving at least 1 hormonal treatment regimen in the metastatic or locally advanced setting.

#### *Exploratory Objectives*

- To evaluate the pharmacodynamic effects of treatment with Compound 1 on biomarkers in plasma and ctDNA.
- To correlate biomarkers of ER $\alpha$  and PR expression with clinical activity of Compound 1.

**[0102]** The endpoints for Part 1 (Dose Escalation) of the study are:

#### *Primary Endpoints*

- Incidence and severity of DLTs.
- MTD and/or RP2D of Compound 1 when administered in combination with ribociclib.
- Incidence and severity of TEAEs and SAEs, as assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI CTCAE, v5.0).
- Plasma levels of Compound 1 (and potential metabolites) and ribociclib at pre-defined intervals to establish PK parameters, including maximum concentration ( $C_{max}$ ), minimum concentration ( $C_{min}$ ), time to maximum concentration ( $T_{max}$ ), area under the curve (AUC), half-life ( $t_{1/2}$ ), and Compound 1 trough concentration at steady state.

#### *Secondary Endpoints*

- ORR by evaluation of tumor response assessments using RECIST 1.1.

- CBR as defined by percent of subjects with CR + PR + SD  $\geq$  24 weeks in subjects without evidence of CNS metastases.
- Duration of response (DoR) and DoR compared with last prior endocrine therapy.

#### *Exploratory Endpoints*

- To explore candidate biomarkers in ctDNA pre- and post-therapy (such as mutESR1, PIK3CA variants, and others).
- Exploratory analyses of metabolites of Compound 1 in plasma may also be conducted, and if so, the results of those analyses will be reported separately by the sponsor
- Percent Ki67 in archived or fresh biopsy samples obtained prior to C1D1.
- Quantitative ER $\alpha$  and PR (percent and Allred score) in biopsy samples obtained in archival or fresh biopsy samples prior to C1D1.

**[0103]** The endpoints for Part 2 (Dose Expansion) of the study are:

#### *Primary Endpoints*

- Incidence and severity of TEAEs and SAEs, as assessed using the NCI CTCAE v 5.0.
- Plasma levels of Compound 1 (and potential metabolites) and ribociclib at pre-defined intervals to establish PK parameters, including maximum concentration (C<sub>max</sub>), minimum concentration (C<sub>min</sub>), time to maximum concentration (T<sub>max</sub>), area under the curve (AUC), half-life (t<sub>1/2</sub>), and Compound 1 trough concentration at steady state.

#### *Secondary Endpoints*

- ORR by evaluation of tumor response assessments using RECIST 1.1
- CBR as defined by percent of subjects with a CR + PR + SD for  $\geq$  24 weeks in subjects without evidence of CNS metastases
- DoR, time to progression, and progression free survival (PFS) in subjects without evidence of CNS metastases

#### *Exploratory Endpoints*

- To explore candidate biomarkers in ctDNA pre- and post-therapy with Compound 1 at (such as mutESR1, PIK3CA variants, and others).
- Exploratory analyses of metabolites of Compound 1 in plasma may also be conducted, and if so, the results of those analyses will be reported separately by the sponsor.
- Percent Ki67 in archived or fresh biopsy samples obtained prior to C1D1.

- Quantitative ER $\alpha$  and PR (percent and Allred score) in biopsy samples obtained in archival or fresh samples prior to C1D1.

#### *Inclusion Criteria*

**[0104]** Subjects are eligible to participate in the study must meet all of the following criteria:

1. Female or male aged  $\geq 18$  years.
2. Willing and able to participate and comply with all study requirements and to provide signed and dated informed consent prior to initiation of any study procedures.
3. Histologically- or cytologically-confirmed locally advanced or MBC for which standard curative measures do not exist.
4. HR+/HER2- disease, as determined in the most recently obtained archival tumor tissue sample from a metastatic site, using locally accepted criteria by the local pathology report.
5. Evaluable disease (measurable and non-measurable).
  - a. Measurable disease, i.e., at least 1 measurable lesion as per RECIST 1.1 (a lesion at a previously irradiated site may only be counted as a target lesion if there is clear sign of progression since the irradiation).
6. Received at least 6 months of a prior continuous endocrine therapy for locally advanced or metastatic disease.
7. Life expectancy  $\geq 6$  months, as judged by the Investigator.
8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
9. Females of childbearing potential must be willing to adhere to highly-effective contraception:
  - a. Highly-effective contraception methods include:
    - i. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - ii. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.

- iii. Male partner sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject and the success of the vasectomy must be medically confirmed as per local practice.
  - iv. Placement of a non-hormonal intrauterine device (IUD).
  - b. Additionally, females of childbearing potential, must meet all of the following criteria:
    - i. Not pregnant, as confirmed by a negative serum pregnancy test ( $\beta$ -human chorionic gonadotropin) before starting study treatment
    - ii. Not breastfeeding
  - c. A female subject is considered to be of childbearing potential unless she:
    - i. Is aged  $\geq 60$  years
    - ii. Has had a hysterectomy, bilateral tube ligation, or bilateral oophorectomy
    - iii. Has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone levels)
    - iv. Is menopausal (amenorrhea  $\geq 12$  months) while off drugs that interfere with ovarian function
10. Male subjects must be willing to adhere to highly-effective contraception. Highly-effective contraception methods must include one of the following criteria:
- a. Successful vasectomy
  - b. For subjects who have not had a successful vasectomy, and are partners of women of childbearing potential, their partners adhere to any one of the following:
    - i. Hormonal contraception + male subject's use of a condom with spermicide
    - ii. IUD (hormonal or non-hormonal)
    - iii. Depo Provera + male subject's use of a condom with spermicide
11. Pre- or peri-menopausal female subjects must be willing to take a luteinizing hormone-releasing hormone (LHRH) agonist  $\geq 2$  weeks before first study drug.
12. No proton pump inhibitor (PPI) use for 7 days prior to first study drug administration and agrees to refrain from PPI therapy for the duration of the study.
13. Subjects must not have received prior endocrine or targeted therapy  $\leq 2$  weeks prior to the first study drug dose.

14. Subjects must not have received prior fulvestrant, chemotherapy, antibody therapy, targeted therapy, or investigational therapy  $\leq 4$  weeks prior to the first study drug dose.
15. Prior radiotherapy must have been completed at least 2 weeks prior to the first study drug dose with recovery of toxicity  $\leq$  Grade 1 (except for alopecia).
16. Major surgery with recovery must have been completed at least 4 weeks prior to administration of the first dose of study drug.
17. Any toxicities from prior therapy must have resolved to  $\leq$  Grade 1 or Baseline, as defined by the NCI CTCAE v5.0 prior to the first study drug dose, with the exception of alopecia.
18. Subjects with brain metastases are eligible for the study if they meet all the following criteria:
  - a. Brain metastases have been treated, or do not require treatment at the time of study enrollment, or are unlikely to require treatment during the study.
  - b. Have been off dexamethasone or are on a stable dose of dexamethasone of  $\leq 2$  mg daily (or an alternate steroid dosed at a level equal to  $\leq 2$  mg daily) for 4 weeks prior to first study drug administration.
19. Has the following laboratory values within 28 days before the first study drug dose:
  - a. Serum creatinine  $\leq$  the upper limit of normal (ULN) or has an estimated glomerular filtration rate (eGFR)  $\geq 30$  mL/min/1.73 m<sup>2</sup> according to the MDRD formula;
  - b. Total bilirubin  $\leq 1.5 \times$  ULN unless prior history of Gilbert's syndrome, in which case total bilirubin is to be  $\leq 3.0 \times$  ULN or direct bilirubin  $\leq 1.5 \times$  ULN;
  - c. Aspartate transaminase (AST) and alanine transaminase (ALT)  $\leq 2.5 \times$  ULN, or  $\leq 5 \times$  ULN if due to liver involvement by tumor;
  - d. Hemoglobin  $\geq 9.0$  g/dL without requirement for red blood cell (RBC) transfusion within the last 4 weeks prior to administration of the first dose of study drug;
  - e. Platelet count  $\geq 100 \times 10^9$  cells/L;
  - f. Absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9$  cells/L (without the use of hematopoietic growth factors within the 3 weeks prior to first dose administration);
  - g. Prothrombin time (PT) and international normalized ratio (INR)  $\leq 1.5 \times$  ULN and activated partial thromboplastin time (aPTT)  $\leq 1.5 \times$  ULN. If on chronic anticoagulation, the PT and aPTT must be in the therapeutic range.
20. Standard 12-lead ECG values defined as the mean of the triplicate ECGs:

- a. QTcF (QT interval corrected for heart rate using Fridericia's correction method) at Screening < 450 msec.
  - b. Mean resting heart rate of 50 to 90 beats per minute (bpm) (determined from ECG).
21. Has received no more than 2 prior hormonal regimens for advanced or metastatic disease. Prior hormonal regimens in combination with CDK4/6 inhibitors are allowed.
22. Has received no more than 1 prior chemotherapy regimen for locally advanced or metastatic disease.
23. The following laboratory values within normal limits or corrected to within normal limits with supplements within 24 hours of the first dose of study drug:
- a. Potassium
  - b. Magnesium
  - c. Total calcium (corrected for serum albumin)
24. Left ventricular ejection fraction greater than 50% as determined by MUGA or echocardiography.

#### *Exclusion Criteria*

**[0105]** Subjects who meet any of the following exclusion criteria will not be eligible to participate in either the Dose Escalation or Dose Expansion Parts of the study:

1. Prior or concurrent malignancy whose natural history or treatment may interfere with the safety or efficacy assessment of the investigational regimen as determined by the medical monitor.
2. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality, including any of the following:
  - a. Myocardial infarction, angina pectoris, symptomatic pericarditis, or coronary artery bypass graft within 6 months prior to first study drug dose.
  - b. Documented cardiomyopathy.
  - c. Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome or risk factors for Torsades de Pointes (TdP), including uncorrected hypocalcemia, hypokalemia, or hypomagnesemia; history of cardiac failure; or history of clinically significant/symptomatic bradycardia.

- d. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular block (e.g., bifascicular block, Mobitz type II, and third degree atrioventricular block).
  - e. Uncontrolled systolic blood pressure >160 or <90 mm Hg.
3. History of cerebral vascular disease within 6 months prior to the first administration of study drug.
  4. History of a pulmonary embolism or deep venous thrombosis within the last 6 months, or subject has an increased risk of thrombosis as determined by the Investigator. (Subjects on chronic anticoagulation regimens are allowed.)
  5. History of pneumonitis or interstitial lung disease (ILD). (The chest computed tomography [CT] scan performed before start of study treatment for the purpose of tumor assessment should be reviewed to confirm that there are no relevant pulmonary complications present.)
  6. Leptomeningeal disease or spinal cord compression.
  7. Medical history or ongoing gastrointestinal (GI) disorders that could affect absorption of oral therapeutics (such as active inflammatory bowel disease, chronic diarrhea, short bowel syndrome, or major upper GI surgery, including gastric resection, and including difficulties swallowing capsules).
  8. Known human immunodeficiency virus (HIV) infection.
  9. Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis (e.g., hepatitis B or hepatitis C virus), current alcohol abuse, or cirrhosis.
  10. History of severe cutaneous reaction, such as Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms.
  11. Active infection that requires antimicrobial therapy or is clinically significant.
  12. Has clinically significant co-morbidities, such as active infection, psychiatric disease, or any other condition that could impact the ability of the subject to participate in this study or otherwise has the potential to confound the study results.
  13. Currently receiving any of the following medications and cannot be discontinued 7 days prior to the start of the treatment:

- a. Concomitant medications, herbal supplements, grapefruit and its juice, and/or Seville oranges and its juice, that are strong inducers or inhibitors of cytochrome P450 (CYP) 3A4/5.
  - b. Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.
14. History of allergic reactions attributed to compounds of similar chemical composition to any study drug.
15. Currently receiving or has received systemic corticosteroids  $\leq 2$  weeks prior to starting study drug, or who have not fully recovered from the adverse effects of such treatment.
- a. Note: The following uses of corticosteroids are permitted:
    - i. Short duration ( $< 5$  days) of systemic corticosteroids).
    - ii. Any duration of topical applications (e.g., rash).
    - iii. Inhaled sprays (e.g., for obstructive airway diseases).
    - iv. Eye drops or local injections (e.g., intra-articular).
16. Currently receiving concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause TdP that cannot be discontinued or replaced by safe alternative medication (e.g., within 5 half-lives or 7 days prior to starting study drug).
17. Inability to determine the QTcF for subject.

#### *Number of Subjects Planned*

**[0106]** The number of subjects planned for each part are provided below:

**[0107]** Part 1 (Dose Escalation): Approximately 9 to 18 subjects are planned to be enrolled; the exact number of subjects to be enrolled is dependent on the dose levels at which DLTs are seen. Subjects who discontinue from Part 1 (Dose Escalation) of the study before completing Cycle 1 (C1) for reasons other than DLT are to be replaced.

**[0108]** Part 2 (Dose Expansion): Twelve subjects are to be enrolled in the Dose Expansion Part of the study. Subjects who discontinue from Part 2 (Dose Expansion) of the study before completing at least 2 cycles of therapy and at least 1 post-baseline disease response assessment are to be replaced.

**[0109]** Thus, up to 30 subjects are to be enrolled in this study.

#### *Study Treatment*

[0110] All subjects will receive Compound 1 in combination with ribociclib in this study.

[0111] Subjects are to take Compound 1 capsules PO QD at approximately the same time of day on an empty stomach. Subjects should be fasted for 2 hours before Compound 1 administration and remain fasting, with the exception of the water allowed to take the study drug, until 1 hour after dosing. Cycles are repeated every 4 weeks (28 days) with continuous Compound 1 dosing.

**Part 1 (Dose Escalation)**

[0112] Cohorts of 3 to 6 subjects will be enrolled at each Compound 1 dose level and each subject will participate in only 1 cohort. Subjects at each dose level will be treated and observed for DLT through the end of the first cycle. At the cohort safety review, PK and safety events will be reviewed and the DLT observation may be extended to 2 cycles.

[0113] A 3+3 dose escalation will be followed, considering DLT observation in Cycle 1. Cohorts of 3 to 6 subjects will be treated at each dose level. Three subjects may be concurrently enrolled in each dose level of the study. Decisions to enroll a new subject onto the current, next highest, or next lowest dose level are made based on available data at the time of new subject enrollment. If 2 or more DLTs at a given dose level are observed, the dose level will be de-escalated. The decision to escalate to the next highest dose level is made by the participating investigators and representatives of the sponsor at a cohort review meeting after at least 3 subjects have completed Cycle 1. Intra-subject dose escalation is not permitted.

[0114] Up to a maximum dose of 120 mg QD of Compound 1 will be administered.

[0115] Dose escalation of Compound 1 will be as per the dosing table below:

| Dose Level Cohort # | Increase From Prior Cohort | Compound 1 Dose Level (mg) |
|---------------------|----------------------------|----------------------------|
| 1                   | -                          | 30                         |
| 2                   | 100%                       | 60                         |
| 3                   | 50%                        | 90                         |
| 4                   | 33%                        | 120                        |

*Dose Limiting Toxicity*

[0116] During C1, subjects will be evaluated for the occurrence of a DLT, which are protocol-defined TEAEs graded by the investigator per the NCI CTCAE v5.0 and that are considered by the investigator to be at least possibly related to Compound 1. For each dose group, TEAEs meeting the definition of a DLT are described separately. At the cohort safety review during dose

escalation, PK and safety events will be reviewed and the DLT observation may be extended to 2 cycles).

[0117] Multiple concurrent TEAEs in an individual subject meeting the definition of DLT will be considered a single DLT.

[0118] Subjects must receive at least 75% (at least 21 of 28 doses) of planned Compound 1 doses in C1 to be evaluated for determination of DLT. Subjects receiving less than 75% of the planned dose for reasons other than DLT will be replaced. (Subjects receiving <75% of the planned dose in C1 will be evaluated in the overall safety analysis but not for the purposes of dose escalation.) In such cases, replacement subjects may be enrolled to receive the same starting dose of Compound 1 as the subjects who withdrew prematurely.

#### *Definition of MTD or R2PD*

[0119] For purposes of defining the MTD and/or RP2D of Compound 1, subjects will be evaluated according to the actual starting dose of Compound 1 during C1. For most subjects, this will be the dose cohort to which they were assigned.

[0120] The MTD is defined as the highest feasible dose tested in which <33% (i.e.,  $\leq 1$  of 6) subjects experienced a DLT.

[0121] The RP2D will be determined after review of all the available safety and PK data.

[0122] At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study drug is required for inclusion in the analysis of a specific safety parameter. To assess change from baseline, a baseline measurement is also required.

#### *Duration of Treatment*

[0123] In the absence of unacceptable treatment-related toxicity or disease progression, subjects may receive study treatment for up to 1 year at the discretion of the investigator and beyond 1 year with the agreement of the investigator and the sponsor. Subjects who discontinue Compound 1 must also discontinue ribociclib within the context of this protocol.

#### *Reference Therapies, Dose, Route, and Regimen*

##### **Ribociclib**

[0124] All subjects will receive Compound 1 in combination with a flat-fixed dose of ribociclib of 600 mg QD, for the first 21 consecutive days of a 28-day cycle, in accordance with the prescribing information. Subjects should take their ribociclib dose at approximately the same time each day after administration of Compound 1.

#### *Criteria for Evaluation*

[0125] Safety: Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, DLTs, laboratory values, ECG results, and vital signs.

[0126] Pharmacokinetics: Pharmacokinetic parameters will be determined for each analyte (Compound 1 and ribociclib) in the PK Analysis Set using standard compartmental or non-compartmental methods.

[0127] Pharmacodynamics: Pharmacodynamic assessment will be made by evaluating ctDNA pre- and post-treatment. ctDNA will be evaluated for ESR1 mutations and other pathways significant to ER activity.

[0128] Efficacy: Radiographic and/or physical assessments of the malignancy will be made at Screening/Baseline (within 28 days prior to the first study drug administration) and after every 2 cycles. After the C8 radiographic assessment, subjects who have been determined to have obtained a clinical benefit from study treatment may decrease the frequency of radiographic and physical assessments of malignancy to every 3 months. ORR and CBR, as determined by the subject's best tumor response, duration of response, and time to progression will be assessed by the investigator using RECIST v1.1. Additional imaging studies and tumor measurements will be performed in subjects obtaining a PR or CR on a second examination  $\geq 4$  weeks after initial response determination.

#### *Statistical Methods*

[0129] Data collected in this study will be displayed using summary tables, data listings, and graphs. Categorical data will be summarized using contingency tables (frequencies and percentages). For continuous data summary statistics of mean, standard deviation, median, minimum, and maximum will be presented. Baseline is defined as the last assessment prior to the first dose of study treatment.

**[0130]** Safety Analyses: The safety data from Part 1 (Dose Escalation) will be summarized by dose cohort. Safety data also will be summarized for Part 2 (Dose Expansion). Safety will be assessed through summaries of AEs, laboratory test results, vital signs, and ECOG PS.

**[0131]** Adverse events will be classified by system organ class and preferred term using MedDRA with severities classified using the CTCAE 5.0 criteria. All collected AE data will be listed. All SAEs will also be listed. All TEAEs regardless of attribution will be summarized by cohort. The changes in hematology, chemistry, and other laboratory values will be summarized descriptively for each scheduled protocol assessment time point. Vital sign results (blood pressure, pulse, respirations, and temperature) will be summarized descriptively for each scheduled protocol time point. ECOG performance status shift tables will be provided by cohort and scheduled visit. The analysis of ECG results will be based on subjects in the Safety Analysis Set with baseline and on treatment ECG data.

**[0132]** Exploratory Efficacy Analyses: The efficacy and biomarker analyses will be conducted for the FAS and the efficacy analysis set populations. The results of these analyses will be presented for the overall cohort, by mutESR1 status, and whether the subjects had prior CDK4/6 inhibitor therapy. For Phase 1, descriptive summaries will be presented by cohort. The ORR (CR+PR) will be estimated in the Dose Expansion Part. The estimate of the ORR will be accompanied by 2-sided 95% exact CIs. The ORR will be determined using RECIST v1.1. CBR (CR+PR+SD >24 weeks) will be estimated and will be accompanied by 2-sided 95% exact CIs. All CRs and PRs to be included in ORR and CBR are confirmed responses. The duration of objective response will be calculated for subjects who achieve CR or PR. For such subjects, the duration of objective response is defined as the number of days from the start date of PR or CR (whichever response is achieved first) to the first date that progressive disease is objectively documented. Disease progression will be determined by the investigator using RECIST v1.1.

**[0133]** Pharmacokinetic Analyses: Pharmacokinetic parameters will be determined for each analyte (Compound 1 and ribociclib) in the PK Analysis Set using standard compartmental or non-compartmental methods. Analyte concentrations will be summarized using appropriate descriptive statistics (e.g., N, arithmetic mean, standard deviation, minimum, median, maximum, coefficient of variation [CV] %, geometric mean and CV associated to the geometric mean) for each cohort per cycle and day.

[0134] Biomarker Analyses: Descriptive statistics will be primarily used to summarize the biomarker data generated in this study. For continuous variables, the number of subjects with non-missing data, mean, either the standard error or standard deviation, median, 25th percentile (first quartile), 75th percentile (third quartile), minimum, and maximum will be presented. For discrete data, the frequency and percent distribution will be presented.

**Example 2. Data from a Phase 1b Open-Label Multicenter Study of Compound 1 in Combination with the CDK4/6 Inhibitor Ribociclib in Adult Subjects with Advanced and/or Metastatic HR Positive, HER2 Negative Breast Cancer**

[0135] The present example reports a phase 1b open-label, 2-part study of Compound 1 in combination with ribociclib. The present example includes participants with evaluable HR+, HER2- advanced or metastatic breast cancer,  $\leq 2$  prior endocrine therapies (prior CDK 4/6 inhibitors allowed) and  $\leq 1$  prior line of chemotherapy. Participants were administered escalating doses of Compound 1 30, 60 and 120 mg oral (PO) once daily (QD) in combination with approved doses of ribociclib 600 mg PO QD (days 1-21 of 28-day cycle) in a 3+3 design to identify the recommended phase 2 dose (RP2D). The dose expansion phase assesses additional safety and PK parameters and the anti-tumor activity of Compound 1 in combination with ribociclib.

*Safety*

[0136] 11 participants were enrolled into dose levels 30 mg (n=3), 60 mg (n=3) and 120 mg (n=3) in the dose escalation phase and n=2 in the dose expansion phase of Compound 1 in combination with ribociclib. No dose limiting toxicities were observed. No maximal tolerated dose was reached.

[0137] The treatment-emergent adverse events (TEAE) that occurred in 2 or more participants are in Table 1. The most common TEAE was neutropenia, which was mostly attributed to ribociclib. Other TEAE that happened in  $\geq 2$  participants were grade 1 or 2. There was no increase in incidence or intensity of TEAE with increased dose of Compound 1. QT duration (corrected per Fredericia's formula; QTcF) was monitored. There was no increase in QTcF beyond grade 2 (one participant had grade 2 increase) or increase in duration of QTcF that required dose reduction or interruption of study treatment. The recommended Compound 1 dose for expansion in combination with ribociclib (600 mg PO QD, days 1-21 of 28-day cycle) was 120 mg.

**Table 1: Summary of all-causality treatment-emergent adverse events (TEAE) by preferred term which occurred in  $\geq 2$  participants.**

| AE Preferred Term                | 30 mg (N=3) |                | 60 mg (N=3) |                | 120 mg (N=5) |                | Total (N=11) |                |
|----------------------------------|-------------|----------------|-------------|----------------|--------------|----------------|--------------|----------------|
|                                  | All Grade   | Grade $\geq 3$ | All Grade   | Grade $\geq 3$ | All Grade    | Grade $\geq 3$ | All Grade    | Grade $\geq 3$ |
| Neutropenia                      | 3           | 3              | 2           | 0              | 2            | 1              | 7 (64)       | 4 (36)         |
| Nausea                           | 3           | 0              | 1           | 0              | 2            | 0              | 6 (55)       | 0              |
| Constipation                     | 2           | 0              | 1           | 0              | 1            | 0              | 4 (36)       | 0              |
| Fatigue                          | 1           | 0              | 1           | 0              | 2            | 0              | 4 (36)       | 0              |
| Anemia                           | 0           | 0              | 2           | 0              | 1            | 0              | 3 (27)       | 0              |
| Hyperglycemia                    | 0           | 0              | 1           | 0              | 2            | 0              | 3 (27)       | 0              |
| Hypotension                      | 1           | 0              | 1           | 0              | 1            | 0              | 3 (27)       | 0              |
| White Blood Cell Count Decreased | 0           | 0              | 2           | 0              | 1            | 0              | 3 (27)       | 0              |
| Diarrhea                         | 1           | 0              | 1           | 0              | 0            | 0              | 2 (18)       | 0              |
| Dizziness                        | 1           | 0              | 1           | 0              | 0            | 0              | 2 (18)       | 0              |
| Hypertension                     | 1           | 0              | 0           | 0              | 1            | 0              | 2 (18)       | 0              |
| Weight Decreased                 | 1           | 0              | 0           | 0              | 1            | 0              | 2 (18)       | 0              |

*Pharmacokinetics*

Objectives and Endpoints

[0138] Pharmacokinetic parameters were determined for each analyte (Compound 1, ribociclib). Analyte concentrations were summarized using appropriate descriptive statistics (e.g., N, arithmetic mean, standard deviation, minimum, median, maximum, coefficient of variation [CV] %, geometric mean and CV associated to the geometric mean) for each cohort per cycle and day. The established primary PK endpoints were the following PK parameters: AUC<sub>0-6</sub>, AUC<sub>0-24</sub>, C<sub>max</sub> and T<sub>max</sub>.

Pharmacokinetic Analysis Considerations

[0139] **Subject disposition:** The PK data contained in this example were based on Compound 1 and ribociclib plasma concentrations from 9 female subjects with metastatic breast cancer (MBC) who received 600 mg ribociclib tablet fasted; 3 subjects received 30 mg Compound 1 capsule, 3 subjects received 60 mg capsule, and 3 subjects received 120 mg capsule. No subjects withdrew or terminated early. Two subjects came off study post Cycle 2. Where incomplete sampling impacted PK parameters, results were excluded from descriptive and inferential statistics.

[0140] **PK Sampling:** Blood samples for PK analysis of Compound 1 in plasma were obtained from all subjects at the following times during Cycle 1: on C1D1 at pre-dose and at 0.5 hour ( $\pm 15$  min), 1 hour ( $\pm 15$  min), 2 hours ( $\pm 30$  min), 4 hours ( $\pm 30$  min), 6 hours ( $\pm 30$  min), optionally 8 hours ( $\pm 30$  min), and 24 hours ( $\pm 2$  hours) post-dose (which is pre-dose on C1D2); and at pre-dose on C1D8 and C1D15. Blood samples for PK analysis of Compound 1 in plasma were obtained from 6 of the 9 subjects at the following times: on C2D1 at pre-dose; on C2D15 at pre-dose, 0.5 hour ( $\pm 15$  min), 1 hour ( $\pm 15$  min), 2 hours ( $\pm 30$  min), 4 hours ( $\pm 30$  min), and 6 hours ( $\pm 30$  min), optionally 8 hours ( $\pm 30$  min); and 24 hours ( $\pm 2$  hours) post-dose (which is predose on C2D16); Samples are also to be collected on C3D1 and C3D15 at pre-dose; and pre-dose on C5D1, C7D1, and C9D1. Blood samples for plasma PK analysis of ribociclib were obtained for all subjects at the same time points as Compound 1 for C1D1, C1D2, C1D8, C1D15, C2D15, and C2D16 and are to be collected for C3D15.

#### Pharmacokinetic Results

[0141] **Pharmacokinetic Profile of Compound 1:** Summaries of key pharmacokinetic parameters for Compound 1 following its administration in combination with ribociclib are presented in Table 2 (Day 1) and Table 3 (steady state). Mean plasma Compound 1 concentration-time plots following its administration in combination with ribociclib are presented in FIG. 1A, FIG. 1B, and FIG. 1C (Day 1) and FIG. 2A and FIG. 2B (steady state).

[0142] **Pharmacokinetic Profile of Ribociclib:** Summaries of key pharmacokinetic parameters for ribociclib following its administration in combination with Compound 1 are presented in Table 4 (Day 1) and Table 5 (steady state). Dot plots of the geometric mean (geometric SD) of plasma ribociclib pharmacokinetic parameters following its administration in combination with Compound 1 are presented in FIG. 3 (Day 1) and FIG. 4 (steady state).

Table 1      Plasma Compound 1 Pharmacokinetic Parameters Following a Single Oral Dose of Compound 1 in Combination with 600 mg Ribociclib

| PK Parameter <sup>a</sup>         | 30 mg Compound 1       |                        | 60 mg Compound 1       |                        | 120 mg Compound 1                        |                            |
|-----------------------------------|------------------------|------------------------|------------------------|------------------------|------------------------------------------|----------------------------|
|                                   | Compound 1 Monotherapy | Compound 1 Combination | Compound 1 Monotherapy | Compound 1 Combination | Compound 1 Monotherapy                   | Compound 1 Combination     |
| AUC <sub>0-6</sub> (h*ng/mL)      | 252 (37%); 5           | 220 (78%); 3           | 417 (51%); 31          | 509 (27%); 3           | 776 (48%); 74 [365 ; 1650] <sup>e</sup>  | 1260 (16%); 3 <sup>d</sup> |
| AUC <sub>0-24</sub> (h*ng/mL)     | 514 (22%); 5           | 597 (15%); 2           | 934 (48%); 31          | 1110 (46%); 3          | 1970 (45%); 74 [955 ; 4050] <sup>e</sup> | 3020 (25%); 3 <sup>d</sup> |
| C <sub>max</sub> (ng/mL)          | 68.8 (62%); 5          | 61.6 (47%); 3          | 112 (55%); 33          | 160 (17%); 3           | 202 (50%); 81 [92.0 ; 446] <sup>e</sup>  | 365 (10%); 3 <sup>d</sup>  |
| T <sub>max</sub> <sup>b</sup> (h) | 2.0 [1.0-6.0]; 5       | 2.0 [2.0-6.0]; 3       | 2.0 [1.0-4.0]; 33      | 2.0 [2.0-4.0]; 3       | 2.0 [1.0-6.0]; 81                        | 2.0 [2.0-4.0]; 3           |

<sup>a</sup>GeoMean (GeoCV); n.  
<sup>b</sup>Median [Min-Max]; n.  
<sup>c</sup>GeoMean (GeoCV); n, [Geo 90% lower CI ; Geo 90% upper CI].  
<sup>d</sup>Within the 90% confidence intervals of the geometric mean for Compound 1 monotherapy.

Table 2 Steady State Plasma Compound 1 Pharmacokinetic Parameters Following Multiple Oral Doses in Combination with 600 mg Ribociclib

| PK Parameter <sup>a</sup>         | 30 mg QD Compound 1    |                        | 60 mg QD Compound 1    |                          |
|-----------------------------------|------------------------|------------------------|------------------------|--------------------------|
|                                   | Compound 1 Monotherapy | Compound 1 Combination | Compound 1 Monotherapy | Compound 1 Combination   |
| AUC <sub>0-6</sub> (h*ng/mL)      | 597 (51%); 5           | 456 (47%); 3           | 1140 (48%); 26         | 1900 (47%); 3            |
| AUC <sub>0-24</sub> (h*ng/mL)     | 1970 (33%); 5          | 1600 (55%); 3          | 3960 (45%); 26         | 11300, 4980 <sup>c</sup> |
| C <sub>max</sub> (ng/mL)          | 139 (50%); 5           | 94.3 (42%); 3          | 241 (47%); 27          | 405 (43%); 3             |
| T <sub>max</sub> <sup>b</sup> (h) | 2.0 [1.0-6.0]; 5       | 4.0 [2.0-4.0]; 3       | 4.0 [1.0-6.0]; 27      | 4.0 [2.0-4.0]; 3         |

<sup>a</sup>GeoMean (GeoCV); n.  
<sup>b</sup>Median [Min-Max]; n.  
<sup>c</sup>Individual values for N=2 (24-hour timepoint not collected).

**Table 3 Plasma Ribociclib Pharmacokinetic Parameters Following a Single Oral Dose of 600 mg Ribociclib**

| PK Parameter <sup>a</sup>         | Ribociclib 600 mg<br>Combined with Compound 1 Dose (mg) |                  |                  | Single Agent Ribociclib <sup>c</sup>           |                                           |
|-----------------------------------|---------------------------------------------------------|------------------|------------------|------------------------------------------------|-------------------------------------------|
|                                   | 30                                                      | 60               | 120              | Based on<br>Accumulation<br>Ratio <sup>c</sup> | Digitized<br>Mean<br>Profile <sup>d</sup> |
| AUC <sub>0-6</sub><br>(h*ng/mL)   | 4616 (26%); 3                                           | 3707 (51%); 3    | 4718 (10%); 3    | N/A                                            | 5003                                      |
| AUC <sub>0-24</sub><br>(h*ng/mL)  | 11565 (11%); 2                                          | 9728 (63%); 3    | 10702 (19%); 2   | 9520 (66%); 54                                 | 13166                                     |
| C <sub>max</sub><br>(ng/mL)       | 1137 (28%); 3                                           | 1069 (36%); 3    | 1213 (19%); 3    | 728 (62%); 57                                  | 1208                                      |
| T <sub>max</sub> <sup>b</sup> (h) | 2.0 [2.0-6.0]; 3                                        | 2.0 [2.0-4.0]; 3 | 2.0 [2.0-4.0]; 3 | 2.4 [0.7, 7.8]; 57                             | N/D                                       |

<sup>a</sup>GeoMean (GeoCV); n, unless otherwise specified.<sup>b</sup>Median [Min-Max]; n.<sup>c</sup> Single dose exposure levels for ribociclib single agent calculated from steady state exposure and accumulation ratio (2.5) from ribociclib product manuscript. %CV reported are from steady state pooled data from patients with cancer receiving intermittent schedule (3 weeks on/1 week off) and patients with cancer with continuous dosing (once daily for 28 days).

N/A= Not Applicable.

<sup>d</sup> Mean single dose exposure levels for ribociclib digitized and calculated from Yan Ji SABCS 2019 poster single dose data.

N/D= Not Done.

**Table 4. Steady State Plasma Ribociclib Dose Normalized Pharmacokinetic Parameters Following 600 mg (3-Weeks-On/1-Week-Off Dosing Schedule) Ribociclib in Combination with Compound 1**

| Dose Normalized /1 mg<br>PK Parameter <sup>a</sup> | Compound 1 <sup>c</sup> + Ribociclib | Single Agent Ribociclib <sup>d</sup> |
|----------------------------------------------------|--------------------------------------|--------------------------------------|
| AUC <sub>0-24</sub><br>(h*ng/mL )                  | 49.0 (57%); 4                        | 39.7 (66%); 54                       |
| C <sub>max</sub><br>(ng/mL )                       | 2.88 (76%); 5                        | 3.0 (62%); 57                        |
| T <sub>max</sub> <sup>b</sup><br>(h)               | 4.0 [2.0 – 4.0]; 5                   | 2.4 [0.7 – 7.8]; 57                  |

<sup>a</sup>GeoMean (GeoCV); N.<sup>b</sup>Median [Min-Max]; n.<sup>c</sup>30 and 60 mg QD Compound 1.<sup>d</sup>Pooled data from patients with cancer receiving intermittent schedule (3 weeks on/ 1 week off) and patients with cancer with continuous dosing (once daily for 28 days).

### Pharmacokinetic Discussion and Conclusion

#### **Compound 1**

**[0143]** *Single dose:* The single dose exposure parameters AUC<sub>0-6</sub>, AUC<sub>0-24</sub>, and C<sub>max</sub> of Compound 1 when dosed in combination with 600 mg ribociclib were comparable to those of Compound 1 when dosed as a single agent. Median T<sub>max</sub> for Compound 1 given alone or in combination with ribociclib was also comparable across the dose levels studied at single dose.

These results suggest that, to date, there is no clear DDI following co-administration with 600 mg ribociclib for single doses of 30, 60 and 120 mg Compound 1. The PK parameters for the 120 mg Compound 1 combination were within the 90% confidence intervals of the geometric mean for Compound 1 monotherapy.

**[0144]** *Steady State:* The steady state exposure parameters  $AUC_{0-6}$ ,  $AUC_{0-24}$ , and  $C_{max}$  of Compound 1 when dosed in combination with 600 mg ribociclib were comparable to those of Compound 1 when dosed as a single agent. Median  $T_{max}$  for Compound 1 given alone or in combination with ribociclib was also comparable across the dose levels of 30 and 60 mg Compound 1. These results suggest that, to date, there is no clear DDI following co-administration with 600 mg ribociclib for doses of 30 and 60 mg Compound 1.

**[0145]** Compound 1 PK was dose proportional in the dose ranges from 30 to 120 mg when Compound 1 was dosed in combination with 600 mg ribociclib.

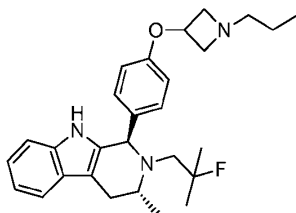
#### ***Ribociclib***

**[0146]** *Single Dose:* The single dose exposure parameters  $AUC_{0-24}$ , and  $C_{max}$  of ribociclib when dosed in combination with 30, 60 or 120 mg Compound 1 were comparable to those of ribociclib when dosed as a single agent (Novartis Pharmaceuticals Canada Inc. 2023. Available at [www.ask.novartispharma.ca/download.htm?res=kisqali\\_scrip\\_e.pdf&resTitleId=1439](http://www.ask.novartispharma.ca/download.htm?res=kisqali_scrip_e.pdf&resTitleId=1439) (Accessed September 26, 2023)). Median  $T_{max}$  for ribociclib given alone or in combination with 30, 60 or 120 mg QD Compound 1 was comparable at single dose. These results suggest that, to date, there was no clear DDI following co-administration with 30, 60 or 120 mg QD Compound 1 for single dose ribociclib.

**[0147]** *Steady State:* The steady state exposure parameters  $AUC_{0-6}$ ,  $AUC_{0-24}$ , and  $C_{max}$  of ribociclib when dosed in combination with 30 or 60 mg Compound 1 QD were comparable to those of ribociclib when dosed as a single agent (Novartis Pharmaceuticals Canada Inc. 2023. Available at [www.ask.novartispharma.ca/download.htm?res=kisqali\\_scrip\\_e.pdf&resTitleId=1439](http://www.ask.novartispharma.ca/download.htm?res=kisqali_scrip_e.pdf&resTitleId=1439) (Accessed September 26, 2023)). These preliminary results suggest that, to date, there was no clear DDI following co-administration with 30 or 60 mg QD Compound 1 for 3 weeks on/ 1 week off administration of 600 mg QD ribociclib.

## CLAIMS

1. A method of treating an estrogen receptor mediated disease, disorder, or condition in a subject comprising administering a composition comprising Compound 1



or a pharmaceutically acceptable salt thereof, wherein Compound 1 is administered in an amount that is about 15 mg to about 360 mg,

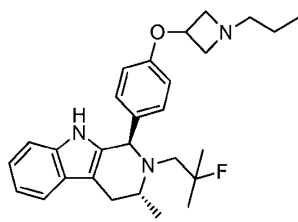
in combination with a composition comprising about 200 to about 800 mg of ribociclib, or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein Compound 1 is administered in an amount that is about 30 mg to about 120 mg.
3. The method of claim 1 or 2, wherein Compound 1 is administered in an amount that is about 30 mg.
4. The method of claim 1 or 2, wherein Compound 1 is administered in an amount that is about 60 mg.
5. The method of claim 1 or 2, wherein Compound 1 is administered in an amount that is about 90 mg.
6. The method of claim 1 or 2, wherein Compound 1 is administered in an amount that is about 120 mg.
7. The method of any one of claims 1-6, wherein ribociclib is administered in an amount that is about 500 to about 700 mg.

8. The method of any one of claims 1-7, wherein ribociclib is administered in an amount that is about 600 mg.
9. The method of any one of claims 1-8, wherein Compound 1 is administered once daily.
10. The method of any one of claims 1-8, wherein ribociclib is administered once daily for 21 days, followed by a 7-day dose holiday.
11. The method of any one of claims 1-10, wherein Compound 1 and ribociclib are administered concomitantly.
12. The method of any one of claims 1-11, wherein the composition comprising Compound 1 or a pharmaceutically acceptable salt thereof is a capsule or a tablet.
13. The method of claim 12, wherein the composition comprising ribociclib or a pharmaceutically acceptable salt thereof is a capsule or a tablet.
14. The method of any one of claims 1-13, wherein the estrogen receptor-mediated disease, disorder, or condition is a cancer.
15. The method of claim 14, wherein the cancer is breast cancer.
16. The method of claim 15, wherein the cancer is HR+/HER2- breast cancer.
17. The method of any one of claims 14-16, wherein the cancer has metastasized to another organ.
18. The method of claim 17, wherein the cancer has metastasized to the brain, bone, lungs, or liver.

19. The method of any one of claims 1-18, wherein the subject has previously received at least one of a CDK4/6 inhibitor, an aromatase inhibitor, chemotherapy, fulvestrant, or a combination thereof.

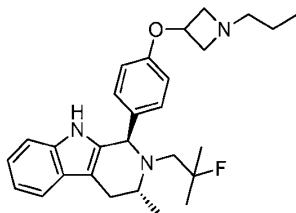
20. In a method of treating a disease, disorder, or condition comprising administering Compound 1



or a pharmaceutically acceptable salt thereof, and ribociclib in combination,

the improvement comprising administering from about 30 mg to about 120 mg Compound 1, or a pharmaceutically acceptable salt thereof, and about 600 mg of ribociclib, or a pharmaceutically acceptable salt thereof.

21. A kit comprising a composition comprising about 30 mg to about 360 mg of Compound 1



or a pharmaceutically acceptable salt thereof, and a composition comprising about 200 to about 800 mg of ribociclib, or a pharmaceutically acceptable salt thereof.

22. The kit of claim 21, wherein the kit comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt thereof.

23. The kit of claim 21, wherein the kit comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt thereof.

24. The kit of claim 21, wherein the kit comprises about 90 mg of Compound 1, or a pharmaceutically acceptable salt thereof.
25. The kit of claim 21, wherein the kit comprises about 120 mg of Compound 1, or a pharmaceutically acceptable salt thereof.
26. The kit of any one of claims 21-25, wherein the kit comprises about 600 mg of ribociclib, or a pharmaceutically acceptable salt thereof.
27. The kit of any one of claims 21-26, wherein the kit further comprises packaging material that comprises a label which indicates that Compound 1 and ribociclib can be used for treating an estrogen-receptor mediated disease, disorder, or condition.
28. The kit of claim 27, wherein the estrogen receptor-mediated disease, disorder, or condition is a cancer.
29. The kit of claim 28, wherein the cancer is breast cancer.
30. The kit of claim 29, wherein the cancer is HR+/HER2- breast cancer.
31. The kit of any one of claims 28-30, wherein the cancer has metastasized to another organ.
32. The kit of claim 31, wherein the cancer has metastasized to the brain, bone, lungs, or liver.