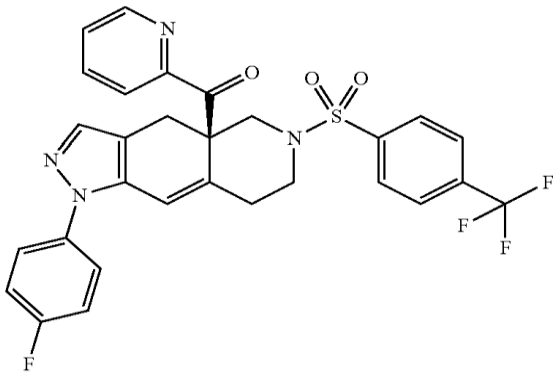
associated with a mutation in the superoxide dismutase 1 (SOD1) gene. However, all patient treatments include palliative care, since the disease progresses despite administration of approved drug treatments.

[0004] Accordingly, in order to provide improved patient care and to slow disease progression improved methods and compositions for use in treating patients suffering from ALS are needed.

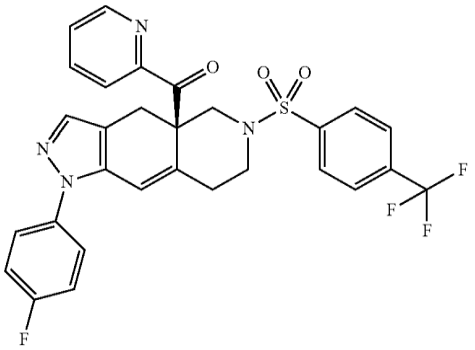
SUMMARY

[0004a] In one aspect, there is provided the use of an effective amount of between about 75 milligrams (mg) to about 500 mg of dazucorilant, (R)-(1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl) sulfonyl)-4, 4a, 5,6,7,8-hexahydro-1-H-pyrazolo[3,4-g]isoquinolin-4a-yl) (pyridin-2-yl)methanone:



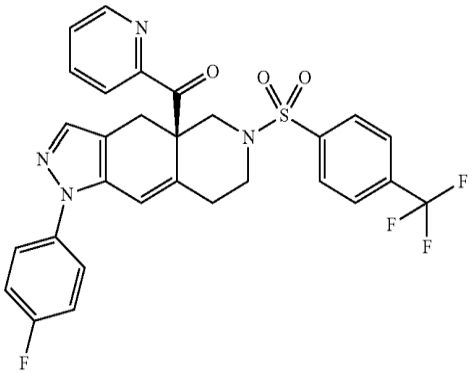
, in the manufacture of a medicament for treating a subject suffering from amyotrophic lateral sclerosis (ALS), wherein said dazucorilant is to be administered daily for at least 7 consecutive days, effective to increase dazucorilant exposure by about 1.7-fold as compared to the dazucorilant exposure resulting from a single day's administration of said effective amount of dazucorilant, effective to treat said ALS.

[0004b] In another aspect, there is provided the use of a heteroaryl ketone fused azadecalin dazucorilant, (R)-(1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl) sulfonyl)-4, 4a, 5,6,7,8-hexahydro-1-H-pyrazolo[3,4-g]isoquinolin-4a-yl) (pyridin-2-yl)methanone:



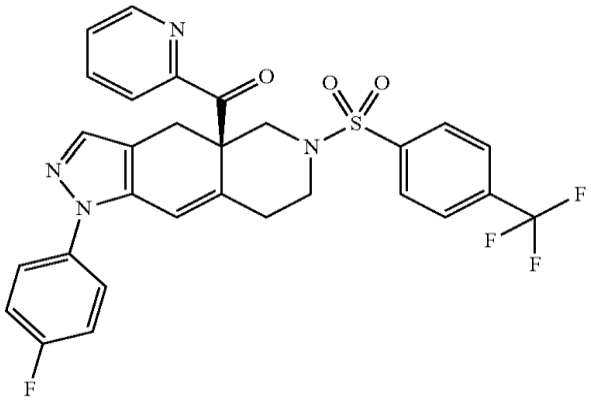
, in the manufacture of a medicament for use with food in the treatment of amyotrophic lateral sclerosis (ALS).

[0004c] In another aspect, there is provided the use of an effective amount of between about 75 milligrams (mg) to about 500 mg of dazucorilant, (R)-(1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl) sulfonyl)-4, 4a, 5,6,7,8-hexahydro-1-H-pyrazolo[3,4-g]isoquinolin-4a-yl) (pyridin-2-yl)methanone:



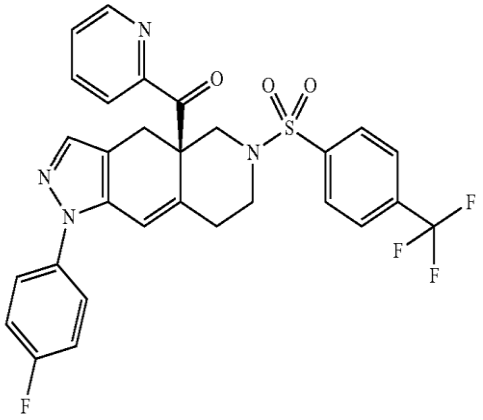
, in the manufacture of a medicament for reducing a symptom associated with amyotrophic lateral sclerosis (ALS) in a subject suffering from ALS, wherein said dazucorilant is to be administered daily for at least 7 consecutive days, effective to increase dazucorilant exposure by about 1.7-fold as compared to the dazucorilant exposure resulting from a single day's administration of said effective amount of dazucorilant, effective to treat said ALS.

[0004d] In another aspect, there is provided the use of the heteroaryl ketone fused azadecalin dazucorilant, (R)-(1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl) sulfonyl)-4, 4a, 5,6,7,8-hexahydro-1-H-pyrazolo[3,4-g]isoquinolin-4a-yl) (pyridin-2-yl)methanone:



, in the manufacture of a medicament for use with food for reducing a symptom associated with amyotrophic lateral sclerosis (ALS).

[0005] Disclosed herein are novel methods for treating amyotrophic lateral sclerosis (ALS). The methods comprise administering to the subject an effective amount of a heteroaryl ketone fused azadecalin compound. Preferably, the heteroaryl ketone fused azadecalin compound is a compound that modulates glucocorticoid receptors (GRs). A compound that modulates a GR is termed a GR modulator (GRM); a GRM compound which has little or no modulatory effect on other steroid hormone receptors (such as, e.g., a progesterone receptor, an aldosterone receptor, or an androgen receptor) is termed a selective GRM (SGRM). In examples, the methods for treating ALS disclosed herein comprise administering to the subject an effective amount of the SGRM heteroaryl ketone fused azadecalin compound (R)-(1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl) sulfonyl)-4, 4a, 5,6,7,8-hexahydro-1-H-pyrazolo[3,4-g]isoquinolin-4a-yl) (pyridin-2-yl)methanone, also termed “dazucorilant” or “CORT133176”, which has the structure:



. Dazucorilant is disclosed in Example 1 of U.S. Patent 8,859,774 (the entire contents of which patent is hereby incorporated by reference in its entirety).

[0006] In examples, the GRM (e.g., a SGRM) is orally administered. In examples, the GRM or SGRM may be administered by injection, infusion, transdermal application, or by other means or routes of administration. In examples, the GRM (e.g., dazucorilant)

may be administered with food, or with water, or with both food and water. In other examples, the GRM (e.g., dazucorilant) may be administered in the absence of food.

[0007] In examples, the effective amount of the GRM (e.g., a SGRM, such as dazucorilant) is a daily dose of between 50 and 500 milligrams per day (mg/day); e.g., in examples, the daily dose of the GRM (e.g., a SGRM, such as dazucorilant) is 50, 75, 100, 125, 150, 200, 225, 250, 300, 350, 375, 400, 450, 500, 525, or 600 mg/day. Typically, administration of the GRM (e.g., a SGRM, such as dazucorilant) is once-daily administration; however, in examples, administration may be twice daily, or three times daily, or may be every other day, or every three days, or every four days, or at other intervals as necessary or convenient. The GRM (e.g., a SGRM, such as dazucorilant) may be administrated to the patient for as long as necessary; for example, administration of the GRM (e.g., a SGRM, such as dazucorilant) may continue for weeks, months, or years as needed.

[0008] The present methods provide improved methods of treating ALS.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIG. 1A shows plasma concentrations of dazucorilant 300 mg with and without food in the PK study of dazucorilant administration to healthy human volunteers. Greater dazucorilant exposure was observed when dazucorilant was administered to fed subjects as compared to the dazucorilant exposure observed in fasted subjects.

[0010] FIG. 1B shows pharmacokinetic parameters of dazucorilant administration to healthy human volunteers. Greater dazucorilant exposure was observed when dazucorilant was administered to fed subjects as compared to the dazucorilant exposure observed in fasted subjects.

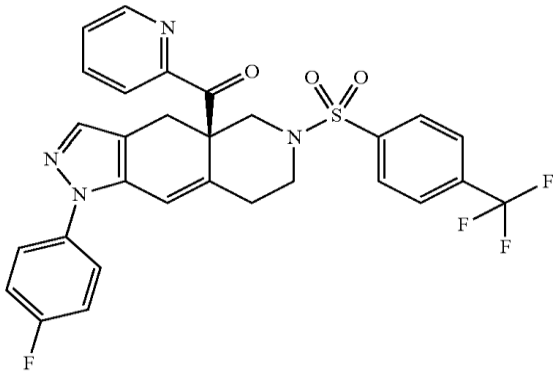
[0011] FIG. 2A shows the dazucorilant steady-state PK profile after 14 days of QD dosing in the brain penetration study.

[0012] FIG. 2B shows pharmacokinetic parameters of dazucorilant administration to healthy human volunteers who were administered dazucorilant daily at the indicated dosages for successive 14 days. Greater than dose-proportional increase in dazucorilant exposures was observed.

[0013] FIG. 3 shows the timeline for the Phase 2 study of dazucorilant for the treatment of ALS disclosed herein.

CLAIMS:

1. Use of an effective amount of between about 75 milligrams (mg) to about 500 mg of dazucorilant, (R)-(1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl) sulfonyl)-4, 4a, 5,6,7,8-hexahydro-1-H-pyrazolo[3,4-g]isoquinolin-4a-yl) (pyridin-2-yl)methanone:



, in the manufacture of a medicament for treating a subject suffering from amyotrophic lateral sclerosis (ALS), wherein said dazucorilant is to be administered daily for at least 7 consecutive days, effective to increase dazucorilant exposure by about 1.7-fold as compared to the dazucorilant exposure resulting from a single day's administration of said effective amount of dazucorilant, effective to treat said ALS.

2. The use of claim 1, wherein said dazucorilant is to be administered with food.

3. The use of claim 1 or claim 2, wherein said effective amount of dazucorilant is selected from about 75 mg, about 150 mg, about 300 mg, about 375 mg, about 450 mg, and about 500 mg of dazucorilant.

4. The use of any of claims 1 to 3, wherein said dazucorilant is to be administered daily dazucorilant for at least 14 consecutive days, effective to achieve a steady-state level of dazucorilant exposure that is at least about 1.6-fold greater than the dazucorilant exposure resulting from a single day's administration of said effective amount of dazucorilant.

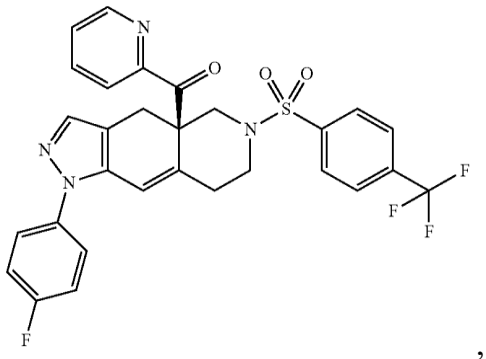
5. The use of any of claims 1 to 4, wherein said effective amount of dazucorilant is contained in one or more softgel capsules.

6. The use of any of claims 1 to 5, further comprising a further therapy to be administered for ALS.

7. The use of claim 6, wherein said further therapy for ALS comprises riluzole or edaravone to be administered.

8. The use of any of claims 1 to 7, wherein said dazucorilant is to be administered orally or enterally.

9. Use of a heteroaryl ketone fused azadecalin dazucorilant, (R)-(1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl) sulfonyl)-4, 4a, 5,6,7,8-hexahydro-1-H-pyrazolo[3,4-g]isoquinolin-4a-yl) (pyridin-2-yl)methanone:



, in the manufacture of a medicament for use with food in the treatment of amyotrophic lateral sclerosis (ALS).

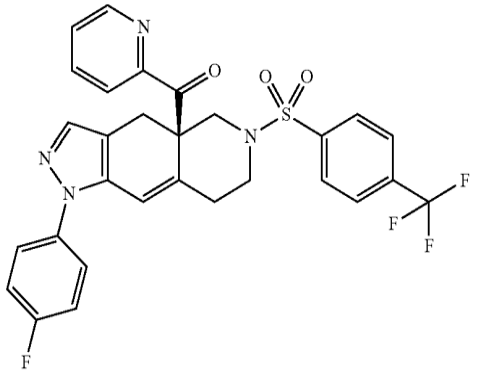
10. The use of claim 9, wherein said medicament is for use with water and with food. 11. The use of claim 9 or claim 10, wherein the amount of dazucorilant is selected from about 75 mg, about 150 mg, about 300 mg, about 375 mg, about 450 mg, and about 500 mg of dazucorilant.

12. The use of any of claims 9 to 11, wherein said medicament comprises dazucorilant contained in a softgel capsule.

13. The use of any of claims 9 to 12, comprising a further therapy for ALS to be used.

14. The use of claim 13, wherein said further therapy for ALS comprises use of riluzole or edaravone.

15. Use of an effective amount of between about 75 milligrams (mg) to about 500 mg of dazucorilant, (R)-(1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl) sulfonyl)-4, 4a, 5,6,7,8-hexahydro-1-H-pyrazolo[3,4-g]isoquinolin-4a-yl) (pyridin-2-yl)methanone:



, in the manufacture of a medicament for reducing a symptom associated with amyotrophic lateral sclerosis (ALS) in a subject suffering from ALS, wherein said dazucorilant is to be administered daily for at least 7 consecutive days, effective to increase dazucorilant exposure by about 1.7-fold as compared to the dazucorilant exposure resulting from a single day's administration of said effective amount of dazucorilant,

effective to treat said ALS.

16. The use of claim 15, wherein said dazucorilant is to be administered with food.

17. The use of claim 15 or claim 16, wherein said effective amount of dazucorilant is selected from about 75 mg, about 150 mg, about 300 mg, about 375 mg, about 450 mg, and about 500 mg of dazucorilant.

18. The use of any of claims 15 to 17, wherein said dazucorilant is to be administered daily for at least 14 consecutive days, effective to achieve a steady-state level of dazucorilant exposure that is at least about 1.6-fold greater than the dazucorilant exposure resulting from a single day's administration of said effective amount of dazucorilant.

19. The use of any of claims 15 to 18, wherein said effective amount of dazucorilant is contained in one or more softgel capsules.

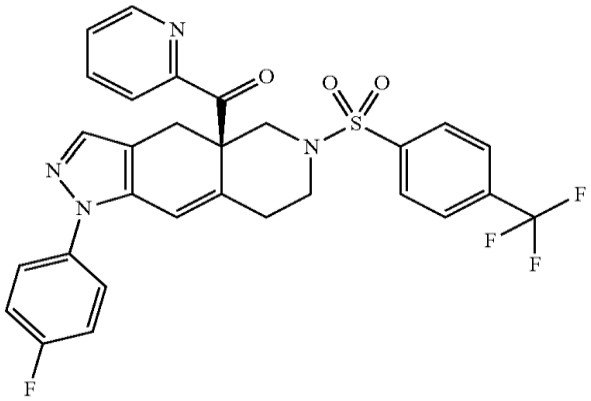
20. The use of any of claims 15 to 19, further comprising a further therapy for ALS.

21. The use of claim 20, wherein said further therapy for ALS comprises riluzole or edaravone to be administered.

22. The use of any of claims 15 to 21, wherein said dazucorilant is to be administered orally or enterally.

23. The use of any of claims 15 to 22, wherein said symptom associated with ALS is a symptom selected from weakness of the upper limbs, weakness of lower limbs, dysarthria, and dysphagia.

24. Use of the heteroaryl ketone fused azadecalin dazucorilant, (R)-(1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl) sulfonyl)-4, 4a, 5,6,7,8-hexahydro-1-H-pyrazolo[3,4-g]isoquinolin-4a-yl) (pyridin-2-yl)methanone:



, in the manufacture of a medicament for use with food for reducing a symptom associated with amyotrophic lateral sclerosis (ALS).

25. The use of claim 24, wherein said medicament is for use with water and with food.

26. The use of claim 24 or claim 25, wherein the amount of dazucorilant is selected from about 75 mg, about 150 mg, about 300 mg, about 375 mg, about 450 mg, and about 500 mg of dazucorilant.

27. The use of any of claims 24 to 26, comprising a further therapy for ALS to be used.

28. The use of claim 27, wherein said further therapy for ALS comprises use of riluzole or edaravone.

29. The use of any of claims 24 to 28, wherein said symptom associated with ALS is a symptom selected from weakness of the upper limbs, weakness of lower limbs, dysarthria, and dysphagia.

30. The use of any of claims 24 to 29, wherein said medicament comprises dazucorilant contained in a softgel capsule.