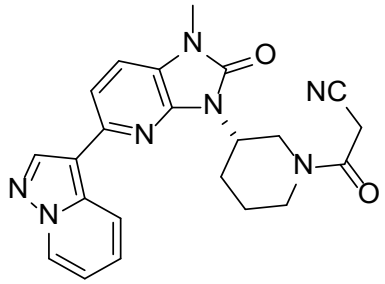
CLAIMS

1. A pharmaceutical formulation comprising:

(a) (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)piperidin-1-yl)-3-oxopropanenitrile:



Compound I,

or a pharmaceutically acceptable salt thereof;

(b) magnesium stearate; and

(c) lactose.

2. The pharmaceutical formulation of claim 1, wherein the formulation comprises:

(a) 0.5-11.0 weight percent Compound I, or a pharmaceutically acceptable salt thereof;

(b) 0.5-2.0 weight percent magnesium stearate; and

(c) 87.0-99.0 weight percent lactose.

3. The pharmaceutical formulation of claim 1 or claim 2, wherein the formulation comprises:

(a) about 1.1 weight percent Compound I, or a pharmaceutically acceptable salt thereof;

(b) about 1.0 weight percent magnesium stearate; and

(c) about 97.9 weight percent lactose.

4. The pharmaceutical formulation of claim 1 or claim 2, wherein the formulation comprises:

(a) about 10.3 weight percent Compound I, or a pharmaceutically acceptable salt thereof;

(b) about 1.2 weight percent magnesium stearate; and

(c) about 88.5 weight percent lactose.

5. The pharmaceutical formulation of any one of claims 1-4, wherein the content uniformity of the pharmaceutical formulation of Compound I has a percent relative standard deviation (RSD) less than or equal to about 5%.

6. The pharmaceutical formulation of any one of claims 1-5, wherein the formulation is suitable for aerosolized delivery to a subject.

7. The pharmaceutical formulation of claim 6, wherein, when aerosolized, the mass median aerodynamic diameter (MMAD) is less than or equal to about 5.0 μm.

8. The pharmaceutical formulation of claim 6 or claim 7, wherein, when aerosolized, the fine particle fraction (FPF) of Compound I is greater than or equal to about 60%.

9. The pharmaceutical formulation of any one of claims 6-8, wherein, when a capsule containing about 1.0-3.0 mg of Compound I is aerosolized, the fine particle mass (FPM) of Compound I is 900-1800 μg.

10. The pharmaceutical formulation of any one of claims 6-9, wherein, when a capsule containing about 3.0-5.0 mg of Compound I is aerosolized, the FPM of Compound I is 1750-2350 μg.

11. The pharmaceutical formulation of any one of claims 6-10, wherein, when aerosolized, the delivered dose of Compound I is at least about 80% of the target dose.

12. The pharmaceutical formulation of any one of claims 6-11, wherein Compound I is a polymorph form having the following diffraction angles (2Theta) based on cupric Kα1:

at approximately 8.25°;
at approximately 13.25°;
at approximately 15.40°;
at approximately 17.65°; and
at approximately 25.39° (Form II).

13. Use of the pharmaceutical formulation of any one of claims 1-12 in the manufacture of a medicament for treating asthma, COPD, or an inflammatory condition associated with eosinophilic inflammation or non-eosinophilic inflammation in a subject in need thereof,

wherein the subject is to be administered the pharmaceutical formulation of any one of claims 1-12.

14. The use of claim 13, wherein the inflammatory condition associated with eosinophilic inflammation or non-eosinophilic inflammation is eosinophilic asthma, nasal polyposis, rhinitis, pulmonary fibrotic disease, interstitial lung disease, or pulmonary hypertension.

15. The use of claim 13 or 14, wherein the subject's FeNO concentration is reduced to at least about 35 parts per billion (ppb).

16. The use of claim 15, wherein the subject's FeNO concentration is reduced to at least about 30 ppb.

17. The use of claim 15 or claim 16, wherein the subject's FeNO concentration is reduced to at least about 25 ppb.

18. The use of any one of claims 15-17, wherein the subject's FeNO concentration is reduced to at least about 20 ppb.

19. The use of any one of claims 15-18, wherein the subject's FeNO concentration is reduced relative to the subject's pre-administration FeNO concentration.

20. The use of claim 13 or 14, wherein the subject's FeNO concentration is reduced by at least about 20%.

21. The use of claim 20, wherein the subject's FeNO concentration is reduced by at least about 30%.

22. The use of claim 20 or claim 21, wherein the subject's FeNO concentration is reduced by at least about 40%.

23. The use of any one of claims 20-22, wherein the subject's FeNO concentration is reduced by at least about 50%.

24. The use of any one of claims 20-23, wherein the subject's FeNO concentration is reduced by at least about 60%.

25. The use of any one of claims 20-24, wherein the subject's FeNO concentration is reduced by at least about 65%.

26. The use of any one of claims 20-25, wherein the subject's FeNO concentration is reduced by at least about 80%.

27. The use of any one of claims 20-26, wherein the subject's FeNO concentration is reduced relative to both the subject's pre-administration FeNO concentration and the FeNO concentration upon placebo treatment.

28. The use of any one of claims 13-27, wherein the formulation is to be administered as a single capsule.

29. The use of any one of claims 13-28, wherein the subject has moderate to severe asthma.

30. The use of claim 29, wherein the subject's moderate to severe asthma is characterized by a Th2-high phenotype.

31. A method for the preparation of a dry powder pharmaceutical formulation comprising (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)piperidin-1-yl)-3-oxopropanenitrile (Compound I), wherein the method comprises:

(a) combining (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)piperidin-1-yl)-3-oxopropanenitrile (Compound I), or a pharmaceutically acceptable salt thereof with magnesium stearate to form a first preblend;

(b) combining magnesium stearate and lactose to form a second preblend;

(c) combining the first preblend with the second preblend;

(d) co-milling the product formed in step (c); and

(e) blending the product formed in step (d) to form the formulation.

32. The method of claim 31, wherein a portion of the second preblend is co-milled prior to step (c).

33. The method of claim 31 or claim 32, wherein the first preblend is 4.0-14.0 weight percent magnesium stearate.

34. The method of any one of claims 31-33, wherein the second preblend is 0.4-1.1 weight percent magnesium stearate.

35. A method for the preparation of a dry powder pharmaceutical formulation comprising (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)piperidin-1-yl)-3-oxopropanenitrile, wherein the method comprises:

(a) combining (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)piperidin-1-yl)-3-oxopropanenitrile, or a pharmaceutically acceptable salt thereof with magnesium stearate to form a first preblend;

(b) combining magnesium stearate and lactose to form a second preblend;

(c) blending the first and second preblends together to form the formulation; and

(d) resting the formulation for 10-120 hours.

36. The method of claim 35, wherein the resting step (d) is 15-65 hours.

37. The method of claim 35 or claim 36, wherein the first and second preblends are each individually co-milled prior to step (c).

38. The method of any one of claims 35-37, wherein the (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)piperidin-1-yl)-3-oxopropanenitrile and magnesium stearate preblend is 4.0-14.0 weight percent magnesium stearate.

39. The method of any one of claims 35-38, wherein the (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridin-3-yl)-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)piperidin-1-yl)-3-oxopropanenitrile and magnesium stearate preblend is 4.0-8.0 weight percent magnesium stearate.

40. The method of any one of claims 35-39, wherein the lactose and magnesium stearate preblend is 0.4-1.1 weight percent magnesium stearate.

41. The method of any one of claims 35-40, wherein the lactose and magnesium stearate preblend is 0.8-1.1 weight percent magnesium stearate.

42. The method of any one of claims 35-41, wherein the method comprises the additional step of:

(e) filling a capsule with the formulation.

43. The dry powder pharmaceutical formulation formed by the method of any one of claims 31-42.