

SOLID STATE FORMS OF GUSACITINIB

RELATED APPLICATIONS

[0001] This application claims priority to and benefit of U.S. Application No. 63/515,864, filed July 27, 2023, the entire contents of which are hereby incorporated by reference in its entirety.

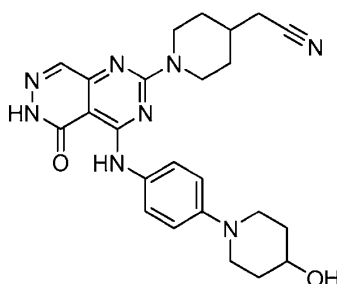
BACKGROUND

[0002] Inhibition of the JAK signaling pathway plays an important role in the treatment of a variety of diseases and disorders, including, for example inflammatory diseases. *See* Schwartz, *et al.*, *Nat. Rev. Drug Discov.* 17(1):78 (2017). Inhibition of spleen tyrosine kinase (SYK) has also shown promise as treatment for immune-mediated diseases. *Id.* Inhibiting both JAK and SYK has been theorized to enhance efficacy by broadening the signaling pathways that are blocked, and cytokines that are targeted. *Id.*; Pavel, *et al.*, *J. of Allergy and Clinical Immunology*, 144(4):1011-1024 (2019).

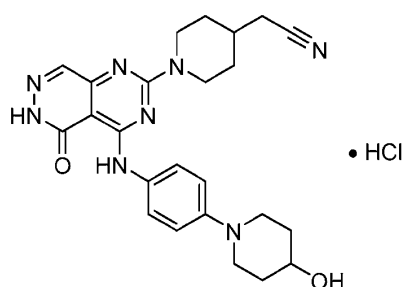
SUMMARY

[0003] Previous JAK/SYK inhibitors have shown promise as treatment of certain autoimmune or inflammatory disorders, but have suffered from exaggerated adverse events. *See* Schwartz, *et al.*, *Nat. Rev. Drug Discov.* 17(1):78 (2017). There remains a need for JAK/SYK inhibitors that can treat certain autoimmune or inflammatory disorders that do not suffer from said side effects, and further are shelf stable and capable of being incorporated into oral dosage forms for ease of administration.

[0004] One compound that is being evaluated for use in treating JAK/SYK mediated disorders is gusacitinib, otherwise known as ASN-002, or 2-(1-(4-((4-(4-hydroxypiperidin-1-yl)phenyl)amino)-5-oxo-5,6-dihydropyrimido[4,5-d]pyridazin-2-yl)piperidin-4-yl)acetonitrile, and having a structure:



Gusacitinib is also being evaluated as a hydrochloride salt, represented by the structure below, and referred to herein as “Compound 1”:



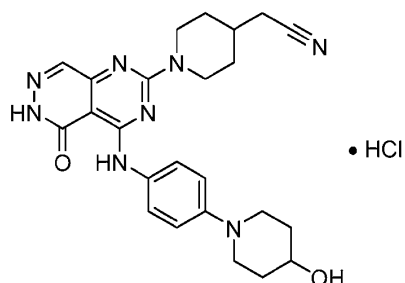
Compound 1

[0005] Gusacitinib is described in WO2013/028818, reported at example 189, and certain formulations of gusacitinib and Compound 1 are described in WO2018/201131, each of which is incorporated herein by reference in its entirety. There remains, however, a need for identifying crystalline, anhydrate, hydrate and/or solvate forms of gusacitinib and/or Compound 1 useful for various therapeutic applications.

[0006] In particular, it is also desirable to identify particular forms of gusacitinib and Compound 1 that are stable in a variety of conditions. Initial attempts to formulate gusacitinib and Compound 1 into a form more amenable for manufacturing and formulation, resulted in a form of Compound 1 that was unstable or hygroscopic. Applicant discovered, however, that particular forms of gusacitinib and Compound 1 were exceptionally stable in a variety of conditions.

[0007] The present disclosure, however, solves the problems identified above and provides crystalline solid forms that, in some embodiments, exhibit desirable characteristics such as improved stability, hygroscopicity, flow properties, compressibility, ease of processing, consistency in manufacturing, particle size distribution, bulk density, pharmacokinetics, bioavailability, and ease of formulation.

[0008] In some embodiments, the present disclosure provides a crystalline solid form of Compound 1:



Compound 1

[0009] In some embodiments, a crystalline solid form of Compound 1 is a hydrate. In some embodiments, a crystalline solid form of Compound 1 is Form 1, as described herein.

[0010] In some embodiments, the present disclosure provides a pharmaceutical formulation comprising a crystalline solid form described herein. In some embodiments, a pharmaceutical formulation is a unit dosage form. In some embodiments, a unit dosage form is in the form of a tablet.

[0011] In some embodiments, the present disclosure provides a method of treating a disease, disorder, or condition, in a subject in need thereof, comprising a step of administering to the subject a crystalline form described herein.

[0012] In some embodiments, the present disclosure provides a method of treating a JAK/SYK-mediated disease, disorder, or condition, in a subject in need thereof, comprising a step of administering to the subject a crystalline solid form described herein.

BRIEF DESCRIPTION OF THE DRAWING

[0013] FIG. 1A is an XRPD spectrum of Compound 1 Form 1.

[0014] FIG. 1B is a DSC and TGA plot of Compound 1 Form 1.

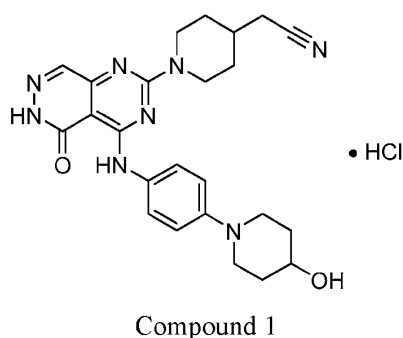
[0015] FIG. 1C is a dynamic vapor sorption (DVS) plot of Compound 1 Form 1.

[0016] FIG. 1D provides a series of XRPD spectra of Compound 1 Form 1 before (top) and after (bottom) heating at 100 °C.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0017] Gusacitinib, otherwise known as 2-(1-(4-((4-(4-hydroxypiperidin-1-yl)phenyl)amino)-5-oxo-5,6-dihydropyrimido[4,5-d]pyridazin-2-yl)piperidin-4-yl)acetonitrile is being evaluated in the treatment of certain diseases, disorders, and conditions associated with the JAK/SYK pathway. The present disclosure provides crystalline solid forms of 2-(1-(4-((4-(4-hydroxypiperidin-1-yl)phenyl)amino)-5-oxo-5,6-dihydropyrimido[4,5-d]pyridazin-2-yl)piperidin-4-yl)acetonitrile as a hydrochloride salt. The present disclosure, among other things, recognizes the surprising discovery that gusacitinib, and certain salts thereof, are capable of forming crystalline solid forms, and further, that those forms exhibit improved stability and other beneficial properties relative to a corresponding amorphous form or other crystalline forms. Further, the present disclosure, among other things, provides particular pharmaceutical formulations (i.e., unit dosage forms) of gusacitinib that are suitable for oral administration.

[0018] In some embodiments, the present disclosure provides crystalline solid forms of a hydrochloride salt form of gusacitinib, represented by the structure below, and referred to herein as "Compound 1":



Definitions

[0019] *About or approximately:* As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In general, those skilled in the art, familiar within the context, will appreciate the relevant degree of variance encompassed by "about" or "approximately" in that context. For example, in some embodiments, the term "approximately" or "about" may encompass a range of values that are within (i.e., $\pm$) 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.

[0020] *Administering:* As used herein, the term "administering" or "administration" typically refers to the administration of a composition to a subject to achieve delivery of an agent that is, or

is included in, a composition to a target site or a site to be treated. Those of ordinary skill in the art will be aware of a variety of routes that may, in appropriate circumstances, be utilized for administration to a subject, for example a human. For example, in some embodiments, administration may be ocular, oral, parenteral, topical, etc. In some particular embodiments, administration may be bronchial (e.g., by bronchial instillation), buccal, dermal (which may be or comprise, for example, one or more of topical to the dermis, intradermal, interdermal, transdermal, etc.), enteral, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intravenous, intraventricular, within a specific organ (e.g., intrahepatic), mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (e.g., by intratracheal instillation), vaginal, vitreal, etc. In some embodiments, administration may be parenteral. In some embodiments, administration may be oral. In some particular embodiments, administration may be intravenous. In some particular embodiments, administration may be subcutaneous. In some embodiments, administration may involve only a single dose. In some embodiments, administration may involve application of a fixed number of doses. In some embodiments, administration may involve dosing that is intermittent (e.g., a plurality of doses separated in time) and/or periodic (e.g., individual doses separated by a common period of time) dosing. In some embodiments, administration may involve continuous dosing (e.g., perfusion) for at least a selected period of time. In some embodiments, administration may comprise a prime-and-boost protocol. A prime-and-boost protocol can include administration of a first dose of a pharmaceutical composition (e.g., an immunogenic composition, e.g., a vaccine) followed by, after an interval of time, administration of a second or subsequent dose of a pharmaceutical composition (e.g., an immunogenic composition, e.g., a vaccine). In the case of an immunogenic composition, a prime-and-boost protocol can result in an increased immune response in a patient.

[0021] Antagonist: As will be understood by those skilled in the art, the term “antagonist” generally refers to an agent whose presence or level correlates with decreased level or activity of a target, as compared with that observed absent the agent (or with the agent at a different level). In some embodiments, an antagonist is one whose presence or level correlates with a target level or activity that is comparable to or less than a particular reference level or activity (e.g., that observed under appropriate reference conditions, such as presence of a known antagonist, e.g., a positive control). In some embodiments, an antagonist may be a direct antagonist in that it exerts its influence directly on (e.g., interacts directly with) the target; in some embodiments, an

antagonist may be an indirect antagonist in that it exerts its influence indirectly (e.g., by acting on, such as interacting with, a regulator of the target, or with some other component or entity).

[0022] 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.

[0023] Carrier: As used herein, the term “carrier” refers to a diluent, adjuvant, excipient, or vehicle with which a composition is administered. In some exemplary embodiments, carriers can include sterile liquids, such as, for example, water and oils, including oils of petroleum, animal, vegetable or synthetic origin, such as, for example, peanut oil, soybean oil, mineral oil, sesame oil and the like. In some embodiments, carriers are or include one or more solid components.

[0024] Combination therapy: As used herein, the term “combination therapy” refers to those situations in which a subject is simultaneously exposed to two or more therapeutic regimens (e.g., two or more therapeutic agents or modality(ies)). In some embodiments, the two or more regimens may be administered simultaneously; 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).

[0025] 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 therebetween 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.

[0026] Composition: Those skilled in the art will appreciate that the term “composition” may be used to refer to a discrete physical entity that comprises one or more specified components. In general, unless otherwise specified, a composition may be of any form – e.g., gas, gel, liquid, solid, etc.

[0027] 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).

[0028] 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).

[0029] 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.

[0030] Modulator: The term “modulator,” as used herein, refers to a compound (e.g., a small molecule) that can alter the activity of another molecule (e.g., a protein). For example, in some

embodiments, a modulator can cause an increase or decrease in the magnitude of a certain activity of a type of molecule as compared to the magnitude of the activity in the absence of the modulator. For example, a modulator can be an agonist or an antagonist of a particular target, as those terms are defined herein. For example, in some embodiments, a modulator is an agonist. In some embodiments, a modulator is an antagonist.

[0031] 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.

[0032] 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.

[0033] 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.

[0034] 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 amount appropriate for administration in a therapeutic or dosing regimen that shows a statistically significant probability of achieving a predetermined therapeutic effect when administered to a relevant population. In some embodiments, pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for

buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces.

[0035] 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.

[0036] 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).

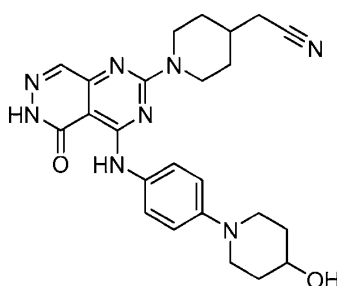
[0037] Prevent or prevention: As used herein, the terms “prevent” or “prevention”, when used in connection with the occurrence of a disease, disorder, and/or condition, refer to reducing the risk of developing the disease, disorder and/or condition and/or to delaying onset of one or more characteristics 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.

[0038] 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.

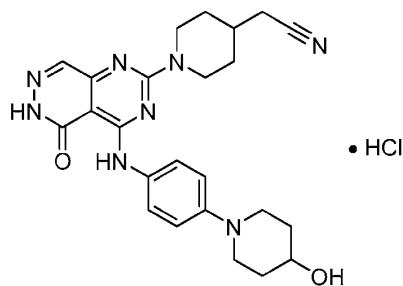
Crystalline Solid Forms of Gusacitinib and Compound 1

[0039] Gusacitinib is being evaluated in the treatment of a certain autoimmune and inflammatory disorders. Gusacitinib is otherwise known as ASN-002, or 2-(1-(4-((4-(4-hydroxypiperidin-1-yl)phenyl)amino)-5-oxo-5,6-dihydropyrimido[4,5-d]pyridazin-2-yl)piperidin-4-yl)acetonitrile, is referred herein as “Compound 2,” and has a structure:



Compound 2

Gusacitinib is also being evaluated as a hydrochloride salt, represented by the structure, and referred to herein as “Compound 1”:



Compound 1

[0040] Compound 2 is reported in WO2013/028818, in example 189, and certain formulations of Compound 1 and Compound 2 are provided in WO2018/201131, each of which is incorporated herein by reference in its entirety. A synthesis of Compound 2 is also provided in WO2013/028818.

[0041] Applicant discovered that Compound 1 can each exist in one or more polymorphic solid forms. As used herein, the term “polymorph” refers to the ability of a compound to exist in one

or more different crystal structures. For example, one or more polymorphs may vary in pharmaceutically relevant physical properties between one form and another, e.g., solubility, stability, and/or hygroscopicity. In some embodiments, the present disclosure provides a crystalline solid form of Compound 1.

[0042] Compound 1 can occur in an amorphous solid form, in a crystalline solid form, or in mixtures of forms. Crystalline solid forms of Compound 1 can exist in one or more unique solid forms, which can additionally comprise one or more molecules of water or solvent (i.e., hydrates or solvates, respectively) in the crystal lattice. As described herein, crystalline forms of Compound 1 each have distinct characteristic XRPD peaks that are not reported in previous disclosures of Compound 1.

[0043] In some embodiments, a crystalline form of Compound 1 exists as a solvate and/or hydrate. As used herein, the term “solvate” refers to a solid form with a stoichiometric or non-stoichiometric amount of one or more solvents incorporated into the crystal structure. For example, a solvated or heterosolvated polymorph can comprise 0.05, 0.1, 0.2, 0.5, 1.0, 1.5, 2.0, etc. equivalents independently of one or more solvents incorporated into the crystal lattice. As used herein, the term “hydrate” refers to a solvate, wherein the solvent incorporated into the crystal structure is water.

[0044] In some embodiments, provided forms (e.g., Compound 1 Form 1) are characterized by having peaks in its XRPD pattern selected from “substantially all” of a provided list, optionally within ± 0.2 degrees 2-theta of the stated value. It will be appreciated that an XRPD pattern having “substantially all” of a provided list of peaks refers to an XRPD pattern that comprises at least 80% (e.g., 80%, 85%, 90%, 95%, 99% or 100%) of the listed peaks. In some embodiments, an XRPD pattern comprises at least 90% of the listed peaks. In some embodiments, an XRPD pattern comprises all of the listed peaks. In some embodiments, an XRPD pattern comprises all but one of the listed peaks. In some embodiments, an XRPD pattern comprises all but two of the listed peaks. In some embodiments, an XRPD pattern comprises all but three of the listed peaks.

[0045] In some embodiments, provided forms (e.g., Compound 1 Form 1) are characterized by having a pattern or spectrum that is “substantially similar” to a Figure provided herein. It will be appreciated that a pattern or spectrum having “substantial similarity” to a Figure provided herein is one that comprises one or more features (e.g., position (degrees 2-theta) values, temperature values, % weight loss values, intensity, shape of curve, etc.) of the provided Figure so

as to enable identification of the form (e.g., solid and/or salt form) characterized by the pattern or spectrum as being the same as the form characterized in the Figure. For example, in some embodiments, an XRPD pattern having substantial similarity to a provided Figure is one that comprises substantially all of the same peaks, optionally within ± 0.2 degrees 2-theta of peaks in the reference Figure. In some embodiments, an XRPD pattern having substantial similarity to a provided Figure is one that comprises substantially all of the same peaks, optionally within ± 0.2 degrees 2-theta of peaks in the reference Figure, with about the same intensities.

Compound 1 Form 1

[0046] In some embodiments, a crystalline solid form of Compound 1 is a hydrate.

[0047] In some embodiments, a hydrate form of Compound 1 is characterized by one or more peaks in its X-ray powder diffraction pattern selected from 5.9, 8.1, 9.5, 16.2, 16.6, 17.8, 18.9, and 32.6 ± 0.2 degrees 2-theta. In some embodiments, a hydrate form of Compound 1 is characterized by two or more peaks in its X-ray powder diffraction pattern selected from 5.9, 8.1, 9.5, 16.2, 16.6, 17.8, 18.9, and 32.6 ± 0.2 degrees 2-theta. In some embodiments, a hydrate form of Compound 1 is characterized by three or more peaks in its X-ray powder diffraction pattern selected from 5.9, 8.1, 9.5, 16.2, 16.6, 17.8, 18.9, and 32.6 ± 0.2 degrees 2-theta. In some embodiments, a hydrate form of Compound 1 is characterized by four or more peaks in its X-ray powder diffraction pattern selected from 5.9, 8.1, 9.5, 16.2, 16.6, 17.8, 18.9, and 32.6 ± 0.2 degrees 2-theta. In some embodiments, a hydrate form of Compound 1 is characterized by five or more peaks in its X-ray powder diffraction pattern selected from 5.9, 8.1, 9.5, 16.2, 16.6, 17.8, 18.9, and 32.6 ± 0.2 degrees 2-theta. In some embodiments, a hydrate form of Compound 1 is characterized by six or more peaks in its X-ray powder diffraction pattern selected from 5.9, 8.1, 9.5, 16.2, 16.6, 17.8, 18.9, and 32.6 ± 0.2 degrees 2-theta. In some embodiments, a hydrate form of Compound 1 is characterized by seven or more peaks in its X-ray powder diffraction pattern selected from 5.9, 8.1, 9.5, 16.2, 16.6, 17.8, 18.9, and 32.6 ± 0.2 degrees 2-theta. In some embodiments, a hydrate form of Compound 1 is characterized by the following peaks in its X-ray powder diffraction pattern: 5.9, 8.1, 9.5, 16.2, 16.6, 17.8, 18.9, and 32.6 ± 0.2 degrees 2-theta.

[0048] In some embodiments, a hydrate form of Compound 1 is characterized by one or more peaks in its X-ray powder diffraction pattern selected from:

$^{\circ}2\theta (\pm 0.2)$
5.9
8.1
9.5
10.6
13.5
15.1
15.8
16.2
16.6
16.9
17.8
18.9
20.7
21.1
21.5
23.2
23.7
24.4
24.9
25.5
27.5
28.6
30.3
32.6
33.5
34.7
36.2
40.8
41.6

[0049] In some embodiments, a hydrate of Compound 1 is characterized by a differential scanning calorimetry (DSC) endotherm having a minima with an onset at about 257.25 °C and/or a peak at about 260.24 °C.

[0050] In some embodiments, a hydrate form of Compound 1 is characterized by a thermogravimetric analysis (TGA) with a weight loss of about 1.386% between 21-150 °C.

[0051] In some embodiments, a hydrate form of Compound 1 is characterized by an X-ray powder diffraction pattern substantially similar to FIG. 1A. In some embodiments, a hydrate of Compound 1 is characterized by a DSC pattern substantially similar to FIG. 1B. In some embodiments, a hydrate of Compound 1 is characterized by a TGA pattern substantially similar to

FIG. 1B. In some embodiments, a hydrate of Compound 1 is characterized by (a) an X-ray powder diffraction pattern substantially similar to FIG. 1A; (b) a DSC pattern substantially similar to FIG. 1B; and (c) a TGA pattern substantially similar to FIG. 1B.

[0052] In some embodiments, a crystalline solid form of Compound 1 is Form 1.

Methods of Preparing Crystalline Solid Forms

[0053] In some embodiments, the present disclosure provides methods of preparing provided crystalline solid forms of Compound 1 (e.g., Compound 1 Form 1). In some embodiments, a crystalline solid form of Compound 1 is prepared by slurrying Compound 1 (amorphous, partially crystalline or crystalline) in a mixture comprising one or more organic solvents.

[0054] In some embodiments, a crystalline solid form of Compound 1 is prepared by slurrying Compound 1 (amorphous, partially crystalline, or crystalline) in a mixture comprising water. In some embodiments, slurrying Compound 1 in a mixture comprising water yields a crystalline solid form of Compound 1 in the form of a hydrate. In some embodiments, a mixture comprising water further comprises an organic solvent.

[0055] In some embodiments, Form 1 of Compound 1 is prepared by: (i) providing Compound 2; (ii) contacting Compound 2 with HCl in a suitable solvent; and (iii) causing Compound 1 to crystallize from the solvent. In some embodiments, a suitable solvent is isopropanol.

Compositions

[0056] In some embodiments, the present disclosure provides compositions comprising a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1). In some embodiments, a provided composition comprises a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1) that is substantially free of impurities. As used herein, the term “substantially free of impurities” means that the composition contains no significant amount of extraneous matter. Such extraneous matter may include starting materials, alternative crystalline forms, residual solvents, or any other impurities that may result from the preparation of and/or isolation of a crystalline solid form. In some embodiments, the composition comprises at least about 90% by weight of a solid crystalline form of Compound 1 (e.g., Compound 1 Form 1).

[0057] In some embodiments, a provided composition comprising a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1) is substantially pure (e.g., comprises at least about 95%, 97%, 97.5%, 98%, 98.5%, 99%, 99.5%, or 99.8% by weight of the provided crystalline solid form based on the total weight of the composition). In some embodiments, a composition comprising a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1) comprises no more than about 5.0 percent of total organic impurities. In some embodiments, a composition comprising a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1) comprises no more than about 3.0 percent of total organic impurities. In some embodiments, a composition comprising a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1) comprises no more than about 1.5 percent of total organic impurities. In some embodiments, a composition comprising a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1) comprises no more than about 1.0 percent of total organic impurities. In some embodiments, a composition comprising a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1) comprises no more than about 0.5 percent of total organic impurities. In some embodiments, the percent of total organic impurities is measured by HPLC.

[0058] In some embodiments, a provided composition comprising a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1) is substantially pure (e.g., comprises at least about 95%, 97%, 97.5%, 98%, 98.5%, 99%, 99.5%, or 99.8% by weight of the provided crystalline solid form based on the total weight of the composition). In some embodiments, a composition comprising a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1) comprises no more than about 5.0 percent of total organic impurities. In some embodiments, a composition comprising a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1) comprises no more than about 3.0 percent of total organic impurities. In some embodiments, a composition comprising a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1) comprises no more than about 1.5 percent of total organic impurities. In some embodiments, a composition comprising a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1) comprises no more than about 1.0 percent of total organic impurities. In some embodiments, a composition comprising a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1) comprises no more than about 0.5 percent of total organic impurities. In some embodiments, the percent of total organic impurities is measured by HPLC.

Pharmaceutical Compositions

[0059] In some embodiments, the present disclosure provides a pharmaceutical composition comprising a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1) and one or more pharmaceutically acceptable excipients. In some embodiments, a pharmaceutical composition comprises a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1) and one or more pharmaceutically acceptable excipients. In some embodiments, a pharmaceutical composition is one described in WO2018/201131, which is incorporated herein by reference in its entirety.

[0060] In some embodiments, a pharmaceutical composition comprises a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), one or more binders, one or more fillers, one or more disintegrants, and/or one or more antioxidants. In some embodiments, a pharmaceutical composition comprises a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1).

[0061] In some embodiments, a pharmaceutical formulation comprises about 10-30% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. As used herein, a person of skill in the art will understand that reference to a “free base weight” or reference to calculating a weight “as a free base” refers to using the weight corresponding to a molar equivalent of a free base of Compound 1 (i.e., 2-(1-(4-((4-(4-hydroxypiperidin-1-yl)phenyl)amino)-5-oxo-5,6-dihydropyrimido[4,5-d]pyridazin-2-yl)piperidin-4-yl)acetonitrile), which is agnostic to any particular salt form. In some embodiments, a pharmaceutical formulation comprises about 10-25% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 10-15% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 10%, about 11%, about 12%, about 13%, about 14%, or about 15% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 10% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 10.5% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 11% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 11.5% by weight of a

crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 12% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 12.5% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base.

[0062] In some embodiments, a pharmaceutical formulation comprises about 15-25% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, or about 25% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 20% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 21% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 22% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 23% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 24% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 25% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base.

[0063] In some embodiments, a pharmaceutical formulation comprises about 1-10% by weight of a binder. In some embodiments, a pharmaceutical formulation comprises about 1-5% by weight of a binder. In some embodiments, a pharmaceutical formulation comprises about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9% or about 10% by weight of a binder. In some embodiments, a pharmaceutical formulation comprises about 1% by weight of a binder. In some embodiments, a pharmaceutical formulation comprises about 2% by weight of a binder. In some embodiments, a pharmaceutical formulation comprises about 3% by weight of a binder. In some embodiments, a pharmaceutical formulation comprises about 4% by weight

of a binder. In some embodiments, a pharmaceutical formulation comprises about 5% by weight of a binder.

[0064] In some embodiments, one or more binders are selected from polyvinylpyrrolidone or hydroxylpropyl cellulose. In some embodiments, a binder is polyvinylpyrrolidone. In some embodiments, a binder is hydroxylpropyl cellulose.

[0065] In some embodiments, a pharmaceutical formulation comprises about 1-10% by weight of a disintegrant. In some embodiments, a pharmaceutical formulation comprises about 4-8% by weight of a disintegrant. In some embodiments, a pharmaceutical formulation comprises about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9% or about 10% by weight of a disintegrant. In some embodiments, a pharmaceutical formulation comprises about 4% by weight of a disintegrant. In some embodiments, a pharmaceutical formulation comprises about 5% by weight of a disintegrant. In some embodiments, a pharmaceutical formulation comprises about 6% by weight of a disintegrant. In some embodiments, a pharmaceutical formulation comprises about 7% by weight of a disintegrant. In some embodiments, a pharmaceutical formulation comprises about 8% by weight of a disintegrant.

[0066] In some embodiments, one or more disintegrants are selected from crospovidone and croscarmellose sodium. In some embodiments, a disintegrant is crospovidone. In some embodiments, a disintegrant is croscarmellose sodium.

[0067] In some embodiments, a pharmaceutical formulation comprises about 0.05-1% by weight of an antioxidant. In some embodiments, a pharmaceutical formulation comprises about 0.05% to about 0.5% by weight of an antioxidant. In some embodiments, a pharmaceutical formulation comprises about 0.05% to about 0.1% by weight of an antioxidant. In some embodiments, a pharmaceutical formulation comprises about 0.05%, about 0.06%, about 0.07%, about 0.08%, about 0.09% or about 0.1% of an antioxidant.

[0068] In some embodiments, one or more antioxidants are selected from vitamin E and butylated hydroxytoluene. In some embodiments, an antioxidant is vitamin E. In some embodiments, an antioxidant is butylated hydroxytoluene.

[0069] In some embodiments, a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1) is micronized.

[0070] In some embodiments, a pharmaceutical composition comprises: about 10-30% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated by free

base weight; about 1-10% by weight of a disintegrant; about 1-10% by weight of a binder; and about 0.1-1% by weight of an antioxidant. In some embodiments, a pharmaceutical composition comprises: about 10-30% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated by free base weight; about 1-10% by weight of croscarmellose sodium; about 1-10% by weight of hydroxypropyl cellulose; and about 0.05-1% by weight of vitamin E.

[0071] In some embodiments, a pharmaceutical composition comprises about 10-15% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated by free base weight; about 3-8% by weight of a disintegrant; about 1-5% by weight of a binder; and about 0.05-1% by weight of an antioxidant. In some embodiments, a pharmaceutical composition comprises about 10-15% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated by free base weight; about 3-8% by weight of croscarmellose sodium; about 1-5% by weight of hydroxypropyl cellulose; and about 0.05-1% by weight of vitamin E. In some embodiments, a pharmaceutical composition comprises about 10% by weight of a crystalline form of Compound 1 (e.g., Compound 1 Form 1); about 3% by weight of a binder; about 6% by weight of a disintegrant; and about 0.1% by weight of an antioxidant. In some embodiments, a pharmaceutical composition comprises about 10% by weight of a crystalline form of Compound 1 (e.g., Compound 1 Form 1); about 3% by weight of hydroxypropyl cellulose; about 6% by weight of a croscarmellose sodium; and about 0.1% by weight of vitamin E. In some embodiments, a pharmaceutical composition comprises about 12% by weight of a crystalline form of Compound 1 (e.g., Compound 1 Form 1); about 3% by weight of a binder; about 6% by weight of a disintegrant; and about 0.08% by weight of an antioxidant. In some embodiments, a pharmaceutical composition comprises about 12% by weight of a crystalline form of Compound 1 (e.g., Compound 1 Form 1); about 3% by weight of hydroxypropyl cellulose; about 6% by weight of a croscarmellose sodium; and about 0.08% by weight of vitamin E.

[0072] In some embodiments, a pharmaceutical composition comprises about 20-25% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated by free base weight; about 3-8% by weight of a disintegrant; about 1-5% by weight of a binder; and about 0.05-1% by weight of an antioxidant. In some embodiments, a pharmaceutical composition comprises about 20-25% by weight of a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1), calculated by free base weight; about 3-8% by weight of croscarmellose sodium; about 1-5% by weight of hydroxypropyl cellulose; and about 0.05-1% by weight of vitamin E. In some

embodiments, a pharmaceutical composition comprises about 20% by weight of a crystalline form of Compound 1 (e.g., Compound 1 Form 1); about 3% by weight of a binder; about 6% by weight of a disintegrant; and about 0.1% by weight of an antioxidant. In some embodiments, a pharmaceutical composition comprises about 20% by weight of a crystalline form of Compound 1 (e.g., Compound 1 Form 1); about 3% by weight of hydroxypropyl cellulose; about 6% by weight of a croscarmellose sodium; and about 0.1% by weight of vitamin E. In some embodiments, a pharmaceutical composition comprises about 23% by weight of a crystalline form of Compound 1 (e.g., Compound 1 Form 1); about 3% by weight of a binder; about 6% by weight of a disintegrant; and about 0.08% by weight of an antioxidant. In some embodiments, a pharmaceutical composition comprises about 23% by weight of a crystalline form of Compound 1 (e.g., Compound 1 Form 1); about 3% by weight of hydroxypropyl cellulose; about 6% by weight of a croscarmellose sodium; and about 0.08% by weight of vitamin E.

[0073] In some embodiments, a pharmaceutical formulation further comprises a filler. In some embodiments, a pharmaceutical composition comprises about 50-80% by weight of a filler. In some embodiments, a pharmaceutical composition comprises about 50% to about 75% by weight of a filler. In some embodiments, a pharmaceutical composition comprises about 50%, about 55%, about 60%, about 65%, about 70%, or about 75% by weight a filler. In some embodiments, a filler is lactose monohydrate.

[0074] In some embodiments, a pharmaceutical formulation further comprises about 5-10% by weight of microcrystalline cellulose. In some embodiments, a pharmaceutical formulation further comprises about 0.5-2% by weight of sodium lauryl sulfate. In some embodiments, a pharmaceutical formulation comprises about 1% by weight of magnesium stearate.

[0075] In some embodiments, a pharmaceutical formulation comprises about 20 mg to about 120 mg of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 40 mg to about 80 mg of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 40 mg of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base. In some embodiments, a pharmaceutical formulation comprises about 80 mg of Compound 1 (e.g., Compound 1 Form 1), calculated as a free base.

[0076] In some embodiments, a pharmaceutical formulation is a unit dosage form. In some embodiments, a unit dosage form in the form of a tablet.

[0077] In some embodiments, a provided pharmaceutical composition is administered once daily (QD). In some embodiments, a provided pharmaceutical composition is administered twice daily (BID). In some embodiments, a provided pharmaceutical composition is administered every other day (QOD). In some embodiments, a provided pharmaceutical composition is administered once weekly (QW). In some embodiments, a provided pharmaceutical composition is administered once every four weeks (Q4W).

Uses

[0078] Provided crystalline solid forms and compositions comprising said crystalline solid forms are useful in the treatment of a variety of diseases and disorders. For example, in some embodiments, a provided crystalline solid form is useful for treating a disease, disorder, or condition that is mediated by the JAK/SYK pathway.

[0079] In some embodiments, the present disclosure provides a method of treating a disease, disorder or condition, comprising administering to a subject in need thereof a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1). In some embodiments, the present disclosure provides a method of treating a disease, disorder or condition, comprising administering to a subject in need thereof a crystalline solid form of Compound 1 (e.g., Compound 1 Form 1).

[0080] In some embodiments, a disease, disorder, or condition is atopic dermatitis, alopecia areata, hand and foot eczema, chronic hand eczema, hidradenitis suppurativa, pemphigus vulgaris, psoriasis, cutaneous lupus, vitiligo, inflammatory bowel disease, rheumatoid arthritis, asthma, allergic rhinitis, systemic lupus erythematosus, psoriatic arthritis, multiple sclerosis, acute myeloid leukemia, graft versus host disease, myelofibrosis, warm hemolytic anemia, idiopathic thrombocytopenic purpura, immunoglobulin A nephropathy, scleroderma, idiopathic pulmonary fibrosis, uveitis, eosinophilic esophagitis, and lupus nephritis. In some embodiments, a disease, disorder, or condition is atopic dermatitis. In some embodiments, a disease, disorder, or condition is alopecia areata. In some embodiments, a disease, disorder, or condition is hand and foot eczema. In some embodiments, a disease, disorder, or condition is chronic hand eczema. In some embodiments, a disease, disorder, or condition is hidradenitis suppurativa. In some embodiments, a disease, disorder, or condition is pemphigus vulgaris. In some embodiments, a disease, disorder, or condition is psoriasis. In some embodiments, a disease, disorder, or condition is cutaneous

lupus. In some embodiments, a disease, disorder, or condition is vitiligo. In some embodiments, a disease, disorder, or condition is inflammatory bowel disease. In some embodiments, a disease, disorder, or condition is rheumatoid arthritis. In some embodiments, a disease, disorder, or condition is asthma. In some embodiments, a disease, disorder, or condition is allergic rhinitis. In some embodiments, a disease, disorder, or condition is systemic lupus erythematosus. In some embodiments, a disease, disorder, or condition is psoriatic arthritis. In some embodiments, a disease, disorder, or condition is multiple sclerosis. In some embodiments, a disease, disorder, or condition is acute myeloid leukemia. In some embodiments, a disease, disorder, or condition is graft versus host disease. In some embodiments, a disease, disorder, or condition is myelofibrosis. In some embodiments, a disease, disorder, or condition is warm hemolytic anemia. In some embodiments, a disease, disorder, or condition is idiopathic thrombocytopenic purpura. In some embodiments, a disease, disorder, or condition is immunoglobulin A nephropathy. In some embodiments, a disease, disorder, or condition is scleroderma. In some embodiments, a disease, disorder, or condition is idiopathic pulmonary fibrosis. In some embodiments, a disease, disorder, or condition is uveitis. In some embodiments, a disease, disorder, or condition is eosinophilic esophagitis. In some embodiments, a disease, disorder, or condition is lupus nephritis.

[0081] In some embodiments, a disease, disorder, or condition is a JAK/SYK-mediated disease, disorder, or condition. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is atopic dermatitis, alopecia areata, hand and foot eczema, chronic hand eczema, hidradenitis suppurativa, pemphigus vulgaris, psoriasis, cutaneous lupus, vitiligo, inflammatory bowel disease, rheumatoid arthritis, asthma, allergic rhinitis, systemic lupus erythematosus, psoriatic arthritis, multiple sclerosis, acute myeloid leukemia, graft versus host disease, myelofibrosis, warm hemolytic anemia, idiopathic thrombocytopenic purpura, immunoglobulin A nephropathy, scleroderma, idiopathic pulmonary fibrosis, uveitis, eosinophilic esophagitis, and lupus nephritis. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is atopic dermatitis. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is alopecia areata. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is hand and foot eczema. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is chronic hand eczema. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is hidradenitis suppurativa. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is pemphigus vulgaris. In some embodiments, a JAK/SYK-mediated

disease, disorder, or condition is psoriasis. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is cutaneous lupus. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is vitiligo. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is inflammatory bowel disease. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is rheumatoid arthritis. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is asthma. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is allergic rhinitis. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is systemic lupus erythematosus. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is psoriatic arthritis. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is multiple sclerosis. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is acute myeloid leukemia. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is graft versus host disease. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is myelofibrosis. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is warm hemolytic anemia. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is idiopathic thrombocytopenic purpura. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is immunoglobulin A nephropathy. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is scleroderma. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is idiopathic pulmonary fibrosis. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is uveitis. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is eosinophilic esophagitis. In some embodiments, a JAK/SYK-mediated disease, disorder, or condition is lupus nephritis.

EXAMPLES

[0082] As described in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present disclosure, the following general methods and other methods known to one of ordinary skill in the art can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

[0083] The following abbreviations may be used in the Examples below: ACN (acetonitrile); DCM (dichloromethane); DMF (N,N-dimethylformamide); DMSO (dimethyl sulfoxide); EA (ethyl acetate); EtOH (ethanol); h (hour or hours); HPLC (*high-performance liquid chromatography*); IPA (isopropyl alcohol); IPAC (isopropyl acetate); LCMS (liquid chromatography-mass spectrometry); methanol (MeOH); MTBE (methyl tert-butyl ether); min (minute or minutes); NMR (nuclear magnetic resonance); RH (relative humidity); rt or RT (room temperature); s (second or seconds); SM (starting material); THF (tetrahydrofuran); and UV (ultraviolet).

Materials and Methods

X-Ray Powder Diffraction (XRPD)

[0084] The solid samples were examined using an X-ray diffractometer (Bruker D8 Focus). The samples were scanned from 3° to 42° (2 θ), at a step size 0.02° (2 θ). The tube voltage and current were 40 kV and 40 mA, respectively. The sample was transferred from the sample container onto a zero background XRPD-holder and planished to make the surface smooth.

Thermal Gravimetric Analysis (TGA)

[0085] TGA analysis was carried out on a TA Instruments TGA Discovery 550. Samples were placed in a tared platinum or aluminum pan, automatically weighed, and inserted into the TGA furnace. The samples were heated at a rate of 10 °C/min to the final temperature. The purge gas was nitrogen for balance at 40 mL/min and for the sample at 60 mL/min, respectively.

Differential Scanning Calorimetric Analysis (DSC)

[0086] DSC analysis was conducted on a TA Instruments Discovery DSC 25. The calibration standard was indium. A sample in weight was placed into a TA DSC pan, and weight accurately recorded. Crimped pans were used for analysis and the samples were heated under nitrogen (50 mL/min) at a rate of 10 °C/min to the final temperature.

Dynamic Vapor Sorption (DVS)

[0087] Dynamic vapor sorption and desorption were studied using an Intrinsic DVS (System Measurement System UK). About 20~30 mg of prepared sample was placed in a sample basket and hung in the measuring chamber. For an isotherm test, the chamber temperature is maintained by a water bath at constant 25 $\pm$ 1 °C. The sample was tested at a targeted RH of 0 to 90% full

cycle in step mode. The analysis was performed in 10% RH increments. Time duration at each RH was set as 60 min so that the sample could reach equilibrium with the chamber environment. Data were collected in 20 second increments.

Example 1: Solubility Analysis

[0088] In the present example, the solubility of Compound 1 was assessed in a variety of solvents. In particular, Compound 1 Form 1 (referred to as “SM” in the table below) was added into an 8-mL glass vial followed by the addition of corresponding solvent at room temperature. The solvent was added step wise until the solution was visually clear or a total volume of 3 mL was reached. The parameters and results are summarized in Table 1.

Table 1

No.	Solvent	Amount of		Observation	Solubility (mg/mL)
		SM (mg)	Solvent (mL)		
1	MeOH	1.8	0.5	Clear	≥ 3.6
2	EtOH	1.8	3	Turbid	< 0.6
3	IPA	2.2	3	Turbid	< 0.7
4	THF	1.8	3	Turbid	< 0.6
5	ACN	2.2	3	Turbid	< 0.7
6	MTBE	1.9	3	Turbid	< 0.6
7	Acetone	2.1	3	Turbid	< 0.7
8	Water	33.3	3	Clear	≥ 11.1
9	EA	1.9	3	Turbid	< 0.6
10	IPAC	2.1	3	Turbid	< 0.7
11	DMSO	45.6	0.5	Clear	≥ 91.2
12	DCM	1.2	3	Turbid	< 0.4
13	DMF	42.9	1	Clear	≥ 42.9
14	Iso-butanol	2.0	3	Turbid	< 0.7
15	Butanone	1.8	3	Turbid	< 0.6
16	Toluene	1.4	3	Turbid	< 0.5

No.	Solvent	Amount of		Observation	Solubility (mg/mL)
		SM (mg)	Solvent (mL)		
17	ACN:Water 1:1	49.4	0.5	Clear	≥98.8
18	Acetone:Water 1:1	18.9	0.5	Clear	≥37.8
19	DMSO:MeOH 4:1	51.1	0.5	Clear	≥102.2
20	MeOH:Water 1:4	51.5	1	Clear	≥51.5

Example 2: Stability Evaluation of Compound 1 Form 1

[0089] Stability of Compound 1 Form 1 was assessed under controlled temperature/humidity conditions. In the present example, about 10 mg solid was put into a 2-mL glass vial. Uncapped vials were stored under stress conditions of 25 °C/60% RH, 40 °C/75% RH and 60 °C/75% RH and capped vials were stored under stress test conditions of 80 °C and light. Then the resulting solid was analyzed by XRPD and HPLC.

[0090] The stability result of the starting material is summarized in Table 2. Compound 1 Form 1 demonstrated some stability after four weeks at 25 °C/60% RH and 40 °C/75% RH, as well as at 80 °C for 1 day and 60 °C/75% RH for one week.

Table 2

Condition	Time	SM Purity	Degradation	XRPD
Initial	N/A	99.45	N/A	N/A
80 °C	1 day	99.66	-0.21	No change
Light	1.2M Lux	97.96	1.49	No change
60 °C/75% RH	1 week	99.53	-0.08	No change
25 °C/60% RH	1 week	99.62	-0.17	No change
	2 weeks	99.68	-0.23	No change
	4 weeks	99.63	-0.18	No change
40 °C/75% RH	1 week	99.62	-0.17	No change
	2 weeks	99.70	-0.25	No change
	4 weeks	99.55	-0.1	No change

Example 3. Preparation of Compound 1 Form 1

[0091] Compound 1 Form 1 was prepared as follows:

[0093] Step 2: SeO₂ (23.3 kg) and DMSO (387.6 kg) were added to a 1000 L reactor under nitrogen atmosphere. Compound 5.3 (35.2 kg) was then added, and nitrogen was bubbled through the resulting mixture for 2-5 min. The mixture was heated to 90-98 °C until area% of 5.3 was ≤ 1.0 % as judged by HPLC. The mixture was then cooled to ambient temperature. The mixture was filtered and the filtrate transferred into a 3000 L reactor containing water (776.1 kg). The mixture was stirred for 1 hour at 25-35 °C and then filtered. The collected solids were added to a reactor containing water (352.2 kg) and the mixture stirred for 1 hour at 25-35 °C. The mixture was then filtered. The collected solids were added to a reactor containing isopropanol (140.4 kg) and stirred for 1 hour at 25-35 °C. The mixture was then heated to 65-75 °C, and hydrazine hydrate (6.8 kg) was added. The mixture was stirred at 65-75 °C until ≥99.7% conversion was confirmed by HPLC. The mixture was then cooled to ambient temperature and stirred for 1 hour, filtered, rinsed twice with isopropyl alcohol and twice with water, and then dried at ≤ 55 °C to give compound **5.4** (23.5 kg, 68.5% yield).

[0094] *Step 3:* Compound **5.4** (23.3 kg) and DMF (178.5 kg) were added to 2000 L reactor under nitrogen atmosphere. The mixture was cooled to 0-10 °C and mCPBA (21.2 kg) was added in five portions. The mixture was stirred at 0-10 °C until area% of 5.4 was ≤ 1.0 % as judged by

HPLC. Then, compound 5.5 (15.6 kg) was added to the mixture in five portions. The mixture was allowed to warm to 25-35 °C and stirred at that temperature until $\geq 99.0\%$ conversion was confirmed by HPLC. The mixture was then warmed to 50-60 °C and filtered. The filtrate was then warmed to 40-50 °C, water (631.9 kg) was added, and the mixture stirred for 1 h at 40-50 °C. The mixture was filtered again, washed twice with water, and the collected solids were added to a reactor containing water (234.8 kg) and sodium bicarbonate (6.1 kg) at 25-35 °C. After stirring for 1 h at 25-35 °C, the mixture was filtered, washed twice with water, and the collected solids were dried at 40-60 °C to give crude Compound 2 (27.8 kg, 84.0% yield).

[0095] Crude Compound 2 (32.2 kg) was added to a 3000 L reactor containing DMF (346.4 kg) and the mixture was stirred at 25-35 °C until a clear solution was obtained. The solution was filtered through an activated carbon cartridge into another 3000 L reactor, heated to 40-50 °C and stirred for 2-4 hours. Water (260.0 kg) was added and the mixture was stirred at 40-50 °C for 2-4 hours, then was cooled to 10-15 °C and stirred for 2-4 hours. The solid was collected by filtration, washed with water and methanol, then dried at 50-65 °C to give Compound 2 (30.3 kg, 94% yield). The isolated Compound 2 (30.2 kg) was added to a 3000 L reactor containing DCM (803.7 kg) and methanol (108.0 kg) and heated to 30-40 °C for 1-2 h with stirring. The mixture was cooled to 15-25 °C, and MTBE (224.5 kg) was added. The mixture was stirred for 4-6 h and then filtered. The collected solids were dried at ≤ 50 °C to give Compound 2 (27.0 kg, 89% yield).

[0096] Step 4: Compound 2 (22.5 kg) was added to a 3000 L reactor containing methanol (340.2 kg) under nitrogen atmosphere. At 15-25 °C, hydrochloric acid (5.4 kg) in isopropanol (36.9 kg) was added. The mixture was stirred at 18-23 °C for 20.5 h, resulting in crystallization. Crystals were collected by filtration, rinsing with methanol and MTBE. The collected solids were dried at ≤ 40 °C to give Compound 1 (21.5 kg, 89% yield).

[0097] Compound 1 prepared from this process was assigned as Compound 1 Form 1. An XRPD spectrum of Compound 1 Form 1 is provided in FIG. 1A.

[0098] As shown in FIG. 1B, about 1.386% of weight loss was observed up to 150 °C in the TGA curve and was attributed to loss of residual solvent or water. The DSC curve (FIG. 1B) shows one main endothermic peak with an onset temperature of 257.25 °C and a peak temperature of 260.24 °C.

[0099] FIG. 1C provides a DVS analysis of Compound 1 Form 1, showing a 3.258% weight increase at 80% RH. DVS indicated that Compound 1 Form 1 is hygroscopic. XRPD analysis of the material before and after DVS was the same.

[0100] When Compound 1 Form 1 was heated to 100 °C, the XRPD pattern remained the same (FIG. 1D). Compound 1 Form 1 may therefore be a channel hydrate, since no change in form was observed after removal of solvent.

Example 4. Pharmaceutical Formulations of Compound 1

[0101] Exemplary formulations of provided solid forms were prepared generally as follows: Compound 1 (e.g., Compound 1 Form 1), lactose monohydrate, and croscarmellose sodium were combined with a solution of hydroxypropyl cellulose and vitamin E in isopropyl alcohol to provide wet granules, which were then dried and milled. The resulting milled granules were then blended with croscarmellose sodium, microcrystalline cellulose, magnesium stearate, and sodium lauryl sulfate to provide the final blend. The final blend was then compressed into a tablet. The tablets were film-coated with a suspension of aesthetic coating in 1:1 alcohol:water.

Exemplary Formulation #1

[0102] An exemplary formulation, without coating, is provided in the following table:

Component	Function	Amount per unit (mg)
Compound 1 (micronized)	Active ingredient	86.34*
Hydroxypropyl cellulose	Binder	11.25
Lactose monohydrate	Filler	216.74
Croscarmellose sodium	Disintegrant	22.50
Vitamin E	Antioxidant	0.30
Microcrystalline cellulose	Filler	28.12
Sodium lauryl sulfate	Wetting agent	6.00
Magnesium stearate	Lubricant	3.75

*Corresponding to 80 mg free base weight of Compound 1.

Exemplary Formulation #2

[0103] An exemplary formulation, without coating, is provided in the following table:

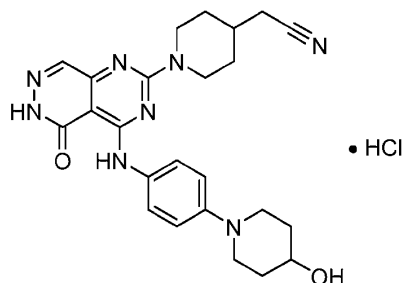
Component	Function	Amount per unit (mg)
Compound 1 (micronized)	Active ingredient	43.17*
Hydroxypropyl cellulose	Binder	11.25
Lactose monohydrate	Filler	262.91
Croscarmellose sodium	Disintegrant	22.50
Vitamin E	Antioxidant	0.30
Microcrystalline cellulose	Filler	28.12
Sodium lauryl sulfate	Wetting agent	3.00
Magnesium stearate	Lubricant	3.75

*Corresponding to 40 mg free base weight of Compound 1.

[0104] The embodiments of the disclosure described above are intended to be merely exemplary, numerous variations and modifications will be apparent to those skilled in the art. All such variations and modifications are intended to be within the scope of the present invention as defined in any appended claims.

CLAIMS

1. A crystalline solid form of Compound 1:



Compound 1

wherein the crystalline solid form is a hydrate and is characterized by one or more peaks in its X-ray powder diffraction pattern selected from 5.9, 8.1, 9.5, 16.2, 16.6, 17.8, 18.9, and 32.6 ± 0.2 degrees 2-theta.

2. The crystalline solid form of claim 1, wherein the crystalline solid form is characterized by one or more peaks in its X-ray powder diffraction pattern selected from:

$^{\circ}2\theta (\pm 0.2)$
5.9
8.1
9.5
10.6
13.5
15.1
15.8
16.2
16.6
16.9
17.8
18.9
20.7
21.1
21.5
23.2
23.7
24.4
24.9
25.5
27.5

$^{\circ}2\theta (\pm 0.2)$
28.6
30.3
32.6
33.5
34.7
36.2
40.8
41.6

3. The crystalline solid form of claim 1 or claim 2, wherein the crystalline solid form is characterized by an X-ray powder diffraction pattern substantially similar to FIG. 1A.
4. The crystalline solid form of any one of claims 1-3, wherein the crystalline solid form is Form 1.
5. A sample comprising the crystalline form of any one of claims 1-4, wherein the sample is substantially free of impurities.
6. A pharmaceutical formulation comprising the crystalline form of any one of claims 1-4, and one or more pharmaceutically acceptable excipients.
7. The pharmaceutical formulation of claim 6, wherein the pharmaceutical formulation comprises:
 - about 10-30% by weight of the crystalline solid form of Compound 1, calculated by free base weight;
 - about 1-10% by weight of a disintegrant;
 - about 1-10% by weight of a binder; and
 - about 0.05-0.5% by weight of an antioxidant.
8. The pharmaceutical formulation of claim 7, further comprising a lubricant.
9. The pharmaceutical formulation of claims 7 or 8, wherein the binder is hydroxypropyl cellulose.

10. The pharmaceutical formulation of any one of claims 7-9, wherein the disintegrant is croscarmellose sodium.
11. The pharmaceutical formulation of any one of claims 7-10, wherein the antioxidant is vitamin E.
12. The pharmaceutical formulation of any one of claims 7-11, wherein the pharmaceutical formulation comprises about 20 mg to about 120 mg of the crystalline solid form of Compound 1, calculated by free base weight.
13. The pharmaceutical formulation of claim 12, wherein the pharmaceutical formulation comprises about 40 mg to about 80 mg of the crystalline solid form of Compound 1, calculated by free base weight.
14. The pharmaceutical formulation of any one of claims 6-13, wherein the pharmaceutical formulation is a unit dosage form.
15. The pharmaceutical formulation of claim 14, wherein the unit dosage form is in the form of a tablet.
16. A method of treating a disease, disorder, or condition, in a subject in need thereof, comprising a step of administering to the subject the crystalline form of any one of claims 1-4 or the pharmaceutical formulation of any one of claims 6-15.
17. The method of claim 16, wherein the disease, disorder, or condition is selected from atopic dermatitis, alopecia areata, hand and foot eczema, chronic hand eczema, hidradenitis suppurativa, pemphigus vulgaris, psoriasis, cutaneous lupus, vitiligo, inflammatory bowel disease, rheumatoid arthritis, asthma, allergic rhinitis, systemic lupus erythematosus, psoriatic arthritis, multiple sclerosis, acute myeloid leukemia, graft versus host disease, myelofibrosis, warm hemolytic

anemia, idiopathic thrombocytopenic purpura, immunoglobulin A nephropathy, scleroderma, idiopathic pulmonary fibrosis, uveitis, eosinophilic esophagitis and lupus nephritis.

18. A method of treating a JAK/SYK-mediated disease, disorder, or condition, in a subject in need thereof, comprising a step of administering to the subject the crystalline form of any one of claims 1-4 or the pharmaceutical formulation of any one of claims 6-15.

19. Use of the crystalline form of any one of claims 1-4, or the pharmaceutical formulation of any one of claims 6-15 in the treatment of a disease, disorder, or condition.

20. The use of claim 19, wherein the disease, disorder, or condition is selected from atopic dermatitis, alopecia areata, hand and foot eczema, chronic hand eczema, hidradenitis suppurativa, pemphigus vulgaris, psoriasis, cutaneous lupus, vitiligo, inflammatory bowel disease, rheumatoid arthritis, asthma, allergic rhinitis, systemic lupus erythematosus, psoriatic arthritis, multiple sclerosis, acute myeloid leukemia, graft versus host disease, myelofibrosis, warm hemolytic anemia, idiopathic thrombocytopenic purpura, immunoglobulin A nephropathy, scleroderma, idiopathic pulmonary fibrosis, uveitis, eosinophilic esophagitis, and lupus nephritis.