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.

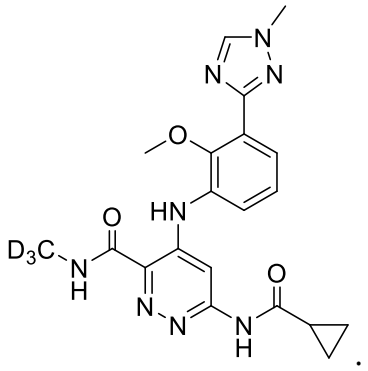
BACKGROUND

[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

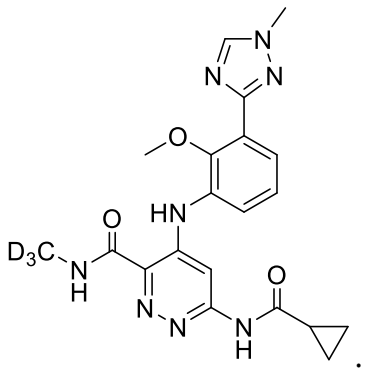
[0003a] In a first aspect, the present disclosure refers to a pharmaceutical composition comprising a therapeutically effective amount of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide, or a pharmaceutically acceptable thereof; and a therapeutically effective amount of the Tyk2 inhibitor



[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 about 1 mg/day to about 15 mg/day, about 1 mg/day to about 14 mg/day, about 2 mg/day to about 14 mg/day, about 2 mg/day to about 12 mg/day, or about 3 mg/day to about 12 mg/day, of the Tyk inhbitor.

3. The pharmaceutical composition of any one of Claim 1 or 2, wherein the composition is formulated for administration of about 2 mg/day, about 3 mg/day, about 4 mg/day, about 5 mg/day, about 6 mg/day, about 7 mg/day, about 8 mg/day, about 9 mg/day, about 10 mg/day, about 11 mg/day, or about 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 about 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 about 1 mg to about 1000 mg per day, about 5 mg to about 500 mg per day, about 10 mg to about 200 mg per day, about 10 mg to about 100 mg per day, about 40 mg to about 100 mg per day, about 20 mg to about 40 mg per day, about 0.1 mg to about 10 mg per day, about 0.5 mg to about 5 mg per day, about 1 mg to about 20 mg per day, and about 1 mg to about 10 mg per day, about 1 mg to about 100 mg per day, about 1 mg to about 80 mg per day, about 5 mg to about 70 mg per day, and about

10 mg to about 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 about 10 mg to about 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 about 10 mg per day, about 15 mg per day, about 20 mg per day, about 25 mg per day, about 30 mg per day, about 35 mg per day, about 40 mg per day, about 45 mg per day, about 50 mg per day, about 55 mg per day, or about 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 about 30 mg per day or about 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 about 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 about 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 about 10 mg to about 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 about 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 about 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.