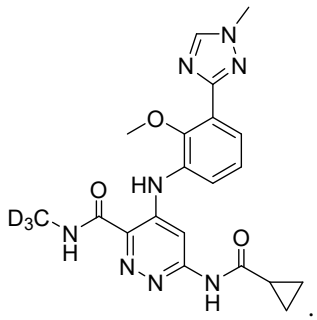
[0004] It was also found that the combination of apremilast and BMS-986165 elicit complementary effects against certain pro-inflammatory cytokines. BMS-986165, for example, increased TNF-α and GM-CSF cytokine in whole blood assay, while apremilast inhibited the production of these cytokines. See e.g., **Table 5** where the % control for 1 μM apremilast was 10.7 and the % control for 0.01 μM BMS-986165 was 143.1 against TNF-α. When administered in combination, however, apremilast corrected the deficiency of BMS-986165 thereby producing a complementary effect of 13.5% inhibition against TNF-α. See e.g., **Table 5**. This trend was also established at 0.1 μM concentrations of BMS-986165 and against cytokine GM-CSF. See e.g., **Table 5**. These results illustrate the synergistic and complementary pharmacological effects of BMS-986165 and apremilast.

[0005] In addition to whole blood assay, the combination of BMS-986165 and apremilast elicit complementary effects against certain pro-inflammatory cytokines in LPS stimulated PBMCs as well. BMS-986165 increased IL-23, IL-12 and TNF-α, while apremilast inhibited the production of these cytokines. See e.g., **Table 6** in the Exemplification section. These results further support the advantage of combining BMS-986165 and apremilast in treatment of Th17 related diseases.

[0006] Provided herein, therefore are methods of treating diseases or disorders responsive to the inhibition of PDE4 in a subject using an effective amount of apremilast, or a pharmaceutically acceptable salt thereof, and an effective amount of a Tyk2 inhibitor such as BMS-986165. Such diseases and disorders include e.g., inflammatory diseases such as psoriasis, psoriatic arthritis, and ulcerative colitis.

[0007] Also provided herein are pharmaceutical compositions comprising an effective amount of apremilast, or a pharmaceutically acceptable salt thereof, and an effective amount of a Tyk2 inhibitor such as BMS-986165.

[0007a] In one 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

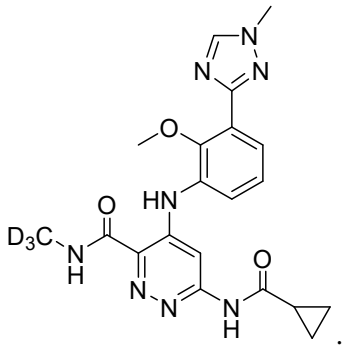


BRIEF DESCRIPTION OF THE DRAWINGS

[0008] **FIG. 1** illustrates interleukin-17a (IL-17a) cytokine production (percent of control) by apremilast and BMS-986165 in anti-CD3/anti-CD28 (Th0) or anti-CD3/anti-CD28, IL-1β, IL-6 and IL-23 (Th17) stimulated whole blood – TruCulture® tube assay.

[0009] **FIG. 2** illustrates interleukin-17A (IL-17A) cytokine production by apremilast and BMS-986165 in anti-CD3/anti-CD28 (Th0) or anti-CD3/anti-CD28, IL-1β, IL-6 and IL-23 (Th17) stimulated whole blood – TruCulture® tube assay.

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 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.