COMBINATION THERAPIES COMPRISING APREMILAST AND TYK2 INHIBITORS

RELATED APPLICATIONS

[0001] This application claims priority to International Application No. PCT/US2019/029772, filed April 30, 2019, the entire contents of which are incorporated herein by reference.

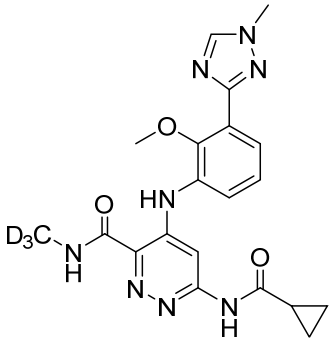
BACKGROUND

[0002] N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide (apremilast), marketed as Otezla®, is a phosphodiesterase type 4 (PDE4) inhibitor currently approved for treating both moderate to severe plaque psoriasis and active psoriatic arthritis. PDE4 inhibition by apremilast elevates cyclic adenosine monophosphate (cAMP) levels in immune cells. This in turn down-regulates inflammatory responses by reducing the expression of pro-inflammatory mediators such as TNF-α, IL-23, IL-17, and other inflammatory cytokines, and increases the production of anti-inflammatory mediators. Studies have shown that a 75% reduction in plaque psoriasis is achievable in some patients in as little as just over 4 months of treatment.

[0003] Tyrosine kinase 2 (Tyk2), an intracellular signaling enzyme, activates signal transducer and activator of transcription (STAT)–dependent gene expression and functional responses of IL-12, IL-23, and type I and III interferon receptors. Amongst other conditions, tyrosine kinase inhibitors (TKIs) have recently gained attention as effective agents for treating psoriasis and related conditions. The TKI inhibitor BMS-986165, for example, recently showed positive results in phase 2 clinical trials in subjects with moderate to severe plaque psoriasis. See Kim Papp, M.D., Phase 2 Trial of Selective Tyrosine Kinase 2 Inhibition in Psoriasis, The New England Journal of Medicine, Sept. 12, 2018.

SUMMARY

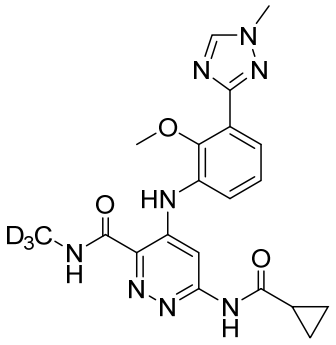
[0003a] In one aspect of the present disclosure, there is provided the use of a therapeutically effective amount of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a 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 wherein the disease or disorder is selected from a viral, genetic, inflammatory, allergic, and autoimmune disease.

[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. 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, wherein the disease or disorder is selected from a viral, genetic, inflammatory, allergic, and autoimmune disease.

2. The use of Claim 1, wherein the effective amount of the Tyk2 inhibitor, or the pharmaceutically acceptable salt ranges from 0.1 mg/day to 250 mg/day.

3. The use of Claim 1 or 2, wherein the effective amount of the Tyk2 inhibitor, or the pharmaceutically acceptable salt ranges from 2 mg/day to 14 mg/day.

4. The use of any one of Claims 1 to 3, wherein the effective amount of the Tyk2 inhibitor is 4 mg/day, 6 mg/day, or 12 mg/day.

5. The use of any one of Claims 1 to 4, 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.

6. The use of any one of Claims 1 to 5, 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.

7. The use of any one of Claims 1 to 6, 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.

8. The use of any one of Claims 1 to 7, 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.

9. The use of any one of Claims 1 to 7, 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.

10. The use of any one of Claims 1 to 7, 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.

11. The use of any one of Claims 1 to 7, 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.

12. The use of any one of Claims 1 to 11, 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.

13. The use of any one of Claims 1 to 12, 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.

14. The use of any one of Claims 1 to 13, 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.

15. The use of any one of Claims 1 to 14, 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.

16. The use of any one of Claims 1 to 15, wherein the disease or disorder is selected from psoriasis and psoriatic arthritis.

17. The use of any one of Claims 1 to 16, wherein the disease or disorder is plaque psoriasis or moderate to severe plaque psoriasis.