[0014] The FDA has recognized and listed various drugs as potential P-gp inhibitors (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers).

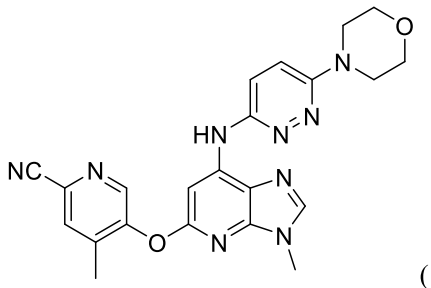
[0015] In addition, the co-administration of a substance acting as P-gp inhibitor, which can also act as CYP inhibitor, may result in a reduced therapeutic effect due to a doble effect. On one side, a P-gp inhibition-mediated, enhanced the intracellular accumulation of the parent drug; and on another side, a CYP inhibition-mediated, may cause excessive drug accumulation of the parent drug and increased its toxicity, resulting in the need to reduce the dose of the therapeutic agent. Therefore, it is crucial to understand which combinations of drugs should be contraindicated or their co-administration avoided (Wandel et al. 1999).

SUMMARY

[0016] The example described herein is based upon the findings that the Compound of the disclosure:

i. when administered at certain dosages provides unexpected advantages in the treatment of inflammatory diseases and/or diseases associated with hypersecretion of IFNα and/or interferons ("interferonopathies", especially type I interferonopathies), IL-12 and/or IL-23; and
ii. is metabolized by CYP3A4 and/or transported by P-gp, which could result in undesired drug-drug interactions when administered in combination with one or more compounds that are CYP inhibitors and/or P-gp inhibitors, particularly CYP3A4 inhibitors and/or P-gp inhibitors, and more particularly strong CYP3A4 inhibitors and/or strong P-gp inhibitors.

[0016a] In an aspect, there is provided the use of compound 1



(1)

or a pharmaceutically acceptable salt/cocrystal thereof, or a solvate or the solvate of a salt/cocrystal thereof, in the manufacture of a medicament for the treatment of an inflammatory disease, a disease associated with hypersecretion of IFNα and/or interferons ("interferonopathies", especially type I interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, ulcerative colitis and/or Crohn's disease, wherein compound 1 is to be administered at a total daily dosage of at least 80 mg per day to 200 mg per day.

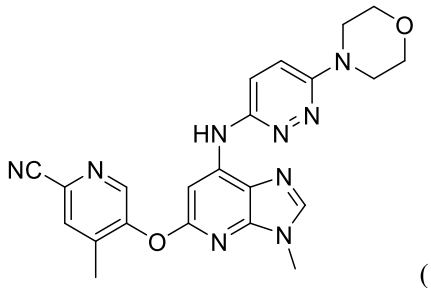
[0016b] In another aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of compound 1 as defined above.

[0016c] In another aspect, there is provided a a package or kit comprising:

i. the compound according to Formula I or a pharmaceutically acceptable salt/cocrystal thereof, or a solvate or the solvate of a salt/cocrystal thereof, and

ii. a package insert, package label, instructions or other labelling comprising instructions to avoid or discontinue or contraindication of concomitant use or co-administration of one or more compounds that are CYP inhibitors and/or P-gp inhibitors.

[0016d] In another aspect, there is provided a pharmaceutical unit dosage composition comprising 80 mg to 200 mg of compound 1:



(1)

or a pharmaceutically acceptable salt/cocrystal thereof, or a solvate or the solvate of a salt/cocrystal thereof, wherein the unit dosage form is suitable for oral administration up to a maximum total dosage of 200 mg of compound 1 per day.

[0016e] In another aspect, there is provided the use of the dosage form as defined above in the manufacture of a medicament for the treatment of an inflammatory disease, a disease associated with hypersecretion of IFNα and/or interferons ("interferonopathies", especially type I interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, ulcerative colitis and/or Crohn's disease.

[0017] Accordingly, in a first example the present disclosure provides the Compound of the disclosure for use in the treatment of an inflammatory disease and/or a disease associated with hypersecretion of IFNα and/or interferons ("interferonopathies", especially type I interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid

arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn's disease, wherein compound 1 is administered at a total daily dosage of at least 80 mg per day to 200 mg per day.

[0018] In a second example the present disclosure provides the compound of the disclosure for use in treating a patient in need of the compound of the disclosure therapy, characterized in that the treating comprises avoiding, contraindicating or discontinuing concomitant use or co-administration of one or more compounds that are CYP inhibitors and/or P-gp inhibitors, particularly CYP3A4 inhibitors and/or P-gp inhibitors, and more particularly strong CYP3A4 inhibitors and/or strong P-gp inhibitors.

[0019] In a further example, the present disclosure also provides the use of the Compound of the disclosure in the manufacture of a medicament for the treatment of an inflammatory disease and/or a disease associated with hypersecretion of IFNα and/or interferons ("interferonopathies", especially type I interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn's disease, wherein compound 1 is administered at a total daily dosage of at least 80 mg per day to 200 mg per day.

[0020] In a another example, the present disclosure provides a method of treating an inflammatory disease and/or a disease associated with hypersecretion of IFNα and/or interferons ("interferonopathies", especially type I interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn's disease, comprising administering to a patient the Compound of the Disclosure at a total daily dosage of at least 80 mg per day to 200 mg per day.

[0021] In another example the present disclosure provides a pharmaceutical unit dosage composition comprising 80 mg to 200 mg of the Compound of the Disclosure, wherein the unit dosage form is suitable for oral administration up to a maximum total dosage of 200 mg per day.

[0022] In a further example, the present disclosure also provides the use of the compound of the disclosure in the manufacture of a medicament for treating a patient in need of therapy using the compound of the disclosure, characterized in that the treating comprises avoiding, contraindicating or discontinuing concomitant use or co-administration of one or more compounds that are CYP inhibitors and/or P-gp inhibitors, particularly CYP3A4 inhibitors and/or P-gp inhibitors, and more particularly strong CYP3A4 inhibitors and/or strong P-gp inhibitors.

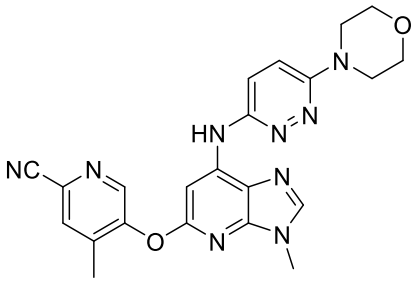
[0023] In another example, the present disclosure provides a method of administering treatment using the compound of the disclosure to a patient in need of therapy using the compound of the disclosure comprising administering the patient a therapeutically effective amount of the compound of the disclosure, and, avoiding, contraindicating or discontinuing concomitant use or co-administration of one or more compounds that are CYP inhibitors and/or P-gp inhibitors, particularly CYP3A4 inhibitors and/or P-gp inhibitors, and more particularly strong CYP3A4 inhibitors and/or strong P-gp inhibitors.

[0024] In specific examples the patient in need of therapy is a patient suffering from inflammatory diseases, and/or diseases associated with hypersecretion of IFNα and/or interferons ("interferonopathies", especially type I interferonopathies), IL-12 and/or IL-23. In particular, diseases such as systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn's disease.

[0025] In specific examples, the one or more compounds that may produce potentially serious side effects or toxicity or exhibit adverse drug interactions when co-administered with the compound of the disclosure are CYP inhibitors and/or P-gp inhibitors, more particularly CYP3A4 inhibitors and/or P-gp inhibitors, even more particularly strong CYP3A4 inhibitors and/or strong P-gp inhibitors.

[0026] In specific examples the disease to be treated or the treatment is for a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, ulcerative colitis and/or Crohn's disease.

[0027] Compound 1 means a compound according to formula I below:



I

[0028] The chemical name of Compound 1 is "4-methyl-5-[3-methyl-7-[(6-morpholin-4-ylpyridazin-3-yl)amino]imidazo[4,5-b]pyridin-5-yl]oxypyridine-2-carbonitrile".

[0029] Moreover, Compound 1, useful in the pharmaceutical compositions and treatment methods disclosed herein, is pharmaceutically acceptable as prepared and used.

[0030] Other examples, objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Shows the Mean (±SD) Compound 1 Plasma Concentration Versus Time Profiles - Part 1 - (SAD) - PK Analysis Set (Linear-linear Scale)

Figure 2. Shows the Mean (±SD) Compound 1 Plasma Concentration Versus Time Profiles - Part 1 - (SAD) - PK Analysis Set (Log-linear Scale)

Figure 3. Shows the Mean (±SD) Compound 1 Plasma Concentration Versus Time Profiles - Part 2 (MAD) - PK Analysis Set (Linear-linear Scale).

Figure 4. Shows the Mean (±SD) Compound 1 Plasma Concentration Versus Time Profiles - Part 2 (MAD) - PK Analysis Set (Log-linear Scale).

Figure 5. Shows Inhibition of the IFN-α-induced Neopterin Release Over Time Following Compound 1 Administration and IFN-α Challenge on Day 11 - Part 2 (MAD) - PD Analysis Set.

Figure 6. Shows a two-dimensional heatmap displaying the effects of oral administration of Compound 1 on IFN-response genes in whole blood of volunteers after *in vivo* IFN-α challenge.

Figure 7. Shows the PASI Cumulative Distribution of percentage change from baseline (% CfB) at Week 4 in the Phase 1b clinical study.

Figure 8. Shows the PASI 50 Response Rate as % number of subjects with PASI 50 response at each visit.

Figure 9. Shows the PASI 75 Response Rate as % number of subjects with PASI 75 response at each visit.

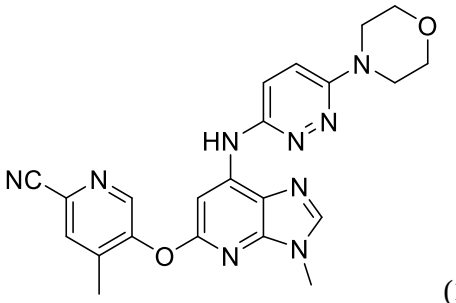
DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0031] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

CLAIMS

1. Use of compound 1



(1)

or a pharmaceutically acceptable salt/cocrystal thereof, or a solvate or the solvate of a salt/cocrystal thereof, in the manufacture of a medicament for the treatment of an inflammatory disease, a disease associated with hypersecretion of IFNα and/or interferons ("interferonopathies", especially type I interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, ulcerative colitis and/or Crohn's disease, wherein compound 1 is to be administered at a total daily dosage of at least 80 mg per day to 200 mg per day.

2. The use of compound 1 according to claim 1, wherein the total daily dosage of compound 1 is to be administered as a once per day dosage (q.d.).

3. The use of compound 1 according to claim 1 or 2, wherein compound 1 is to be administered at a total daily dosage of at least 90 mg per day to 200 mg per day, preferably 150 mg per day to 200 mg per day.

4. The use of compound 1 according to any of claims 1, 2 or 3, wherein compound 1 is to be administered at a total daily dosage of 90 mg per day, 100 mg per day, 110 mg per day, 120 mg per day, 125 mg per day, 130 mg per day, 140 mg per day, 150 mg per day, 160 mg per day, 170 mg per day, 175 mg per day, 180 mg per day, 190 mg per day or 200 mg per day.

5. The use of compound 1 according to any of claims 1, 2, 3 or 4, wherein compound 1 is to be administered at a total daily dosage of 90 mg per day or 150 mg per day or 200 mg per day.

6. The use of compound 1 according to any of claims 1, 2, 3, 4 or 5, wherein compound 1 is to be administered orally.

7. The use of compound 1 according to any of claims 1, 2, 3, 4, 5 or 6, wherein compound 1 is to be administered orally to a patient in a fed state.

8. The use of compound 1 according to any of claims 1, 2, 3, 4, 5, 6 or 7, further comprising avoiding or contraindicating or discontinuing concomitant use or co-administration one or more compounds that are CYP inhibitors and/or P-gp inhibitors.

9. The use of compound 1 according to any of claims 1, 2, 3, 4, 5, 6, 7 or 8, wherein the patient in need of therapy thereof is currently undergoing treatment with one or more compounds that are CYP inhibitors and/or P-gp inhibitors.

10. The use of compound 1 according to any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9, comprising discontinuing the use of or treatment of one or more compounds that are CYP inhibitors and/or P-gp inhibitors prior to or at the same time as starting the therapy.

11. The use of compound 1 according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, comprising discontinuing the use of or treatment of one or more compounds that are CYP inhibitors and/or P-gp inhibitors, at least 12 hours, preferably at least 24 hours, prior to commencing therapy thereof.

12. The use of compound 1 according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11, further comprising concomitant use or co-administration of a medicament from the same class or mechanism of action or known to be a suitable alternative medicament for the respective therapy thereof and that is a medicament or one or more compounds that are not CYP inhibitors and/or P-gp inhibitors, particularly not CYP3A4 inhibitors and/or not P-gp inhibitors, and more particularly not strong CYP3A4 inhibitors and/or strong not P-gp inhibitors.

13. The use of compound 1 according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, comprising discontinuing treatment with one or more compounds that are CYP inhibitors and/or P-gp inhibitors and commencing treatment with a medicament from the same class or mechanism of action or known to be a suitable alternative medicament for the respective therapy thereof and that is a medicament or one or more compounds that are not CYP inhibitors and/or P-gp inhibitors, particularly not CYP3A4 inhibitors and/or not P-gp inhibitors, and more particularly not strong CYP3A4 inhibitors and/or strong not P-gp inhibitors.

14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of compound 1 according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13.

15. A package or kit comprising:

    i. the compound according to Formula I or a pharmaceutically acceptable salt/cocrystal thereof, or a solvate or the solvate of a salt/cocrystal thereof, and

ii. a package insert, package label, instructions or other labelling comprising instructions to avoid or discontinue or contraindication of concomitant use or co-administration of one or more compounds that are CYP inhibitors and/or P-gp inhibitors.

16. A package or kit according to claim 15 further comprising one or more of the features according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16.

17. The use of compound 1 according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, or the kit according to claim 15 or 16, wherein the CYP inhibitor is a CYP3A4 inhibitor.

18. The use of compound 1 according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 13 or 17, or the kit according to claim 15, 16 or 17, wherein the CYP inhibitor is a CYP3A4 inhibitor and is one or more medicaments selected from Atazanavir, Boceprevir, Clarithromycin, Cobicistat, Conivaptan, Danoprevir, Darunavir, Delavirdine, Diltiazem, Elvitegravir, grapefruit juice, Idelalisib, Indinavir, Itraconazole, Ketoconazole, Lonafarnib, Lopinavir, Nefazodone, Nelfinavir, Nilotinib, Posaconazole, Ritonavir, Saquinavir, Stiripentol, Telithromycin, Tipranavir, Troleandomycin, Voriconazole, Aprepitant, Ciprofloxacin, Crizotinib, Cyclosporine, Dronedarone, Erythromycin, Fluconazole, Fluvoxamine, Imatinib, Verapamil, Chlorzoxazone, Cilostazol, Cimetidine, Fosaprepitant, Istradefylline, Ivacaftor, Lomitapide, Ranitidine, Ranolazine, Ticagrelor, (S)-omeprazole (esomeprazole)- high dose, ACT-178882, ACT-539313, Almorexant, AMD070, ANS-6637, Apararenone, ASP8477, Atorvastatin, AZD2327, Azithromycin, Berberine, Berotralstat, Bicalutamide, Brodalumab, Casopitant, Ceritinib, Clotrimazole, cranberry juice, Duvelisib, Entrectinib, Evacetrapid, Everolimus, Faldaprevir, Fedratinib, Fenebrutinib, FK1706, Fostamatinib, ginkgo (Ginkgo biloba), Glecaprevir / Pibrentasvir, Goldenseal (Hydrastis canadensis), Grazoprevir (ingredient of Zepatier), GSK2248761, Isavuconazole, Lapatinib, Larotrectinib, LCL161, Lefamulin, Letermovir, Lumateperone, Lurasidone, M100240, Mibefradil, Netupitant, obeticholic acid, Olaparib, Osilodrostat, Palbociclib, Pazopanib, Posaconazole, Propiverine, Ravuconazole, Ribociclib, Rimegepant, Roxithromycin, Rucaparib, Schisandra sphenanthera, Scutellarin (Breviscapine), Selpercatinib, Simeprevir, Suvorexant, Tabimorelin, Tacrolimus, Telaprevir, Teriflunomide, Tofisopam, Tucatinib, Verapamil and Voxelotor.

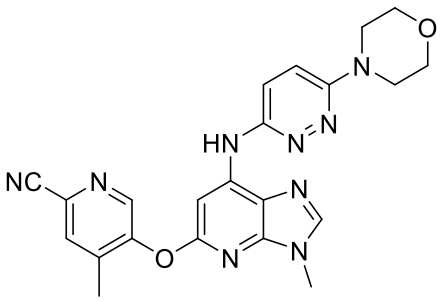
19. The use of compound 1 according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, 17 or 18, or the kit according to claim 15, 16, 17 or 18, wherein the CYP inhibitor is a strong CYP3A4 inhibitor and is one or more medicaments selected from Boceprevir, Clarithromycin, Cobicistat, Conivaptan, Danoprevir, Elvitegravir, Idelalisib, Indinavir, Itraconazole, Ketoconazole, Lonafarnib, Lopinavir, Nefazodone, Nelfinavir, Posaconazole, Ribociclib, Ritonavir, Saquinavir, Telaprevir, Telithromycin, Tipranavir, Troleandomycin, Voriconazole, Ceritinib, grapefruit juice, LCL161, Mibefradil and Tucatinib.

20. The use of compound 1 according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, 17, 18 or 19, or the kit according to claim 15, 16, 17, 18 or 19, wherein the P-gp inhibitor is one or more medicaments selected from Amiodarone, Azithromycin, Cannabidiol, Capmatinib, Carvedilol, Clarithromycin, Cobicistat, Cyclosporine, Daclatasvir, Diosmin, Dronedarone, Elagolix, Elagolix-Estradiol-Norethindrone, Eliglustat, Elexacaftor-tezacaftor-ivacaftor, Erythromycin, Flibanserin, Fostamatinib, Glecaprevir-pibrentasvir, Ketoconazole, Itraconazole, Ivacaftor, Ketoconazole, Lapatinib, Ledipasvir, Levoketoconazole, Neratinib, Ombitasvir-paritaprevir-ritonavir, Osimertinib, Propafenone, Quinidine, Quinine, Ranolazine, Ritonavir, Rolapitant, Roxithromycin, Simeprevir, Tamoxifen, Telithromycin, Tepotinib, Tezacaftor-Ivacaftor, Ticagrelor, Tucatinib, Velpatasvir, Vemurafenib, Verapamil, and Voclosporin.

21. The use of compound 1 according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, 17, 18, 19 or 20, or the kit according to claim 15, 16, 17, 18, 19 or 20, wherein the P-gp inhibitor is a strong P-gp inhibitor and is one or more medicaments selected from Amiodarone, Azithromycin, Clarithromycin, Erythromycin, Roxithromycin, Telithromycin, Cyclosporine, Itraconazole, Ketoconazole, Tamoxifen, and Verapamil.

22. The use of compound 1 according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, 17, 18, 19, 20 or 21, or the kit according to claim 15, 16, 17, 18, 19, 20 or 21, wherein the one or more compounds that are CYP inhibitors and/or P-gp inhibitors are combined CYP3A4/P-gp inhibitors, in particular Itraconazole.

23. A pharmaceutical unit dosage composition comprising 80 mg to 200 mg of compound 1:



(1)

or a pharmaceutically acceptable salt/cocrystal thereof, or a solvate or the solvate of a salt/cocrystal thereof, wherein the unit dosage form is suitable for oral administration up to a maximum total dosage of 200 mg of compound 1 per day.

24. The dosage form of claim 23 comprising from 90 mg to 200 mg of compound 1 in unit dosage form.

25. The dosage form of claim 23 or 24 comprising from 90 mg, 100 mg, 110 mg, 120 mg, 125 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 175 mg, 180 mg, 190 mg or 200 mg of compound 1 in unit dosage form.

26. The dosage form according to any of claims 23, 24 or 25, wherein the unit dosage is in a form selected from a liquid, a tablet, a capsule, or a gelcap.

27. The dosage form according to any of claims 23, 24, 25 or 26, wherein the unit dosage is in the form of a tablet or capsule.

28. Use of the dosage form according to any of claims 23, 24, 25, 26 or 27 in the manufacture of a medicament for the treatment of an inflammatory disease, a disease associated with hypersecretion of IFNα and/or interferons ("interferonopathies", especially type I interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, ulcerative colitis and/or Crohn's disease.