

Crystalline IRAK4 Inhibitors

The present specification claims right of priority to European Patent Application No. 23191039, filed 11 August 2023, the contents of which are hereby incorporated by reference in their entirety for all purposes.

- 5 The specification relates to stable solid forms of *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido) cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide (herein Compound (I)) and *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido) cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide (herein Compound (II)). These compounds are potent inhibitors of IRAK4. The specification also relates to
- 10 pharmaceutical compositions containing Compounds (I) and (II) and their use in therapy.

- Interleukin-1 receptor (IL-1R)-associated kinase 4 (IRAK4) is a key regulator of immune signaling. IRAK4 is expressed by multiple cell types and mediates signal transduction from Toll-like receptors (TLRs) and receptors of the interleukin-1 (IL-1) family, including IL-1R, IL-18R and the IL-33 receptor ST2. TLRs recognize and respond to ligands derived from microbes, such as lipopolysaccharide (LPS)
- 15 or microbial RNA or DNA, while receptors of the IL-1 family can be activated by endogenous ligands produced by TLR-activated cells (IL-1 β and IL-18) or by tissue damage (IL-1 α and IL-33). Upon activation of TLRs or IL-1 receptors by their ligands, the adaptor protein myeloid differentiation primary response 88 (MyD88) is recruited to the receptor and forms a multimeric protein complex, called the "Myddosome", together with proteins of the IRAK family (IRAK1, IRAK2 and IRAK4). The
- 20 Myddosome serves as a signaling platform to induce nuclear factor κ B (NF- κ B) and mitogen-activated protein kinase (MAPK) signal transduction pathways, culminating in the activation of transcription factors NF- κ B, activator protein 1 (AP1), c-AMP response element-binding protein (CREB) and interferon regulatory factor 5 (IRF5), driving transcription of inflammatory cytokines and chemokines. Mice lacking IRAK4 are viable but lack inflammatory cytokine response to IL-1 β , IL-18 and LPS. Humans
- 25 presenting loss-of-function mutations in IRAK4 display an immunocompromised phenotype and their immune cells show an abrogated cytokine response to TLR agonists and IL-1 receptor ligands.

- IRAK4 is characterized by an N-terminal death domain that mediates the interaction with MyD88 and a centrally located kinase domain. Myddosome formation promotes IRAK4 auto-phosphorylation which modulates the stability and downstream signaling of the Myddosome. The kinase activity of
- 30 IRAK4 is required for cytokine induction by TLRs and IL-1R, as shown by studies in knock-in mice expressing a kinase-dead IRAK4, as well as in studies using small molecule IRAK4 kinase inhibitors.

Given its critical role in eliciting an inflammatory response, IRAK4 constitutes a target for drugs that exert an anti-inflammatory effect.

Asthma and COPD (chronic obstructive pulmonary disease) are chronic lung diseases constituting a major unmet medical need around the world. Asthma and COPD are characterized by chronic airway inflammation, involving abnormal cytokine release, dysregulated immune cell activation and airway remodeling. In asthma, insults to the airways such as allergenic, viral and bacterial insults activate the TLR receptors via pathogen associated molecular patterns (PAMPs), and the IL-1R and ST2 receptors via the release of alarmins, including IL-33 and IL-1 α , as well as by IL-1 β released upon inflammasome activation. TLRs and receptors of the IL-1 family are present in multiple cell types in the airways, including macrophages, dendritic cells, mast cells, monocytes and epithelial cells, and respond to their ligands by releasing inflammatory cytokines (TNF- α , IL-6, IL-8, GM-CSF, IL-5) leading to airway inflammation, recruitment of inflammatory cells such as neutrophils and eosinophils, airway hyperresponsiveness and mucus production. IRAK4 inhibition has the potential to suppress these inflammatory pathways in the airways. Gene expression analysis of lung samples from asthma and COPD patients, have revealed an upregulated expression of genes associated with the IL-1R and TLR2/4 inflammatory pathways in subsets of severe patients. Although IRAK4 inhibitors have not, to the best of our knowledge, been explored in the clinic for the treatment of respiratory diseases, pre-clinical data from several research groups indicates that interfering with IRAK4-regulated pathways attenuates airway inflammation in animal models of both asthma and COPD. For instance, mice lacking MyD88, the central component of the myddosome, are protected against airway inflammation induced by allergens or IL-33, as are mice treated with a small molecule mimetics blocking the interaction between IRAK2 and IRAK4. Blocking IL-1 β with a monoclonal antibody has also been found to suppress airway inflammation induced by allergens and bacteria in a steroid-resistant mouse model of asthma. Moreover, the treatment of mice with the IL-1R antagonist anakinra at the time of allergen challenge ameliorates asthma-like symptoms in a mouse model of allergic asthma. Chronic exposure to cigarette smoke is a major contributing factor to the development of COPD. In mice exposed to cigarette smoke, IL-1 signaling is central in mediating neutrophilic airway inflammation, and blocking IL-1 signaling with antibodies against IL-1 α , IL-1 β or the IL-1R can ameliorate the neutrophilic inflammation in the lung and reduce bacteria- or virus-induced exacerbations in cigarette smoke-exposed mice. Taken together, IRAK4 inhibition has potential to provide a broad anti-inflammatory effect in inflammatory respiratory diseases by simultaneously blocking several disease-relevant signaling pathways.

As a central regulator of the Myddosome, IRAK4 is also a promising therapeutic target in other inflammatory diseases driven by IL-1R-, TLR- or ST2-mediated mechanisms. As previously disclosed, IRAK4 plays a role in autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus (SLE) (see e.g. WO2017207386 & WO2015150995). In SLE, immunocomplexes
5 composed by autoantibodies and self-antigens, can drive TLR-dependent pathological signaling. In SLE pathogenesis, IRAK4 inhibition reportedly blocks the release of type I interferons and pro-inflammatory cytokines mediated by TLR7 and TLR9 activation in plasmacytoid dendritic cells. Mice expressing a kinase-dead mutant of IRAK4 or treated with IRAK4 kinase inhibitor compounds, are resistant to experimentally induced arthritis and lupus (see e.g. WO2017207386). The approved use
10 of anakinra (an IL-1 receptor antagonist) for the treatment of rheumatoid arthritis, also support the role of pathogenic IL-1R signaling in this disease. In Sjögren's syndrome, TLRs are upregulated in PBMCs (peripheral blood mononuclear cells) and salivary glands and TLR activation can stimulate release of interferon and other inflammatory cytokines, suggested to be implicated in Sjögren's pathogenesis. MyD88 knockout mice also display reduced disease manifestations in an experimental
15 mouse model of Sjögren's syndrome. Systemic sclerosis is a severe autoimmune disorder where IL-1R, TLR4, TLR8 and ST2-signaling can drive pathogenic mechanisms, including microvascular damage and fibrosis. Inhibition of IRAK4 as a treatment in systemic sclerosis would thus block multiple disease-relevant pathways simultaneously. In myositis, elevated levels of IL-1 α and IL-1 β can contribute to muscle tissue inflammation. Myositis patients have also been characterized with high type I interferon
20 gene signature, that may be partly driven by TLR7/9 activation, and the relevance of IL-1R signaling was supported by an improved clinical outcome in myositis patients treated with anakinra in a smaller mechanistic clinical trial. As a central regulator of the IL-1R pathway, IRAK4 is also a promising target in the treatment of gout. Monosodium urate crystals, characteristically formed in gout sufferers, can trigger the activation of the inflammasome and release of IL-1 β . The use of both canakinumab, an
25 anti IL-1 β monoclonal antibody or anakinra has demonstrated clinical efficacy in the treatment of gout flares. Elevated levels of IL-1 β and IL-33 have also been found in patients with endometriosis. The importance of IRAK4 in the disease process of endometriosis was shown in a mouse model where oral administration of an IRAK4 inhibitor suppressed lesion formation. MyD88 knockout mice were also protected against the development of endometriosis in the same mouse model. IL-33/ST2 signaling is
30 a key mechanism in atopic dermatitis, involved in the regulation of skin inflammation, epithelial barrier integrity and eosinophil recruitment. IL-33 can trigger eczema and dermatitis in mice in a MyD88-dependent manner. As a regulator of ST2 signaling and a central component of the myddosome, IRAK4 inhibition has the potential to inhibit pathogenic IL-33/ST2 signaling in atopic dermatitis. Both TLR7 and IL-1R mediated mechanisms have been suggested to be involved in

psoriasis. Imiquimod (TLR/8 agonist) can induce psoriasis-like disease in mice in a MyD88-dependent manner. IL-1 β is upregulated in psoriatic skin lesions and the IL-1 β /IL-1R axis has been suggested to contribute to skin inflammation and regulate the production of IL-17, a critical cytokine released from TH17 cells in psoriasis pathogenesis. IRAK4 kinase activity has further been shown to be required for the regulation of TH17 differentiation and TH17-mediated diseases in vivo.

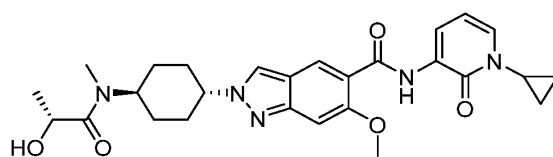
In addition to the above, there is widespread interest in the application of IRAK4 inhibitors for the treatment of various cancers, especially haematological malignancies such as myelodysplastic syndromes (MDS, a group of disease characterised by ineffective haematopoiesis and myelodysplasia see e.g. Cazzola M. *N Engl J Med* 2020; 383:1358–1374), Waldenstrom's macroglobulinemia (WM), non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), primary central nervous system lymphoma (PCNSL), Splenic Marginal Zone Lymphoma (SMZL), small lymphocytic lymphoma (SLL), leukaemias (chronic lymphocytic leukaemia (CLL)) and monoclonal gammopathy of undetermined significance (MGUS-IgM+). For example, IRAK4 overexpression has been associated with adverse clinical features (e.g. lower platelet counts, higher RBC transfusion needs and higher leukemic blast counts) in human myelodysplastic syndromes (see Choudhary *et al*, *eLife*. 2022; 11: e78136 (doi: 10.7554/eLife.78136). IRAK4 inhibition has been shown to lead to a reduction in MDS clones in *in vivo* models of MDS (*ibid.*). The potential of IRAK4 inhibitors for the treatment of MDS is presently being explored in the clinic.

A number of IRAK4 kinase inhibitors are known and have been developed principally for use in oncology or inflammatory disease (see e.g. WO2015150995, WO2017207386, WO2017009806, WO2016174183, WO2018234342). A number of clinical trials exploring the therapeutic utility of IRAK4 inhibitors are in progress.

N-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (I), and *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (II), are disclosed in PCT/EP2023/053416 (published as International Publication Pamphlet WO2023/152349) as compounds 12 and 11, respectively, alongside their activities as inhibitors of IRAK4 enzyme (IC₅₀ 0.6 nM & 0.9 nM, respectively) and IRAK4 activity in Karpas-299 cells (IC₅₀ 24 nM & 23 nM, respectively). Accordingly, these compounds have clear potential for use in medicine due to their ability to selectively inhibit IRAK4. Notwithstanding this there is a need to identify solid forms of Compound (I) and (II) with the appropriate chemical and physical stability for pharmaceutical development. It is an object of the present application to provide

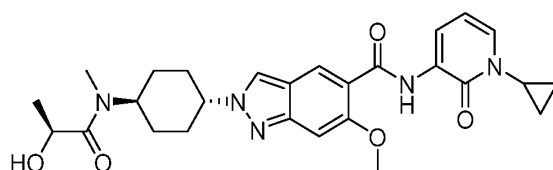
solid forms of Compounds (I) and (II) that are suitable for pharmaceutical development and that can be used for formulation into medicinal products.

- In the formulation of drug substances, it is important for the drug substance (active compound) to be in a form in which it can be conveniently handled and processed. This is of importance, not only from the point of view of obtaining a commercially-viable manufacturing process for the drug substance itself, but also from the point of view of subsequent manufacture of pharmaceutical formulations comprising the active compound and suitable excipients. The chemical stability and the physical stability of the active compound are important factors in determining the suitability of a solid form for use in the development of pharmaceutical formulations. The active compound, and formulations containing it, should be capable of being effectively stored over appreciable periods of time, without exhibiting any significant change in its physico-chemical characteristics (e.g. chemical composition, density, hygroscopicity and solubility) of the active compound. It is an object of the present specification to provide solid forms of *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide
- Compound (I) and *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (II), that are suitable for pharmaceutical development. As the skilled person will appreciate, Compound (I) and Compound (II) are enantiomeric forms of the same molecule and their structures are identical other than their absolute stereochemical configuration.
- In a first aspect, the present specification provides crystalline forms of *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide (hereafter "Compound (I)"). The structure of Compound (I) is shown below:



Compound (I).

- In a related aspect, the present specification provides crystalline forms of *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (II).



Compound (II).

In a related aspect, the specification provides an anhydrous crystalline form of Compound (I). In aspects, the specification provides the anhydrous crystalline Form A of Compound (I), or Compound
 5 (I), Form A that characteristically provides an X-ray diffraction pattern substantially as shown in Figure 1.

In a related aspect, the specification provides an anhydrous crystalline form of Compound (II). In aspects, the specification provides the anhydrous crystalline Form A of Compound (II), or Compound
 10 (II), Form A that characteristically provides an X-ray diffraction pattern substantially as shown in Figure 5.

In a related aspect, the specification provides a hydrated crystalline form (such as a tetrahydrate crystalline form) of Compound (II). In aspects, the specification provides the hydrated crystalline Form B of Compound (II), or Compound (II), Form B that characteristically provides an X-ray
 diffraction pattern substantially as shown in Figure 9.

15 As the skilled reader will appreciate and would expect, crystalline Form A of Compound (I) and crystalline Form A of Compound (II) give, within the limits of experimental reproducibility, the same X-ray Powder Diffractograms because, as is noted above, Compounds (I) and (II) are enantiomeric forms of the same molecule and thus when each compound is crystallised under the same conditions their crystallisation behaviour and the resultant crystalline forms are equivalent.
 20 Accordingly, the 2-theta values of the 10 most prominent peaks in each of Figures 1 and 5, as presented in Tables 1 and 3, respectively, are identical. Likewise, crystallisation conditions, chemical behaviour and analytical data for Form A of Compounds (I) and Form A of Compound (II) are essentially the same, again within the limits of experimental reproducibility.

In a further aspect there is provided *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-
 25 ((*S*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide for use in the treatment of myelodysplastic syndromes (MDS).

In a further aspect there is provided *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide for use in the treatment of myelodysplastic syndromes (MDS).

In a further aspect there is provided a method of treatment comprising administering *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide to a patient in need thereof, wherein the patient has myelodysplastic syndrome.

In a further aspect there is provided a method of treatment comprising administering *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide to a patient in need thereof, wherein the patient has myelodysplastic syndrome.

In a further aspect there is provided *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide for use in the manufacture of a medicament wherein the medicament is for the treatment of myelodysplastic syndromes (MDS).

In a further aspect there is provided *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide for use in the manufacture of a medicament wherein the medicament is for the treatment of myelodysplastic syndromes (MDS).

In a further aspect there is provided a crystalline form of Compound (I) for use in the manufacture of a medicament. In such aspects, the crystalline form of Compound (I) for use in the manufacture of a medicament may be Compound (I), Form A.

In a further aspect there is provided a crystalline form of Compound (I) for use in the manufacture of a medicament for use in the prevention or treatment of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). In a further aspect there is provided a crystalline form of Compound (I) for use in the manufacture of a medicament for use in the treatment of cancers, for example a haematological malignancies selected from myelodysplastic syndromes (MDS), Waldenstrom's macroglobulinemia (WM), non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), primary central nervous system lymphoma (PCNSL), Splenic Marginal Zone Lymphoma (SMZL), small lymphocytic lymphoma (SLL), leukaemias (chronic lymphocytic leukaemia (CLL)) and monoclonal gammopathy of undetermined significance (MGUS-IgM+). In a further aspect

there is provided a crystalline form of Compound (I) for use in the manufacture of a medicament for use in the prevention or treatment of inflammatory diseases and of autoinflammatory/autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, myositis, Sjögren's syndrome, systemic sclerosis, gout, endometriosis, atopic dermatitis and psoriasis. In such aspects, the crystalline
5 form of Compound (I) for use in the manufacture of a medicament may be Compound (I), Form A.

In a further aspect there is provided a crystalline form of Compound (II) for use in the manufacture of a medicament. In such aspects, the crystalline form of Compound (II) for use in the manufacture of a medicament may be Compound (II), Form A. In other aspects, the crystalline form of Compound (II) for use in the manufacture of a medicament may be Compound (II), Form B.

10 In a further aspect there is provided a crystalline form of Compound (II) for use in the manufacture of a medicament for use in the prevention or treatment of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). In a further aspect there is provided a crystalline form of Compound (II) for use in the manufacture of a medicament for use in the treatment of cancers, for example a haematological malignancies selected from myelodysplastic syndromes (MDS),
15 Waldenstrom's macroglobulinemia (WM), non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), primary central nervous system lymphoma (PCNSL), Splenic Marginal Zone Lymphoma (SMZL), small lymphocytic lymphoma (SLL), leukaemias (chronic lymphocytic leukaemia (CLL)) and monoclonal gammopathy of undetermined significance (MGUS-IgM+). In a further aspect there is provided a crystalline form of Compound (II) for use in the manufacture of a medicament for
20 use in the prevention or treatment of inflammatory diseases and of autoinflammatory/autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, myositis, Sjögren's syndrome, systemic sclerosis, gout, endometriosis, atopic dermatitis and psoriasis. In such aspects, the crystalline form of Compound (II) for use in the manufacture of a medicament may be Compound (II), Form A. In other aspects, the crystalline form of Compound (II) for use in the manufacture of a medicament may
25 be Compound (II), Form B.

In a further aspect there is provided a pharmaceutical composition comprising Compound (I), Form A and at least one pharmaceutically acceptable excipient.

In a further aspect there is provided a pharmaceutical composition comprising Compound (II), Form A and at least one pharmaceutically acceptable excipient.

30 In a further aspect there is provided a pharmaceutical composition comprising Compound (II), Form B and at least one pharmaceutically acceptable excipient.

In a further aspect there is provided a method of treatment, comprising administering a pharmaceutical composition comprising Compound (I), Form A to a patient in need thereof.

In a further aspect there is provided a method of treatment, comprising administering a pharmaceutical composition comprising Compound (II), Form A to a patient in need thereof.

- 5 In a further aspect there is provided a method of treatment, comprising administering a pharmaceutical composition comprising Compound (II), Form B to a patient in need thereof.

In a further aspect there is provided a pharmaceutical composition comprising Compound (I), Form A and at least one pharmaceutically acceptable excipient for use in the treatment of a haematological malignancy. In such aspects the haematological malignancy may be selected from myelodysplastic syndrome (MDS), Waldenstrom's macroglobulinemia (WM), non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), primary central nervous system lymphoma (PCNSL), Splenic Marginal Zone Lymphoma (SMZL), small lymphocytic lymphoma (SLL), leukaemias (chronic lymphocytic leukaemia (CLL)) and monoclonal gammopathy of undetermined significance (MGUS-IgM+).

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In a further aspect there is provided a pharmaceutical composition comprising Compound (II), Form A and at least one pharmaceutically acceptable excipient for use in the treatment of a haematological malignancy. In such aspects the haematological malignancy may be selected from myelodysplastic syndrome (MDS), Waldenstrom's macroglobulinemia (WM), non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), primary central nervous system lymphoma (PCNSL), Splenic Marginal Zone Lymphoma (SMZL), small lymphocytic lymphoma (SLL), leukaemias (chronic lymphocytic leukaemia (CLL)) and monoclonal gammopathy of undetermined significance (MGUS-IgM+).

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In a further aspect there is provided a pharmaceutical composition comprising Compound (II), Form B and at least one pharmaceutically acceptable excipient for use in the treatment of a haematological malignancy. In such aspects the haematological malignancy may be selected from myelodysplastic syndrome (MDS), Waldenstrom's macroglobulinemia (WM), non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), primary central nervous system lymphoma (PCNSL), Splenic Marginal Zone Lymphoma (SMZL), small lymphocytic lymphoma (SLL), leukaemias (chronic lymphocytic leukaemia (CLL)) and monoclonal gammopathy of undetermined significance (MGUS-IgM+).

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In a further aspect there is provided a kit comprising a pharmaceutical composition comprising Compound (I), Form A and at least one pharmaceutically acceptable excipient and instructions for its use in the treatment of a haematological malignancy, for example a haematological malignancy selected from myelodysplastic syndrome (MDS), Waldenstrom's macroglobulinemia (WM), non-

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Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), primary central nervous system lymphoma (PCNSL), Splenic Marginal Zone Lymphoma (SMZL), small lymphocytic lymphoma (SLL), leukaemias (chronic lymphocytic leukaemia (CLL)) and monoclonal gammopathy of undetermined significance (MGUS-IgM+).

- 5 In a further aspect there is provided a kit comprising a pharmaceutical composition comprising Compound (II), Form A and at least one pharmaceutically acceptable excipient and instructions for its use in the treatment of a haematological malignancy, for example a haematological malignancy selected from myelodysplastic syndrome (MDS), Waldenstrom's macroglobulinemia (WM), non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), primary central nervous system lymphoma (PCNSL), Splenic Marginal Zone Lymphoma (SMZL), small lymphocytic lymphoma (SLL),
10 leukaemias (chronic lymphocytic leukaemia (CLL)) and monoclonal gammopathy of undetermined significance (MGUS-IgM+).

- In a further aspect there is provided a kit comprising a pharmaceutical composition comprising Compound (II), Form B and at least one pharmaceutically acceptable excipient and instructions for its
15 use in the treatment of a haematological malignancy, for example a haematological malignancy selected from myelodysplastic syndrome (MDS), Waldenstrom's macroglobulinemia (WM), non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), primary central nervous system lymphoma (PCNSL), Splenic Marginal Zone Lymphoma (SMZL), small lymphocytic lymphoma (SLL), leukaemias (chronic lymphocytic leukaemia (CLL)) and monoclonal gammopathy of undetermined
20 significance (MGUS-IgM+).

In the aspects above, the use, composition for use or method of treatment is intended for use in humans.

So that the specification may be fully understood, reference to the following Figures is made herein.

- Figure 1** X-ray powder diffraction pattern of Compound (I), Form A, an anhydrous physical form of *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide. Characteristic peak positions of Compound (I) Form A are listed in Table 1.
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- Figure 2** A representative DSC thermogram for Compound (I), Form A recorded on heating from 0 to 230 °C. Exothermic events are plotted in the upward direction. The melting endotherm shown in Fig.
30 2 has an onset temperature of about 217 °C and an enthalpy of approximately 89 J/g.

Figure 3 A representative TGA thermogram for Compound (I), Form A. Form A exhibited a minimal weight loss of (less than about 0.1 %) upon heating from about 25 °C to 150 °C, which confirms that Form A is thus confirmed as an anhydrate solid form of Compound (I).

5 **Figure 4** A representative GVS plot for Compound (I), Form A recorded during the sorption/desorption cycle. Form A exhibited a reversible moisture uptake of about 0.12 mass % between 20% relative humidity and 80% relative humidity at 25 °C ± 0.1 °C. The desorption curve indicates that Form A lost moisture at a similar rate to the moisture gained during sorption, with limited hysteresis. No form change was observed after the GVS experiment as confirmed by XRPD.

10 **Figure 5** X-ray powder diffraction pattern of Compound (II), Form A, an anhydrous physical form of *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido) cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (II). Characteristic peak positions of Compound (II) Form A are listed in Table 3.

15 **Figure 6** A representative DSC thermogram for Compound (II), Form A recorded on heating from 0 to 230 °C. Exothermic events are plotted in the upward direction. The melting endotherm shown in Fig. 6 has an onset temperature of about 217 °C and an enthalpy of approximately 90 J/g.

Figure 7 A representative TGA thermogram for Compound (II), Form A. Form A exhibited a minimal weight loss (less than about 0.1 %) upon heating from about 25 °C to 150 °C, Form A is thus confirmed as an anhydrate solid form of Compound (II).

20 **Figure 8** A representative GVS plot for Compound (II), Form A recorded during the sorption/desorption cycle. Form A exhibited a reversible moisture uptake of about 0.12 mass % between 20% relative humidity and 80% relative humidity at 25 °C ± 0.1 °C. The desorption curve indicates that Form A lost moisture at a similar rate to the moisture gained during sorption, with limited hysteresis. No form change was observed after the GVS experiment as confirmed by XRPD. According to the European Pharmacopoeia (EP) classification, Form A is therefore identified as a non-hygroscopic (i.e., < 0.2% weight increase) solid form of Compound (II).

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Figure 9 X-ray powder diffraction pattern of Compound (II), Form B, a hydrated physical form of *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido) cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (II). Characteristic peak positions of Compound (II) Form B are shown in Table 4.

Figure 10 A representative DSC thermogram for Compound (II), Form B. Conversion of Compound (II) Form B to amorphous Compound (II) and subsequent crystallisation to Compound (II) Form A is denoted by the endo- and exothermic events.

Figure 11 A representative TGA thermogram for Compound (II), Form B. Mass loss of Compound (II) Form B is shown, suggesting that this form is a hydrated form of Compound (II).

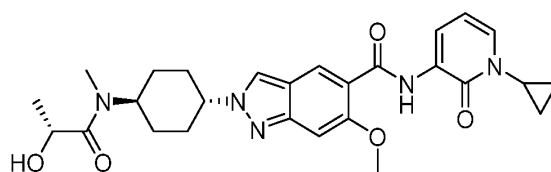
Figure 12 A representative GVS plot for Compound (II), Form B. Relative humidity dependent interconversion between lower and higher hydrated forms is observed.

As noted above, the present specification provides crystalline forms of *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide (Compound (I)).

In addition, the present specification provides crystalline forms of *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide (Compound (II)).

Although not further detailed herein, polymorph screening studies revealed several other crystalline or semi-crystalline solid forms of Compound (I) and (II). These were typically non-stoichiometric hydrates, solvates or mixed hydrate-solvate forms. In comparison to Form A, these other solid forms exhibited inferior physical and/or chemical stability on exposure to heating or high relative humidity conditions. Form A of Compound (I) and Form A of Compound (II) were thus identified as suitable candidates for pharmaceutical development due to their superior physical and chemical stability. Compound (II) Form B, which is a hydrated crystalline form of Compound (II), was identified as a further crystalline form.

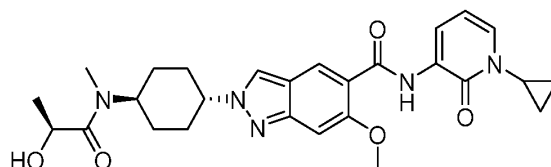
In a first embodiment the specification provides a crystalline form of *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide (Compound (I)) or a pharmaceutically acceptable salt or solvate thereof:



Compound (I).

In embodiments the crystalline form of Compound (I) is an anhydrous crystalline form. In one such embodiment the crystalline form is Compound (I), Form A and is characterised in providing at least one of the following 2θ values measured using Cu K_{α} radiation: 16.3° and 23.0° .

In embodiments, the specification provides a crystalline form of *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide (Compound (II)) or a pharmaceutically acceptable salt or solvate thereof:



Compound (II).

In embodiments the crystalline form of Compound (II) is an anhydrous crystalline form. In one such embodiment the crystalline form is Compound (II), Form A and is characterised in providing at least one of the following 2θ values measured using Cu K_{α} radiation: 16.3° and 23.0° .

In embodiments the crystalline form of Compound (II) is a hydrated crystalline form, such as a tetrahydrate crystalline form. In one such embodiment the crystalline form is Compound (II), Form B and is characterised in providing at least one of the following 2θ values measured using Cu K_{α} radiation: 3.8° and 5.5° .

Compound (I) Form A

Compound (I) Form A, an anhydrous physical form of *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, is characterised in providing at least one of the following 2θ values measured using Cu K_{α} radiation: : 16.3° and 23.0° . Compound (I) Form A is characterised in providing an X-ray powder diffraction pattern, substantially as shown in Figure 1. The ten most prominent peaks are shown in Table 1:

Table 1 Ten most prominent peaks of X-ray powder diffraction pattern of Compound (I) Form A

$2\theta (^{\circ})$	Relative Intensity
9.0	Strong
13.1	Strong
13.6	Very strong
14.3	Strong

15.6	Strong
16.3	Very strong
19.5	Very strong
22.4	Strong
23.0	Very strong
25.9	Very strong

Table 2 Definition of relative intensity

% Relative Intensity*	Definition
25 - 100	vs (very strong)
10 - 25	s (strong)
3 - 10	m (medium)
1 - 3	w (weak)

* The relative intensities are derived from diffractograms measured with fixed slits.

According to the present specification there is provided a crystalline form, Compound (I) Form A,
5 which has an X-ray powder diffraction pattern with at least one specific peak at about 2-theta = 16.3°.

According to the present specification there is provided a crystalline form, Compound (I) Form A,
which has an X-ray powder diffraction pattern with at least one specific peak at about 2-theta = 23.0°.

According to the present specification there is provided a crystalline form, Compound (I) Form A,
which has an X-ray powder diffraction pattern with at least two specific peaks at about 2-theta = 16.3
10 and 23.0°.

According to the present specification there is provided a crystalline form, Compound (I) Form A,
which has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 13.6, 16.3, 19.5,
23.0, and 25.9°.

According to the present specification there is provided a crystalline form, Compound (I) Form A,
15 which has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 9.0, 13.1, 13.6,
14.3, 15.6, 16.3, 19.5, 22.4, 23.0 and 25.9°.

According to the present specification there is provided Compound (I) Form A which has an X-ray
powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in
Figure 1.

According to the present specification there is provided a crystalline form, Compound (I) Form A, wherein said has an X-ray powder diffraction pattern with at least one specific peak at $2\text{-theta} = 13.6^\circ$ plus or minus 0.2° 2-theta .

5 According to the present specification there is provided a crystalline form, Compound (I) Form A, wherein said has an X-ray powder diffraction pattern with at least one specific peak at $2\text{-theta} = 23.0^\circ$ plus or minus 0.2° 2-theta .

According to the present specification there is provided a crystalline form, Compound (I) Form A, wherein said has an X-ray powder diffraction pattern with at least two specific peaks at $2\text{-theta} = 13.6$ and 23.0° wherein said values may be plus or minus 0.2° 2-theta .

10 According to the present specification there is provided a crystalline form, Compound (I) Form A, wherein said has an X-ray powder diffraction pattern with specific peaks at about $2\text{-theta} = 13.6, 16.3, 19.5, 23.0,$ and 25.9° plus or minus 0.2° 2-theta .

According to the present specification there is provided a crystalline form, Compound (I) Form A, wherein said has an X-ray powder diffraction pattern with specific peaks at about $2\text{-theta} = 9.0, 13.1,$
15 $13.6, 14.3, 15.6, 16.3, 19.5, 22.4, 23.0$ and 25.9° plus or minus 0.2° 2-theta .

It will be understood that in embodiments above the 2-theta values are measured using $\text{Cu K}\alpha$ radiation.

When it is stated that the present specification relates to a crystalline form of Compound (I) Form A, the degree of crystallinity is conveniently greater than about 60%, optionally greater than about 80%,
20 greater than about 90% or greater than about 95%. In embodiments the degree of crystallinity is greater than about 98%.

The Compound (I) Form A provides X-ray powder diffraction patterns substantially the same as the X-ray powder diffraction patterns shown in Figure 1 and has substantially the ten most prominent peaks (angle 2-theta values) shown in Table 1. It will be understood that the 2-theta values of the X-ray
25 powder diffraction pattern may vary slightly from one machine to another or from one sample to another, and so the values quoted are not to be construed as absolute.

It is known that an X-ray powder diffraction pattern may be obtained which has one or more measurement errors depending on measurement conditions (such as equipment or machine used). In particular, it is generally known that intensities in an X-ray powder diffraction pattern may fluctuate
30 depending on measurement conditions. Therefore it should be understood that the Compound (I)

Form A of the present specification is not limited to the crystals that provide X-ray powder diffraction patterns identical to the X-ray powder diffraction pattern shown in Figure 1, and any crystals providing X-ray powder diffraction patterns substantially the same as those shown in Figure 1 fall within the scope of the present specification. A person skilled in the art of X-ray powder diffraction is able to
5 judge the substantial identity of X-ray powder diffraction patterns.

In order to further characterise Compound (I) Form A, a series of further experiments were performed. Ramp Differential Scanning Calorimetry (DSC) was used to establish the melting point of the material and to identify any thermal transitions in the solid state structure below the melting point. As can be seen from Figure 2, Compound (I) Form A the melting endotherm shown in Figure 2 has an onset
10 temperature of about 217 °C and an enthalpy of approximately 89 J/g. The absence of thermal events in the DSC signal prior to the melting onset temperature indicates that Compound (I) Form A is thermally stable in the temperature range 0 to 210 °C under these experimental conditions. The observed thermal stability range indicates that the material is suitable for formulation development.

Thermal gravimetric analysis of Compound (I) Form A was performed and the results are presented in
15 Figure 3. As can be seen from Figure 3, minimal weight loss (less than about 0.1%) was observed upon heating from 25 °C to 150 °C. This, in conjunction with Karl Fischer analysis (not shown), confirms that Compound (I) Form A is an anhydrate solid form of Compound (I).

In order to study the hygroscopicity of Compound (I) Form A, a Gravimetric Vapor Sorption (GVS) experiment was performed. Results with Compound (I) Form A recorded during the
20 sorption/desorption cycle are presented in Figure 4. In this GVS experiment Form A exhibited a reversible moisture uptake of about 0.12 mass % between 20% relative humidity and 80% relative humidity at 25 °C ± 0.1 °C. The desorption curve indicates that Form A lost moisture at a similar rate to the moisture gained during sorption, with limited hysteresis. No form change was observed by XRPD after the GVS experiment. According to the European Pharmacopoeia (EP) classification, Form
25 A is therefore identified as a non-hygroscopic (i.e., < 0.2% weight increase) solid form of Compound (I). In addition, crystals of Compound (I) Form A were analysed with scanning electron microscopy (not shown), which revealed that the crystals were suitable for pharmaceutical development. Compound (I) Form A was found to be soluble in phosphate buffer at pH 7.3.

To summarise the above, Compound (I) Form A has been shown to be a non-hygroscopic anhydrate
30 solid form of Compound (I) with sufficient thermal stability and of a suitable crystal form for further pharmaceutical development. Data sets presented herein for Compound (II) Form A likewise

demonstrate its suitability for further pharmaceutical development on the basis that it possesses the same combination of properties as Compound (I) Form A.

In embodiments the specification provides a crystalline form of Compound (I) which has a DSC thermogram substantially as shown in Figure 2. In embodiments the specification provides a crystalline form of Compound (I) which has a TGA thermogram substantially as shown in Figure 3. In
5 embodiments the specification provides a crystalline form of Compound (II) which has a DSC thermogram substantially as shown in Figure 6. In embodiments the specification provides a crystalline form of Compound (II) which has a TGA thermogram substantially as shown in Figure 7.

Compound (II) Form A

10 Compound (II) Form A, an anhydrous physical form of *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, is characterised in providing at least one of the following 2θ values measured using Cu K_{α} radiation: : 16.3° and 23.0°. Compound (II) Form A is characterised in providing an X-ray powder diffraction pattern, substantially as shown in Figure 5. The ten most prominent peaks are shown in
15 Table 3:

Table 3 Ten most prominent peaks of X-ray powder diffraction pattern of Compound (II) Form A

2θ (°)	Relative Intensity
9.0	Strong
13.1	Strong
13.6	Very strong
14.3	Strong
15.6	Strong
16.3	Very strong
19.5	Very strong
22.4	Strong
23.0	Very strong
25.9	Very strong

According to the present specification there is provided a crystalline form, Compound (II) Form A, which has an X-ray powder diffraction pattern with at least one specific peak at about 2-theta = 16.3°.

20 According to the present specification there is provided a crystalline form, Compound (II) Form A, which has an X-ray powder diffraction pattern with at least one specific peak at about 2-theta = 23.0°.

According to the present specification there is provided a crystalline form, Compound (II) Form A, which has an X-ray powder diffraction pattern with at least two specific peaks at about 2-theta = 16.3 and 23.0°.

5 According to the present specification there is provided a crystalline form, Compound (II) Form A, which has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 13.6, 16.3, 19.5, 23.0, and 25.9°.

According to the present specification there is provided a crystalline form, Compound (II) Form A, which has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 9.0, 13.1, 13.6, 14.3, 15.6, 16.3, 19.5, 22.4, 23.0 and 25.9°.

10 According to the present specification there is provided Compound (II) Form A which has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 5.

According to the present specification there is provided a crystalline form, Compound (II) Form A, wherein said has an X-ray powder diffraction pattern with at least one specific peak at 2-theta = 13.6°
15 plus or minus 0.2° 2-theta.

According to the present specification there is provided a crystalline form, Compound (II) Form A, wherein said has an X-ray powder diffraction pattern with at least one specific peak at 2-theta = 23.0° plus or minus 0.2° 2-theta.

According to the present specification there is provided a crystalline form, Compound (II) Form A,
20 wherein said has an X-ray powder diffraction pattern with at least two specific peaks at 2-theta = 13.6 and 23.0° wherein said values may be plus or minus 0.2° 2-theta.

According to the present specification there is provided a crystalline form, Compound (II) Form A, wherein said has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 13.6, 16.3, 19.5, 23.0, and 25.9° plus or minus 0.2° 2-theta.

25 According to the present specification there is provided a crystalline form, Compound (II) Form A, wherein said has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 9.0, 13.1, 13.6, 14.3, 15.6, 16.3, 19.5, 22.4, 23.0 and 25.9° plus or minus 0.2° 2-theta.

It will be understood that in embodiments above the 2-theta values are measured using Cu K_α radiation.

When it is stated that the present specification relates to a crystalline form of Compound (II) Form A, the degree of crystallinity is optionally greater than about 60%, greater than about 80%, greater than about 90% or greater than about 95%. In embodiments the degree of crystallinity is greater than about 98%.

- 5 The Compound (II) Form A provides X-ray powder diffraction patterns substantially the same as the X-ray powder diffraction patterns shown in Figure 5 and has substantially the ten most prominent peaks (angle 2-theta values) shown in Table 3. It will be understood that the 2-theta values of the X-ray powder diffraction pattern may vary slightly from one machine to another or from one sample to another, and so the values quoted are not to be construed as absolute.
- 10 It is known that an X-ray powder diffraction pattern may be obtained which has one or more measurement errors depending on measurement conditions (such as equipment or machine used). In particular, it is generally known that intensities in an X-ray powder diffraction pattern may fluctuate depending on measurement conditions. Therefore, it should be understood that the Compound (II) Form A of the present specification is not limited to the crystals that provide X-ray powder diffraction
- 15 patterns identical to the X-ray powder diffraction pattern shown in Figure 5, and any crystals providing X-ray powder diffraction patterns substantially the same as those shown in Figure 5 fall within the scope of the present specification. A person skilled in the art of X-ray powder diffraction is able to judge the substantial identity of X-ray powder diffraction patterns.

Compound (II) Form B

- 20 Compound (II) Form B is a hydrated physical form of *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide. The most prominent peaks are shown in Table 4:

Table 4 Most prominent peaks of X-ray powder diffraction pattern of Compound (II) Form B

2θ (°)	Relative intensity
3.8	Strong
4.8	Medium
5.5	Very strong
9.5	Medium
13.2	Medium
14.4	Medium
17.5	Medium
25.7	Strong
26.4	Strong

According to the present specification there is provided a crystalline form, Compound (II) Form B, which has an X-ray powder diffraction pattern with at least one specific peak at about $2\text{-theta} = 5.5^\circ$.

According to the present specification there is provided a crystalline form, Compound (II) Form B, which has an X-ray powder diffraction pattern with at least one specific peak at about $2\text{-theta} = 3.8^\circ$.

- 5 According to the present specification there is provided a crystalline form, Compound (II) Form B, which has an X-ray powder diffraction pattern with specific peaks at about $2\text{-theta} = 3.8^\circ$ and 5.5° .

According to the present specification there is provided a crystalline form, Compound (II) Form B, which has an X-ray powder diffraction pattern with specific peaks at about $2\text{-theta} = 3.8^\circ$, 5.5° , 9.5° , 25.7° and 26.4° .

- 10 According to the present specification there is provided a crystalline form, Compound (II) Form B, which has an X-ray powder diffraction pattern with specific peaks at about $2\text{-theta} = 3.8^\circ$, 4.8° , 5.5° , 9.5° , 13.2° , 14.4° , 17.5° , 25.7° and 26.4° .

According to the present specification there is provided a crystalline form, Compound (II) Form B, which has an X-ray powder diffraction pattern with at least one specific peak at about $2\text{-theta} = 5.5^\circ$

- 15 plus or minus $0.2^\circ 2\text{-theta}$.

According to the present specification there is provided a crystalline form, Compound (II) Form B, which has an X-ray powder diffraction pattern with at least one specific peak at about $2\text{-theta} = 3.8^\circ$ plus or minus $0.2^\circ 2\text{-theta}$.

According to the present specification there is provided a crystalline form, Compound (II) Form B, which has an X-ray powder diffraction pattern with specific peaks at about $2\text{-theta} = 3.8^\circ$ and 5.5° plus or minus $0.2^\circ 2\text{-theta}$.

- 20

According to the present specification there is provided a crystalline form, Compound (II) Form B, which has an X-ray powder diffraction pattern with specific peaks at about $2\text{-theta} = 3.8^\circ$, 5.5° , 9.5° , 25.7° and 26.4° plus or minus $0.2^\circ 2\text{-theta}$.

- 25 According to the present specification there is provided a crystalline form, Compound (II) Form B, which has an X-ray powder diffraction pattern with at least one specific peak at about $2\text{-theta} = 3.8^\circ$, 4.8° , 5.5° , 9.5° , 13.2° , 14.4° , 17.5° , 25.7° and 26.4° plus or minus $0.2^\circ 2\text{-theta}$.

According to the present specification there is provided Compound (II) Form B which has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 9.

5 It will be understood that in embodiments above the 2-theta values are measured using Cu K_{α} radiation.

When it is stated that the present specification relates to a crystalline form of Compound (II) Form B, the degree of crystallinity is optionally greater than about 60%, greater than about 80%, greater than about 90% or greater than about 95%. In embodiments the degree of crystallinity is greater than about 98%.

10 It is known that an X-ray powder diffraction pattern may be obtained which has one or more measurement errors depending on measurement conditions (such as equipment or machine used). In particular, it is generally known that intensities in an X-ray powder diffraction pattern may fluctuate depending on measurement conditions. Therefore, it should be understood that the Compound (II) Form B of the present specification is not limited to the crystals that provide X-ray powder diffraction
15 patterns identical to the X-ray powder diffraction pattern shown in Figure 9, and any crystals providing X-ray powder diffraction patterns substantially the same as those shown in Figure 9 fall within the scope of the present specification. A person skilled in the art of X-ray powder diffraction is able to judge the substantial identity of X-ray powder diffraction patterns.

In embodiments the specification provides a crystalline form of Compound (II) which has a DSC
20 thermogram substantially as shown in Figure 10. In embodiments the specification provides a crystalline form of Compound (II) which has a TGA thermogram substantially as shown in Figure 11.

X-ray Powder Diffraction Analysis

The X-ray powder diffraction analysis was performed according to standard methods, which can be found in e.g. Kitaigorodsky, A.I. (1973), *Molecular Crystals and Molecules*, Academic Press, New York;
25 Bunn, C.W. (1948), *Chemical Crystallography*, Clarendon Press, London; or Klug, H.P. & Alexander, L.E. (1974), *X-ray Diffraction Procedures*, John Wiley & Sons, New York.

Persons skilled in the art of X-ray powder diffraction will realize that the relative intensity of peaks can be affected by, for example, grains above 30 microns in size and non-unitary aspect ratios, which may affect analysis of samples. The skilled person will also realize that the position of reflections can be
30 affected by the precise height at which the sample sits in the diffractometer and the zero calibration

of the diffractometer. The surface planarity of the sample may also have a small effect. Hence the diffraction pattern data presented are not to be taken as absolute values. (Jenkins, R & Snyder, R.L. 'Introduction to X-Ray Powder Diffractometry' John Wiley & Sons 1996; Bunn, C.W. (1948), Chemical Crystallography, Clarendon Press, London; Klug, H. P. & Alexander, L. E. (1974), X-Ray Diffraction Procedures).

Generally, a measurement error of a diffraction angle in an X-ray powder diffractogram is about 5% or less, in particular plus or minus 0.2° 2-theta, and such degree of a measurement error should be taken into account when considering the X-ray powder diffraction patterns in Figure 1, Figure 5 and Figure 9, and when reading Table 1, Table 3 and Table 4. Furthermore, it will be understood that intensities may fluctuate depending on experimental conditions and sample preparation (preferred orientation). Definition of relative intensity is described in Table 2.

The XRPD pattern was determined by mounting a sample on a zero-background sample holder with a small depression filled with some of the ground material. A glass slide was used to get an evenly distributed sample with the correct sample height and sample peak position was adjusted with reference to a second sample containing an internal Corundum standard.

The powder X-ray diffraction was recorded with a theta-two theta scan axis and in one dimensional scan with Rigaku Miniflex 600 (wavelength of X-rays $1.5418 \text{ \AA}$ nickel-filtered Cu K α radiation, 40 kV, 15 mA) equipped with D/Tex Ultra detector.

Fixed divergence and receiving slits were used together with an automatic variable anti-scatter screen. The samples were rotated at 30 revolutions per minute during measurement. Samples were scanned from $3 - 50^\circ$ 2-theta (2θ) using a 0.01° and $1^\circ/\text{min}$ step width and scan speed respectively.

A person skilled in the art understands that the value or range of values observed in a particular compound's DSC Thermogram will show variation between batches of different purities. Therefore, whilst for one compound the range may be small, for others the range may be quite large. Generally, a measurement error in DSC thermal events is approximately plus or minus 5°C , and such degree of a measurement error should be taken into account when considering the DSC data included herein.

Crystallisation of the desired form in a process described herein may be aided by seeding with crystals of the desired form. The seed crystals may be obtained using one of the methods described in the Examples. The use of seeding is particularly advantageous in larger-scale manufacture.

In the present specification in instances where the compound is described as having a "X-ray powder diffraction pattern with at least one specific peak at 2θ about = " the XRPD of the compound may contain one or more of the 2θ values listed. For example, one or more of the 2θ values, 2 or more of the 2θ values or 3 or more of the 2θ values listed.

- 5 In the preceding paragraphs defining the X-ray powder diffraction peaks for the crystalline form of Compound (I), the term "about=" is used in the expression" ... at 2θ about= ... "to indicate that the precise position of peaks (i.e. the recited 2-theta angle values) should not be construed as being absolute values because, as will be appreciated by those skilled in the art, the precise position of the peaks may vary slightly between one measurement apparatus and another, from one sample to another, or as a result of slight variations in measurement conditions utilised. It is also stated in the preceding paragraphs that the crystalline form of Compound (I) provide X-ray powder diffraction patterns 'substantially' the same as the X-ray powder diffraction patterns shown in Figure 1 has substantially the most prominent peaks (2-theta angle values) shown in Table 1. It is to be understood that the use of the term 'substantially' in this context is also intended to indicate that the 2-theta angle values of the X-ray powder diffraction patterns may vary slightly from one apparatus to another, from one sample to another, or as a result of slight variations in measurement conditions utilised, so the peak positions shown in a Figure or quoted in the corresponding Table are again not to be construed as absolute values. The same considerations apply equally to Compound (II), the values in Tables 3 and 4, and the interpretation of Figures 5 and 9.
- 20 The person skilled in the art of X-ray powder diffraction will realize that the relative intensity of peaks can be affected by, for example, grains above approximately 30 micrometer in size and non-unitary aspect ratios which may affect analysis of samples. Furthermore, it should be understood that intensities may fluctuate depending on experimental conditions and sample preparation such as preferred orientation of the particles in the sample. The use of automatic or fixed divergence slits will also influence the relative intensity calculations. A person skilled in the art can handle such effects when comparing diffraction patterns.

The person skilled in the art of X-ray powder diffraction will also realize that due to difference in sample heights and errors in the calibration of the detector position, a small shift in the 2θ positions could occur. Generally, a difference of $\pm 0.1^\circ$ from the given value are to be considered correct.

- 30 Compound (I) and Compound (II) forms described herein may also be characterised and/or distinguished from other physical forms using other suitable analytical techniques, for example NIR spectroscopy or solid-state nuclear magnetic resonance spectroscopy.

The chemical structure of Compound (I) and Compound (II) forms described herein can be confirmed by routine methods for example proton nuclear magnetic resonance (NMR) analysis.

Compound (I) and Compound (II) forms may be prepared as described in the Examples hereinafter.

Medical and pharmaceutical use

- 5 A crystalline form of Compound (I) or Compound (II) may be useful in the prevention or treatment of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), of cancer, of inflammatory diseases and of autoinflammatory/autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, myositis, Sjögren's syndrome, systemic sclerosis, gout, endometriosis, atopic dermatitis and psoriasis in a mammal, particularly a human.
- 10 A crystalline form of Compound (I) or Compound (II) may be useful in the treatment of cancers, for example in the treatment of haematological malignancies selected from myelodysplastic syndromes (MDS), Waldenstrom's macroglobulinemia (WM), non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), primary central nervous system lymphoma (PCNSL), Splenic Marginal Zone Lymphoma (SMZL), small lymphocytic lymphoma (SLL), leukaemias (chronic lymphocytic leukaemia (CLL)) and monoclonal gammopathy of undetermined significance (MGUS-IgM+).

The specification also provides *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide for use in the treatment of myelodysplastic syndromes (MDS). The compound may equally be used in a method of treating this condition or in the manufacture of a medicine for treating this condition.

- 20 The specification also provides *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide for use in the treatment of myelodysplastic syndromes (MDS). The compound may equally be used in a method of treating this condition or in the manufacture of a medicine for treating this condition.

Combination therapy

- 25 A crystalline form of Compound (I) or Compound (II) may also be administered in conjunction with other compounds used for the treatment of the above conditions.

In another embodiment, there is a combination therapy wherein a compound of a crystalline form of Compound (I) or Compound (II), and a second active ingredient are administered concurrently, sequentially or in admixture, for the treatment of one or more of the conditions listed above. Such a

combination may be used in combination with one or more further active ingredients. In
embodiments of the specification the second active agent may be a Bruton's tyrosine kinase
inhibitor, for example when the combination therapy is directed to the treatment of a
haematological malignancy selected from myelodysplastic syndromes (MDS), Waldenstrom's
5 macroglobulinemia (WM), non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL),
primary central nervous system lymphoma (PCNSL), Splenic Marginal Zone Lymphoma (SMZL), small
lymphocytic lymphoma (SLL), leukaemias (chronic lymphocytic leukaemia (CLL)) and monoclonal
gammopathy of undetermined significance (MGUS-IgM+).

Administration

10 There is provided a method of treatment of a condition where inhibition of IRAK4 is required, which
method comprises administration of a therapeutically effective amount of a crystalline form of
Compound (I) or Compound (II) to a person suffering from, or susceptible to, such a condition.

A crystalline form of Compound (I) or Compound (II), will normally be administered via the oral,
parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal,
15 vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical
preparations comprising the active ingredient in a pharmaceutically acceptable dosage form.
Depending upon the disorder and patient to be treated and the route of administration, the
compositions may be administered at varying doses.

Dosage forms suitable for oral use form one aspect of the specification.

20 The compositions of the specification may be obtained by conventional procedures using
conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral
use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative
agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert
25 diluents; granulating and disintegrating agents; binding agents starch; and lubricating agents. Tablet
formulations may be uncoated or coated using conventional coating agents and procedures well
known in the art.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of
Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press
30 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration.

Suitable daily doses of a crystalline form of Compound (I) or Compound (II), in therapeutic treatment of humans are about 0.0001-100 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.1 mg to 1000 mg.

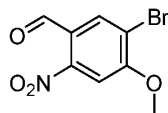
For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

According to a further aspect, there is thus provided a pharmaceutical composition including a crystalline form of Compound (I) or Compound (II) in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

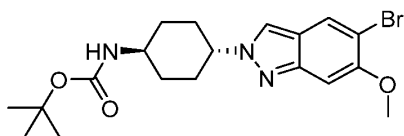
Examples

Abbreviations used for analytical data, are consistent with the common usage in the field (see J Med Chem Standard Abbreviations and Acronyms http://pubsapp.acs.org/paragonplus/submission/jmcmr/jmcmr_abbreviations.pdf). The compound names provided below are generated using PerkinElmer ChemDraw Professional, Version 20.0.2.51. In instances where there is uncertainty as to the absolute stereochemistry, relative stereochemistry is specified as far as possible.

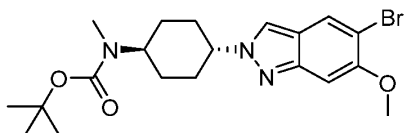
5-Bromo-4-methoxy-2-nitrobenzaldehyde (Int 1)



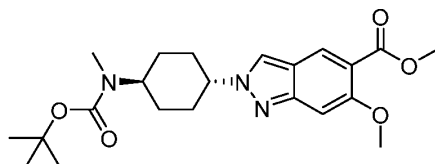
Sodium methoxide (10.9 g, 60.6 mmol) in MeOH (46 mL) was added to 5-bromo-4-fluoro-2-nitrobenzaldehyde (10.0 g, 40.3 mmol) in MeOH (150 mL) at rt. After stirring for 16 h the reaction was quenched with water (300 mL), the formed solid was filtered off and washed with water (100 mL) to afford 5-bromo-4-methoxy-2-nitrobenzaldehyde (6.6 g, 63%) as a pale-yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.03 (s, 1H), 8.15 (s, 1H), 7.78 (s, 1H), 4.04 (s, 3H).

Int 2: *tert*-Butyl ((1*r*,4*r*)-4-(5-bromo-6-methoxy-2*H*-indazol-2-yl)cyclohexyl)carbamate

To a solution of *tert*-butyl ((1*r*,4*r*)-4-aminocyclohexyl)carbamate (10.5 g, 49.0 mmol) in *i*-PrOH (200 mL) at rt was added 5-bromo-4-methoxy-2-nitrobenzaldehyde (**Int 1**) (12.7 g, 49.0 mmol) under N₂ atmosphere. The resulting mixture was stirred at 80 °C for 1 h, followed by the addition of tri-*n*-butylphosphine (29.7 g, 147.0 mmol). The reaction mixture was stirred at 80 °C for 13 h. The mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with 9 – 50% EtOAc in PE) to afford *tert*-butyl ((1*r*,4*r*)-4-(5-bromo-6-methoxy-2*H*-indazol-2-yl)cyclohexyl)carbamate (**Int 2**) (14.2 g, 68%) as a colorless solid. MS ESI, *m/z* = 424/426 [M+H]⁺.

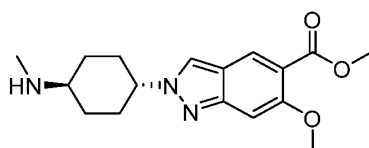
***tert*-Butyl ((1*r*,4*r*)-4-(5-bromo-6-methoxy-2*H*-indazol-2-yl)cyclohexyl)(methyl)carbamate**

To a solution of *tert*-butyl ((1*r*,4*r*)-4-(5-bromo-6-methoxy-2*H*-indazol-2-yl)cyclohexyl)carbamate (**Int 2**) (4.2 g, 9.9 mmol) in DMF (50 mL) at 0 °C was added NaH (60 wt.%) (792 mg, 19.8 mmol). The resulting mixture was stirred at 25 °C for 30 min followed by the addition of iodomethane (1.24 mL, 19.8 mmol). The reaction mixture was stirred at rt for 13 h, then quenched with water (150 mL). The precipitate was filtered, washed with water (150 mL) and dried *in vacuo* to afford *tert*-butyl ((1*r*,4*r*)-4-(5-bromo-6-methoxy-2*H*-indazol-2-yl)cyclohexyl)(methyl)carbamate (4.36 g, 100 %) as a colorless solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.28 (s, 1H), 7.96 (s, 1H), 7.11 (s, 1H), 4.42 (ddt, 1H), 3.87 – 4.06 (m, 1H), 3.86 (s, 3H), 2.71 (s, 3H), 2.09 – 2.23 (m, 2H), 1.87 – 2.08 (m, 2H), 1.62 – 1.87 (m, 4H), 1.42 (s, 9H). MS ESI, *m/z* = 438/440 (1 :1) [M+H]⁺.

Methyl 2-((1*r*,4*r*)-4-((*tert*-butoxycarbonyl)(methyl)amino)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxylate (Int 3**)**

A suspension of *tert*-butyl ((1*r*,4*r*)-4-(5-bromo-6-methoxy-2*H*-indazol-2-yl)cyclohexyl)(methyl)carbamate (4.3 g, 9.8 mmol), Pd(dppf)Cl₂ (714 mg, 1.0 mmol) and TEA (13.6 mL, 97.6 mmol) in MeOH (125 mL) was stirred under CO atmosphere at 15 atm and 100 °C for 15 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with 30 – 50% EtOAc in PE) to afford methyl 2-((1*r*,4*r*)-4-((*tert*-butoxycarbonyl)(methyl)amino)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxylate (**Int 3**) (3.8 g, 93%) as a yellow solid. MS ESI, *m/z* = 418 [M+H]⁺.

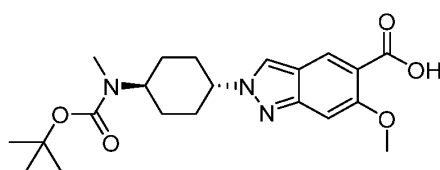
Int 4: Methyl 6-methoxy-2-((1*r*,4*r*)-4-(methylamino)cyclohexyl)-2*H*-indazole-5-carboxylate



10

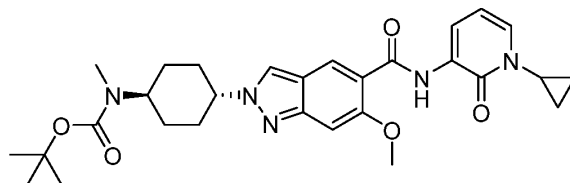
To a solution of methyl 2-((1*r*,4*r*)-4-((*tert*-butoxycarbonyl)(methyl)amino)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxylate (**Int 3**) (2.5 g, 6.0 mmol) in DCM (50 mL) was added 4*N* HCl in dioxane (15 mL, 59.9 mmol) at 25 °C under N₂ atmosphere. The resulting mixture was stirred at 25 °C for 18 h and then concentrated under reduced pressure to afford the HCl salt of (**Int 4**) methyl 6-methoxy-2-((1*r*,4*r*)-4-(methylamino)cyclohexyl)-2*H*-indazole-5-carboxylate (2.1 g, 100 %), which was used without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.77 (br. s, 1H), 8.43 (s, 1H), 8.05 (s, 1H), 7.01 (s, 1H), 4.36 – 4.56 (m, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.53 (s, 3H), 2.95 – 3.14 (m, 1H), 2.11 – 2.26 (m, 4H), 1.92 (br. q, 2H), 1.60 (br. q, 2H). MS ESI, *m/z* = 318 [M+H]⁺.

Int 5: 2-((1*r*,4*r*)-4-((*tert*-Butoxycarbonyl)(methyl)amino)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxylic acid



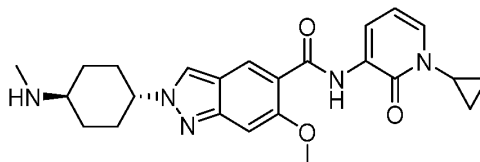
To a solution of methyl 2-((1*r*,4*r*)-4-((*tert*-butoxycarbonyl)(methyl)amino)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxylate (**Int 3**) (2.9 g, 6.9 mmol) in MeOH (50 mL) / water (25 mL) at rt was added NaOH (556 mg, 13.9 mmol). The resulting solution was stirred at 30 °C for 12 h. The reaction mixture was cooled to rt and acidified to pH ~6 with 4*N* HCl. The precipitate was filtered, washed with water (200 mL) and dried *in vacuo* to afford 2-((1*r*,4*r*)-4-((*tert*-butoxycarbonyl)(methyl)amino)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxylic acid (**Int 5**) (2.7 g, 95%) as a pale-yellow solid. MS ESI, *m/z* = 404 [M+H]⁺.

***tert*-Butyl ((1*r*,4*r*)-4-(5-((1-cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)carbamoyl)-6-methoxy-2*H*-indazol-2-yl)cyclohexyl)(methyl)carbamate**



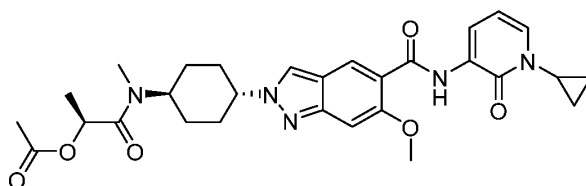
To a solution of 2-((1*r*,4*r*)-4-((*tert*-butoxycarbonyl)(methyl)amino)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxylic acid (**Int 5**) (300 mg, 0.7 mmol), HATU (339 mg, 0.9 mmol) and DIPEA (519 μ L, 3.0 mmol) in DMF (5 mL) at 25°C under N₂ atmosphere was added 3-amino-1-cyclopropylpyridin-2(1*H*)-one hydrochloride (167 mg, 0.9 mmol). The reaction mixture was stirred at 25 °C for 15 h. The mixture was purified directly by C18-flash chromatography (eluting with 0 – 100% MeCN in water (0.05% NH₄OH)) to afford to afford *tert*-butyl ((1*r*,4*r*)-4-(5-((1-cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)carbamoyl)-6-methoxy-2*H*-indazol-2-yl)cyclohexyl)(methyl)carbamate (300 mg, 75 %) as a colorless solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.05 (s, 1H), 8.53 – 8.59 (m, 2H), 8.42 (dd, 1H), 7.29 (dd, 1H), 7.22 (s, 1H), 6.27 (t, 1H), 4.37 – 4.54 (m, 1H), 4.07 (s, 3H), 3.76 – 4.03 (m, 1H), 3.39 – 3.49 (m, 1H), 2.71 (s, 3H), 2.09 – 2.26 (m, 2H), 1.87 – 2.08 (m, 2H), 1.59 – 1.86 (m, 4H), 1.41 (s, 9H), 0.97 – 1.09 (m, 2H), 0.81 – 0.93 (m, 2H). MS ESI, *m/z* = 536 [M+H]⁺.

***N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-6-methoxy-2-((1*r*,4*r*)-4-(methylamino)cyclohexyl)-2*H*-indazole-5-carboxamide**



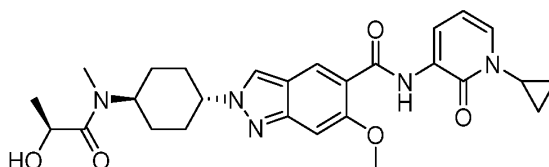
To a solution of *tert*-butyl ((1*r*,4*r*)-4-(5-((1-cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)carbamoyl)-6-methoxy-2*H*-indazol-2-yl)cyclohexyl)(methyl)carbamate (295 mg, 0.6 mmol) in DCM (1 mL) was added 4*N* HCl in dioxane (688 μ L, 2.8 mmol) at 25°C under N₂ atmosphere. The resulting mixture was stirred at 25 °C for 17 h and then concentrated under reduced pressure to afford the HCl salt of *N*-(1-cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-6-methoxy-2-((1*r*,4*r*)-4-(methylamino)cyclohexyl)-2*H*-indazole-5-carboxamide (260 mg, 100 %) as a colorless solid, which was used without further purification. ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.04 (s, 1H), 8.57 (s, 2H), 8.42 (dd, 1H), 7.29 (dd, 1H), 7.21 (s, 1H), 6.27 (t, 1H), 4.43 – 4.58 (m, 1H), 4.07 (s, 3H), 3.39 – 3.48 (m, 1H), 2.97 – 3.13 (m, 1H), 2.54 (t, 3H), 2.13 – 2.31 (m, 4H), 1.86 – 2.06 (m, 2H), 1.52 – 1.71 (m, 2H), 0.97 – 1.10 (m, 2H), 0.85 – 0.93 (m, 2H). MS ESI, *m/z* = 436 [M+H]⁺.

(S)-1-(((1*r*,4*S*)-4-(5-((1-cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)carbamoyl)-6-methoxy-2*H*-indazol-2-yl)cyclohexyl)(methyl)amino)-1-oxopropan-2-yl acetate



To a solution of the HCl salt of *N*-(1-cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-6-methoxy-2-((1*r*,4*r*)-4-(methylamino)cyclohexyl)-2*H*-indazole-5-carboxamide (255 mg, 0.5 mmol) and TEA (226 μ L, 1.6 mmol) in DCM (20 mL) was added (*S*)-1-chloro-1-oxopropan-2-yl acetate (114 mg, 0.8 mmol) at 0 °C under N₂ atmosphere. The resulting mixture was stirred at 25 °C for 30 min, then quenched with water (25 mL) and extracted with DCM (15 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by C18-flash chromatography (eluting with 0 – 100% MeCN in water (0.05% NH₄OH)) to afford (*S*)-1-(((1*r*,4*S*)-4-(5-((1-cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)carbamoyl)-6-methoxy-2*H*-indazol-2-yl)cyclohexyl)(methyl)amino)-1-oxopropan-2-yl acetate (295 mg, 99 %) as a colorless solid. ¹H NMR (300 MHz, DMSO-*d*₆) (2 : 3 mixture of rotamers) δ 11.05 (s, 1H), 8.50 – 8.59 (m, 2H), 8.42 (dd, 1H), 7.29 (dd, 1H), 7.22/7.20 (s, 1H) (rotamers), 6.27 (t, 1H), 5.45/ 5.27 (q, 1H) (rotamers), 4.40 – 4.56 (m, 1H), 4.26 – 4.39/3.71 – 3.86 (m, 1H) (rotamers), 4.07 (s, 3H), 3.39 – 3.49 (m, 1H), 2.90/2.74 (s, 3H) (rotamers), 1.69 – 2.28 (m, 10H), 1.54 – 1.68 (m, 1H), 1.31 (t, 3H), 0.98 – 1.11 (m, 2H), 0.84 – 0.94 (m, 2H). MS ESI, *m/z* = 550 [M+H]⁺.

***N*-(1-cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (II)**



To a solution of (*S*)-1-(((1*r*,4*S*)-4-(5-((1-cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)carbamoyl)-6-methoxy-2*H*-indazol-2-yl)cyclohexyl)(methyl)amino)-1-oxopropan-2-yl acetate (290 mg, 0.5 mmol) in MeOH (10 mL) at 25 °C under N₂ atmosphere was added LiOH (38 mg, 1.6 mmol) in water (10 mL). The resulting solution was stirred at 25 °C for 15 h. The reaction mixture was purified directly by C18-flash chromatography (eluting with 20 – 50% MeCN in water (0.05% NH₄OH)) to afford *N*-(1-cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide (250 mg, 93 %, 99.8% *ee*), **Compound (II)**, as a colorless solid. ¹H NMR (400 MHz, DMSO-*d*₆) (2 : 3 mixture of rotamers) δ 11.05 (s, 1H), 8.53 – 8.61 (m, 2H), 8.42 (dd, 1H), 7.29 (dd, 1H), 7.22/7.19 (s, 1H) (rotamers), 6.27 (t, 1H), 4.91/4.75 (br.s, 1H) (rotamers), 4.32 –

4.56/3.91 – 4.03 (m, 3H) (rotamers), 4.07 (s, 3H), 3.40 – 3.48 (m, 1H), 2.90/2.75 (s, 3H) (rotamers), 1.71 – 2.27 (m, 7H), 1.60 – 1.70 (m, 1H), 1.21/1.17 (d, 3H) (rotamers), 0.99 – 1.08 (m, 2H), 0.86 – 0.92 (m, 2H). MS ESI, m/z = 508 $[M+H]^+$.

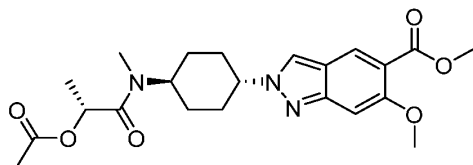
Compound (II) Form A

- 5 Samples of amorphous *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (II), (5 mg) were slurried in separate vials containing 25 μ L of isopropyl alcohol (IPA), methyl ethyl ketone (MEK), toluene, and ethyl acetate and stirred at 25°C for two days. The resultant precipitated powders from each of these slurrying experiments were isolated by filtration. Analysis of the respective powder
- 10 samples revealed that the resultant powders were crystalline. Furthermore, XRPD of each powder produced equivalent diffractograms as per that presented as Figure 5 herein. Further analysis as described herein revealed the material to be an anhydrate solid form, Form A, of Compound (II). For details of the XRPD technique see X-ray Powder Diffraction Analysis above.

Compound (II) Form B

- 15 A sample of amorphous *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (II) was slurried in water at room temperature for two weeks. Analysis of the residual solid, as described herein, revealed the material to be a hydrated solid form (likely a tetrahydrate solid form), Form B, of Compound (II). Compound (II) Form B converts to Compound (II) Form A under vacuum drying. For
- 20 details of the XRPD technique see X-ray Powder Diffraction Analysis above.

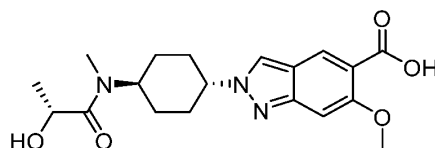
Methyl 2-((1*R*,4*r*)-4-((*R*)-2-acetoxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxylate



- To a solution of the HCl salt of methyl 6-methoxy-2-((1*r*,4*r*)-4-(methylamino)cyclohexyl)-2*H*-indazole-5-carboxylate (**Int 4**) (800 mg, 2.3 mmol) and TEA (945 μ L, 6.8 mmol) in DCM (30 mL) at 0 °C under N_2
- 25 atmosphere was added (*R*)-1-chloro-1-oxopropan-2-yl acetate (511 mg, 3.4 mmol). The resulting solution was stirred at 25 °C for 15 h and then concentrated under reduced pressure. The residue was purified by C18-flash chromatography (eluting with 10 – 100% MeCN in water (0.1% NH_4OH)) to afford

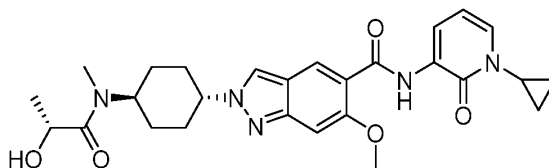
methyl 2-((1*R*,4*r*)-4-((*R*)-2-acetoxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxylate (910 mg, 93 %) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) (4 : 5 mixture of rotamers) δ 8.46/8.43 (s, 1H) (rotamers), 8.09/8.07 (s, 1H) (rotamers), 7.06/7.04 (s, 1H) (rotamers), 5.45/5.28 (q, 1H) (rotamers), 4.39 – 4.55 (m, 1H), 4.28 – 4.39/3.33 – 3.41 (m, 1H) (rotamers), 3.82 (s, 3H), 3.78 (s, 3H), 2.90 /2.75 (s, 3H) (rotamers), 2.15 – 2.25 (m, 2H), 1.72 – 2.14 (m, 8H), 1.56 – 1.69 (m, 1H), 1.29 – 1.36 (m, 3H). MS ESI, *m/z* = 432 [M+H]⁺.

2-((1*R*,4*r*)-4-((*R*)-2-Hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxylic acid (Int 6)



To a solution of methyl 2-((1*R*,4*r*)-4-((*R*)-2-acetoxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxylate (900 mg, 2.1 mmol) in MeOH (10 mL) at 25 °C under N₂ atmosphere was added LiOH monohydrate (525 mg, 12.5 mmol) in water (10 mL). The resulting solution was stirred at 25 °C for 16 h. The pH of the reaction mixture was adjusted to pH 7 with 1N HCl. The mixture was purified by C18-flash chromatography (eluting with 5 – 100% MeCN in water (0.1% FA)) to afford 2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxylic acid (**Int 6**) (750 mg, 96 %) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) (4 : 5 mixture of rotamers) δ 8.43/8.40 (s, 1H) (rotamers), 8.25 (s, 1H), 8.04/8.03 (s, 1H) (rotamers), 7.01/7.00 (s, 1H) (rotamers), 4.38 – 4.58 (m, 2H), 4.32 – 4.41/3.93 – 4.02 (m, 1H) (rotamers), 3.81 (s, 3H), 2.90 /2.76 (s, 3H) (rotamers), 1.94 – 2.24 (m, 4H), 1.71 – 1.94 (m, 3H), 1.59 – 1.71 (m, 1H), 1.17 – 1.26 (m, 3H). MS ESI, *m/z* = 376 [M+H]⁺.

***N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (I)**



To a solution of 2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxylic acid (**Int 6**) (200 mg, 0.5 mmol), 3-amino-1-cyclopropylpyridin-2(1*H*)-one (120 mg, 0.8 mmol) and DIPEA (372 μL, 2.1 mmol) in DMF (2 mL) under N₂ atmosphere was added HATU (243 mg, 0.6 mmol). The reaction mixture was stirred at 20 °C for 17 h. The reaction mixture was purified directly by C18-flash chromatography (eluting with 0 – 100% MeCN in water (0.05% FA)) and further by prep. HPLC (YMC-Actus Triart C18 5μm 30 × 150 mm; elution gradient 15 – 40% MeCN in

water (10 mM (NH₄)₂CO₃ + 0.1% NH₄OH) over 10 min; 60 mL/min) to afford *N*-(1-cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide (32 mg, 12%), as a colorless solid. ¹H NMR (400 MHz, DMSO-*d*₆) (4 : 5 mixture of rotamers) δ 11.05 (s, 1H), 8.54 – 8.61 (m, 2H), 8.43 (dd, 1H), 7.29 (dd, 1H), 7.23/7.20 (s, 1H) (rotamers), 6.28 (t, 1H), 4.91/4.73 (d, 1H) (rotamers), 4.37 – 4.56 (m, 2H), 4.34 – 4.45/3.93 – 4.04 (m, 1H) (rotamers), 4.08 (s, 3H), 3.45 (tt, 1H), 2.91/2.77 (s, 3H) (rotamers), 2.15 – 2.28 (m, 2H), 1.96 – 2.15 (m, 2H), 1.72 – 1.96 (m, 3H), 1.68 (s, 1H), 1.16 – 1.26 (m, 3H), 1 – 1.09 (m, 2H), 0.87 – 0.95 (m, 2H). MS ESI, *m/z* = 508 [M+H]⁺.

As described for its enantiomer above, amorphous *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido)cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (I), was slurried in isopropyl alcohol (IPA) and stirred for room temperature for 2 days at 25 °C. The resultant precipitated powder was isolated by filtration. Analysis revealed this powder to be crystalline, with XRPD producing the diffractogram presented in Figure 1. Further analysis as described herein revealed the material to be an anhydrate solid form, Form A, of Compound (I). For details of the XRPD technique see X-ray Powder Diffraction Analysis above.

Ramp Differential Scanning Calorimetry (DSC)

The melting point temperature onset (*T*_m) for Compound (I), Form A and Compound (II), Form A determined by Differential Scanning Calorimetry using a TA Instruments DSC, model Q2000 (see https://www.tainstruments.com/pdf/2011_Thermal.pdf). Briefly, each sample (approximately 1-3 mg) was weighed into an aluminium sample pan, packed to the bottom of the sample pan and covered with a lid with a pin hole. The instrument was purged with nitrogen gas at 50 mL/min and data collected between 0 °C and 230 °C, using a heating rate of 10 °C/minute.

Representative DSC thermograms for Compound (I), Form A and Compound (II), Form A are presented as Figures 2 and 6, respectively. In each case exothermic events are plotted in the upward direction.

The melting endotherm shown in Figure 2 has an onset temperature of about 217 °C and an enthalpy of approximately 89 J/g. The absence of any thermal events detected in the DSC signal prior to the melting onset temperature indicates that Compound (I) Form A is thermally stable in the temperature range 0 to 210 °C under these experimental conditions. Accordingly, Compound (I), Form A is identified as having appropriate thermal stability for further formulation development.

As would be expected, DSC analysis of Compound (II), Form A as shown in Figure 6 is analogous to that observed for its enantiomer in Figure 2. The melting endotherm shown in Figure 6 has an onset temperature of about 217 °C and an enthalpy of approximately 90 J/g.

- 5 DSC analysis of Compound (II), Form B (Figure 10) shows a large endothermic event at 67°C, which likely corresponds to the removal of water and conversion to amorphous Compound (II). Crystallisation to Compound (II) Form A is observed as the exothermic event at about 172°C, followed by a melting endotherm at about 215 °C and an enthalpy of approximately 72 J/g.

Thermogravimetric Analysis (TGA)

- 10 Thermal gravimetric analysis is performed using a TA Instruments TGA, model TGA550 (see tainstruments.com). A sample (approximately 5 mg) of each of Compound (I), Form A and Compound (II), Form A was transferred into a tared sample holder. The instrument was in each case purged with nitrogen (oven 60 mL/min and balance 40 mL/min), and data are collected between room temperature and 350 °C, using a heating rate of 3 °C/min. During heating, the buoyancy effect results in an observed weight increase. This buoyancy effect can be reduced by using more than 15 mg of material or by performing a baseline subtraction on the sample curve.

As can be seen in Figure 3 which is a representative TGA thermogram for Compound (I), Form A, a minimal weight loss of (less than about 0.1 %) is observed upon heating from about 25 °C to 150 °C, indicating that Form A is likely as an anhydrate solid form of Compound (I). Karl Fischer analysis of Compound (I), Form A confirmed that Form A is an anhydrate.

- 20 Likewise, Figure 7 is a representative TGA thermogram for Compound (II), Form A. As can be seen in Figure 7 a minimal weight loss of (less than about 0.1 %) is observed upon heating from about 25 °C to 150 °C, indicating that Form A is likely as an anhydrate solid form of Compound (II). Karl Fischer analysis of Compound (II), Form A confirmed that Form A is an anhydrate. Karl Fischer analysis of Compound (II), Form A confirmed that Form A is an anhydrate.

- 25 Figure 11 is a representative TGA thermogram of Compound (II), Form B. A weight loss of approximately 12.8% upon heating is observed, which corresponds to the loss of four moles of water. These data indicate that Compound (II), Form B is a hydrated solid form of Compound (II), and likely a tetrahydrate solid form of Compound (II).

Gravimetric Vapor Sorption (GVS)

Gravimetric vapor sorption analysis on each of Compound (I), Form A and Compound (II), Form A was performed using a DVS Resolution instrument from Surface Measurement Systems (<https://surfacemeasurementsystems.com/solutions/products/>). A sample of each compound (approximately 5-10 mg) was transferred to a tared sample holder. The instrument was initially purged with dry nitrogen, at 25 °C and data was then collected at a range of relative humidities (%RH) by mixing wet and dry nitrogen flows. The GVS experiment was started at 20% RH and ramped up to 80% RH in 10% RH increments in a stepwise manner before stepping down, again in 10% RH increments and then down stepwise to 0% RH. The equilibrium criteria for moving to the next %RH is reached when the drift criteria (dm/dt) is below 0.002 for 10 min. The mass at the end of the 0% RH stage is used as the reference mass for calculation of the change in mass over the course of the experiment.

Hygroscopicity can be assessed using the GVS technique, for example, according to the European Pharmacopoeia (EP) classification materials can be classified as: non-hygroscopic: < 0.2%; slightly hygroscopic: $\geq 0.2\%$ and < 2%; hygroscopic: $\geq 2\%$ and < 15%; very hygroscopic: $\geq 15\%$; deliquescent: sufficient water is absorbed to form a liquid; all values measured as weight increase at 80% RH and 25 °C).

As can be seen from Figure 4, Compound (I), Form A exhibited a reversible moisture uptake of about 0.12 mass % between 20% relative humidity and 80% relative humidity at 25 °C $\pm$ 0.1 °C. The desorption curve indicates that Form A lost moisture at a similar rate to the moisture gained during sorption, with limited hysteresis. No form change was observed by XRPD after the GVS experiment. According to the European Pharmacopoeia (EP) classification, Form A is therefore identified as a non-hygroscopic (i.e., < 0.2% weight increase) solid form of Compound (I).

Similarly, Figure 8 reveals Compound (II), Form A exhibited a reversible moisture uptake of less than 0.1 mass % between 20% relative humidity and 80% relative humidity at 25 °C $\pm$ 0.1 °C. The desorption curve indicates that Form A lost moisture at a similar rate to the moisture gained during sorption, with limited hysteresis. No form change was observed by XRPD after the GVS experiment. According to the European Pharmacopoeia (EP) classification, Form A is therefore identified as a non-hygroscopic (i.e., < 0.2% weight increase) solid form of Compound (II).

Figure 12 suggests that Compound (II), Form B exhibits reversible conversion between lower and higher hydrated forms, converting to the higher hydrated form (likely the tetrahydrate form) at about 60% relative humidity, and to the lower hydrated form (which may be a monohydrate, dihydrate or trihydrate form) below about 60% relative humidity.

The physical and chemical stability of Compound (II), Form A was assessed under stressed conditions over a period of 21 days according to standard protocols. Briefly, samples of Form A material were weighed into sample vials, the sample vials were placed in separate jars each containing a MadgeTech temperature and humidity logger, and in a separate vial a saturated solution of salts were used to
5 control the humidities from 11% RH to 75% RH.

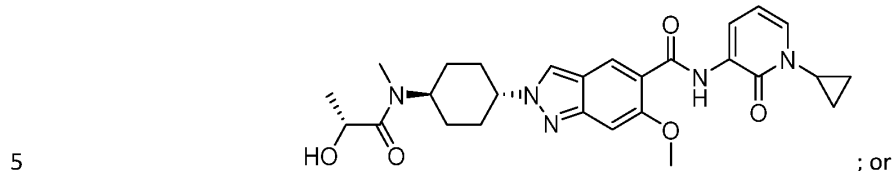
The jars were then sealed and placed in temperature-controlled calibrated ovens for a period of up to 21 days. Control samples were maintained in sealed vials in a refrigerator for the duration of the study. Experiments were performed at 60°C/75% RH, 70°C/11% RH and 70°C/50% RH for 21 days and 80°C/11% RH and 80°C/50% RH for 14 days.

10 Analysis of the samples by UHPLC (ultra-high performance liquid chromatography) revealed that no organic impurities developed in the samples stored at low or high relative humidity over the course of the experiment. Furthermore, XRPD confirmed that the physical form of the material over the course of the study was unchanged. It could thus be concluded that no chemical degradation of the samples or change in their physical form occurred on storage under stressed conditions. Accordingly, the
15 suitability of Compound (II), Form A, and by extension its enantiomer, Compound (I), Form A, for further development in pharmaceutical formulations was established.

Claims

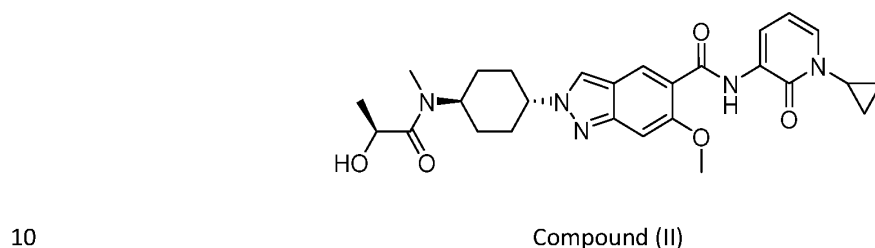
1) A crystalline form of

i) *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido) cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (I):



Compound (I)

ii) *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido) cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (II):



or a pharmaceutically acceptable salt or solvate thereof.

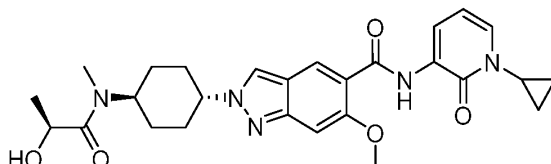
2) A crystalline form according to claim 1, that is Compound (I), Form A characterised in that it has an X-ray powder diffraction pattern with specific peaks at about 2-theta 16.3 and 23.0°, when measured using CuKα radiation.

15 3) A crystalline form according to claim 1, that has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 1, when measured using CuKα radiation.

4) A crystalline form according to claim 1, that is Compound (II), Form A characterised in that it has an X-ray powder diffraction pattern with specific peaks at about 2-theta 16.3 and 23.0°, when
20 measured using CuKα radiation.

5) A crystalline form according to claim 1, that has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 5, when measured using CuK α radiation.

- 5 6) A crystalline form of *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido) cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (II):



Compound (II),

that is Compound (II), Form B characterised in that it has an X-ray powder diffraction pattern with
10 specific peaks at about 2-theta 8° and 5.5°, when measured using CuK α radiation.

7) The crystalline form according to claim 6, that has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 3.8°, 4.8°, 5.5°, 9.5°, 13.2°, 14.4°, 17.5°, 25.7° and 26.4°, when measured using CuK α radiation.

8) The crystalline form according to claim 6, that has an X-ray powder diffraction pattern
15 substantially the same as the X-ray powder diffraction pattern shown in Figure 9.

9) A pharmaceutical formulation comprising a crystalline form according to any preceding claim and at least one pharmaceutically acceptable excipient.

10) A crystalline form according to any of claims 1 to 8 for use as a medicament or a method of treatment comprising administering a crystalline form according to any of claims 1 to 8 or a
20 composition according to claim 9 to a patient in need thereof.

11) The use or method according to claim 10 or the pharmaceutical composition of claim 9 for use in the treatment of a haematologic malignancy selected from myelodysplastic syndrome (MDS), Waldenstrom's macroglobulinemia (WM), non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), primary central nervous system lymphoma (PCNSL), Splenic Marginal Zone Lymphoma (SMZL), small lymphocytic lymphoma (SLL), leukaemias (chronic lymphocytic leukaemia (CLL)) and monoclonal gammopathy of undetermined significance (MGUS-IgM+).

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- 12) A crystalline form of *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido) cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide according to any of claims 1 to 3 or *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido) cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide according to claims 1 or 4
5 to 8, for use in the manufacture of a medicine.
- 13) *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido) cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (I), or *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido) cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (II), for use in the treatment of
10 myelodysplastic syndrome.
- 14) A method of treatment of myelodysplastic comprising administering *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido) cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (I), or *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido) cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide,
15 Compound (II), to a patient in need thereof.
- 15) *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*R*,4*r*)-4-((*R*)-2-hydroxy-*N*-methylpropanamido) cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (I), or *N*-(1-Cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)-2-((1*S*,4*r*)-4-((*S*)-2-hydroxy-*N*-methylpropanamido) cyclohexyl)-6-methoxy-2*H*-indazole-5-carboxamide, Compound (II), for use in the manufacture of a
20 medicament, wherein the medicament is for the treatment of myelodysplastic syndrome.