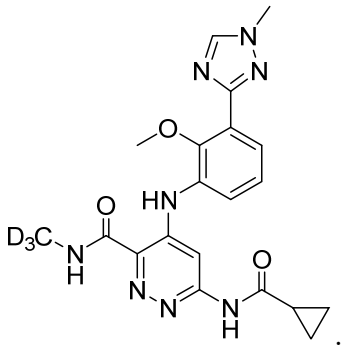
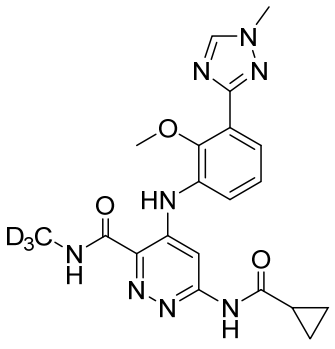
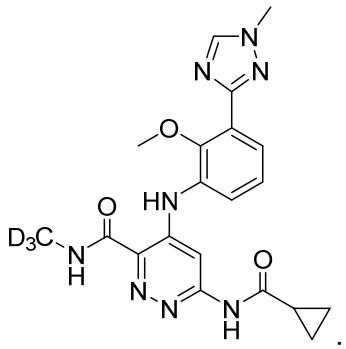


[0003b] In another aspect of the present disclosure, there is provided the use of a therapeutically effective amount of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or disorder responsive to the inhibition of phosphodiesterase type 4 (PDE4) in a subject, wherein said medicament is to be administered in combination with a therapeutically effective amount of the Tyk2 inhibitor , or a pharmaceutically acceptable salt thereof.

[0004] It has now been found that the combination of apremilast and the Tyk2 inhibitor 6-(cyclopropanecarboxamido)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)-N-(methyl-d3)pyridazine-3-carboxamide (BMS-986165) synergistically reduces pro-inflammatory cytokines expressed in a whole blood assay under conditions that stimulate Th17 cells. For example, there was over a 2-fold increase in the inhibition of IL-17F expression using the combination of 0.01 μM BMS-986165 and 1 μM apremilast when compared to the use of each drug alone. See e.g., **Table 5** in the Exemplification section.

Claims

1. A pharmaceutical composition comprising a therapeutically effective amount of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or a pharmaceutically acceptable thereof; and a therapeutically effective amount of the Tyk2 inhibitor



2. The pharmaceutical composition of Claim 1, wherein the composition is formulated for administration of from 1 mg/day to 15 mg/day, 1 mg/day to 14 mg/day, 2 mg/day to 14 mg/day, 2 mg/day to 12 mg/day, or 3 mg/day to 12 mg/day, of the Tyk inhbitor.

3. The pharmaceutical composition of Claim 1 or 2, wherein the composition is formulated for administration of 2 mg/day, 3 mg/day, 4 mg/day, 5 mg/day, 6 mg/day, 7 mg/day, 8 mg/day, 9 mg/day, 10 mg/day, 11 mg/day, or 12 mg/day of the Tyk inhibitor.

4. The pharmaceutical composition of any one of Claims 1 to 3, wherein the composition is formulated for administration of 6 mg/day of the Tyk inhibitor.

5. The pharmaceutical composition of any one of Claims 1 to 4, wherein the composition is formulated for administration of from 1 mg to 1000 mg per day, 5 mg to 500 mg per day, 10 mg to 200 mg per day, 10 mg to 100 mg per day, 40 mg to 100 mg per day, 20 mg to 40 mg per day, 0.1 mg to 10 mg per day, 0.5 mg to 5 mg per day, 1 mg to 20 mg per day, and 1 mg to 10 mg per day, 1 mg to 100 mg per day, 1 mg to 80 mg per day, 5 mg to 70 mg per day, and 10 mg to 60 mg per day of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or the pharmaceutically acceptable salt thereof.

6. The pharmaceutical composition of any one of Claims 1 to 5, wherein the composition is formulated for administration of from 10 mg to 60 mg per day of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or the pharmaceutically acceptable salt thereof.

7. The pharmaceutical composition of any one of Claims 1 to 6, wherein the composition is formulated for administration of 10 mg per day, 15 mg per day, 20 mg per day, 25 mg per day, 30 mg per day, 35 mg per day, 40 mg per day, 45 mg per day, 50 mg per day, 55 mg per day, or 60 mg per day of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or the pharmaceutically acceptable salt thereof.

8. The pharmaceutical composition of any one of Claims 1 to 7, wherein the composition is formulated for administration of 30 mg per day or 60 mg per day of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or the pharmaceutically acceptable salt thereof.

9. The pharmaceutical composition of any one of Claims 1 to 8, wherein the composition is formulated for administration of 30 mg once daily of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or the pharmaceutically acceptable salt thereof.

10. The pharmaceutical composition of any one of Claims 1 to 8, wherein the composition is formulated for administration of 30 mg twice daily of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or the pharmaceutically acceptable salt thereof.

11. The pharmaceutical composition of any one of Claims 1 to 6, wherein the composition is formulated for administration of from 10 mg to 40 mg per day of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or the pharmaceutically acceptable salt thereof.

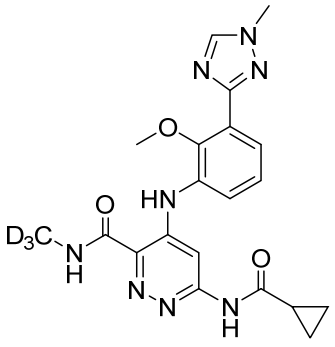
12. The pharmaceutical composition of any one of Claims 1 to 6, wherein the composition is formulated for administration of from 10 mg once or twice daily of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or the pharmaceutically acceptable salt thereof.

13. The pharmaceutical composition of any one of Claims 1 to 6, wherein the composition is formulated for administration of from 20 mg once or twice daily of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or the pharmaceutically acceptable salt thereof.

14. The pharmaceutical composition of any one of Claims 1 to 13, wherein the pharmaceutical composition is in the form of a tablet or a capsule.

15. The pharmaceutical composition of any one of Claims 1 to 14, wherein the pharmaceutical composition is formulated for extended release.

16. The pharmaceutical composition of any one of Claims 1 to 14, wherein the pharmaceutical composition is formulated for immediate release.

17. Use of a therapeutically effective amount of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or disorder responsive to the inhibition of phosphodiesterase type 4 (PDE4) in a subject, wherein said medicament is to be administered in combination with a therapeutically effective amount of the Tyk2 inhibitor , or a pharmaceutically acceptable salt thereof.

18. The use of Claim 17, wherein the effective amount of the Tyk2 inhibitor, or the pharmaceutically acceptable salt ranges from 0.1 mg/day to 250 mg/day.

19. The use of Claim 17 or 18, wherein the effective amount of the Tyk2 inhibitor, or the pharmaceutically acceptable salt ranges from 2 mg/day to 14 mg/day.

20. The use of any one of Claims 17 to 19, wherein the effective amount of the Tyk2 inhibitor is 4 mg/day, 6 mg/day, or 12 mg/day.

21. The use of any one of Claims 17 to 20, wherein the N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide is greater than 95% stereomerically pure.

22. The use of any one of Claims 17 to 21, wherein the effective amount of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or the pharmaceutically acceptable salt thereof, ranges from 0.5 mg to 1000 mg per day.

23. The use of any one of Claims 17 to 22, wherein the effective amount of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or the pharmaceutically acceptable salt thereof, ranges from 10 mg to 60 mg per day.

24. The use of any one of Claims 17 to 23, wherein the effective amount of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or the pharmaceutically acceptable salt thereof, is 20 mg per day, 40 mg per day, or 60 mg per day.

25. The use of any one of Claims 17 to 23, wherein the effective amount of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or the pharmaceutically acceptable salt thereof, is 30 mg per day or 60 mg per day.

26. The use of any one of Claims 17 to 23, wherein the effective amount of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide is 30 mg administered once daily.

27. The use of any one of Claims 17 to 23, wherein the effective amount of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide is 30 mg administered twice daily.

28. The use of any one of Claims 17 to 27, wherein the N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide is formulated as part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

29. The use of any one of Claims 17 to 28, wherein the N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide is to be administered orally.

30. The use of any one of Claims 17 to 29, wherein the N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide is to be administered orally in the form of a tablet or a capsule.

31. The use of any one of Claims 17 to 30, wherein the disease or disorder is selected from a viral, genetic, inflammatory, allergic, and autoimmune disease.

32. The use of any one of Claims 17 to 31, wherein the disease or disorder is selected from chronic obstructive pulmonary disease, asthma, chronic pulmonary inflammatory disease, hyperoxic alveolar injury, inflammatory skin disease, psoriasis, psoriatic arthritis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, atopic dermatitis, rheumatoid spondylitis, depression, osteoarthritis, contact dermatitis, ankylosing spondylitis, lupus, lupus nephritis, cutaneous lupus erythematosus, systemic lupus erythrematosus, erythema nodosum leprosum, Sjögren's syndrome, inflammatory bowel disease, Crohn's Disease, Behçet's Disease, and ulcerative colitis.

33. The use of any one of Claims 17 to 32, wherein the disease or disorder is selected from psoriasis and psoriatic arthritis.

34. The use of any one of Claims 17 to 33, wherein the disease or disorder is plaque psoriasis or moderate to severe plaque psoriasis.