COMPOUNDS FOR TREATING MDS-ASSOCIATED ANEMIAS AND OTHER CONDITIONS

Related Applications

[0001] This application claims priority to U.S. Provisional Application No. 63/280,069, filed November 16, 2021 and U.S. Provisional Application No. 63/357,240, filed June 30, 2022, each of which are incorporated herein in their entirety.

BACKGROUND

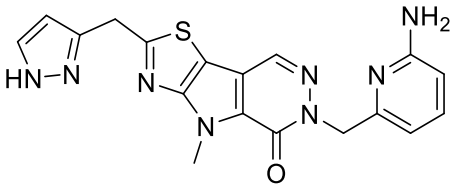
[0002] Myelodysplastic syndromes (MDS) are a heterogeneous group of rare hematological malignancies characterized by dysfunctional hematopoiesis, progressive cytopenia, and an increased risk of progression to acute myeloid leukemia (AML). MDS occurs when the blood-forming cells in the bone marrow become abnormal (dysplastic) and have problems making new blood cells. Many of the blood cells formed by the bone marrow cells often die or are destroyed by the body, thus leaving the individual without enough normal blood cells. Although different cell types are affected by this phenomenon, the most common finding in MDS is a shortage of red blood cells (anemia). However, hemolytic anemia has also been found to occur, albeit rarely, in patients suffering from MDS. See, for example, Leukemia Research Reports, Vol. 5, 2016, pp 23-26.

[0003] With an average age at diagnosis of 71 years, MDS patients can be severely impacted by chronically low levels of hemoglobin. This can lead to fatigue, worsening cardiopulmonary function, increased falls, and significant cognitive decline. As such, treatment of anemia is essential for overall health and quality of life. Currently, transfusions of packed red blood cells (PRBC) is the standard of care for MDS-associated anemia. The problem with transfusion dependent MDS-associated anemia patients, however, is that these patients are at a higher risk of iron overload and transfusion reactions and report a decreased quality of life.

[0004] Alternative approaches for treating MDS-associated anemias are therefore needed.

SUMMARY

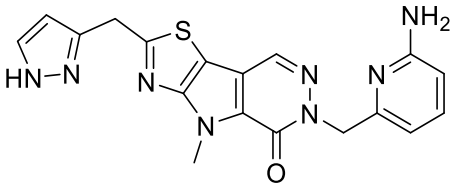
[004a] In a first aspect of the present disclosure, there is provided a use of a compound having the structural formula:



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or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating anemia associated with myelodysplastic syndrome (MDS) in a subject suffering from MDS.

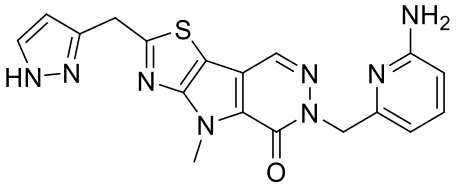
[004b] In another aspect of the present disclosure, there is provided a use of a compound having the structural formula:



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or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating hemolytic anemia associated with myelodysplastic syndrome (MDS) in a subject suffering from MDS.

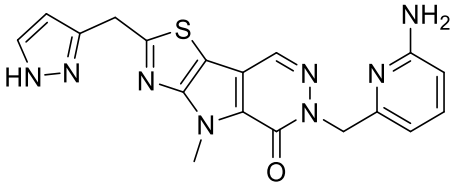
[004c] In yet another aspect of the present disclosure, there is provided a use of a compound having the structural formula:



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or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for increasing the hemoglobin level in a subject suffering from myelodysplastic syndrome (MDS).

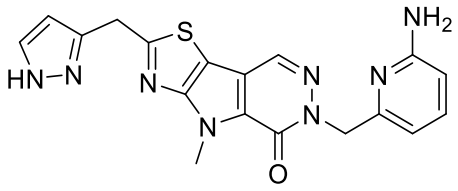
[004d] In a further aspect of the present disclosure, there is provided a use of a compound having the structural formula:



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or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating acquired PK deficiency (PKD) in a subject suffering from myelodysplastic syndrome (MDS).

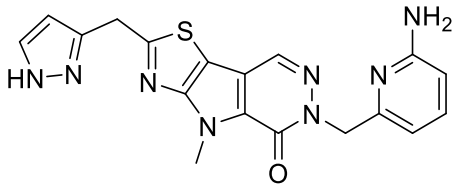
[004e] In another aspect of the present disclosure, there is provided a use of a compound having the structural formula:



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or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating anemia associated with acquired PK deficiency (PKD) in a subject suffering from myelodysplastic syndrome (MDS).

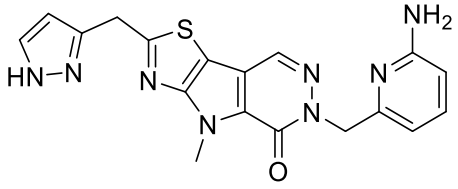
[004f] In yet another aspect of the present disclosure, there is provided a use of a compound having the structural formula:



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or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cytopenia in a subject suffering from myelodysplastic syndrome (MDS).

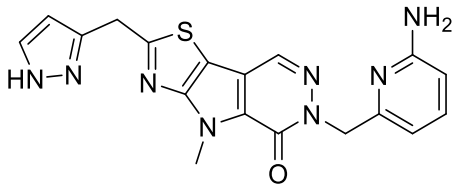
[004g] In a further aspect of the present disclosure, there is provided a use of a compound having the structural formula:



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or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating anemia associated with low-risk myelodysplastic syndrome (MDS) in a subject suffering from MDS, wherein an amount that is equivalent to 2 mg daily, 3 mg daily, or 5 mg daily of the compound is to be orally administered to the subject daily, and wherein the subject is classified as being non-transfused, of low transfusion burden, or of high transfusion burden prior to administration.

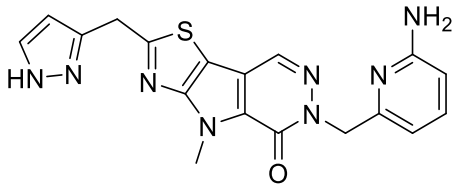
[004h] In another aspect of the present disclosure, there is provided a use of a compound having the structural formula



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or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or disorder associated with mitochondrial dysfunction in a subject in need thereof.

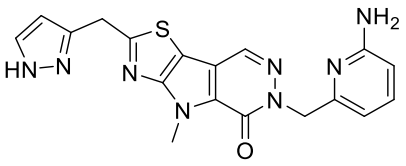
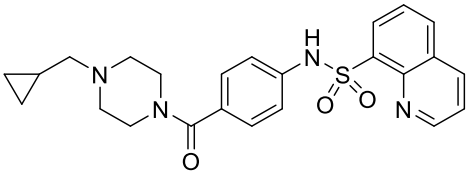
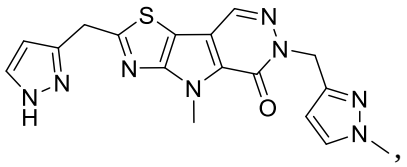
[004i] In yet another aspect of the present disclosure, there is provided a use of a compound having the structural formula



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or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or disorder associated with ineffective erythropoiesis in a subject in need thereof.

[0005] It has now been found that certain activators of pyruvate kinase may also be effective in treating MDS-associated anemia, particularly anemia associated with very low-risk, low-risk and intermediate-risk MDS. These activators include those having the following structure formulae:



, and

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as well as pharmaceutically acceptable salts thereof. In one example, the disclosed pyruvate kinase activators have been found to increase hemoglobin levels, decrease reticulocyte count, and/or improve red blood cell (RBC) functionality in animal models of MDS. See, e.g., **FIGs 1** and **2**.

[0006] Provided herein, therefore, are methods of treating MDS-associated anemias and other conditions in a subject, comprising administering to the subject one or more of the disclosed pyruvate kinase activators, or a pharmaceutically acceptable salt or composition thereof.

[0007] Also provided are methods for increasing the hemoglobin level in a subject suffering from MDS, comprising administering to the subject one or more of the disclosed pyruvate kinase activators, or a pharmaceutically acceptable salt or composition thereof.

[0008] Also provided are methods of treating acquired PK deficiency (PKD) in a subject suffering from MDS, comprising administering to the subject one or more of the disclosed pyruvate kinase activators, or a pharmaceutically acceptable salt or composition thereof.

[0009] Also provided are methods of treating anemias associated with acquired PKD in a subject suffering from MDS, comprising administering to the subject one or more of the disclosed pyruvate kinase activators, or a pharmaceutically acceptable salt or composition thereof.

[0010] Also provided are methods of treating cytopenia in a subject suffering from MDS, comprising administering to the subject one or more of the disclosed pyruvate kinase activators, or a pharmaceutically acceptable salt or composition thereof.

[0011] Further provided are methods of treating hemolytic anemia in a subject suffering from MDS, comprising administering to the subject one or more of the disclosed pyruvate kinase activators, or a pharmaceutically acceptable salt or composition thereof.

[0012] Further provided are methods of treating ineffective erythropoiesis in a subject suffering from MDS, comprising administering to the subject one or more of the disclosed pyruvate kinase activators, or a pharmaceutically acceptable salt or composition thereof.

[0013] Further provided are methods of reducing disease progression in subjects suffering from MDS. In some examples, administering to the subject one or more of the disclosed pyruvate kinase activators, or a pharmaceutically acceptable salt or composition thereof reduces inflammation within the subject's bone marrow thereby reducing disease progression in the subject.

[0014] Still further provided are methods of treating diseases related to mitochondrial dysfunction in a subject in need thereof, comprising administering to the subject one or more of the disclosed pyruvate kinase activators, or a pharmaceutically acceptable salt or composition thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] **FIGS. 1A-D** show the hemoglobin level effect in an MDS-associated anemia mouse model following administration of mitapivat in chow for 6 weeks (**FIG. 1A**), 8 weeks (**FIG. 1B**), 12 weeks (**FIG. 1C**), and 18 weeks (**FIG. 1D**).

[0016] **FIGS. 2A-D** show hematological parameter results for red blood cell count (RBC) (**FIG. 2A**), reticulocyte percentage (**FIG. 2B**), reticulocyte concentration (**FIG. 2C**), and hematocrit percentage (**FIG. 2D**) from an MDS-associated anemia mouse model following administration of mitapivat.

[0017] **FIG. 3** shows a multi-phase clinical trial design for the treatment of MDS-associated anemia.

[0018] **FIG. 4** shows an overview of a Phase 2a study design with Compound 1 in subjects with anemia due to lower-risk myelodysplastic syndromes (LR-MDS).

[0019] **FIG. 5** shows an overview of a Phase 2b study design with Compound 1 in subjects with anemia due to lower-risk myelodysplastic syndromes (LR-MDS).

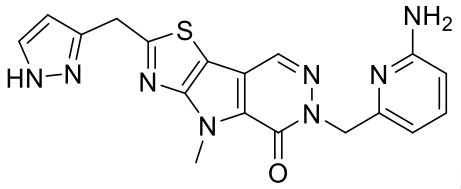
[0020] **FIGs. 6A-E** show flow cytometry data of bone marrow aspirates from $Polg^{D257A}$ mice following treatment with Compound 1.

[0021] **FIGs. 7A-D** show flow cytometry data of bone marrow aspirates from NHD13 mice following treatment with mitapivat or Compound 1.

[0022] **FIGs. 8A-C** show hematological parameter results for hemoglobin (**FIG. 8A**), RBC (**FIG. 8B**), and reticulocyte concentration (**FIG. 8C**) from NHD13 mice following treatment with mitapivat or Compound 1.

Listing of Claims:

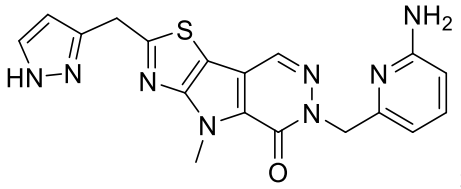
1. Use of a compound having the structural formula:



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or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating anemia associated with myelodysplastic syndrome (MDS) in a subject suffering from MDS.

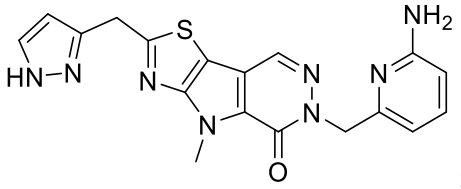
2. Use of a compound having the structural formula:



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or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating hemolytic anemia associated with myelodysplastic syndrome (MDS) in a subject suffering from MDS.

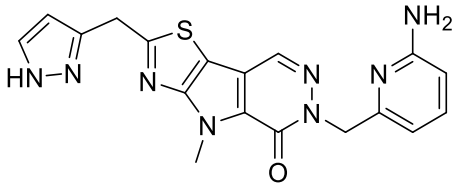
3. Use of a compound having the structural formula:



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or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for increasing the hemoglobin level in a subject suffering from myelodysplastic syndrome (MDS).

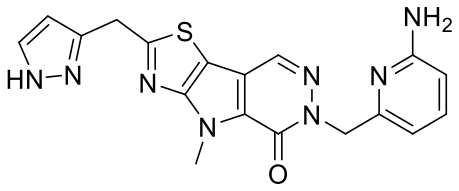
4. Use of a compound having the structural formula:



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or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating acquired PK deficiency (PKD) in a subject suffering from myelodysplastic syndrome (MDS).

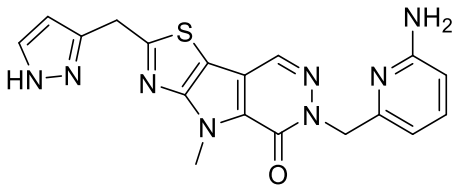
5. Use of a compound having the structural formula:



;

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating anemia associated with acquired PK deficiency (PKD) in a subject suffering from myelodysplastic syndrome (MDS).

6. Use of a compound having the structural formula:



;

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cytopenia in a subject suffering from myelodysplastic syndrome (MDS).

7. The use of any one of claims 1 to 6, wherein the hemoglobin level of the subject improves over a period of at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 14 weeks, at least 16 weeks, at least 18 weeks, or at least 20 weeks during treatment.

8. The use of any one of claims 1 to 6, wherein the hemoglobin level of the subject increases from baseline from week 1 through week 20, from week 1 through week 18, from week 1 through week 16, from week 4 through week 20, from week 4 through

week 18, from week 4 through week 16, from week 6 through week 20, from week 6 through week 18, from week 6 through week 16, from week 8 through week 20, from week 8 through week 18, from week 8 through week 16, from week 10 through week 20, from week 10 through week 18, or from week 10 through week 16 during treatment.

9. The use of any one of claims 1 to 8, wherein the hemoglobin level of the subject increases from baseline from week 8 through week 16 during treatment.

10. The use of any one of claims 1 to 9, wherein the hemoglobin level of the subject increases from baseline at ≥ 2, ≥ 3, ≥ 4, ≥ 5, or ≥ 6 consecutive time points from week 1 through week 20, from week 1 through week 18, from week 1 through week 16, from week 4 through week 20, from week 4 through week 18, from week 4 through week 16, from week 6 through week 20, from week 6 through week 18, from week 6 through week 16, from week 8 through week 20, from week 8 through week 18, from week 8 through week 16, from week 10 through week 20, from week 10 through week 18, or from week 10 through week 16 during treatment.

11. The use of any one of claims 1 to 10, wherein the hemoglobin level of the subject increases from baseline at ≥ 2 consecutive time points from week 8 through week 16 during treatment.

12. The use of any one of claims 1 to 11, wherein the hemoglobin level of the subject increases from baseline by ≥ 1.0 g/dL during treatment.

13. The use of any one of claims 1 to 12, wherein the hemoglobin level of the subject increases from baseline by ≥ 1.5 g/dL during treatment.

14. The use of any one of claims 1 to 13, wherein the hemoglobin level of the subject increases from baseline by ≥ 2.0 g/dL during treatment.

15. The use of any one of claims 1 to 14, wherein the subject becomes transfusion independent during treatment.

16. The use of any one of claims 1 to 15, wherein the subject is classified as having a low transfusion burden prior to treatment.

17. The use of any one of claims 1 to 16, wherein the subject becomes transfusion independent for ≥ 1 consecutive week, for ≥ 2 consecutive weeks, for ≥ 3 consecutive weeks, for ≥ 4 consecutive weeks, for ≥ 5 consecutive weeks, for ≥ 6 consecutive weeks, for ≥ 7 consecutive weeks, for ≥ 8 consecutive weeks, for ≥ 9 consecutive weeks, or for ≥ 10 consecutive weeks during treatment.

18. The use of any one of claims 1 to 17, wherein the subject becomes transfusion independent for ≥ 8 consecutive weeks during treatment.

19. The use of any one of claims 1 to 18, wherein the total transfused red blood cell (RBC) units of the subject are reduced from baseline by ≥ 10%, ≥ 20%, ≥ 30%, ≥ 40%, ≥ 50%, ≥ 60%, ≥ 70%, or ≥ 80% during treatment.

20. The use of any one of claims 1 to 19, wherein the total transfused red blood cell (RBC) units of the subject are reduced from baseline by ≥ 50% during treatment.

21. The use of any one of claims 1 to 20, wherein the total transfused red blood cell (RBC) units of the subject are reduced from baseline by ≥ 50% over a period of ≥ 1 consecutive week, ≥ 2 consecutive weeks, ≥ 3 consecutive weeks, ≥ 4 consecutive weeks, ≥ 5 consecutive weeks, ≥ 6 consecutive weeks, ≥ 7 consecutive weeks, ≥ 8 consecutive weeks, ≥ 9 consecutive weeks, or ≥ 10 consecutive weeks during treatment.

22. The use of any one of claims 1 to 21, wherein the total transfused red blood cell (RBC) units of the subject are reduced from baseline by ≥ 50% over a period of ≥ 8 consecutive weeks during treatment

23. The use of any one of claims 1 to 22, wherein the MDS is low risk MDS (as characterized by the Revised International Prognostic Scoring System (IPSS-R) for MDS).

24. The use of any one of claims 1 to 22, wherein the MDS is very low risk MDS (as characterized by the Revised International Prognostic Scoring System (IPSS-R) for MDS).

25. The use of any one of claims 1 to 22, wherein the MDS is intermediate risk MDS (as characterized by the Revised International Prognostic Scoring System (IPSS-R) for MDS).

26. The use of any one of claims 1 to 25, wherein the subject is male.

27. The use of any one of claims 1 to 25, wherein the subject is female.

28. The use of any one of claims 1 to 27, wherein a therapeutically effective amount of 2 mg, 3 mg, or 5 mg of the compound is to be administered daily to the subject.

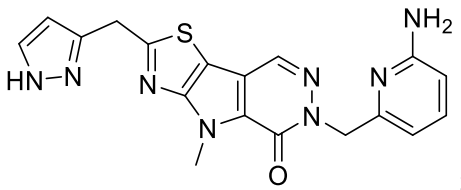
29. The use of any one of claims 1 to 28, wherein a therapeutically effective amount of 2 mg QD, 3 mg QD, or 5 mg QD of the compound is to be administered to the subject.

30. The use of any one of claims 1 to 29, wherein the compound or pharmaceutically acceptable salt is to be administered orally.

31. The use of any one of claims 1 to 30, wherein the compound or pharmaceutically acceptable salt are in the form of a tablet or one or more granules.

32. The use of any one of claims 1 to 31, wherein the compound or pharmaceutically acceptable salt are in the form of one or more granules.

33. Use of a compound having the structural formula:



;

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating anemia associated with low-risk myelodysplastic syndrome (MDS) in a

subject suffering from MDS, wherein an amount that is equivalent to 2 mg daily, 3 mg daily, or 5 mg daily of the compound is to be orally administered to the subject daily, and wherein the subject is classified as being non-transfused, of low transfusion burden, or of high transfusion burden prior to administration.

34. The use of Claim 33, wherein the subject is classified as having a low transfusion burden prior to treatment.

35. The use of Claim 34, wherein the compound or pharmaceutically acceptable salt is to be administered to the subject for a period of 16 weeks.

36. The use of Claim 34 or 35, wherein the subject becomes transfusion independent for ≥ 8 consecutive weeks during the 16 week administration period.

37. The use of any one of Claims 34 to 36, wherein the hemoglobin level of the subject increases from baseline by ≥ 1.0 g/dL, ≥ 1.5 g/dL or ≥ 2.0 g/dL from week 8 through week 16 of the 16 week administration period.

38. The use of Claim 34, wherein the compound or pharmaceutically acceptable salt is to be administered to the subject for a period of 24 weeks.

39. The use of Claim 38, wherein the subject becomes transfusion independent for ≥ 8 consecutive weeks during the 24 week administration period.

40. The use of Claim 33, wherein the subject is classified as being non-transfused prior to treatment.

41. The use of Claim 40, wherein the compound or pharmaceutically acceptable salt is to be administered to the subject for a period of 24 weeks.

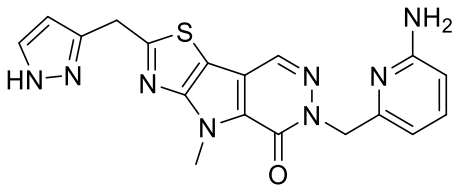
42. The use of Claim 41, wherein the hemoglobin level of the subject increases from baseline by ≥ 1.0 g/dL, ≥ 1.5 g/dL or ≥ 2.0 g/dL for ≥ 8 consecutive weeks during the 24 week administration period.

43. The use of Claim 33, wherein the subject is classified as having a high transfusion burden prior to treatment.

44. The use of Claim 42, wherein the compound or pharmaceutically acceptable salt is to be administered to the subject for a period of 24 weeks.

45. The use of Claim 43, wherein the total transfused red blood cell (RBC) units of the subject are reduced from baseline by ≥ 50% over a period of ≥ 8 consecutive weeks during the 24 week administration period.

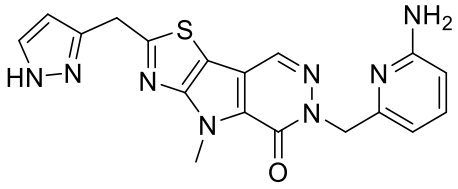
46. Use of a compound having the structural formula



;

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or disorder associated with mitochondrial dysfunction in a subject in need thereof.

47. Use of a compound having the structural formula



;

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or disorder associated with ineffective erythropoiesis in a subject in need thereof.

48. The use of any one of claims 1 to 27, wherein a therapeutically effective amount in the range of from 0.25 mg to 15 mg of the compound is to be administered daily to the subject.

49. The use of any one of claims 1 to 27, wherein a therapeutically effective amount in the range of from 0.25 mg to 2 mg QD or BID or from 1.5 mg to 5.5 mg QD or BID

or from 4 mg to 6 mg QD or BID of the compound is to be administered to the subject.

50. The use of any of claims 5 and 7 to 32 wherein the anemia associated with acquired PK deficiency (PKD) is hemolytic anemia.

51. The use of any one of claims 33 to 45 wherein the anemia associated with acquired PK deficiency (PKD) is hemolytic anemia.