METHODS FOR THE TREATMENT OF CHILDHOOD-ONSET FLUENCY DISORDER

BACKGROUND

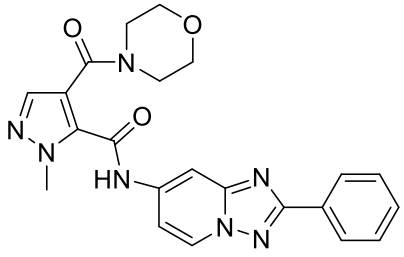
[001] Childhood-Onset Fluency Disorder (COFD; aka stuttering or development stuttering or stammer) is a neuro-developmental speech disorder that involves frequent and significant problems with normal fluency and flow of speech. COFD, typically characterized by recurrent prolongations, reverberations or blocs of sounds, syllables, phrases or words, can lead to significant secondary effects, including negative self-perception and negative perception by others, anxiety, and occasionally depression. It affects about 5% to 10% of preschoolers and about 1% of adults. (R. W. Sander, et al. American Family Physician, 2019, 100(9): 556-560).

[002] There are currently no approved pharmacological treatments for COFD. Disorder management include speech therapy, psychotherapy, and antipsychotics, but with limited effectiveness. Antipsychotics are often used off label and are associated with serious side effects.

[003] Therefore, there is an unmet medical need to develop new methods that can effectively treat COFD without serious side effects.

SUMMARY

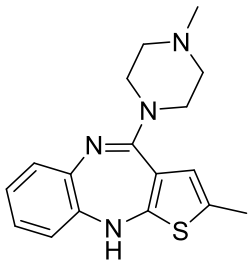
[003a] In an aspect of the present disclosure, there is provided a use of a composition containing a therapeutically effective amount of a therapeutic agent, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Childhood Onset Fluency Disorder (COFD) in a subject in need thereof, wherein the therapeutic agent is a compound of Formula I:



(I).

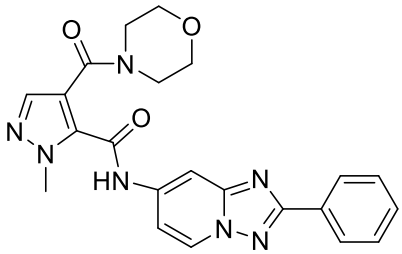
[003b] In another aspect of the present disclosure, there is provided a use of:

a compound of Formula III:



(III); and

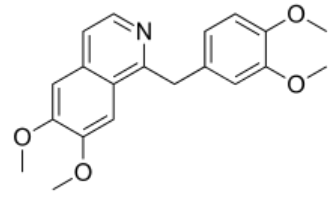
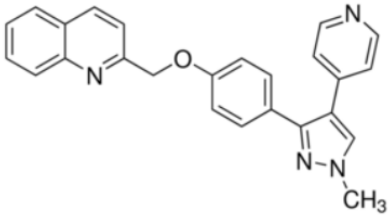
a compound of Formula I:

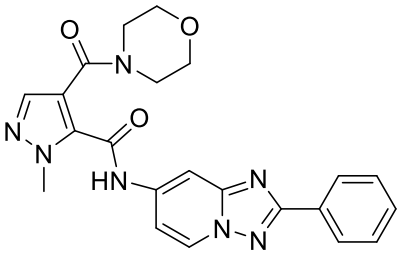
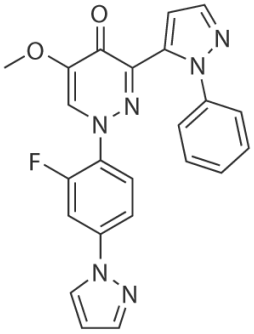


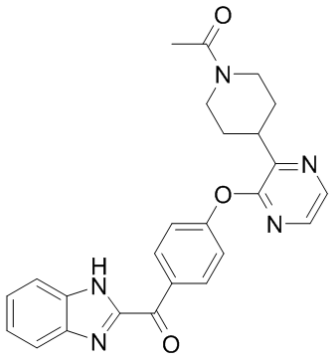
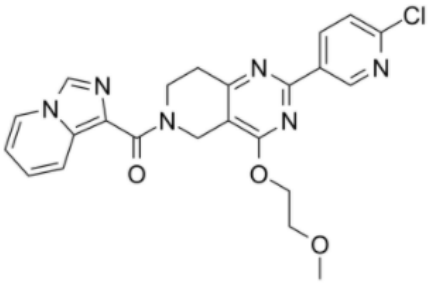
(I);

[004] or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Childhood Onset Fluency Disorder (COFD) in a subject in need thereof.The disclosure is directed to, in one example, a method of treating Childhood-Onset Fluency Disorder (COFD), wherein the method comprises administering to a subject in need thereof a composition containing a therapeutically effective amount of a phosphodiesterase 10A (PDE10A) inhibitor or a pharmaceutically acceptable salt thereof. In another example, a method of treating Childhood-Onset Fluency Disorder (COFD), wherein the method comprises administering to a subject in need thereof a composition containing a therapeutically effective amount of a phosphodiesterase 10A (PDE10A) inhibitor (e.g., compound of Formula I) or a pharmaceutically acceptable salt thereof, and a compound of Formula III, or a pharmaceutically acceptable salt thereof. Each of these different examples can be described more particularly by the various examples described herein, which examples can be equally applicable to the different examples.

[005] Examples of the PDE10A inhibitor include, but are not limited to, papaverine, PF-02545920 (aka MP-10), RO5545965, TAK-063, AMG 579, and THPP-1. The structures of these PDE10A inhibitors are shown below:

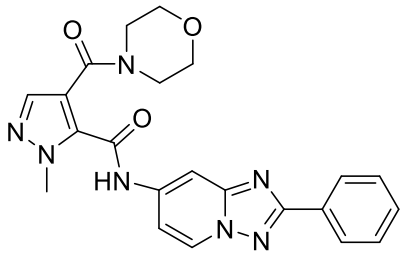
Papaverine , PF-02545920 , RO5545965

, TAK-063 , AMG 579

, THPP-1 .

[006] In certain examples, the method comprises administering the PDE10A inhibitor, or a pharmaceutically acceptable salt thereof, once daily. In certain examples, the method comprises administering orally the PDE10A inhibitor, or a pharmaceutically acceptable salt thereof. In certain examples, the method comprises administering the PDE10A inhibitor, or a pharmaceutically acceptable salt thereof, as a unit dose.

[007] In another example, provided herein is a method of treating COFD, 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 (also refered to herein as RO5545965):



(I).

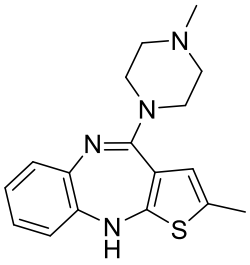
[008] In a further example, provided herein is a method of treating COFD, comprising administering to a subject in need thereof a composition containing a therapeutically effective amount of a therapeutic agent or a pharmaceutically acceptable salt thereof, wherein the therapeutic agent is a compound of Formula I (i.e., RO5545965), wherein the compound in free base, or a pharmaceutically acceptable salt thereof, is administered in an amount of about 5 mg to about 15 mg once daily. In certain examples, the therapeutic agent is a compound of Formula I (i.e., RO5545965) in free base, or a pharmaceutically acceptable salt thereof, is administered in an amount of about 2.5 mg to about 15 mg once daily. In certain examples, the therapeutic agent is a compound of Formula I (i.e., RO5545965) in free base, or a pharmaceutically acceptable salt thereof, is administered in an amount of about 2.5 mg, about 5.0 mg, about 10 mg, or about 15 mg once daily.

[009] Still another example of this disclosure is a method of treating COFD, comprising administering to a subject in need thereof a composition containing a therapeutically effective amount of a crystalline solid of the compound of Formula I above, wherein said crystalline solid has a melting point onset as determined by differential scanning calorimetry (DSC) of about 210 °C to about 214 °C, and said administering comprises administering to the subject the crystalline solid in an amount of about 5 mg to about 15 mg once daily. In certain examples, a therapeutically effective amount of a crystalline solid of the compound of Formula I is administered in an amount of about 2.5 mg to about 15 mg once daily. In certain examples, a therapeutically effective amount of a crystalline solid of the compound of Formula I is administered in an amount of about 2.5 mg, about 5.0 mg, about 10 mg, or about 15 mg once daily.

[0010] In some examples, the crystalline solid set forth above has an XRPD pattern as substantially as substantially shown in FIG. 1. In some examples, the crystalline solid set forth above has a DSC curve as substantially shown in FIG. 2.

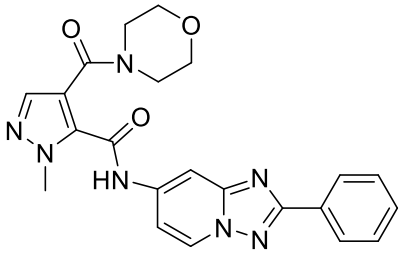
[0011] Also provided herein is a method of treating Childhood-Onset Fluency Disorder (COFD) in a subject in need thereof, comprising administering to a subject in need thereof a therapeutically effective amount of:

a compound of Formula III:



(III); and

a compound of Formula I:

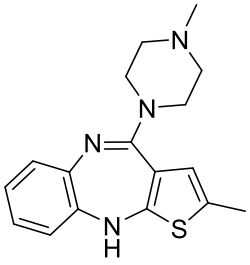


(I);

or a pharmaceutically acceptable salt thereof.

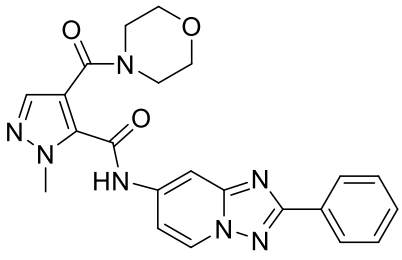
[0012] In certain examples, the compound of Formula III, or a pharmaceutically acceptable salt thereof, is administered at about 2.5 mg to about 5.0 mg once daily; and the compound of Formula I, or a pharmaceutically acceptable salt thereof, is administered at about 5.0 mg to about 15 mg once daily.

[0013] Also provided herein is a compound of the compound of Formula III:



(III); and

a crystalline solid of Formula I:


(I),

wherein said crystalline solid has a melting point onset as determined by DSC of about 210 °C to about 214 °C; or a pharmaceutically acceptable salt thereof. In certain examples, the compound of Formula III, or a pharmaceutically acceptable salt thereof, is administered at about 2.5 mg to about 5.0 mg once daily; and the crystalline solid of Formula I, or a pharmaceutically acceptable salt thereof, is administered at about 5.0 mg to about 15 mg once daily.

[0014] The details of one or more examples of the disclosure are set forth in the description below. Other features, objects, and advantages of the disclosure will be apparent from the drawings, description and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. 1 depicts an exemplary XRPD pattern of a crystalline solid of the free base of the compound of Formula I.

[0016] FIG. 2 depicts an exemplary DSC curve of a crystalline solid of the free base of the compound of Formula I.

[0017] FIG. 3 depicts the glucose level during oral glucose tolerance test in Sprague Dawley rats after acute treatment with Olanzapine (compound of Formula III) or Haloperidol.

[0018] FIG. 4 depicts the insulin level of Sprague Dawley rats after oral glucose challenge (2g/kg).

[0019] FIG. 5 depicts the oral glucose tolerance test and glucose level in Sprague Dawley rats after acute treatment with Olanzapine (compound of Formula III) or Haloperidol.

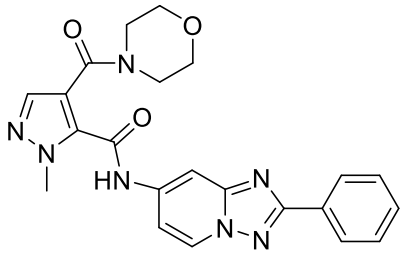
[0020] FIG. 6 depicts the body weight and food intake of Sprague Dawley rats during treatment of Olanzapine (compound of Formula III) or RO5545965 (compound of Formula I).

[0021] FIG. 7 depicts the oral glucose tolerance test and glucose level in Sprague Dawley rats after sub-chronic treatment with Olanzapine (compound of Formula III), RO5545965 (compound

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a composition containing a therapeutically effective amount of a therapeutic agent, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Childhood Onset Fluency Disorder (COFD) 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 compound of Formula I is to be administered to the subject in its free base form.

3. 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.

4. The use of claim 1, wherein the therapeutic agent is to be administered to the subject in an amount of about 1 mg to about 17 mg once daily.

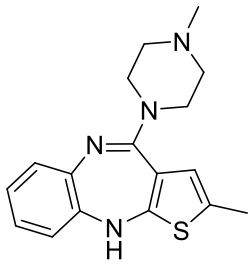
5. The use of claim 1, wherein the therapeutic agent is to be administered to the subject in an amount of about 5 mg to about 15 mg once daily.

6. The use of claim 1, wherein the therapeutic agent is to be administered to the subject in an amount of about 2.5 mg to about 15 mg once daily.

7. The use of claim 1, wherein the therapeutic agent is to be administered to the subject in an amount of about 2.5 mg, about 5.0 mg, about 10 mg, or about 15 mg once daily.

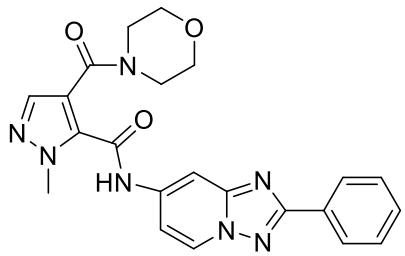
8. Use of:

a compound of Formula III:



(III); and

a compound of Formula I:



(I);

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Childhood Onset Fluency Disorder (COFD) in a subject in need thereof.

9. The use of claim 8, wherein the compound of Formula III, or a pharmaceutically acceptable salt thereof, is to be administered to the subject at about 1 mg to about 50 mg once daily; and the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered to the subject at about 1 mg to about 50 mg once daily.

10. The use of claim 8, wherein the compound of Formula III, or a pharmaceutically acceptable salt thereof, is to be administered to the subject at about 1 mg to about 30 mg once daily; and the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered to the subject at about 500 µg to about 20 mg once daily.

11. The use of claim 8, wherein the compound of Formula III, or a pharmaceutically acceptable salt thereof, is to be administered to the subject at about 2.5 mg to about 5.0 mg once

daily; and the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered to the subject at about 5.0 mg to about 15 mg once daily.

12. The use of claim 8, wherein the compound of Formula III and the compound of Formula I, or a pharmaceutically acceptable salt thereof, are to be administered to the subject simultaneously or to be administered to the subject successively.

13. The use of claim 8, wherein the compound of Formula III is present in a single dosage form and the compound of Formula I is present in a separate dosage form.

14. The use of claim 8, wherein the compound of Formula III, the compound of Formula I, or both the compound of Formula III and the compound of Formula I, or pharmaceutically acceptable salt thereof, are to be administered to the subject intravenously, intramuscularly, or orally.

15. The use of claim 8, wherein the compound of Formula III and the compound of Formula I are comprised in a composition, wherein the composition is an aerosol, an inhalable powder, an injectable, a liquid, a solid, a capsule or a tablet form.

16. The use of claim 1, wherein therapeutic efficacy of the treatment is determined by assessing improvement based on the Stuttering Severity Instrument–Fourth Edition (SSI-4), Subject-rated Self Assessment of Stuttering, Sheehan Disability Scale, Maguire-Leal-Garibaldi Self-rated Stuttering Scale (MLGSSS), Patient global impression of severity (PGI-S), or Clinician global impression of change (CGI-C).

17. The use of claim 1, wherein therapeutic efficacy of the treatment is determined by assessing improvement based on stuttering freedom, rating of the medication satisfaction questionnaire, or clinician-rated stuttering severity instrument-4.

18. The use of claim 8, wherein therapeutic efficacy of the treatment is determined by assessing improvement based on the Stuttering Severity Instrument–Fourth Edition (SSI-4), Subject-rated Self Assessment of Stuttering, Sheehan Disability Scale, Maguire-Leal-Garibaldi

Self-rated Stuttering Scale (MLGSSS), Patient global impression of severity (PGI-S), or Clinician global impression of change (CGI-C).

19. The use of claim 8, wherein therapeutic efficacy of the treatment is determined by assessing improvement based on stuttering freedom, rating of the medication satisfaction questionnaire, or clinician-rated stuttering severity instrument-4.