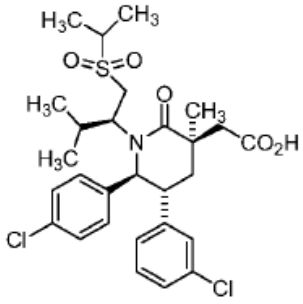
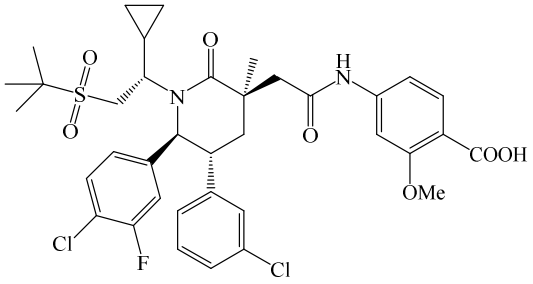


(I)



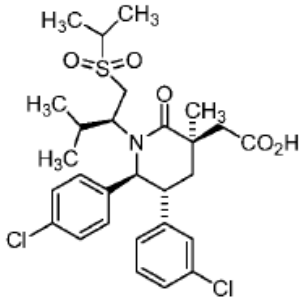
(II)

or a pharmaceutically acceptable salt thereof. In one aspect, the present disclosure refers to a use of a MDM2 inhibitor in the manufacture of a medicament for treating a myeloproliferative neoplasm (MPN) in a human subject in need thereof, wherein the MDM2 inhibitor is a compound of Formula (I) ~~or Formula (II) or a compound of Formula (II)~~ or a pharmaceutically acceptable salt thereof. In an example, the MPN is selected from the group consisting of polycythemia vera (PV), myelofibrosis, primary myelofibrosis, thrombocythemia, essential thrombocythemia, idiopathic myelofibrosis, systemic mastocystosis (SM), chronic neutrophilic leukemia (CNL), myelodysplastic syndrome (MDS), and systemic mast cell disease (SMCD). In an example, the MPN is selected from the group consisting of polycythemia vera (PV), primary myelofibrosis, and essential thrombocythemia. In an example, the MPN is polycythemia vera (PV). In an example, the MPN is essential thrombocythemia. In an example, the MPN is myelofibrosis. In an example, myelofibrosis is selected from primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF), and post-essential thrombocythemia myelofibrosis (post-ET MF). In an example, the human subject failed Ruxolitinib therapy for any of the above MPN. In an example, the human subject failed Ruxolitinib therapy for myelofibrosis. In an example, the human subject failed Ruxolitinib therapy for primary myelofibrosis (PMF). In an example, the human subject failed Ruxolitinib therapy for post-

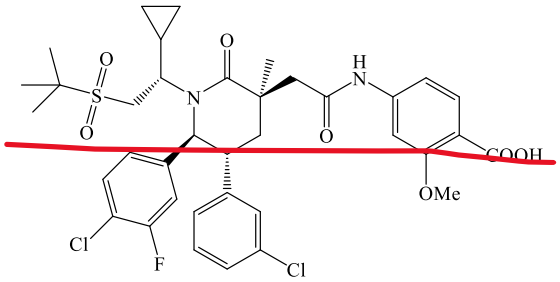
CLAIMS

We claim:

1. Use of a MDM2 inhibitor in the manufacture of a medicament for treating a myeloproliferative neoplasm (MPN) in a human subject in need thereof, wherein the MDM2 inhibitor is a compound of Formula (I) ~~or Formula (II) or a compound of Formula (II)~~:



(I)



~~(II)~~

or a pharmaceutically acceptable salt thereof.

2. The use of claim 1, wherein the MPN is polycythemia vera (PV).

3. The use of claim 2, wherein the MPN is phlebotomy-dependent polycythemia vera.

4. The use of claim 1, wherein the MPN is thrombocythemia.

5. The use of claim 4, wherein thrombocythemia is essential thrombocythemia (ET).

6. The use of claim 1, wherein the MPN is myelofibrosis.

7. The use of claim 6, wherein myelofibrosis is selected from primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF), and post-essential thrombocythemia myelofibrosis (post-ET MF).

8. The use of claim 7, wherein the human subject did not respond to prior Ruxolitinib therapy.

~~9. The use of claim 1, wherein the MPN is systemic mastocystosis (SM).~~

~~10. The use of claim 1, wherein the MPN is chronic neutrophilic leukemia (CNL).~~

~~11. The use of claim 1, wherein the MPN is myelodysplastic syndrome (MDS).~~

~~12. The use of claim 1, wherein the MPN is systemic mast cell disease (SMCD).~~

~~13. The use of claim 1, wherein the MPN is chronic eosinophilic leukemia.~~

~~14. The use of claim 1, wherein the MPN is chronic myelomonocytic leukemia (CMML).~~

~~15. The use of claim 1, wherein the MPN is atypical chronic myeloid leukemia (aCML).~~

~~16. The use of claim 1, wherein the MPN is juvenile myelomonocytic leukemia (JMML).~~

~~17. The use of claim 1, wherein the MPN is hypereosinophilic syndromes (HES).~~

~~18. The use of claim 1, wherein the MPN is myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).~~

~~19. The use of any one of claims 1 to 18, wherein the compound of Formula (I) or Formula (II) is in a crystalline form.~~

~~20.~~ ~~The use of any one of claims 1 to 18, wherein the compound of Formula (I) or Formula (II) is in a free form.~~

~~21.~~9. The use of any one of claims 1 to ~~20~~8, wherein the MDM2 inhibitor is a pharmaceutically acceptable salt of a compound of Formula (I) ~~or Formula (II)~~.

~~22. The use of any one of claims 1 to 20, wherein the compound of Formula (I) or Formula (II) is in an amorphous form.~~

~~23. The use of claim 19, wherein the crystalline form is characterized by a powder X-ray diffraction pattern comprising at least three peaks at diffraction angle 2 theta degrees selected from a group consisting of peaks at approximately 11.6, 12.4, 18.6, 19.0, 21.6 and 23.6 ± 0.1.~~

~~24.~~10. The use of any one of claims 1 to ~~23~~8, wherein the compound of Formula (I) ~~or Formula (II)~~ is to be administered once daily at a dose selected from the group consisting of 15 mg, 25 mg, 30 mg, 50 mg, 60 mg, 75 mg, 90 mg, 100 mg, 120 mg, 150 mg, 175 mg, 180 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, and 480 mg.

~~25.~~11. The use of any one of claims 1 to ~~23~~8, wherein the compound of Formula (I) ~~or Formula (II)~~ is to be administered twice daily at a dose selected from the group consisting of 15 mg, 25 mg, 30 mg, 50 mg, 60 mg, 75 mg, 90 mg, 100 mg, 120 mg, 150 mg, 175 mg, 180 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, and 480 mg.

~~26.~~12. The use of any one of claims 1 to ~~25~~8, wherein the human is to be treated with the MDM2 inhibitor on days 1-7 of 21-day cycle, wherein on days 8-21 the human is not to be treated with the MDM2 inhibitor.

~~27.~~13. The use of any one of claims 1 to ~~26~~8, wherein the compound of Formula (I) ~~or Formula (II)~~ is to be orally administered.

~~28.~~14. The use of any one of claims 1 to ~~27~~8, wherein the therapeutically effective amount of the MDM2 inhibitor is 120 mg.

~~29.~~15. The use of any one of claims 1 to ~~28~~8, wherein the MPN is characterized by JAK2V617F mutation.