USE OF A PHOSPHODIESTERASE 10 INHIBITOR FOR THE TREATMENT OF TOURETTE SYNDROME

CROSS-REFERENCE TO RELATED APPLICATION

[001] This application claims priority to U.S.S.N. 63/035,310 filed on June 5, 2020, and U.S.S.N. 63/160,302 filed on March 12, 2021, the contents of each of which is incorporated herein by reference in its entirety.

BACKGROUND

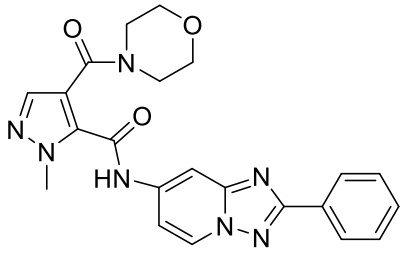
[002] Tourette Syndrome (TS) is a neurologic disorder that is characterized by tics, which are involuntary vocalizations or repetitive, purposeless movements. It is estimated that up to 200,000 Americans have the most severe form of TS, and as many as one in 100 Americans show milder and less complex TS symptoms that may include chronic motor or vocal tics (NIH Handbook on Tourette Syndrome (2012)). The prevalence of TS is estimated to be 0.3% in US children aged 6-17 years, although there are suggestions that this may be an underestimation of its prevalence (Cohen S, et al. Neurosci Biobehav Rev. 37(6): 997-1007 (2013)).

[003] There is currently no medication that is helpful to all patients with TS. While neuroleptic drugs (i.e., antipsychotics) have been effective for treatment of tics in some patients, these medications are associated with significant side effects, and they do not entirely eliminate tic symptoms. In addition, treatment of neurobehavioral disorders associated with TS, such as ADHD, may be complicated as some medications used to treat ADHD are contraindicated in patients with TS (see Prescribing Information for Ritalin) (2013).

[004] Therefore, there is an unmet need to develop new treatments for the spectrum of symptoms of TS, including tics and neurobehavioral disorders.

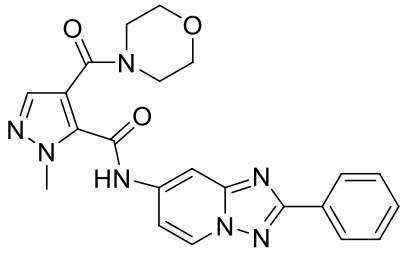
SUMMARY

[004a] In one aspect of the present disclosure, there is provided a use of a composition containing a therapeutic agent or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Tourette Syndrome in a subject in need thereof, wherein the therapeutic agent is a compound of Formula I:



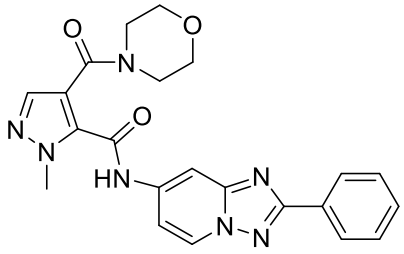
(I).

[004b] In another aspect of the present disclosure, there is provided a use of a composition containing a therapeutic agent or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Tourette Syndrome in a subject in need thereof, wherein the subject has a total tic score of at least 22 on the Yale Global Tic Severity Scale at the start of treatment and the therapeutic agent is a compound of Formula I:



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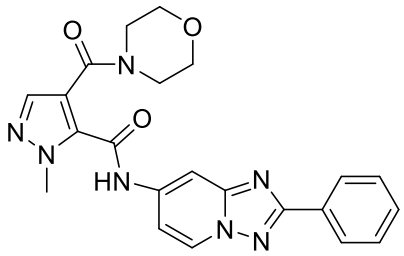
[004c] In a further aspect of the present disclosure, there is provided a use of a composition containing a phosphodiesterase 10 (PDE10) inhibitor or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Tourette Syndrome in a subject in need thereof, wherein the PDE10 inhibitor is a compound of Formula I:



(I).

[004d] In another aspect of the present disclosure, there is provided a use of a composition containing a therapeutic agent or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Tourette Syndrome in a subject in need thereof, wherein the subject

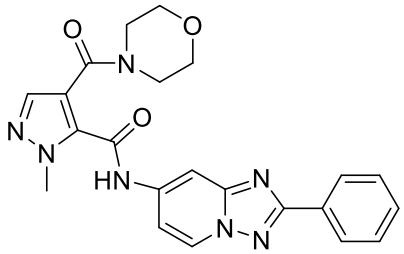
has a total tic score of at least 22 on the Yale Global Tic Severity Scale at the start of treatment and the therapeutic agent is a compound of Formula I:



(I),

wherein the subject is to be administered the compound of Formula I, or a pharmaceutically acceptable salt thereof, in an amount of about 5 mg to about 15 mg once daily.

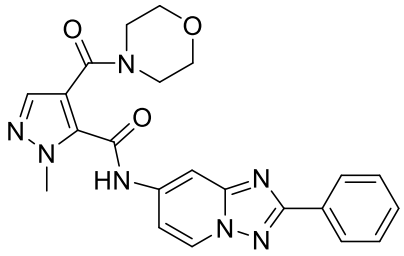
[004e] In a further aspect of the present disclosure, there is provided a solid form of a compound of Formula I:



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wherein the solid form is a crystalline solid of the free base of the compound of Formula I, and the crystalline solid has a melting point onset as determined by differential scanning calorimetry (DSC) of about 210-214 °C.

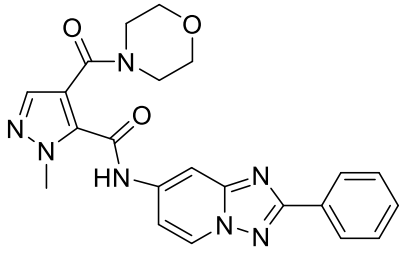
[004f] In another aspect of the present disclosure, there is provided a use of a composition containing a crystalline solid of the free base of the compound of Formula I:



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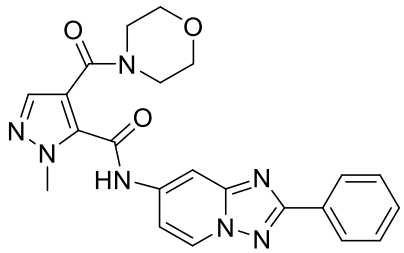
in the manufacture of a medicament for treating Tourette Syndrome in a subject in need thereof, wherein said crystalline solid has a melting point onset as determined by DSC of about 210-214 °C.

[005] In one example, provided herein are methods of treating Tourette Syndrome, comprising administering to a subject in need thereof a composition containing a therapeutically effective amount of a therapeutic agent or a pharmaceutically acceptable salt thereof, wherein the therapeutic agent is a compound of Formula I:


(I).

[006] In certain examples, the subject has a total tic score of at least 22 on the Yale Global Tic Severity Scale.

[007] In another example, provided herein are methods of treating Tourette Syndrome, comprising administering to a subject in need thereof a composition containing a therapeutically effective amount of a therapeutic agent or a pharmaceutically acceptable salt thereof, wherein the subject has a total tic score of at least 22 on the Yale Global Tic Severity Scale and the therapeutic agent is a compound of Formula I:


(I).

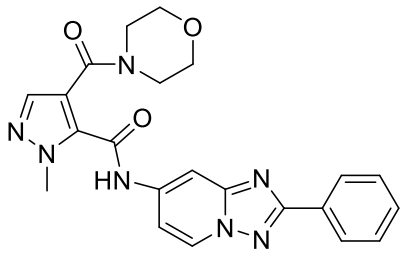
[008] In certain examples, the subject has previously been administered another therapy for Tourette Syndrome. In certain examples, the previous administration of another therapy for Tourette Syndrome is administration of pimozide, haloperidol, or aripiprazole. In certain examples, the previous administration of another therapy for Tourette Syndrome is administration of a psychostimulant (e.g., methylphenidate, dextroamphetamine, or lisdexamfetamine) or an alpha 2 adrenergic receptor antagonist (e.g., atipamezole, efaroxan, or idazoxan).

[009] In certain examples, administering a therapeutically effective amount of the compound of Formula I, or a pharmaceutically acceptable salt thereof, comprises administering from about 2.5 mg to about 5 mg of the compound of Formula I, or a pharmaceutically acceptable salt thereof. In certain examples, the compound of Formula I, or a pharmaceutically acceptable salt thereof, is administered once daily. In certain examples, the compound of Formula I, or a pharmaceutically acceptable salt thereof, is administered orally. In

certain examples, the compound of Formula I, or a pharmaceutically acceptable salt thereof, is administered as a unit dose.

[0010] In certain examples, the compound of Formula I is administered in free base form. In certain examples, the compound of Formula I is administered in the form of a pharmaceutically acceptable salt.

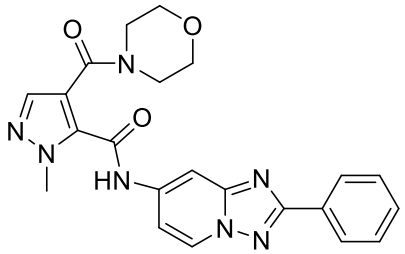
[0011] In another example, provided herein are methods of treating Tourette Syndrome, comprising administering to a subject in need thereof a composition containing a therapeutically effective amount of a phosphodiesterase 10 (PDE10) inhibitor or a pharmaceutically acceptable salt thereof, wherein the PDE10 inhibitor is a compound of Formula I:



(I).

[0012] In certain examples, the subject has attention-deficit hyperactivity disorder (ADHD). In certain examples, the subject is free of ADHD. In certain examples, the subject has obsessive-compulsive disorder (OCD). In certain examples, the subject is free of OCD.

[0013] Still within the scope of this disclosure is a solid form of a compound of Formula I:



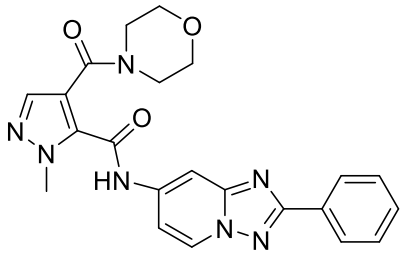
(I),

wherein the solid form is a crystalline solid of the free base of the compound of Formula I, and the crystalline solid has a melting point by differential scanning calorimetry (DSC) of about 210-214 °C (e.g., about 210 °C, about 211 °C, about 212 °C, about 213 °C, or about 214 °C).

[0014] In some examples, the above described solid form is a crystalline solid of the free base of Formula I, having an X-ray powder diffraction (XRPD) pattern as substantially shown in FIG. 1.

[0015] In some examples, the above described solid form is a crystalline solid of the free base of Formula I, having a DSC figure as substantially shown in FIG. 2.

[0016] The present disclosure also covers a method of treating Tourette Syndrome, comprising administering to a subject in need thereof a composition containing a therapeutically effective amount of a crystalline solid of the free base of a compound of Formula I:



(I),

wherein the crystalline solid has a melting point by DSC of about 210-214 °C.

[0017] In some examples, the above described method comprises a crystalline solid of the free base of Formula I, having an X-ray powder diffraction (XRPD) pattern as substantially shown in FIG. 1.

[0018] In some examples, the above described method comprises a crystalline solid of the free base of Formula I, having a DSC figure as substantially shown in FIG. 2.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] FIG. 1 depicts an exemplary XRPD pattern of a crystalline solid of the free base of the compound of Formula I.

[0020] FIG. 2 depicts an exemplary DSC curve of a crystalline solid of the free base of the compound of Formula I.

DETAILED DESCRIPTION

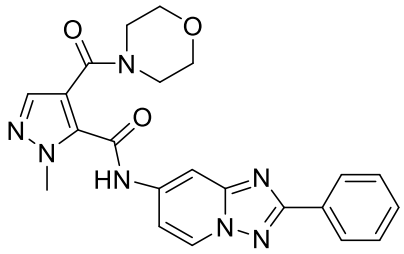
[0021] As generally described herein, the present disclosure provides methods of treating Tourette Syndrome in a subject in need thereof. The present disclosure also describes a crystalline form of the free base of the compound of Formula I, and uses thereof.

Definitions

[0022] To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

CLAIMS

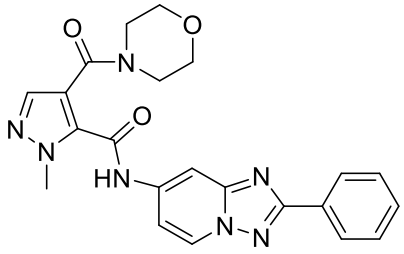
1. Use of a composition containing a therapeutic agent or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Tourette Syndrome in a subject in need thereof, wherein the therapeutic agent is a compound of Formula I:



(I).

2. The use of claim 1, wherein the subject has a total tic score of at least 22 on the Yale Global Tic Severity Scale at the start of treatment.

3. Use of a composition containing a therapeutic agent or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Tourette Syndrome in a subject in need thereof, wherein the subject has a total tic score of at least 22 on the Yale Global Tic Severity Scale at the start of treatment and the therapeutic agent is a compound of Formula I:



(I).

4. The use of any one of claims 1-3, wherein the subject has previously been administered another therapy for Tourette Syndrome.

5. The use of claim 4, wherein the previous administration of another therapy for Tourette Syndrome is administration of pimozide, haloperidol, aripiprazole, methylphenidate, dextroamphetamine, lisdexamfetamine, atipamezole, efaroxan, or idazoxan.

6. The use of claim 5, wherein the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered to the subject once daily.

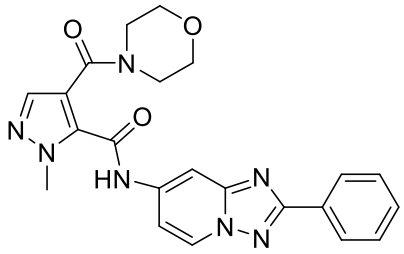
7. The use of claim 5, whereinthe compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered to the subject orally.

8. The use of claim 5, wherein the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered to the subject as a unit dose.

9. The use of claim 1, wherein the compound of Formula I is to be administered to the subject in its free base form.

10. The use of claim 1, wherein the compound of Formula I is to be administered to the subject in the form of a pharmaceutically acceptable salt thereof.

11. Use of a composition containing a phosphodiesterase 10 (PDE10) inhibitor or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Tourette Syndrome in a subject in need thereof, wherein the PDE10 inhibitor is a compound of Formula I:



(I).

12. The use of any one of claims 1-11, wherein the composition comprises the compound of Formula I, or a pharmaceutically acceptable salt thereof, as the sole active agent.

13. The use of any one of claims 1-11, wherein the composition comprises the compound of Formula I, or a pharmaceutically acceptable salt thereof, in combination with aother active agent.

14. The use of claim 13, wherein the other active agent is olanzapine or risperidone.

15. The use of any one of claims 1-14, wherein the composition comprises inactive agents selected from the group consisting of mannitol, microcrystalline cellulose, sodium starch glycolate, sucrose monopalmitate, hydroxypropyl methylcellulose, colloidal silicon dioxide, and sodium stearyl fumarate.

16. The use of any one of claims 1-15, wherein the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered to the subject in a capsule.

17. The use of claim 16, wherein the capsule shell consists of gelatine, titanium dioxide, red iron oxide, and yellow iron oxide.

18. The use of claim 16, wherein the capsule comprises about 1 mg to about 10 mg of the compound of Formula I, or a pharmaceutically acceptable salt thereof.

19. The use of claim 18, wherein the capsule comprises about 2.5 mg to about 5 mg of the compound of Formula I, or a pharmaceutically acceptable salt thereof.

20. The use of any one of claims 1-19, wherein the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered to the subject in an amount of about 2.5 mg to about 5 mg once daily.

21. The use of any one of claims 1-19, wherein the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered to the subject in an amount of about 5 mg to about 15 mg once daily.

22. The use of claim 21, wherein the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered to the subject in an amount of about 5 mg, about 7.5 mg, about 10 mg, about 12.5 mg, or about 15 mg once daily.

23. The use of any one of claims 1-22, wherein the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered to the subject in an immediate release formulation.

24. The use of any one of claims 1-22, wherein the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered to the subject in an extended release formulation.

25. The use of any one of claims 1-24, wherein the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered to the subject, wherein the administering maintains efficacy throughout the day.

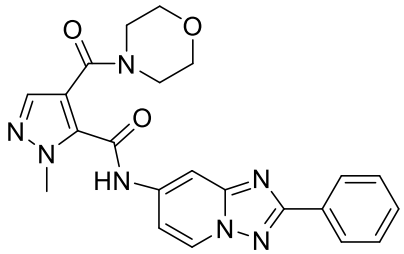
26. The use of any one of claims 1-25, wherein the subject has attention-deficit hyperactivity disorder (ADHD).

27. The use of any one of claims 1-25, wherein the subject is free of ADHD.

28. The use of any one of claims 1-25, wherein the subject has obsessive-compulsive disorder (OCD).

29. The use of any one of claims 1-25, wherein the subject is free of OCD.

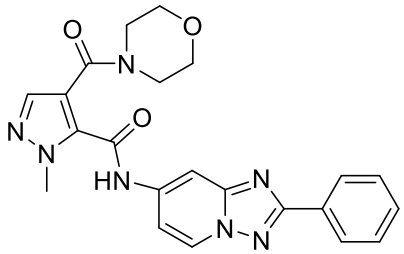
30. Use of a composition containing a therapeutic agent or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Tourette Syndrome in a subject in need thereof, wherein the subject has a total tic score of at least 22 on the Yale Global Tic Severity Scale at the start of treatment and the therapeutic agent is a compound of Formula I:



(I),

wherein the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered to the subject in an amount of about 5 mg to about 15 mg once daily.

31. A solid form of a compound of Formula I:



(I),

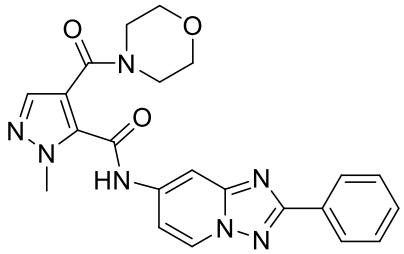
wherein the solid form is a crystalline solid of the free base of the compound of Formula I, and the crystalline solid has a melting point onset as determined by differential scanning calorimetry (DSC) of about 210-214 °C.

32. The solid form of claim 31, wherein the crystalline solid has an X-ray powder diffraction (XRPD) pattern as substantially shown in Figure 1.

33. The solid form of claim 31, wherein the crystalline solid has a DSC curve as substantially shown in Figure 2.

34. The solid form of any one of claims 31-33, wherein the crystalline solid is present in a capsule in an amount of about 1 mg to about 10 mg.

35. Use of a composition containing a crystalline solid of the free base of the compound of Formula I:



(I),

in the manufacture of a medicament for treating Tourette Syndrome in a subject in need thereof, wherein said crystalline solid has a melting point onset as determined by DSC of about 210-214 °C.

36. The use of claim 35, wherein the crystalline solid has an XRPD pattern as substantially as substantially shown in Figure 1.

37. The use of claim 35, wherein the crystalline solid has a DSC curve as substantially shown in Figure 2.