COMBINATION OF A BTK INHIBITOR AND A FUMARIC ACID ESTER FOR USE IN THE TREATMENT OF MULTIPLE SCLEROSIS

RELATED APPLICATIONS

[0001] This application claims the benefit of the filing date, under 35 U.S.C. § 119(e), of U.S. Provisional Application No. 63/464,290, filed on May 5, 2023 and U.S. Provisional Application No. 63/541,968, filed on October 2, 2023, the entire contents of each of above-referenced applications are incorporated herein by reference.

BACKGROUND

[0002] Multiple sclerosis (MS) is a chronic, autoimmune, demyelinating disorder of the central nervous system (CNS) that is characterized by inflammation, demyelination, and axonal injury as well as oligodendrocyte and neuronal loss. It is the most common demyelinating disorder of the CNS, affecting approximately 2.5 million people worldwide. Relapsing multiple sclerosis (RMS) includes patients with clinically isolated syndrome (CIS), relapsing-remitting multiple sclerosis (RRMS), and active secondary progressive multiple sclerosis (SPMS). In the relapsing-remitting phase of the disease, patients experience episodes of neurological dysfunction (relapses) separated by periods of relative stability. Other types of MS include primary progressive multiple sclerosis (PPMS) and non-relapsing SPMS. Patients with radiologically isolated syndrome (RIS) may go on to develop MS.

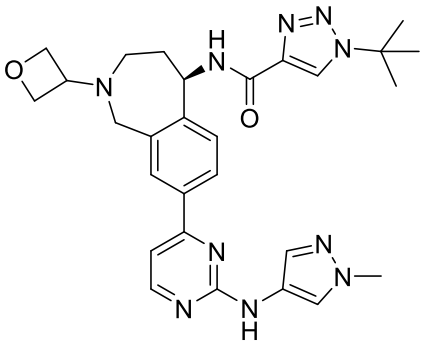
[0003] While there has been substantial progress in MS care over the last 25 years with the approval of a number of medicinal products, many patients with MS continue to experience permanent disability progression, and many receive therapies with limited tolerability, burdensome monitoring, or risk of severe adverse events (SAEs) or even life-threatening side effects. There remains an important unmet need for tolerable MS therapies that are highly efficacious and include new options for treating the inflammatory component of MS seen across the spectrum of RMS through progressive multiple sclerosis (PMS) types, as well as effectively treating disability progression independent of relapse activity.

SUMMARY

[0004] The present disclosure provides methods of treating multiple sclerosis in a subject in need thereof comprising administering to the subject an effective amount of Compound 1 or a

pharmaceutically acceptable salt thereof and an effective amount of a fumaric acid ester (FAE) (*e.g.*, DRF). The disclosure provides safe and effective dosing regimens for Compound 1 and DRF. More specifically, the disclosure provides a total oral daily dose of 200 mg to 1000 mg Compound 1 or a pharmaceutically acceptable salt thereof in an amount equivalent to 200 mg to 1000 mg of Compound 1 for use in the methods of the present disclosure.

[0004a] In one aspect, the present disclosure relates to use of Compound 1:

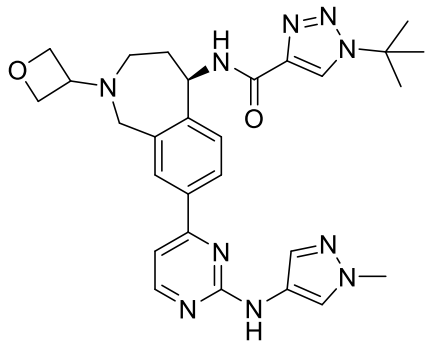


Compound 1;

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a human subject with multiple sclerosis (MS), wherein the subject is to be orally administered an amount equivalent to a total daily dose of 200 mg to 1000 mg of Compound 1, and wherein the subject is to be co-administered with an effective amount of a fumaric acid ester (FAE).

[0005] In one example, the present disclosure provides a method of treating a subject with MS, comprising administering to the subject in need thereof orally an effective amount of Compound 1 or a pharmaceutically acceptable salt thereof and co-administering an effective amount of a fumaric acid ester (FAE). In one example, the FAE is diroximel fumarate (DRF).

[0006] Compound 1 represented by the structure below:



or a pharmaceutically acceptable salt thereof, is used in the methods of the present disclosure.

[0007] In another example, 200 mg to 1000 mg of Compound 1 or a pharmaceutically acceptable salt thereof in an amount equivalent to 200 mg to 1000 mg of Compound 1 is provided for oral and daily use in treating a subject with MS, in combination with an effective amount of DRF.

DETAILED DESCRIPTION OF THE INVENTION

[0008] The present disclosure provides combination therapies for treating MS in a subject in need thereof. The methods comprise administering to the subject an effective amount of Compound 1, a BTK inhibitor, in combination with an effective amount of a fumaric acid ester (FAE), *e.g.*, DRF.

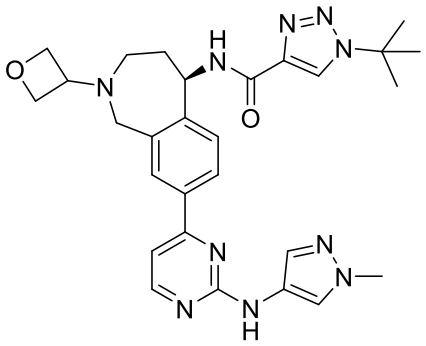
BTK Inhibitors

[0009] Bruton's tyrosine kinase (BTK), a member of the tyrosine kinase hepatocellular carcinoma (TEC) family of protein tyrosine kinases, is expressed in many

CLAIMS

What is claimed is:

1. Use of Compound 1:



Compound 1;

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a human subject with multiple sclerosis (MS), wherein the subject is to be orally administered an amount equivalent to a total daily dose of 200 mg to 1000 mg of Compound 1, and wherein the subject is to be co-administered with an effective amount of a fumaric acid ester (FAE).

2. The use of claim 1, wherein the MS is relapsing form of MS.

3. The use of claim 1, wherein the MS is relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS).

4. The use of claim 1, wherein the MS is primary progressive MS (PPMS).

5. The use of any one of claims 1-4, wherein the subject is to be administered a total daily dose of 300 mg to 900 mg of Compound 1.

6. The use of any one of claims 1-4, wherein the subject is to be administered a total daily dose of 400 mg to 800 mg of Compound 1.

7. The use of any one of claims 1-4, wherein the subject is to be administered a total daily dose of 500 mg to 700 mg of Compound 1.

8. The use of any one of claims 1-4, wherein the subject is to be administered a total daily dose of 200 mg of Compound 1.

9. The use of any one of claims 1-4, wherein the subject is to be administered a total daily dose of 300 mg of the Compound 1.

10. The use of any one of claims 1-4, wherein the subject is to be administered a total daily dose of 400 mg of the Compound 1.

11. The use of any one of claims 1-4, wherein the subject is to be administered a total daily dose of 500 mg of the Compound 1.

12. The use of any one of claims 1-4, wherein the subject is to be administered a total daily dose of 600 mg of the Compound 1.

13. The use of any one of claims 1-4, wherein the subject is to be administered a total daily dose of 700 mg of the Compound 1.

14. The use of any one of claims 1-4, wherein the subject is to be administered a total daily dose of 800 mg of the Compound 1.

15. The use of any one of claims 1-4, wherein the subject is to be administered a total daily dose of 900 mg of the Compound 1.

16. The use of any one of claims 1-4, wherein the subject is to be administered a total daily dose of 1000 mg of the Compound 1.

17. The use of any one of claims 1-16, wherein Compound 1 is to be administered to the subject once daily.

18. The use of any one of claims 1-16, wherein Compound 1 is to be administered to the subject twice daily.

19. The use of claim 18, wherein 100 mg to 500 mg of Compound 1 is to be administered to the subject twice daily.

20. The use of claim 18, wherein 150 mg to 450 mg of Compound 1 is to be administered to the subject twice daily.

21. The use of claim 18, wherein 200 mg to 400 mg of Compound 1 is to be administered to the subject twice daily.

22. The use of claim 18, wherein 250 mg to 350 mg of Compound 1 is to be administered to the subject twice daily.

23. The use of claim 18, wherein 200 mg of Compound 1 is to be administered to the subject twice daily.

24. The use of claim 18, wherein 250 mg of Compound 1 is to be administered to the subject twice daily.

25. The use of claim 18, wherein 275 mg of Compound 1 is to be administered to the subject twice daily.

26. The use of claim 18, wherein 300 mg of Compound 1 is to be administered to the subject twice daily.

27. The use of claim 18, wherein 325 mg of Compound 1 is to be administered to the subject twice daily.

28. The use of claim 18, wherein 350 mg of Compound 1 is to be administered to the subject twice daily.

29. The use of claim 18, wherein 375 mg of Compound 1 is to be administered to the subject twice daily.

30. The use of claim 18, wherein 400 mg of Compound 1 is to be administered to the subject twice daily.

31. The use of claim 18, wherein 450 mg of Compound 1 is to be administered to the subject twice daily.

32. The use of claim 18, wherein 500 mg of Compound 1 is to be administered to the subject twice daily.

33. The use of any one of claims 1-32, wherein Compound 1 is to be administered to the subject right after a regular meal.

34. The use of any one of claims 1-33, wherein the FAE is diroximel fumarate (DRF).

35. The use of any one of claims 1-33, wherein 231 mg of DRF is to be administered to the subject twice daily.

36. The use of any one of claims 1-33, wherein 350 mg of DRF is to be administered to the subject twice daily.

37. The use of any one of claims 1-33, wherein 462 mg of DRF is to be administered to the subject twice daily.

38. The use of any one of claims 1-33, wherein 231 mg of DRF is to be administered to the subject twice daily for the first 7 days and then 350 mg of DRF is to be administered to the subject twice daily.

39. The use of any one of claims 1-33, wherein 231 mg of DRF is to be administered to the subject twice daily for the first 7 days and then 462 mg of DRF is to be administered to the subject twice daily.