

the unbalanced immune homeostasis in MALT1 protease dead knock-in mice may be caused by incomplete deficiency in T and B cell but severe deficiency of immunoregulatory cells (Jaworski et al., EMBO J. 2014; Gewies et al., Cell Reports 2014; Bornancin et al., J. Immunology 2015; Yu et al., PLOS One 2015). Similarly, MALT deficiency in humans has been associated with combined immunodeficiency disorder (McKinnon et al., J. Allergy Clin. Immunol. 2014, 133, 1458-1462; Jabara et al., J. Allergy Clin. Immunol. 2013, 132, 151-158; Punwani et al., J. Clin. Immunol. 2015, 35, 135-146). Given the difference between genetic mutation and pharmacological inhibition, a phenotype of MALT1 protease dead knock-in mice might not resemble that of patients treated with MALT1 protease inhibitors. A reduction of immunosuppressive T cells by MALT1 protease inhibition may be beneficial to cancer patients by potentially increasing antitumor immunity.

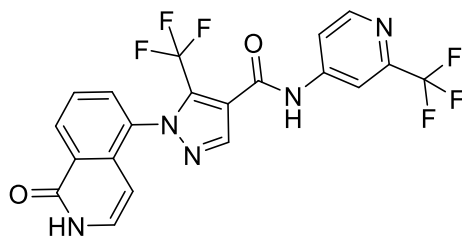
Thus, MALT1 inhibitors may provide a therapeutic benefit to patients suffering from cancer and/or immunological diseases.

WO 2018/119036, which is incorporated herein by reference, discloses compounds that inhibit MALT1, including 1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-N-[2-(trifluoromethyl)pyridin-4-yl]-1H-pyrazole-4-carboxamide (recited in WO 2018/119036 as compound 158).

There is a need to provide alternate forms of 1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-N-[2-(trifluoromethyl)pyridin-4-yl]-1H-pyrazole-4-carboxamide.

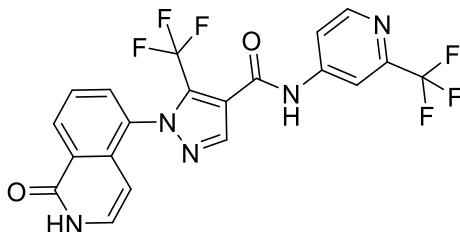
SUMMARY

The present disclosure, is directed to crystalline Form III of 1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide (Compound A) monohydrate:



Compound A.

In one aspect, the present disclosure relates to crystalline form of 1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-*N*-[2-(trifluoromethyl)pyridin-4-yl]-1*H*-pyrazole-4-carboxamide (Compound A) monohydrate:



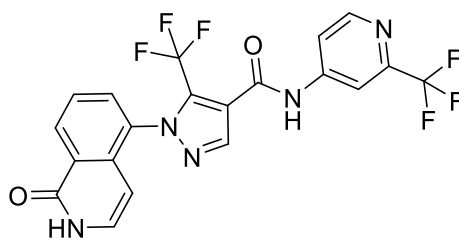
5

Compound A

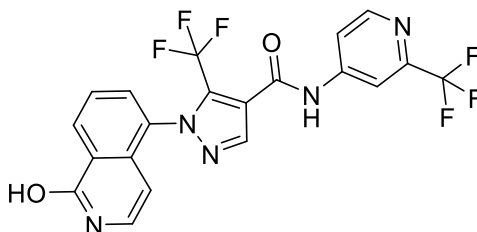
wherein the crystalline form is Form III, producing an X-ray powder diffraction pattern comprising peaks at 16.4, 23.7 and 25.7 degrees two theta $\pm$ 0.2 degrees two theta.

A person of ordinary skill in the art would recognize that other tautomeric arrangements of

10 Compound A are possible. For example, it is understood that



can occur in another tautomeric arrangement



Within the context of this disclosure, in a crystalline Form of Compound A, Compound A
 5 may be in either one of the above tautomeric arrangements or may be a mixture thereof, the
 exact tautomeric arrangement being unknown. For simplicity, only one possible tautomeric
 arrangement of the groups of Compound A is utilized in describing the compounds, but it
 should be clear to a person of ordinary skill in the art that in a crystalline Form of
 Compound A, such as crystalline Form III of Compound A monohydrate, Compound A may
 10 be in one of the above tautomeric arrangements or may be a mixture thereof.

An example of the present disclosure is directed to a pharmaceutical composition
 comprising crystalline Form III of Compound A monohydrate.

The present disclosure also provides a pharmaceutical composition comprising,
 15 consisting of and/or consisting essentially of a pharmaceutically acceptable carrier, a
 pharmaceutically acceptable excipient, and/or a pharmaceutically acceptable diluent and
 crystalline Form III of Compound A monohydrate.

In another aspect, the present disclosure relates to a pharmaceutical composition
 comprising the crystalline form as defined herein and at least one of a pharmaceutically
 20 acceptable carrier, a pharmaceutically acceptable excipient, and a pharmaceutically
 acceptable diluent.

Also provided are processes for making a pharmaceutical composition comprising,
 consisting of, and/or consisting essentially of admixing crystalline Form III of Compound A
 monohydrate, and a pharmaceutically acceptable carrier, a pharmaceutically acceptable
 25 excipient, and/or a pharmaceutically acceptable diluent.

The present disclosure further provides methods for treating or ameliorating a disease, syndrome, condition, or disorder in a subject, including a mammal and/or human in which the disease, syndrome, condition, or disorder is affected by the inhibition of

MALT1, including but not limited to, cancer and/or immunological diseases, using crystalline Form III of Compound A monohydrate.

The present disclosure is also directed to the use of crystalline Form III of Compound A monohydrate in the preparation of a medicament wherein the medicament is prepared for treating a disease, syndrome, disorder or condition that is affected by the inhibition of MALT1, such as cancer and/or immunological diseases.

In another aspect, the present disclosure relates to use of a crystalline form as defined herein in the preparation of a medicament for treating a disease, syndrome, disorder or condition in a subject in need thereof, wherein said disease, syndrome, condition, or disorder is affected by the inhibition of MALT1. Exemplifying the disclosure are methods of treating a disease, syndrome, condition, or disorder mediated by MALT1, selected from the group consisting of lymphomas, leukemias, carcinomas, and sarcomas, e.g. non-Hodgkin's lymphoma (NHL), B-cell NHL, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT) lymphoma, marginal zone lymphoma, T-cell lymphoma, Hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia, lymphoblastic T cell leukemia, chronic myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, megakaryoblastic leukemia, acute megakaryocyte leukemia, promyelocytic leukemia, erythroleukemia, brain (gliomas), glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer including non-small-cell, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma, thyroid cancer, bladder cancer, head and neck cancer, testicular cancer, Ewing's sarcoma, rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer, urothelial cancer, vulval cancer, esophageal cancer, salivary gland cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, and GIST (gastrointestinal stromal tumor), comprising, consisting of, and/or consisting essentially of, administering to a subject in need thereof a therapeutically effective amount of crystalline Form III of Compound A monohydrate.

In another example, the present disclosure is directed to crystalline Form III of Compound A monohydrate for use as a medicament.

In another aspect, the present disclosure relates to a compound in crystalline form as defined herein for use in the treatment of a disease, syndrome, condition, or disorder in a subject in need thereof, wherein said disease, syndrome, condition, or disorder is affected by the inhibition of MALT1. In another example, the present disclosure is directed to crystalline

- 5 Form III of Compound A monohydrate for use in the treatment of a disease, syndrome, condition, or disorder affected by the inhibition of MALT1, selected from the group consisting of lymphomas, leukemias, carcinomas, and sarcomas, e.g. non-Hodgkin's lymphoma (NHL), B-cell NHL, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL),

follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT) lymphoma,
 marginal zone lymphoma, T-cell lymphoma, Hodgkin's lymphoma, Burkitt's lymphoma,
 multiple myeloma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma
 (SLL), Waldenström macroglobulinemia, lymphoblastic T cell leukemia, chronic
 5 myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia,
 plasmacytoma, immunoblastic large cell leukemia, megakaryoblastic leukemia, acute
 megakaryocyte leukemia, promyelocytic leukemia, erythroleukemia, brain (gliomas),
 glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer including
 non-small-cell, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver
 10 cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma,
 thyroid cancer, bladder cancer, head and neck cancer, testicular cancer, Ewing's sarcoma,
 rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer,
 urothelial cancer, vulval cancer, esophageal cancer, salivary gland cancer, nasopharyngeal
 cancer, buccal cancer, cancer of the mouth, and GIST (gastrointestinal stromal tumor).
 15 In another example, the present disclosure is directed to a composition comprising
 crystalline Form III of Compound A monohydrate for the treatment of a disease, syndrome,
 condition, or disorder affected by inhibition of MALT1, selected from the group consisting
 of lymphomas, leukemias, carcinomas, and sarcomas, e.g. non-Hodgkin's lymphoma (NHL),
 B-cell NHL, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL),
 20 follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT) lymphoma,
 marginal zone lymphoma, T-cell lymphoma, Hodgkin's lymphoma, Burkitt's lymphoma,
 multiple myeloma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma
 (SLL), Waldenström macroglobulinemia, lymphoblastic T cell leukemia, chronic
 myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia,
 25 plasmacytoma, immunoblastic large cell leukemia, megakaryoblastic leukemia, acute
 megakaryocyte leukemia, promyelocytic leukemia, erythroleukemia, brain (gliomas),
 glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer including
 non-small-cell, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver
 cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma,
 30 thyroid cancer, bladder cancer, head and neck cancer, testicular cancer, Ewing's sarcoma,
 rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer,
 urothelial cancer, vulval cancer, esophageal

cancer, salivary gland cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, and GIST (gastrointestinal stromal tumour).

In another example, the present disclosure is directed to a composition comprising crystalline Form III of Compound A monohydrate for the treatment of a disease, syndrome,
5 condition, or disorder affected by inhibition of MALT1, selected from the group consisting of diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), and mucosa-associated lymphoid tissue (MALT) lymphoma.

An example of the present disclosure is directed to a composition comprising crystalline Form III of Compound A monohydrate for the treatment of immunological
10 diseases that are affected by the inhibition of MALT1, including but not limited to, autoimmune and inflammatory disorders, e.g. arthritis, inflammatory bowel disease, gastritis, ankylosing spondylitis, ulcerative colitis, pancreatitis, Crohn's disease, celiac disease, multiple sclerosis, systemic lupus erythematosus, lupus nephritis, rheumatic fever, gout, organ or transplant rejection, chronic allograft rejection, acute or chronic graft-versus-
15 host disease, dermatitis including atopic, dermatomyositis, psoriasis, Behcet's diseases, uveitis, myasthenia gravis, Grave's disease, Hashimoto thyroiditis, Sjogren's syndrome, blistering disorders, antibody-mediated vasculitis syndromes, immune-complex vasculitides, allergic disorders, asthma, bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pneumonia, pulmonary diseases including oedema, embolism,
20 fibrosis, sarcoidosis, hypertension and emphysema, silicosis, respiratory failure, acute respiratory distress syndrome, BENTA disease, berylliosis, and polymyositis.

In another example, the present disclosure is directed to a composition comprising crystalline Form III of Compound A monohydrate for the treatment of a disease, syndrome,
condition, or disorder affected by inhibition of MALT1, selected from the group consisting
25 of rheumatoid arthritis (RA), psoriatic arthritis (PsA), psoriasis (Pso), ulcerative colitis (UC), Crohn's disease, systemic lupus erythematosus (SLE), asthma, and chronic obstructive pulmonary disease (COPD).

The present disclosure is also directed to the preparation of crystalline Form III of Compound A monohydrate.

In another aspect, the present disclosure relates to a process for preparing the crystalline form as defined herein, comprising the step of recrystallising Compound A, wherein the recrystallisation comprises the steps of:

5 a) adding Compound A, or a hydrate or solvate thereof, to a mixture of ethyl acetate and ethanol, and heating to a temperature in the range of from about 30 °C to solvent reflux temperature;

b) adding water to the mixture and filtering off any precipitate, maintaining said temperature;

10 c) adding n-heptane to the mixture, seeding with crystalline Form III, and maintaining said temperature; and

d) cooling to room temperature, to yield a precipitate of the crystalline form as defined herein;

wherein the quantity of water is from about 0.1 w/w% to about 3.0 w/w%, relative to the total weight of solvent.

15 In another aspect, the present disclosure relates to a process for preparing the crystalline form as defined herein, comprising the step of recrystallising Compound A, wherein the recrystallisation comprises the steps of:

20 a) adding Compound A, or a hydrate or solvate thereof, to a mixture of water and isopropyl alcohol, and heating to a temperature in the range of from about 30 °C to solvent reflux temperature;

b) adding n-heptane to the mixture, seeding with crystalline Form III, and maintaining said temperature; and

c) cooling to room temperature, to yield a precipitate of the crystalline form as defined herein;

25 wherein the quantity of water is from about 1.0 w/w% to about 6.0 w/w%, relative to the total weight of solvent

BRIEF DESCRIPTION OF THE DRAWINGS

30 The summary, as well as the following detailed description, is further understood when read in conjunction with the appended drawings. For the purpose of illustrating the