networks, modulation of cell surface receptors, ion channels, the secretory pathway, DNA repair and biogenesis of organelles.

[0006] Aberrations in the process have recently been implicated in the pathogenesis of several diseases, both inherited and acquired. These diseases fall into two major groups: (a) those that result from loss of function with the resultant stabilization of certain proteins, and (b) those that result from gain of function, i.e. abnormal or accelerated degradation of the protein target.

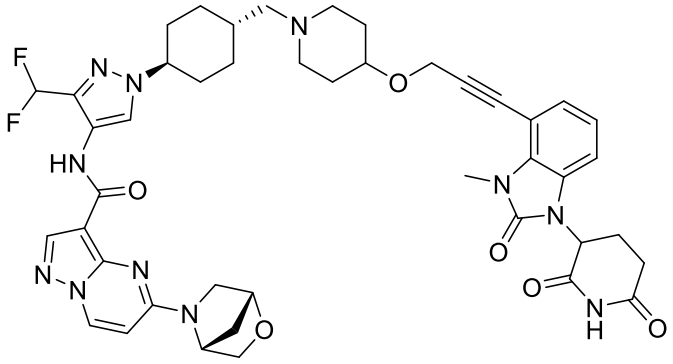
[0007] The UPP is used to induce selective protein degradation, including use of fusion proteins to artificially ubiquitinate target proteins and synthetic small-molecule probes to induce proteasome-dependent degradation. Bifunctional compounds composed of a target protein- binding ligand and an E3 ubiquitin ligase ligand, induced proteasome-mediated degradation of selected proteins via their recruitment to E3 ubiquitin ligase and subsequent ubiquitination. These drug-like molecules offer the possibility of temporal control over protein expression. Such compounds are capable of inducing the inactivation of a protein of interest upon addition to cells or administration to an animal or human, and could be useful as biochemical reagents and lead to a new paradigm for the treatment of diseases by removing pathogenic or oncogenic proteins (Crews C, Chemistry & Biology, 2010, 17(6):551-555; Schnnekloth JS Jr., Chembiochem, 2005, 6(l):40-46).

[0008] An ongoing need exists in the art for effective treatments for disease, especially autoinflammatory and autoimmune diseases with high unmet medical need. However, non-specific effects, and the inability to target and modulate certain classes of proteins altogether, such as transcription factors, remain as obstacles to the development of effective anti-cancer agents. As such, small molecule therapeutic agents that leverage E3 ligase mediated protein degradation to target cancer-associated proteins such as interleukin-1 receptor-associated kinases ("IRAK") hold promise as therapeutic agents. Accordingly, there remains a need to find compounds that are IRAK degraders useful as therapeutic agents.

SUMMARY

[0009] It has now been found that novel forms of 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-(difluoromethyl)-1-((1r,4R)-4-((4-((3-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)prop-2-yn-1-yl)oxy)piperidin-1-yl)methyl)cyclohexyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide, as described in the present disclosure, and compositions thereof, are useful modulators of targeted ubiquitination of IRAK kinases and exhibit desirable characteristics for the same. In general, salt forms or freebase forms, and pharmaceutically acceptable compositions thereof, are useful for treating or lessening the severity of a variety of diseases or disorders as described in detail herein.

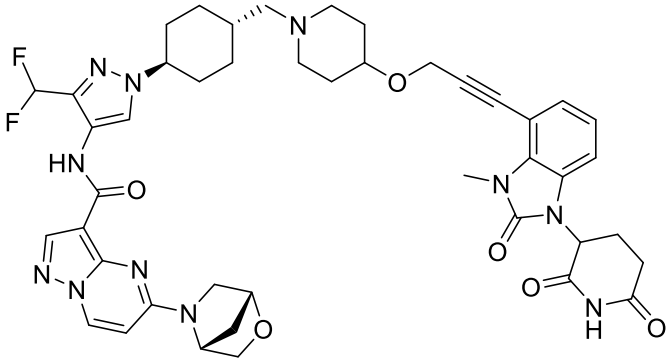
[0009a] In an aspect of the present disclosure, there is provided a crystalline solid form of Compound 1:



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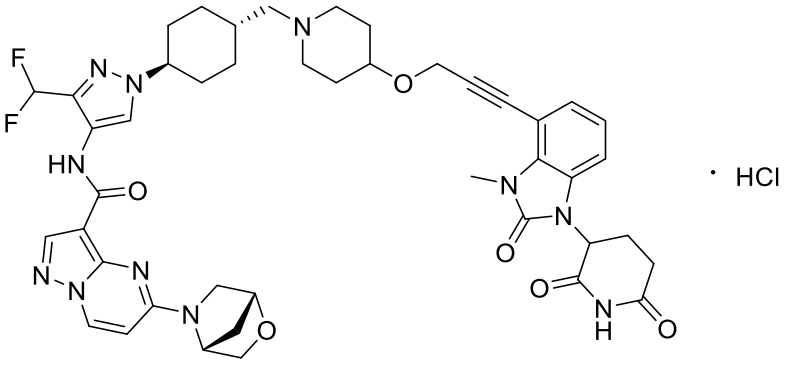
selected from Form A and Form B.

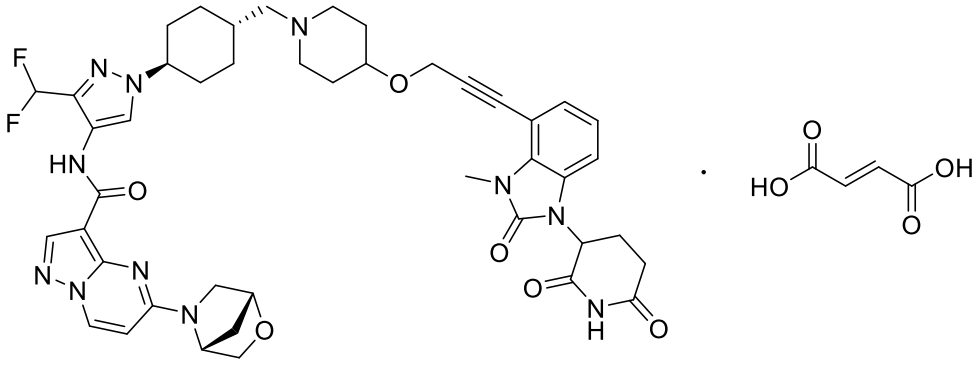
[0009b] In another aspect of the present disclosure, there is provided a salt form of compound **1:**

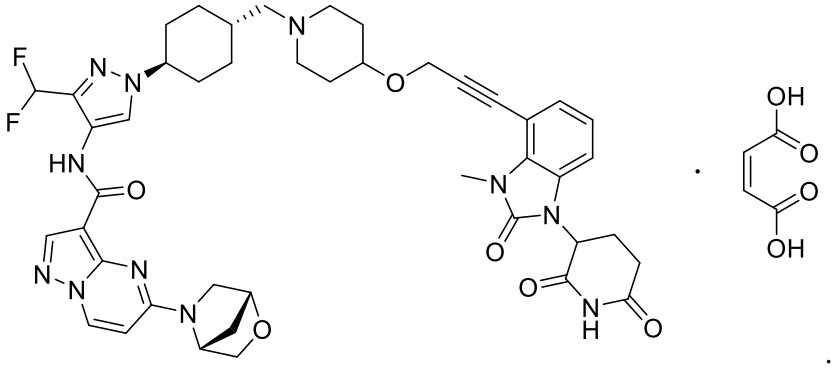


1

selected from:

Compound **2**:  ;

Compound **3**:  ; and

Compound **4**:  .

[0009c] In a further aspect of the present disclosure, there is provided a composition comprising a crystalline solid form or salt form disclosed herein, and a pharmaceutically acceptable carrier or excipient.

[0009d] In another aspect of the present disclosure, there is provided a use of a crystalline solid form or salt form disclosed herein, or a pharmaceutical composition thereof, in the manufacture of a medicament for degrading IRAK1, IRAK2 and/or IRAK4 protein kinase in a patient or biological sample.

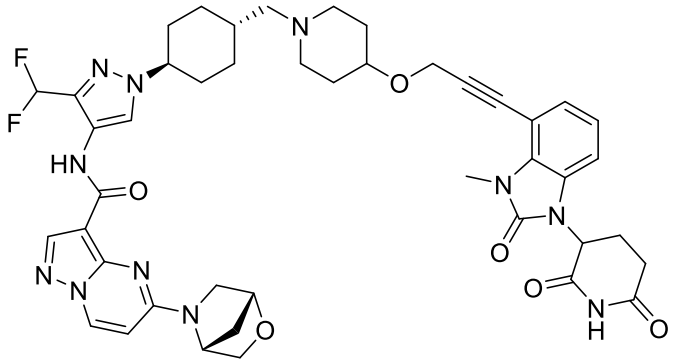
[0009e] In a further aspect of the present disclosure, there is provided use of a crystalline solid form or salt form disclosed herein, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating an IRAK1-mediated, IRAK2-mediated and/or IRAK4-mediated disorder, disease, or condition in a patient.

[0009f] In another aspect of the present disclosure, there is provided a crystalline solid form or salt form disclosed herein, or a pharmaceutical composition thereof, for use in therapy.

CLAIMS

What is claimed is:

1. A crystalline solid form of Compound 1:



1

selected from Form A and Form B.

2. The crystalline solid form according to claim 1, wherein said compound is a crystalline solid substantially free of amorphous compound **1**.

3. The crystalline solid form according to claim 1, wherein said compound is substantially free of impurities.

4. The crystalline solid form according to any one of claims 1-3, wherein the crystalline solid form is Form A of Compound **1**.

5. The crystalline solid form according to claim 4, having one or more peaks in its X-ray powder diffraction pattern selected from those at about 6.0, about 16.5, about 17.2, about 23.0, and about 23.9 degrees 2-theta.

6. The crystalline solid form according to claim 4, having two or more peaks in its X-ray powder diffraction pattern selected from those at about 6.0, about 16.5, about 17.2, about 23.0, and about 23.9 degrees 2-theta.

7. The crystalline solid form according to claim 4, having three or more peaks in its X-ray powder diffraction pattern selected from those at about 6.0, about 16.5, about 17.2, about 23.0, and about 23.9 degrees 2-theta.

8. The crystalline solid form according to claim 4, having four or more peaks in its X-ray powder diffraction pattern selected from those at about 6.0, about 16.5, about 17.2, about 23.0, and about 23.9 degrees 2-theta.

9. The crystalline solid form according to claim 4, having five peaks in its X-ray powder diffraction pattern selected from those at about 6.0, about 16.5, about 17.2, about 23.0, and about 23.9 degrees 2-theta.

10. The crystalline solid form according to claim 4, having an X-ray powder diffraction pattern substantially as shown in **FIG. 1A**.

11. The crystalline solid form according to any one of claims 1-3, wherein the crystalline solid form is Form B.

12. The crystalline solid form according to claim 11, having one or more peaks in its X-ray powder diffraction pattern selected from those at about 3.2, about 16.2, about 16.5, about 17.1, and about 18.2 degrees 2-theta.

13. The crystalline solid form according to claim 11, having two or more peaks in its X-ray powder diffraction pattern selected from those at about 3.2, about 16.2, about 16.5, about 17.1, and about 18.2 degrees 2-theta.

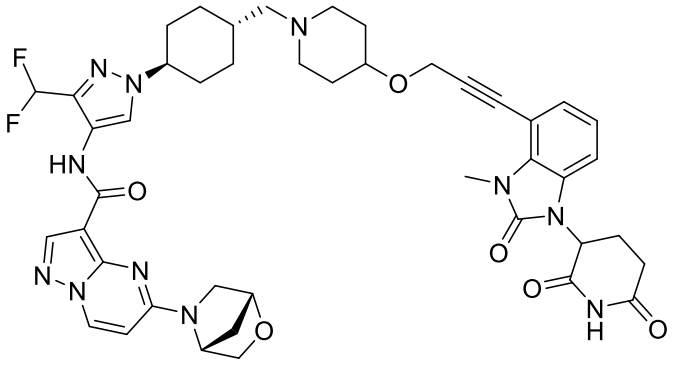
14. The crystalline solid form according to claim 11, having three or more peaks in its X-ray powder diffraction pattern selected from those at about 3.2, about 16.2, about 16.5, about 17.1, and about 18.2 degrees 2-theta.

15. The crystalline solid form according to claim 11, having four or more peaks in its X-ray powder diffraction pattern selected from those at about 3.2, about 16.2, about 16.5, about 17.1, and about 18.2 degrees 2-theta.

16. The crystalline solid form according to claim 11, having five peaks in its X-ray powder diffraction pattern selected from those at about 3.2, about 16.2, about 16.5, about 17.1, and about 18.2 degrees 2-theta.

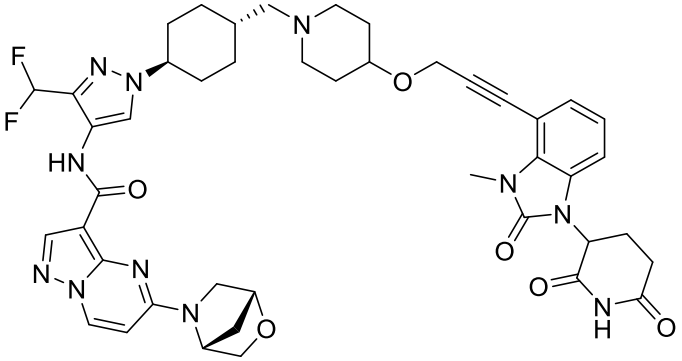
17. The crystalline solid form according to claim 11, having an X-ray powder diffraction pattern substantially as shown in **FIG. 2A**.

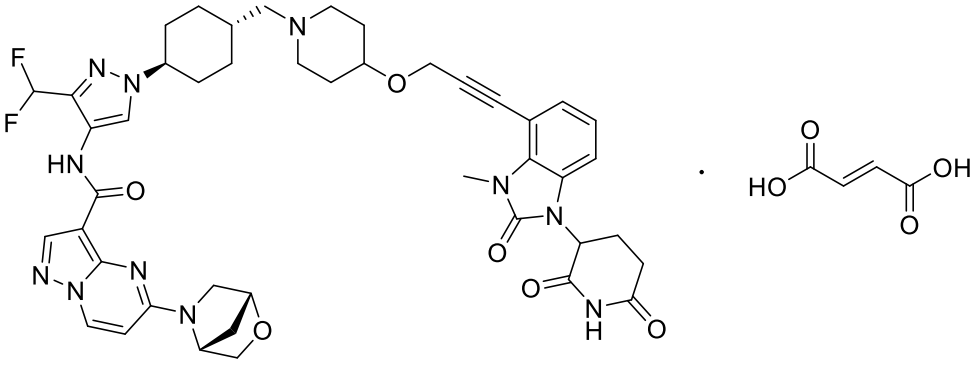
18. A salt form of compound **1:**

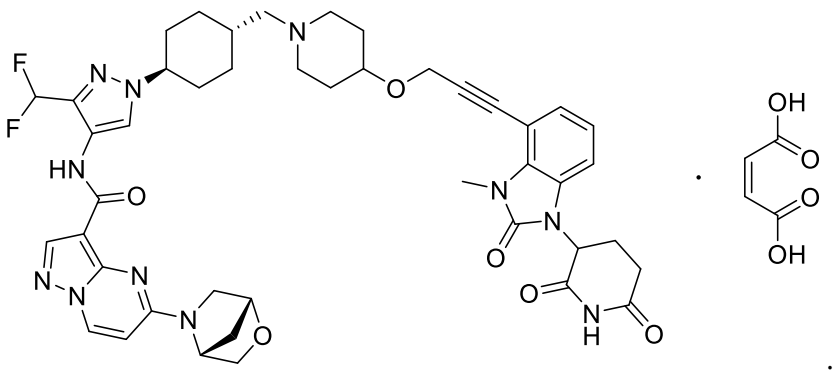


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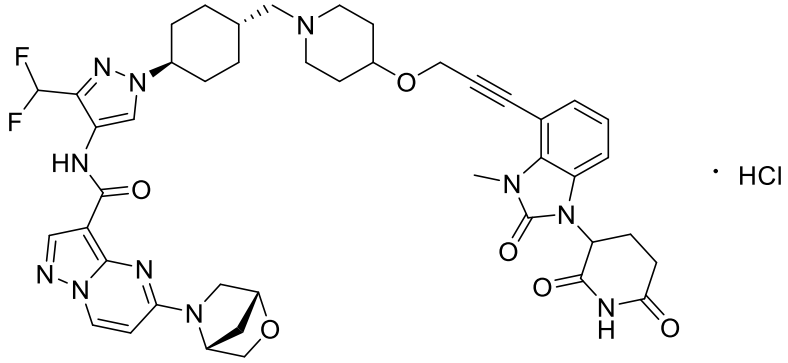
selected from:

Compound **2**:  ;

Compound **3**:  ; and

Compound **4**: .

19. The salt form of claim 18, wherein the salt form of Compound **1** is Compound **2**:



2.

20. The salt form according to claim 19, wherein said salt form is crystalline.

21. The salt form according to claim 19, wherein said salt form is a crystalline solid substantially free of amorphous compound **2**.

22. The salt form according to any one of claims 19-21, wherein said salt form is substantially free of impurities.

23. The salt form according to any one of claims 19-22, wherein said salt form is Form A of Compound **2**.

24. The salt form according to claim 23, having one or more peaks in its X-ray powder diffraction pattern selected from those at about 14.1, about 17.0, about 17.3, about 19.0, about 21.0, about 21.2 and about 23.3 degrees 2-theta.

25. The salt form according to claim 23, having two or more peaks in its X-ray powder diffraction pattern selected from those at about 14.1, about 17.0, about 17.3, about 19.0, about 21.0, about 21.2 and about 23.3 degrees 2-theta.

26. The salt form according to claim 23, having three or more peaks in its X-ray powder diffraction pattern selected from those at about 14.1, about 17.0, about 17.3, about 19.0, about 21.0, about 21.2 and about 23.3 degrees 2-theta.

27. The salt form according to claim 23, having four or more peaks in its X-ray powder diffraction pattern selected from those at about 14.1, about 17.0, about 17.3, about 19.0, about 21.0, about 21.2 and about 23.3 degrees 2-theta.

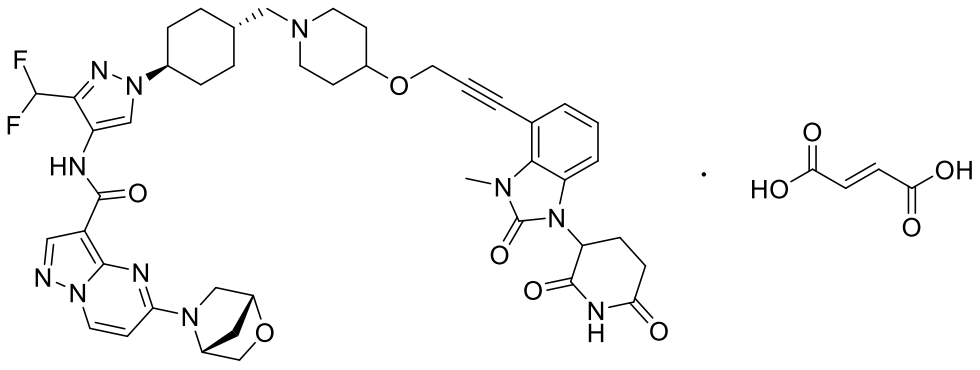
28. The salt form according to claim 23, having five or more peaks in in its X-ray powder diffraction pattern selected from those at about 14.1, about 17.0, about 17.3, about 19.0, about 21.0, about 21.2 and about 23.3 degrees 2-theta.

29. The salt form according to claim 23, having six or more peaks in its X-ray powder diffraction pattern at about 14.1, about 17.0, about 17.3, about 19.0, about 21.0, about 21.2 and about 23.3 degrees 2-theta.

30. The salt form according to claim 23, having seven peaks in its X-ray powder diffraction pattern at about 14.1, about 17.0, about 17.3, about 19.0, about 21.0, about 21.2 and about 23.3 degrees 2-theta.

31. The salt form according to claim 23, having an XRPD substantially as shown in **FIG. 3A**.

32. The salt form of claim 18, wherein the salt form of Compound **1** is Compound **3**:



3.

33. The salt form according to claim 32, wherein said salt form is crystalline.

34. The salt form according to claim 32, wherein said salt form is a crystalline solid substantially free of amorphous compound **3**.

35. The salt form according to any one of claims 32-34, wherein said salt form is substantially free of impurities.

36. The salt form according to any one of claims 32-35, wherein said salt form is Form A of Compound **3**.

37. The salt form according to claim 36, having one or more peaks in its X-ray powder diffraction pattern selected from those at about 6.4, about 11.9, about 16.2, about 17.2, and about 20.9 degrees 2-theta.

38. The salt form according to claim 36, having two or more peaks in its X-ray powder diffraction pattern selected from those at about 6.4, about 11.9, about 16.2, about 17.2, and about 20.9 degrees 2-theta.

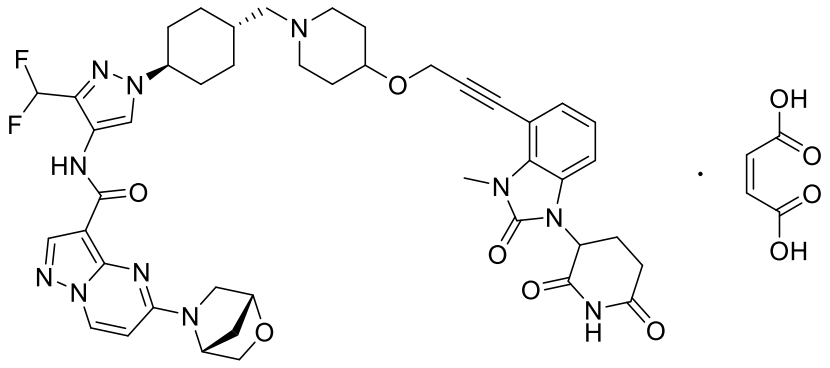
39. The salt form according to claim 36, having three or more peaks in its X-ray powder diffraction pattern selected from those at about 6.4, about 11.9, about 16.2, about 17.2, and about 20.9 degrees 2-theta.

40. The salt form according to claim 36, having four or more peaks in its X-ray powder diffraction pattern selected from those at about 6.4, about 11.9, about 16.2, about 17.2, and about 20.9 degrees 2-theta.

41. The salt form according to claim 36, having five peaks in in its X-ray powder diffraction pattern selected from those at about 6.4, about 11.9, about 16.2, about 17.2, and about 20.9 degrees 2-theta.

42. The salt form according to claim 36, having an XRPD substantially as shown in **FIG. 4A**.

43. The salt form of claim 18, wherein the salt form of Compound **1** is Compound **4**:



4.

44. The salt form according to claim 43, wherein said salt form is crystalline.

45. The salt form according to claim 43, wherein said salt form is a crystalline solid substantially free of amorphous compound **4**.

46. The salt form according to any one of claims 43-45, wherein said salt form is substantially free of impurities.

47. The salt form according to any one of claims 43-46, wherein said salt form is Form A of Compound **4**.

48. The salt form according to claim 47, having one or more peaks in its X-ray powder diffraction pattern selected from those at about 3.3, about 6.4, and about 16.7 degrees 2-theta.

49. The salt form according to claim 47, having two or more peaks in its X-ray powder diffraction pattern selected from those at about 3.3, about 6.4, and about 16.7 degrees 2-theta.

50. The salt form according to claim 47, having three peaks in its X-ray powder diffraction pattern selected from those at about 3.3, about 6.4, and about 16.7 degrees 2-theta.

51. The salt form according to claim 47, having an XRPD substantially as shown in **FIG. 5A**.

52. A composition comprising a crystalline solid form or salt form according to any one of claims 1-51 and a pharmaceutically acceptable carrier or excipient.

53. The pharmaceutical composition according to claim 52, further comprising an additional therapeutic agent.

54. Use of a crystalline solid form or salt form according to any of one of claims 1-51, or a pharmaceutical composition thereof, in the manufacture of a medicament for degrading IRAK1, IRAK2 and/or IRAK4 protein kinase in a patient or biological sample.

55. Use of a crystalline solid form or salt form according to any of one of claims 1-51, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating an IRAK1-mediated, IRAK2-mediated and/or IRAK4-mediated disorder, disease, or condition in a patient.

56. The use according to claim 55, wherein the crystalline solid form or salt form, or the pharmaceutical composition thereof, is to be administered to the patient, and wherein an additional therapeutic agent is to be further administered.

57. The use according to claim 55, wherein the IRAK1-mediated, IRAK2-mediated and/or IRAK4-mediated disorder, disease or condition is an inflammatory disorder.

58. The use according to claim 57, wherein the inflammatory disorder is selected from the group consisting of ocular allergy, conjunctivitis, keratoconjunctivitis sicca, vernal conjunctivitis; allergic rhinitis, hemolytic anemia, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia or another inflammatory disease in which autoimmune reactions are implicated or which have an autoimmune component or etiology, systemic lupus erythematosus, rheumatoid arthritis,

polychondritis, scleroderma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, ulcerative colitis, Crohn's disease or another autoimmune inflammatory bowel disease, irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), Sjogren's syndrome, vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, nephritis, diverticulitis, interstitial cystitis, glomerulonephritis (with and without nephrotic syndrome, optionally including idiopathic nephrotic syndrome or minal change nephropathy), chronic granulomatous disease, endometriosis, leptospiriosis renal disease, glaucoma, retinal disease, aging, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle wasting, catabolic disorders, obesity, fetal growth retardation, hyperchlolesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ecodermal dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma (allergic, non-allergic, mild, moderate, severe, bronchitic, or exercise-induced), acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, nasal sinusitis, silica induced diseases, COPD (reduction of damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression), pulmonary disease, cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, Type 1 diabetes, Type 2 diabetes, appendicitis, atopic dermatitis, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, vaginitis, vasculitis, vulvitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Juvenile rheumatoid arthritis, Cryopyrin Associated Periodic Syndrome (CAPS), and osteoarthritis.

59. A crystalline solid form or salt form according to any of one of claims 1-51, or a pharmaceutical composition thereof, for use in therapy.