

Description

Title of Invention: DOSE INITIATION FOR SCHIZOPHRENIA OR BIPOLAR I DISORDER TREATMENT WITH Aripiprazole

Technical Field

[0001] The present application claims priority to U.S. Provisional Application Nos. 63/498,313, filed 26 April 2023, 63/506,624, filed 7 June 2023, and 63/637,079, filed on 22 April 2024; the content of each application is incorporated herein by reference in its entirety.

Background Art

[0002] Schizophrenia and bipolar I disorder (BP-I) are complex, chronic mental health disorders, with affected individuals typically experiencing multiple relapses of symptoms that are separated by periods of remission. While daily oral antipsychotic agents have proven effective for many patients achieving and maintaining symptom control, it relies on their consistent and long-term use. Suboptimal adherence to oral medication, however, is common, with data indicating that 30-50% of patients with schizophrenia or BP-I do not take their medication as prescribed. Various strategies for improving adherence to treatment are available, including the use of long-acting injectable (LAI) antipsychotics; LAI formulations offer dosing intervals ranging from 2 weeks to 6 months, reducing the adherence demands on patients, compared with daily dosing. Indeed, data from several real-world studies indicate that LAI formulations of antipsychotics are associated with significant improvements in treatment adherence versus oral antipsychotics in patients with schizophrenia or BP-I.

[0003] Aripiprazole is an antipsychotic agent that exerts partial agonist activity at dopamine D2 and serotonin 5-HT1A receptors, full agonist activity at dopamine D3 receptors, and antagonist activity at serotonin 5-HT2A receptors. Aripiprazole is available in a once-daily oral formulation and as an extended-release suspension of aripiprazole monohydrate for intramuscular injection, known as aripiprazole, once-monthly (AOM). Additionally, a novel ready-to-use (RTU) LAI formulation of aripiprazole monohydrate, administered as a gluteal intramuscular injection once every two months, has recently been approved for the treatment of schizophrenia or BP-I in the United States. The novel formulation contains aripiprazole monohydrate in doses of 960 mg or 720 mg, with the latter dose used in case of any tolerability concerns, in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers, and in patients who are taking concomitant strong inhibitors of CYP2D6 or CYP3A4.

Summary of Invention

- [0004] Aripiprazole 2-month ready-to-use 960 mg (Ari 2MRTU 960) was developed to extend the maintenance of therapeutic plasma concentrations of aripiprazole from one month with AOM 400 mg (AOM 400) to two months; this is achieved through several considerations, such as an increase in the administered dose, while maintaining minimum aripiprazole concentrations that are similar to those after multiple doses of AOM and other formulation and administration considerations. Less frequent dosing, among other things, with Ari 2MRTU 960 (i.e., 6 injections per year, versus 12 with AOM) may reduce the medication burden for patients and clinicians and improve adherence to antipsychotic treatment in adult patients with schizophrenia or BP-I.
- [0005] As part of the development of Ari 2MRTU 960 and Ari 2MRTU 720 (i.e., Aripiprazole 2-month ready-to-use 720 mg), a previously developed and validated population pharmacokinetic (popPK) model for characterizing aripiprazole plasma concentrations following administration of oral aripiprazole, or AOM at the gluteal or deltoid sites, was expanded to include the novel RTU LAI formulation of aripiprazole (Ari RTU LAI). The expanded popPK modeling resulted in additional options for dose initiations of aripiprazole treatment of patients.
- [0006] For example, the present disclosure is directed to methods of dose initiation for an aripiprazole treatment to a patient in need thereof by administering two, separate injections of aripiprazole with a first aripiprazole injection of a long acting injectable (LAI) and a second aripiprazole injection of a once-monthly injectable (AOM) with a single dose of oral aripiprazole on a first day of the aripiprazole treatment. Simulations of the dose initiation regimen of two injections of the aripiprazole LAI and AOM injectables at separate gluteal and/or deltoid injection sites on the first day of treatment has shown to be sufficient with a PK exposure profile that was comparable to AOM, with a longer dosing interval.
- [0007] In some embodiments, the present disclosure is directed to methods of dose initiation for an aripiprazole treatment to a patient in need thereof comprising: administering two, separate injections of aripiprazole, wherein a first injection comprises 960 mg or 720 mg of aripiprazole in a long-acting injectable (LAI), and a second injection comprises 400 mg or 300 mg of aripiprazole in a once-monthly (AOM) injectable, to the patient with an injection site chosen from a gluteal site, a deltoid site, and combinations thereof, and a single dose of oral aripiprazole, wherein the step of administering occurs on a first day of the aripiprazole treatment.
- [0008] In some embodiments, the present disclosure is directed to methods of treating schizophrenia or bipolar I disorder in a patient in need thereof comprising: administering two, separate injections of aripiprazole, wherein a first injection comprises 960 mg or 720 mg of aripiprazole in a long-acting injectable (LAI), and a second injection comprises 400 mg or 300 mg of aripiprazole in a once-monthly (AOM) injectable, to

the patient with an injection site chosen from a gluteal site, a deltoid site, and combinations thereof, and a single dose of oral aripiprazole, wherein the step of administering occurs on a first day of the aripiprazole treatment and wherein the dose of oral aripiprazole ranges from about 10 mg to about 20 mg of aripiprazole; and continuing administering with a maintenance dose of the LAI comprising 960 mg or 720 mg of aripiprazole, wherein the maintenance dose is administered about two months after the first day of the aripiprazole treatment.

Brief Description of Drawings

- [0009] [Fig.1]FIG. 1 is a diagram of the base model describing aripiprazole pharmacokinetics following oral, AOM and Ari RTU LAI administration.
- [0010] [Fig.2]FIG. 2 is a graph illustrating the simulated pharmacokinetic profile from the final model according to the retained covariates (gender and CYP2D6 status) following six repeated administration of Ari 2MRTU 960 mg of aripiprazole every 8 weeks.
- [0011] [Fig.3]FIG. 3A-3D are graphs of the goodness-of-fit plots for the final aripiprazole population pharmacokinetic model.
- [0012] [Fig.4]FIG. 4A-4G are graphs of the prediction-corrected visual predictive checks for the final aripiprazole population pharmacokinetic model.
- [0013] [Fig.5]FIG. 5A-5F are graphs of the simulated median aripiprazole concentration-time profiles following initiation of Ari 2MRTU 960 mg of aripiprazole across various prior treatment scenarios.
- [0014] [Fig.6]FIG. 6 is a graph of the simulated median aripiprazole concentration-time profiles following Ari 2MRTU 960 mg of aripiprazole as scheduled or after a delay of 2, 4, 6, or 8 weeks in patients already stabilized on Ari 2MRTU 960 mg of aripiprazole.
- [0015] [Fig.7]FIG. 7 is a graph of simulated median aripiprazole concentration-time profile for Ari 2MRTU 960 on Day 28 following AOM on Day 0 (with overlapping oral aripiprazole 20 mg in patients without prior oral aripiprazole stabilization).
- [0016] [Fig.8]FIG. 8A-8D are graphs of simulated median aripiprazole concentration-time profiles following a two-injection start with Ari 2MRTU 960 plus AOM 400 across various prior treatment scenarios.
- [0017] [Fig.9]FIG. 9 is a graph of simulated median steady-state aripiprazole concentration-time profile following administration of Ari 2MRTU 720 in CYP2D6 poor metabolizers.
- [0018] [Fig.10]FIG. 10 is a graph of simulated median steady-state aripiprazole concentration-time profiles following administration of Ari 2MRTU 720 with strong inhibitors of CYP3A4 or CYP2D6.
- [0019] [Fig.11]FIG. 11 is a graph of simulated median Aripiprazole concentration time profile

following administration of Ari 2MRTU 960 (Day 0) with AOM 400 (Day 0) and 20 mg Oral Aripiprazole (Day 0) in all subject (solid line) and in CYP2D6 poor metabolizers (dashed line) or Ari 2MRTU 720 (Day 0) with AOM 300 (Day 0) and 20 mg oral Aripiprazole (Day 0) in CYP2D6 poor metabolizers in subjects already stabilized on 10 mg oral Aripiprazole (dotted line).

[0020] [Fig.12]FIG. 12 is a graph of simulated median Aripiprazole concentration time profile following administration of Ari 2MRTU 960 (Day 0) with AOM 400 (Day 0) and 20 mg oral Aripiprazole (Day 0) in all subject (solid line) and in CYP2D6 poor metabolizers (dashed line) or Ari 2MRTU 720 (Day 0) with AOM 300 (Day 0) and 20 mg oral Aripiprazole (Day 0) in CYP2D6 poor metabolizers in subjects without prior oral Aripiprazole stabilization (dotted line).

[0021] [Fig.13]FIG. 13 diagrams mean (SD) aripiprazole plasma concentration time profiles following administration of a single dose of 780 mg (N=18) or 1200 mg (N=13) aripiprazole 2M RTU long acting injectable ready to use to the gluteal muscle of subjects with schizophrenia.

Description of Embodiments

[0022] As used herein, “a” or “an” entity refers to one or more of that entity, e.g., “a compound” refers to one or more compounds or at least one compound unless stated otherwise. As such, the terms “a” (or “an”), “one or more”, and “at least one” are used interchangeably herein.

[0023] As used herein, the term “about” means approximately, in the region of, roughly, or around. When the term “about” is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term “about” is used herein to modify a numerical value above and below the stated value by a variance of 5%.

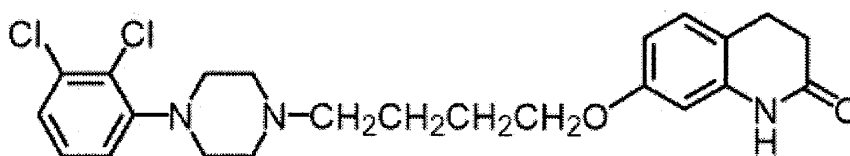
[0024] As used herein, the term “treat,” “treating,” or “treatment,” when used in connection with a disorder or condition, includes any effect, e.g., lessening, reducing, modulating, ameliorating, or eliminating, that results in the improvement of the disorder or condition. Improvements in or lessening the severity of any symptom of the disorder or condition can be readily assessed according to standard methods and techniques known in the art. In some embodiments, the presently disclosed methods or depot formulations can be used to treat schizophrenia and bipolar I disorder, as maintenance monotherapy.

[0025] As used herein, a “mammal” refers to domesticated animals (e.g., dogs, cats, and horses) and humans. In some embodiments, the mammal is a human.

[0026] As used herein, reference to “aripiprazole” is to aripiprazole or a salt thereof, the crystalline form of aripiprazole or a salt thereof. Aripiprazole or a salt thereof may be

in a monohydrate form (aripiprazole hydrate A) or in various anhydrous forms, which are known to exist in the form of anhydrous crystal B, anhydrous crystal C, anhydrous crystal D, anhydrous crystal E, anhydrous crystal F, and anhydrous crystal G. All of those crystalline forms may be used as aripiprazole or a salt thereof in the injectable preparation of the present disclosure and further for example, aripiprazole is a monohydrate form. As used herein, the term “aripiprazole” or salt thereof refers to a compound having the structure:

[Chem.1]



[0027] The empirical formula is $C_{23}H_{27}Cl_2N_3O_2 \cdot H_2O$ and its molecular weight is 466.40. The present disclosure is directed to methods of dose initiation for an aripiprazole treatment to a patient in need thereof by administering two, separate injections of aripiprazole, wherein a first injection comprises 960 mg or 720 mg of aripiprazole in a long-acting injectable (LAI), and a second injection comprises 400 mg or 300 mg of aripiprazole in a once-monthly (AOM) injectable with a single dose or oral aripiprazole, to the patient with an injection site chosen from a gluteal site, a deltoid site, and combinations thereof, and a single dose of oral aripiprazole, wherein the step of administering occurs on a first day of the aripiprazole treatment.

[0028] Embodiments

[0029] Without limitation, some embodiments of the present disclosure include, but are not limited to:

[0030] 1. A method of dose initiation for an aripiprazole treatment to a patient in need thereof comprising: administering two, separate injections of aripiprazole, wherein a first injection comprises 960 mg or 720 mg of aripiprazole in a first long-acting injectable (LAI) formulation, and a second injection comprises 400 mg or 300 mg of aripiprazole in a second LAI formulation, to the patient with an injection site chosen from a gluteal site, a deltoid site, and combinations thereof, and a single dose of oral aripiprazole, wherein the step of administering occurs on a first day of the aripiprazole LAI treatment.

[0031] 2. The method according to embodiment 1, wherein the first LAI formulation is in the form of a gel when allowed to stand, and changes to a sol when subjected to an impact.

[0032] 3. The method according to embodiment 1, wherein the second LAI formulation is a suspension prepared from lyophilized powder and water for injection.

- [0033] 4. The method according to any one of embodiments 1 to 3, wherein the first injection comprises 960 mg of aripiprazole.
- [0034] 5. The method according to any one of embodiments 1 to 4, further comprising after the first day of the aripiprazole LAI treatment, administering a maintenance dose of the first LAI formulation once in about two months.
- [0035] 6. The method according to embodiment 5, wherein the maintenance dose of the first LAI formulation is chosen from 960 mg and 720 mg of aripiprazole.
- [0036] 7. The method according to embodiment 6, wherein when the patient is a CYP2D6 poor metabolizer or is taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days, the maintenance dose of the first LAI formulation is 720 mg of aripiprazole.
- [0037] 8. The method according to any one of embodiments 1 to 7, wherein the two, separate injections of aripiprazole are administered at separate gluteal injection sites of the patient.
- [0038] 9. The method according to any one of embodiments 1 to 7, wherein the two, separate injections of aripiprazole are administered at gluteal and deltoid injection sites of the patient.
- [0039] 10. The method according to any one of embodiments 1 to 7, wherein the two, separate injections of aripiprazole are administered at separate deltoid injection sites of the patient.
- [0040] 11. The method according to any one of embodiments 1 to 10, wherein the patient has schizophrenia.
- [0041] 12. The method according to any one of embodiments 1 to 10, wherein the patient has bipolar I disorder.
- [0042] 13. The method according to any one of embodiments 1 to 12, wherein the dose of oral aripiprazole ranges from about 10 mg to about 20 mg of aripiprazole.
- [0043] 14. The method according to embodiment 13, wherein the dose of oral aripiprazole comprises about 20 mg of aripiprazole.
- [0044] 15. The method according to embodiment 13, wherein the dose of oral aripiprazole comprises about 10 mg of aripiprazole.
- [0045] 16. The method according to any one of embodiments 1 to 15, wherein the patient has not been previously stabilized on oral aripiprazole before the treatment.
- [0046] 17. The method according to embodiment 1, wherein the patient is a CYP2D6 poor metabolizer or is taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days, the first injection comprises 720 mg of aripiprazole, the second injection comprises 400 mg or 300 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 10 mg or about 20 mg of aripiprazole.
- [0047] 18. The method according to embodiment 17, wherein the patient is a CYP2D6 poor

metabolizer or is taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days, the first injection comprises 720 mg of aripiprazole, the second injection comprises 300 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 20 mg of aripiprazole.

- [0048] 19. The method according to embodiment 1, wherein the first injection comprises 960 mg of aripiprazole, the second injection comprises 400 mg or 300 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 10 mg or about 20 mg of aripiprazole.
- [0049] 20. The method according to embodiment 19, wherein the first injection comprises 960 mg of aripiprazole, the second injection comprises 400 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 20 mg of aripiprazole.
- [0050] 21. A method of treating schizophrenia or bipolar I disorder in a patient in need thereof comprising: administering two, separate injections of aripiprazole, wherein a first injection comprises 960 mg or 720 mg of aripiprazole in a first long-acting injectable (LAI) formulation, and a second injection comprises 400 mg or 300 mg of aripiprazole in a second LAI formulation, to the patient with an injection site chosen from a gluteal site, a deltoid site, and combinations thereof, and a single dose of oral aripiprazole, wherein the step of administering occurs on a first day of the aripiprazole LAI treatment and wherein the dose of oral aripiprazole ranges from about 10 mg to about 20 mg of aripiprazole; and continuing administering with a maintenance dose of the first LAI formulation comprising 960 mg or 720 mg of aripiprazole, wherein the maintenance dose is administered once in about two months after the first day of the aripiprazole LAI treatment.
- [0051] 22. The method according to embodiment 21, wherein the first injection comprises 960 mg of aripiprazole, the second injection comprises 400 mg or 300 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 10 mg or about 20 mg of aripiprazole.
- [0052] 23. The method according to embodiment 22, wherein the first injection comprises 960 mg of aripiprazole, the second injection comprises 400 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 20 mg of aripiprazole.
- [0053] 24. The method according to embodiment 21, wherein the first injection comprises 720 mg of aripiprazole, the second injection comprises 400 mg or 300 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 10 mg or about 20 mg of aripiprazole.
- [0054] 25. The method according to embodiment 24, wherein the first injection comprises 720 mg of aripiprazole, the second injection comprises 300 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 20 mg of aripiprazole.
- [0055] 26. The method according to embodiment 21, wherein the dose of oral aripiprazole

comprises about 20 mg of aripiprazole.

[0056] 27. The method according to embodiment 21, wherein the about two months ranges from 54 days to 58 days.

[0057] 28. A long-acting injectable (LAI) comprising 960 mg or 720 mg of aripiprazole, for use in a method of dose initiation for an aripiprazole treatment to a patient in need thereof, the method comprising:

administering two, separate injections of aripiprazole, wherein a first injection comprises 960 mg or 720 mg of aripiprazole in a first long-acting injectable (LAI) formulation, and a second injection comprises 400 mg or 300 mg of aripiprazole in a second LAI formulation, to the patient with an injection site chosen from a gluteal site, a deltoid site, and combinations thereof, and a single dose of oral aripiprazole,

wherein the step of administering occurs on a first day of the aripiprazole LAI treatment.

[0058] 29. Use of aripiprazole in the manufacture of a medicament for an aripiprazole treatment of schizophrenia or bipolar I disorder, the treatment comprising:

administering two, separate injections of aripiprazole, wherein a first injection comprises 960 mg or 720 mg of aripiprazole in a first long-acting injectable (LAI) formulation, and a second injection comprises 400 mg or 300 mg of aripiprazole in a second LAI formulation, to a patient in need thereof with an injection site chosen from a gluteal site, a deltoid site, and combinations thereof, and a single dose of oral aripiprazole,

wherein the step of administering occurs on a first day of the aripiprazole LAI treatment.

[0059] 30. Use of aripiprazole for treating a patient with schizophrenia or bipolar I disorder, wherein the aripiprazole is for administering two, separate injections of aripiprazole, wherein a first injection comprises 960 mg or 720 mg of aripiprazole in a first long-acting injectable (LAI) formulation, and a second injection comprises 400 mg or 300 mg of aripiprazole in a second LAI formulation, to a patient in need thereof with an injection site chosen from a gluteal site, a deltoid site, and combinations thereof, and a single dose of oral aripiprazole,

wherein the step of administering occurs on a first day of the aripiprazole LAI treatment.

[0060] 31. A kit equipped with a prefilled syringe comprising a long-acting injectable (LAI) comprising 960 mg or 720 mg of aripiprazole, for use in a method of dose initiation for an aripiprazole treatment to a patient in need thereof, the method comprising:

administering two, separate injections of aripiprazole, wherein a first injection comprises 960 mg or 720 mg of aripiprazole in a first long-acting injectable (LAI) formulation, and a second injection comprises 400 mg or 300 mg of aripiprazole in a

second LAI formulation, to the patient with an injection site chosen from a gluteal site, a deltoid site, and combinations thereof, and a single dose of oral aripiprazole, wherein the step of administering occurs on a first day of the aripiprazole LAI treatment.

[0061] Aripiprazole Dose Initiation Treatment

[0062] The present disclosure is directed to methods of dose initiation for an aripiprazole treatment to a patient in need thereof by administering two, separate injections of aripiprazole with a first aripiprazole injection of a first long acting injectable (LAI) formulation and a second aripiprazole injection of a second LAI formulation (a once-monthly injectable (AOM)) on a first day of the aripiprazole LAI treatment with a single dose of oral aripiprazole. This dose initiation regimen is also called a "two injection start" in the present disclosure. This dose initiation regimen provides for an Ari RTU LAI PK exposure profile that was comparable to AOM, with a longer dosing interval. Maintenance dosing occurs once in about two months after the first day of the aripiprazole LAI treatment using a maintenance dose of the LAI; for example, maintenance dose follows once in about two months thereafter of 960 mg or 720 mg of aripiprazole first LAI depot formulation. The alternative initiation regimen is applicable to both the deltoid and gluteal administration sites.

[0063] The present disclosure utilizes two, separate aripiprazole injections with a first injection comprising 960 mg or 720 mg of aripiprazole in a long-acting injectable (LAI) formulation, and a second injection comprising 400 mg or 300 mg of aripiprazole in a second LAI formulation (a once-monthly (AOM) injectable) and a single dose of oral aripiprazole. For example, the methods of the present disclosure administer two, separate LAI and AOM aripiprazole injections to the patient at separate gluteal and/or deltoid injection sites with administration occurring on a first day of the LAI treatment. In some embodiments, the two, separate LAI and AOM aripiprazole injections are administered at separate gluteal injection sites or at separate deltoid sites of the patient. In a further embodiment, the two, separate LAI and AOM aripiprazole injections are administered at a gluteal and a deltoid injection site of the patient.

[0064] The present disclosure is further directed to methods of treating schizophrenia or bipolar I disorder in a patient in need thereof comprising: administering two, separate injections of aripiprazole, wherein a first injection comprises 960 mg or 720 mg of aripiprazole in a first long-acting injectable (LAI) formulation, and a second injection comprises 400 mg or 300 mg of aripiprazole in a second LAI formulation (a once-monthly (AOM) injectable), to the patient with an injection site chosen from a gluteal site, a deltoid site, and combinations thereof, and a single dose of oral aripiprazole, wherein the step of administering occurs on a first day of the aripiprazole LAI treatment; and continuing administering with a maintenance dose of the first LAI for-

mulation comprising 960 mg or 720 mg of aripiprazole, wherein the maintenance dose is administered once in about two months after the first day of the aripiprazole treatment.

- [0065] In the present disclosure, aripiprazole treatment may exclude administration for establishment of tolerability with oral aripiprazole prior to initiation of LAI treatment with an injection that comprises 960 mg or 720 mg of aripiprazole in a first long-acting injectable (LAI) formulation.
- [0066] In some embodiments, the methods of the present disclosure comprise wherein the two, separate injections of aripiprazole are administered at separate gluteal injection sites of the patient. In some embodiments, the methods of the present invention comprise wherein the two, separate injections of aripiprazole are administered at gluteal and deltoid injection sites of the patient. In some embodiments, the methods of the present disclosure comprise wherein the two, separate injections of aripiprazole are administered at separate deltoid injection sites of the patient.
- [0067] In some embodiments, the methods of the present disclosure comprise wherein the patient has schizophrenia or bipolar I disorder. In some embodiments, the methods of the present disclosure comprise wherein the patient has schizophrenia. In some embodiments, the methods of the present disclosure comprise wherein the patient has bipolar I disorder.
- [0068] In some embodiments, on the day of initiation, two separate injections of aripiprazole, wherein a first injection comprises 960 mg or 720 mg of aripiprazole in a first long-acting injectable (LAI) formulation, and a second injection comprises 400 mg or 300 mg of aripiprazole in a second LAI formulation (a once-monthly (AOM) injectable) are administered at two different injection sites, along with one 20 mg dose of oral aripiprazole.
- [0069] In some embodiments, when initiating with the two injection start, it is preferable to inject into two different sites in two different muscles. It is preferable not to inject both injections concomitantly into the same deltoid or gluteal muscle. For known CYP2D6 poor metabolizers, it is preferable to administer in either two separate deltoid muscles or one deltoid and one gluteal muscle. It is preferable not to inject into two gluteal muscles.
- [0070] In some embodiments, it is preferable to administer one injection which comprises 960 mg or 720 mg of aripiprazole in a first long-acting injectable (LAI) formulation at gluteal site and one injection which comprises 400 mg or 300 mg of aripiprazole in a second LAI formulation (a once-monthly (AOM) injectable) at gluteal or deltoid site with a single dose of 10 mg or 20 mg of oral aripiprazole on the first day of treatment.
- [0071] In some embodiments, oral aripiprazole is not administered from 1 to 13 days after the first day of the aripiprazole LAI treatment.

- [0072] The rationale for the selection of the alternative initiation regimen dose is based on simulations from a population pharmacokinetic(s) (popPK) model. For example, a previously developed and validated population pharmacokinetic (popPK) model for characterizing aripiprazole plasma concentrations following administration of oral aripiprazole or aripiprazole once-monthly (AOM) intramuscular injection was expanded to include the RTU LAI formulation of aripiprazole (Ari RTU LAI). Overall, 8,899 aripiprazole pharmacokinetic (PK) samples from 1,191 adults from ten clinical trials were included in the final combined analysis dataset. Aripiprazole plasma concentration-time profiles were simulated for various Ari RTU LAI initiation and maintenance scenarios in 1,000 virtual patients. The final popPK model, which incorporated data for oral aripiprazole, AOM and Ari RTU LAI, was found to be a good fit, with absorption of Ari RTU LAI modeled by a parallel zero-order and lagged first-order process. Simulations across multiple scenarios were performed to inform dosing recommendations, including various treatment initiation regimens for a 2-monthly formulation of Ari RTU LAI in patients with or without prior stabilization on oral aripiprazole, and for patients switching from AOM. Additional simulations accounted for missed/delayed doses, CYP2D6 metabolizer status, and concomitant use of CYP2D6 or CYP3A4 inhibitors. Overall, simulations across a variety of scenarios demonstrated an Ari RTU LAI PK exposure profile that was comparable to AOM, with a longer dosing interval.
- [0073] First long-acting injectable (LAI) formulation (Aripiprazole Long-Acting Injectable (LAI))
- [0074] In the methods of the present disclosure, a first injection comprises 960 mg or 720 mg of aripiprazole in a first long-acting injectable (LAI) formulation. In some embodiments, the first injection comprises 960 mg of aripiprazole in the first LAI formulation. In some embodiments, the first injection comprises 720 mg of aripiprazole in the first LAI formulation. Additionally, the methods of the present disclosure comprise administering a maintenance dose of the first LAI formulation. In some embodiments, the maintenance dose of the first LAI formulation comprises 960 mg or 720 mg of aripiprazole. In some embodiments, the maintenance dose comprises 960 mg of aripiprazole in the first LAI formulation. In some embodiments, the maintenance dose comprises 720 mg of aripiprazole in the first LAI formulation.
- [0075] In some embodiments, the first LAI formulation comprises a composition comprising aripiprazole, a specific suspending agent (suspending agent (A)), and a dispersion medium. For example, the injectable preparation of the present disclosure comprises at least water as a dispersion medium. Water, or an aqueous solvent comprising water and an organic solvent can be used as a dispersion medium comprising at least water. In some embodiments, the dispersion medium is water, and further for example, sterile

water for injection.

- [0076] The specific suspending agent (suspending agent A) contained in the first LAI formulation comprises at least one suspending agent chosen from (i) and (ii): (i) polyvinylpyrrolidone, and (ii) polyethylene glycol and carboxymethyl cellulose or a salt thereof.
- [0077] In some embodiments, the first LAI formulation comprises aripiprazole or a salt thereof, water, and at least one suspending agent chosen from groups (i) and (ii): (i) polyvinylpyrrolidone, and (ii) polyethylene glycol and carboxymethylcellulose or a salt thereof, wherein aripiprazole or a salt thereof has a mean primary particle diameter ranging from about 0.5 μm to about 30 μm and the concentration of aripiprazole or a salt thereof ranges from about 200 mg/mL to about 600 mg/mL. The presently disclosed, first LAI formulation, two months ready to use (RTU) or long acting injectable (LAI), injectable preparation is described in U.S. Pat. No. 10,517,951, which is incorporated herein by reference in its entirety. The injectable preparation of the LAI preparation is, for example, Abilify Asimtufii (R), Abilify Maintena (R) 720 mg prolonged-release suspension for injection in pre-filled syringe or Abilify Maintena (R) 960 mg prolonged-release suspension for injection in pre-filled syringe.
- [0078] For example, when the injectable preparation of the present disclosure comprises aripiprazole or a salt thereof (which hereafter may be referred to as “the aripiprazole injectable preparation of the present disclosure”) the concentration of aripiprazole or a salt thereof ranges from about 200 mg/mL to about 600 mg/mL. (α) The first LAI formulation of aripiprazole become a gel upon standing, which precipitation and caking of the particles of aripiprazole can be inhibited, thereby providing excellent storage stability. Furthermore, because (β) the injectable preparation, even in the form of a gel, can easily gain fluidity when subjected to a mild impact, the preparation can be easily injected at the time of use (at the time of injection). Further, because the gelled injectable preparation (gel composition) gains fluidity (forms a sol state) by simply pressing the plunger of a syringe and ejecting the preparation through a syringe needle, the preparation can be smoothly ejected through the needle as is. Therefore, the preparation can have a thixotropic property, and be well dispersed intramuscularly or subcutaneously with relatively less local disturbance and pain at the time of injection.
- [0079] That is, when the concentration of aripiprazole or a salt thereof is 100 mg/mL or below, the production of an injectable preparation that can form a gel may not occur even if the suspending agent A is used (or an aging treatment is further performed). Therefore, the first LAI formulation of the present disclosure comprises aripiprazole or a salt thereof, a combination of the use of a specific suspending agent (suspending agent A) and a specific concentration of aripiprazole or a salt thereof (from about 200 mg/mL to about 600 mg/mL, such as from about 250 mg/mL to about 450 mg/mL, and

from about 300 mg/mL to about 400 mg/mL) is used. When the first LAI formulation of the present disclosure comprises a salt of aripiprazole, the concentration described above is calculated as aripiprazole.

- [0080] In some embodiments, the first LAI formulation comprises aripiprazole in a concentration of about 200 mg/mL to about 600 mg/mL, such as about 200 mg/mL to about 500 mg/mL, for example, about 250 mg/mL to about 450 mg/mL, further for example, about 300 mg/mL to about 400 mg/mL, and further for example, about 300 mg/mL.
- [0081] In some embodiments, in the first LAI formulation of the present disclosure, when (i) polyvinylpyrrolidone is contained as suspending agent A, the concentration of polyvinylpyrrolidone ranges from about 0.1 mg/mL to about 100 mg/mL, such as about 1 mg/mL to about 50 mg/mL, and further for example about 2 mg/mL to about 20 mg/mL.
- [0082] In some embodiments, when the first LAI formulation of the present disclosure comprises (i) polyvinylpyrrolidone as suspending agent A, and further comprises one or more other suspending agents, at least one member is chosen from polyethylene glycol and carboxymethylcellulose or a salt thereof be contained as the one or more other suspending agents. For example, these injectable preparations of the present disclosure comprise (i) polyvinylpyrrolidone as suspending agent A, and when they further comprise one or more other suspending agents, they comprise suspending agents of any combination of (i-1) to (i-3) shown below.
- [0083] (i-1) polyvinylpyrrolidone and polyethylene glycol
- [0084] (i-2) polyvinylpyrrolidone and carboxymethylcellulose or a salt thereof, and
- [0085] (i-3) polyvinylpyrrolidone, polyethylene glycol, and carboxymethylcellulose or a salt thereof.
- [0086] Regardless of which combination of (i-1) to (i-3) these injectable preparations of the present disclosure comprise, the concentration of polyvinylpyrrolidone is, as described above, about 0.1 mg/mL to about 100 mg/mL, such as about 1 mg/mL to about 50 mg/mL, and further for example, about 2 mg/mL to about 20 mg/mL. In (i-1) or (i-3), the concentration of polyethylene glycol is about 0.05 mg/mL to about 100 mg/mL and for example, about 0.1 mg/mL to about 50 mg/mL. In (i-2) or (i-3), the concentration of carboxymethylcellulose or a salt thereof is about 0.5 mg/mL to about 50 mg/mL, such as about 1 mg/mL to about 30 mg/mL, and further for example, about 2 mg/mL to about 20 mg/mL.
- [0087] By containing carboxymethylcellulose or a salt thereof, an increase in viscosity during production can be suppressed. This allows aripiprazole or a salt thereof, to be pulverized into a desirable particle size in an efficient manner. In some embodiments, the molecular weight of carboxymethylcellulose or a salt thereof ranges from 49,000 to

300,000. Furthermore, by containing polyethylene glycol, syneresis can be prevented even when the resulting injectable preparation is stored for a long period of time. In some embodiments, the molecular weight of polyethylene glycol ranges from 400 to 4,000. In some embodiments, (i-3) is present in the injectable preparation.

[0088] In some embodiments, the average molecular weight of carboxymethylcellulose or a salt thereof is, for example, 5,000 or more, preferably 10,000 or more, more preferably 20,000 or more, more preferably 30,000 or more, more preferably 40,000 or more, more preferably 50,000 or more. In other embodiments, the average molecular weight of carboxymethylcellulose or a salt thereof is, for example, 300,000 or less, preferably 250,000 or less, more preferably 200,000 or less, more preferably 150,000 or less. In still other embodiments, the average molecular weight of carboxymethylcellulose or a salt thereof is, for example, between 5,000 and 300,000, preferably between 10,000 and 250,000, preferably between 20,000 and 200,000, preferably 50,000 and 150,000.

[0089] In some embodiments, the viscosity of a 2% (weight/volume) aqueous solution of carboxymethylcellulose or a salt thereof is, for example, 1,000 mPa · s or less, preferably 800 mPa · s or less. In other embodiments, the viscosity is, for example, 10 mPa · s or more, preferably 50 mPa · s or more. In still other embodiments, the viscosity is, for example, between 10 and 1,000 mPa · s, preferably between 50 and 800 mPa · s. The viscosity can be measured according to the method described in the USP-NF (for example, the 2019 edition USP42-NF37).

[0090] In some embodiments, when the first LAI formulation of the present disclosure comprises (ii) polyethylene glycol and carboxymethylcellulose or a salt thereof as suspending agent A, the concentration of polyethylene glycol is about 0.05 mg/mL to about 2 mg/mL and further for example, about 0.1 mg/mL to about 1 mg/mL. In other embodiments, the concentration of carboxymethylcellulose or a salt thereof is about 0.5 mg/mL to about 50 mg/mL, such as about 1 mg/mL to about 30 mg/mL, and such as about 2 mg/mL to about 20 mg/mL.

[0091] In some embodiments, when the first LAI formulation of the present disclosure comprises (ii) polyethylene glycol and carboxymethylcellulose or a salt thereof as suspending agent A, and further comprises one or more other suspending agents, polyvinylpyrrolidone can be contained as the one or more other suspending agents. For example, the injectable preparation of the present disclosure comprises, as suspending agent A, (ii) polyethylene glycol and carboxymethylcellulose or a salt thereof, and when it further comprises one or more other suspending agents, the suspending agents of (i-3) are contained. In this case, the concentrations of polyethylene glycol, carboxymethylcellulose or a salt thereof, and polyvinylpyrrolidone are the same as described in (i-3) above.

[0092] In some embodiments, in the first LAI formulation of the present disclosure, when

the suspending agents of (i-3) are used, the composition comprises about 0.5 mg/mL to about 20 mg/mL of polyvinylpyrrolidone, about 0.1 mg/mL to about 100 mg/mL of polyethylene glycol, about 0.5 mg/mL to about 50 mg/mL of carboxymethylcellulose or a salt thereof, and about 250 mg/mL to about 450 mg/mL (such as about 300 mg/mL to about 400 mg/mL) of aripiprazole or a salt thereof. In this case, the polyethylene glycol may be polyethylene glycol 400 or polyethylene glycol 4000. In some embodiments, the polyvinylpyrrolidone has a K value of about 12 to about 20. In further aspects, the aripiprazole or a salt thereof has a mean primary particle diameter of about 1 μm to 10 μm .

[0093] Because an unduly large mean primary particle diameter of the aripiprazole or a salt thereof, may cause precipitation, the mean primary particle diameter ranges from about 0.5 μm to about 30 μm and for example, about 1 μm to about 20 μm . When the injectable preparation of the present disclosure is in a dosage form that is administered once every two months, the aripiprazole or a salt thereof has a mean primary particle diameter of about 1 μm to about 50 μm , such as about 1 μm to about 10 μm , and further for example, about 2 μm to about 5 μm . The mean secondary particle diameter is up to but not exceeding three times and further for example, up to but not exceeding twice the mean primary particle diameter.

[0094] In some embodiments, the first LAI formulation of the present disclosure is suitably formulated into a dosage form that can be administered once every two months. For example, the concentration of aripiprazole or a salt thereof in the first LAI formulation of the present disclosure that is administered once every two months, is, calculated as aripiprazole, about 200 mg/mL to about 600 mg/mL, such as about 250 mg/mL to about 500 mg/mL, further for example, about 300 mg/mL to 400 mg/mL, and further for example, about 300 mg/mL. When the injectable preparation is administered once every two months, the dosage volume is about 2 mL to about 4 mL, such as about 2.2 mL to about 3.5 mL, further for example, about 2.3 mL to about 3.4 mL, and further for example, about 3.2 mL.

[0095] In some embodiments, the first LAI formulation of the present disclosure achieves the effects (α) and (β) described above. They may be in the form of a gel or they may have fluidity (i.e., they may be in the form of a sol). As described above, the achievement of the effects of the effects (α) and (β) can objectively confirmed by the use of a rotary rheometer. The first LAI formulation may be formulated into a dosage form of a prefilled sol-gel formed injection (also herein referred to as a “prefilled sol-gel formed injectable preparation”). This injectable formulation exhibits a thixotropic property. And the formulation may be in the form of a gel when allowed to stand, and may change to a sol when subjected to an impact.

[0096] In some embodiments, a method for producing the first LAI formulation comprises

preparing a liquid mixture of the starting materials and pulverizing aripiprazole or a salt thereof, contained in the liquid mixture to a desired mean primary particle diameter, optionally followed by aging.

[0097] In some aspects, a method for producing the gel first LAI formulation according to the present invention comprises allowing a liquid mixture to stand at 5 to 70°C for 5 minutes or more, the liquid mixture comprising aripiprazole or a salt thereof with a mean primary particle diameter of about 0.5 μm to about 30 μm in a concentration of about 200 mg/mL to about 600 mg/mL, water, and at least one suspending agent chosen from (i) and (ii): (i) polyvinylpyrrolidone and (ii) polyethylene glycol and carboxymethyl cellulose or a salt thereof.

[0098] For example, in some further embodiments, a production method comprising the following steps can be used: pulverizing aripiprazole or a salt thereof to a mean primary particle diameter of about 0.5 μm to about 30 μm in a liquid mixture comprising the aripiprazole or a salt thereof in a concentration of about 200 mg/mL to about 600 mg/mL, water, and at least one suspending agent selected from the group consisting of (i) and (ii): (i) polyvinylpyrrolidone and (ii) polyethylene glycol and carboxymethyl cellulose or a salt thereof; and allowing the pulverized liquid mixture to stand at 5°C to 70°C for 5 minutes or more.

[0099] In some embodiments, the present disclosure comprises the administration of the first LAI formulation resulting in a total amount of aripiprazole of 960 mg or 720 mg, for example 960 mg, further for example from 720 mg, administered to the patient, wherein the injectable preparation may be optionally administered in one or more divided injections. In some further embodiments, the administration of the first LAI formulation results in a total amount of aripiprazole of about 960 mg to the patient, wherein one or more injectable formulations are administered. For example, to obtain a total amount of 960 mg of aripiprazole administered to the patient, one (1) injection of the first LAI formulation comprising 960 mg/mL of aripiprazole is administered. The 960 mg dosage may be optionally administered in separate injections at short intervals. In some embodiments, the first injection comprises 960 mg of aripiprazole. In some embodiments, the administration of the first LAI formulation results in a total amount of aripiprazole of about 720 mg to the patient, wherein one or more injectable formulations are administered. For example, to obtain a total amount of 720 mg of aripiprazole administered to the patient, one (1) injection of the first LAI formulation comprising 720 mg/mL of aripiprazole is administered. In some embodiments, the first injection comprises 720 mg of aripiprazole. The 720 mg dosage may be optionally administered in separate injections at short intervals. The number of injections and the concentration of the aripiprazole varies in view of the total amount of aripiprazole to be administered and the concentration of aripiprazole contained in each of the in-

jectable preparations, as described above.

- [0100] In some embodiments, the administration of the first LAI formulation to the subject is injected intramuscularly. In some embodiments, administering intramuscularly is at a site chosen from a deltoid, a gluteal muscle, and combinations thereof. In some embodiments, the site is the gluteal muscle. For example, depending on the number of injections for administration, the injection site may encompass various locations of the deltoid and/or gluteal muscles.
- [0101] In some embodiments, maintenance dosing occurs once in about two months after the first day of the aripiprazole LAI treatment using a maintenance dose of the first LAI formulation; for example, maintenance dose follows once in about two months thereafter of 960 mg or 720 mg of first LAI formulation. As with the traditional dose initiation regimen, the alternative initiation regimen is applicable to both the deltoid and gluteal administration sites. For example, the methods of administering the first LAI formulation of aripiprazole disclosed herein occur at a frequency of about once every two months. In some embodiments, the first LAI formulation is administered about once every 42 to 70 days or at any integer in between and including the end points, e.g., every 49 to 63 days, e.g., every 50 to 60 days, i.e., 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61 or 62 days. In further aspects, the first LAI formulation is administered about once every 56 days, e.g., once every 54 days to 58 days. In further aspects, the first LAI formulation is administered about once every 8 weeks, e.g., once every 6 weeks to 10 weeks. In some embodiments, the maintenance dose is 960 mg of the first LAI formulation. In some embodiments, the maintenance dose is 720 mg of the first LAI formulation.
- [0102] In some embodiments, the present disclosure is further directed when the patient is a CYP2D6 poor metabolizer or is taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days, the maintenance dose of the first LAI formulation is 720 mg of aripiprazole.
- [0103] In some embodiments, the first LAI formulation of the present disclosure can be filled as is into a syringe for use as a prefilled syringe. This simplifies the structure of the syringe and reduces size and weight. In some embodiments, the first LAI formulation comprises 960 mg of aripiprazole in a prefilled syringe. In some embodiments, the first LAI formulation comprises 720 mg of aripiprazole in a prefilled syringe. When the first LAI formulation of the present disclosure is filled into a syringe, in a further embodiment, a sol suspension can be administered by simply pressing the plunger rod of the syringe and ejecting the first LAI formulation of the present disclosure through a syringe needle. This provides a prefilled syringe that offers clinical convenience and operability, thus is highly useful medically and industrially. An example of producing such a prefilled syringe is such that the first LAI

formulation is produced in the manner as described above, the formulation is prefilled into a syringe, and then left to stand in the manner as described above to cause the first LAI formulation to gel.

- [0104] In some embodiments, the first LAI formulation comprises 720 mg or 960 mg dose strength in pre-filled syringes and the strengths are calculated based on the anhydrous form (aripiprazole). The concentration of aripiprazole is 200 mg/mL to 600 mg/mL. In some embodiments, inactive ingredients are carboxymethylcellulose sodium (0.5 mg/mL to 50 mg/mL), polyethylene glycol 400 (0.05 mg/mL to 2 mg/mL), povidone (0.1 mg/mL to 100 mg/mL), sodium chloride (0.1 mg/mL to 50 mg/mL), sodium phosphate monobasic monohydrate (0.1 mg/mL to 10 mg/mL), sodium hydroxide (to adjust pH) and water for injection (q.s.).
- [0105] In some embodiments, the first LAI formulation comprises 720 mg or 960 mg dose strength in pre-filled syringes and the strengths are calculated based on the anhydrous form (aripiprazole). Inactive ingredients are carboxymethylcellulose sodium (5 mg/mL), polyethylene glycol 400 (1 mg/mL), povidone (4 mg/mL), sodium chloride (6.1 mg/mL), sodium phosphate monobasic monohydrate (0.74 mg/mL), sodium hydroxide (to adjust pH) and water for injection (q.s.). In some embodiments, the first LAI formulation comprises 960 mg dose strength of aripiprazole in a pre-filled syringe with a volume of about 3.2 mL. In some embodiments, the first LAI formulation comprises 720 mg dose strength of aripiprazole in a pre-filled syringe with a volume of about 2.4 mL.
- [0106] In some embodiments, the present disclosure also includes a kit equipped with the above-described prefilled syringe.
- [0107] Second LAI formulation (Aripiprazole Once-Monthly Injectable (AOM))
- [0108] In the methods of the present disclosure, a second injection comprises 400 mg or 300 mg of aripiprazole in a second LAI formulation (a once-monthly (AOM) injectable). In some embodiments, the second injection comprises 400 mg of aripiprazole in the second LAI formulation (AOM injectable). In some embodiments, the second injection comprises 300 mg of aripiprazole in the second LAI formulation (AOM injectable).
- [0109] In some embodiments, aripiprazole intramuscular depot formulation comprises aripiprazole monohydrate; aripiprazole monohydrate is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyryl monohydrate.
- [0110] For example, in some embodiments, the second injection is aripiprazole intramuscular (IM) depot formulation which is an extended-release injectable suspension in 400-mg or 300-mg strength in pre-filled dual chamber syringes and 400-mg or 300-mg strength vials. In some embodiments, the second injection comprising 400 mg or 300 mg of aripiprazole in a second LAI formulation (a once-monthly (AOM) injectable)

includes lyophilized powder or lyophilized cake for injectable suspension. The labeled strengths are calculated based on the anhydrous form (aripiprazole). In some embodiments, inactive ingredients (per administered dose) for 400-mg and 300-mg strength products, respectively, include carboxymethyl cellulose sodium (16.64 mg and 12.48 mg), mannitol (83.2 mg and 62.4 mg), sodium phosphate monobasic monohydrate (1.48 mg and 1.11 mg) and sodium hydroxide (pH adjuster). In further embodiments, the extended-release injectable suspension in 400-mg or 300-mg strength in pre-filled dual chamber syringes and 400-mg or 300-mg strength vials can be used to make dosage adjustments; that is, in patients who are CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors. Dosage adjustments for 200 mg and 160 mg can be obtained by using the 300-mg or 400-mg strength vials for intramuscular deltoid or gluteal injection for patients taking CYP2D6 inhibitors, CYP3A4 inhibitors, or CYP3A4 for greater than 14 days. The presently disclosed second LAI formulation (aripiprazole IM depot formulation), Abilify Maintena(R), for suspension in an extended-release form is described in U.S. Pat. Nos. 7,807,680, 8,030,313, 8,338,427, 8,338,428, 8,399,469, 8,722,679, 8,759,351, 8,993,761, 9,089,567, and 10,525,057; all of which are incorporated herein by reference in their entirety.

- [0111] In some embodiments, the activity of the aripiprazole intramuscular depot formulation is presumably primarily due to the parent drug, aripiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole, which has been shown to have affinities for D2 receptors similar to the parent drug and represents about 29% of the parent drug exposure in plasma.
- [0112] Aripiprazole absorption into the systemic circulation is slow and prolonged following intramuscular injection due to low solubility of aripiprazole particles. Following a single-dose administration of the aripiprazole intramuscular depot formulation in the deltoid and gluteal muscle, the extent of absorption (AUC_t , AUC_∞) of aripiprazole was similar for both injection sites, but the rate of absorption (C_{max}) was 31% higher following administration to the deltoid compared to the gluteal site. However, at steady state, AUC and C_{max} were similar for both sites of injection. Following multiple intramuscular doses, the plasma concentrations of aripiprazole gradually rise to maximum plasma concentrations at a median T_{max} of about 5-7 days for the gluteal muscle and about 4 days for the deltoid muscle. After gluteal administration, the mean apparent aripiprazole terminal elimination half-life was about 29.9 days and about 46.5 days after multiple injections for every 4-week injection of the aripiprazole intramuscular depot formulation 300 mg and 400 mg, respectively. Steady state concentrations for the typical subject were attained by the fourth dose for both sites of administration. Approximate dose-proportional increases in aripiprazole and dehydro-aripiprazole

exposure were observed after every four-week of the aripiprazole intramuscular depot formulation injections of 300 mg and 400 mg.

- [0113] Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4. Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation.
- [0114] Aripiprazole Oral Formulation
- [0115] In some embodiments, the methods of the present disclosure comprise administering a single dose of oral aripiprazole. In some embodiments, the dose of oral aripiprazole ranges from about 10 mg to about 20 mg of aripiprazole. In some embodiments, the dose of oral aripiprazole is 20 mg. In some embodiments, the dose of oral aripiprazole is 10 mg. In some embodiments, the methods are administered when the patient has or has not been previously stabilized on oral aripiprazole before the treatment. In some embodiments, the methods are administered when the patient has been previously stabilized on oral aripiprazole before the treatment. In some embodiments, the methods are administered when the patient has not been previously stabilized on oral aripiprazole before the treatment.
- [0116] In some embodiments, oral tablets of aripiprazole are available in, e.g., 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg strengths. Inactive ingredients in oral tablets, e.g., include cornstarch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. Colorants can include, e.g., ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake.
- [0117] Aripiprazole is well absorbed after administration of a tablet, with peak plasma concentrations occurring, e.g., within 3 hours to 5 hours; the absolute oral bioavailability of the tablet formulation is about 87%. Oral tablets of aripiprazole can be administered with or without food. For example, administration of a 15 mg oral tablet of aripiprazole with a standard high-fat meal did not significantly affect the C_{max} or AUC of aripiprazole or its active metabolite, dehydro-aripiprazole, but delayed T_{max} by 3 hours for aripiprazole and 12 hours for dehydro-aripiprazole.
- [0118] Aripiprazole is metabolized primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on in vitro studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in the systemic circulation. At steady-state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.
- [0119] Following a single oral dose of [¹⁴C]-labeled aripiprazole, approximately 25% and 55% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged aripiprazole was excreted in the urine and ap-

proximately 18% of the oral dose was recovered unchanged in the feces.

[0120] The present disclosure utilizes an oral tablet of aripiprazole at a single oral dose chosen from about 10 mg to about 20 mg, such as single oral doses of 10 mg, 15 mg, and 20 mg of aripiprazole. In some embodiments, the single oral dose ranges from about 10 mg to about 20 mg of aripiprazole, such as about 20 mg of aripiprazole. In some embodiments, the single oral dose is chosen from 10 mg and 20 mg of aripiprazole. In further embodiments, the single oral dose is 20 mg of aripiprazole. In some embodiments, the single oral dose is 10 mg of aripiprazole.

[0121] In some embodiments, the present disclosure is directed to methods comprising wherein the patient is a CYP2D6 poor metabolizer or is taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days, the first injection comprises 720 mg of aripiprazole, the second injection comprises 300 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 20 mg of aripiprazole.

[0122] In some embodiments, the present disclosure is directed to methods comprising wherein the first injection comprises 960 mg of aripiprazole, the second injection comprises 400 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 20 mg of aripiprazole.

Examples

[0123] Population Pharmacokinetic Model Development

[0124] Source Data

[0125] PK data from ten clinical trials were used for the development of the popPK model. Data for oral aripiprazole and AOM injected at the gluteal or deltoid site were from a previously developed and validated popPK model, as described by Wang and colleagues.[Wang et al. 2021] The previously developed model used data from healthy adults (n=52) or adult patients with schizophrenia (n=765), from four Phase 1 trials, two Phase 1b trials, and one Phase 3 trial. The previous model was expanded to include data for the RTU LAI formulation of aripiprazole, which were derived from three clinical trials undertaken in 374 patients with schizophrenia or BP-I. Across the three trials, 240 patients received at least one dose of Ari RTU LAI. In all, the final combined analysis dataset comprised 1,191 individuals with 8,899 aripiprazole concentration samples.

[0126] Model Development

[0127] The starting point for the popPK model development was the prior popPK model for oral aripiprazole and AOM, as described above. In brief, this was a 3 compartment model with linear elimination, sigmoid absorption (zero order followed by first order) for oral administration, and first-order absorption for the AOM formulation. Covariate effects included: CYP2D6 metabolizer status on apparent clearance (CL/F); co admin-

istration of strong inhibitors of CYP2D6 or CYP3A4 on clearance; and the effect of gender and body mass index (BMI) on the first-order absorption rate constant (K_a) for the AOM formulation. PK data for the Ari RTU LAI formulation were added to the analysis data, and an absorption compartment specific to the Ari RTU LAI formulation was added to the model. Covariate effects from the prior model for oral aripiprazole and AOM were retained, while additional covariates related to the absorption and relative bioavailability of the Ari RTU LAI formulation were explored (i.e., injection site and volume). Age, gender, and BMI were also evaluated as standard demographic variables. As a first step, potential relationships were investigated graphically by plotting individual random effects versus covariates (scatter plots for continuous covariates, side-by-side box plots for categorical covariates). Next, formal testing of potential covariate effects on the absorption parameters of the Ari RTU LAI formulation comprised a modified stepwise approach using forward selection of all statistically significant variables on univariate analysis ($p < 0.01$ threshold [difference in minimum value of objective function (ΔMVOF) of ≥ 6.63 for 1 degree of freedom (df)]) and standard stepwise backward elimination ($p < 0.001$ threshold [ΔMVOF of ≥ 10.83 for 1 df]). Relationships between PK parameters and continuous covariates were evaluated using a power function, while relationships between PK parameters and categorical covariates were evaluated using a proportional function.

[0128] Model Evaluation

[0129] The goodness of fit of the final model was assessed by standard diagnostic plots (e.g., observed concentration versus population predictions [PRED], observed concentration versus individual predictions, conditional weighted residuals [CWRES] versus PRED and time after first dose). The predictive performance of the final model was evaluated using visual predictive checks (VPCs) by simulating 500 replicates of the combined dataset. If significant categorical covariate effects were identified in the final model, simulations were performed to visualize these effects on the concentration-time profile following repeated administration of Ari 2MRTU 960.

[0130] Bioanalytical Methods

[0131] Across all ten trials, aripiprazole plasma concentrations were assayed using validated high-performance liquid chromatography with tandem mass spectrophotometry. A linear calibration curve was used, with the calibration range varying across the different trials, as follows: 1-250 ng/mL in Studies 31-98-206, 31-98-207, and CN138020; 0.5-250 ng/mL in Studies 31-05-244 and 31-07-246; and 0.5-500 ng/mL in Studies 31-11-290, 31-12-298, 031-201-00104, 031-201-00181, and 031-201-00279.

[0132] Population Pharmacokinetic Model Simulations

[0133] Following development of the final PopPK model, multiple simulations were conducted to explore aspects of Ari RTU LAI dosing. This included various treatment

initiation scenarios, including a switch from AOM 400, prior stabilization on oral aripiprazole 10 mg, 20 mg, or 30 mg, and no prior stabilization on oral aripiprazole. For each initiation scenario, two start strategies were considered: an overlap of the first dose of Ari RTU LAI with 14 days of oral aripiprazole 10 mg or 20 mg, or a two-injection start (one dose of Ari 2MRTU 960 and one dose of AOM 400 at separate injection sites combined with a single oral dose of aripiprazole 20 mg on treatment Day 1). Additional simulations included: missed/delayed doses (to evaluate the impact of a lack of adherence, as defined by different scenarios, with Ari 2MRTU 960 doses delayed by 2, 4, 6, and 8 weeks); CYP2D6 metabolizer status (to evaluate lower dosing in CYP2D6 poor metabolizers); and drug-drug interactions (to evaluate lower dosing with concomitant use of strong inhibitors of CYP2D6 or CYP3A4). For comparison, an initiation scenario with Ari RTU LAI 960, Ari RTU LAI 960 and oral aripiprazole was simulated.

[0134] For the simulations, a population of 1,000 virtual patients was created. Individual PK parameters for the virtual patients were derived from patient covariates and random effects according to the popPK model and were used to simulate individual PK profiles according to each dosing scenario. Model covariates (i.e., gender, BMI, and CYP2D6 metabolizer status, as included in the popPK model) were assigned to the virtual patients by resampling from the total patient population used to develop the final popPK model (n=1,191). To best reflect the target patient population, random effects and covariates were resampled from individuals with the most relevant and robust information for each parameter of interest. Across almost all simulation scenarios, the virtual patient population remained constant, comprising a mixture of normal and poor metabolizers of CYP2D6 as obtained by the resampling procedure with poor metabolizers making up approximately 5% of the population. The only exception to this was for scenarios that required all patients to be normal or poor CYP2D6 metabolizers; in this situation, the status was changed accordingly for the whole virtual patient population. For simulations involving AOM the site of administration was the gluteal muscle to allow easier comparison to Ari RTU LAI, which is gluteal only.

[0135] Simulation results were presented graphically by plotting median values over time, with reference lines added to mark certain concentration levels of interest (i.e., to facilitate interpretation of the results and comparisons across different plots). These included 95 ng/mL (the plasma concentration identified as the lower efficacy threshold for the prevention of impending relapse); this was based on an exposure-response model analysis for AOM 400 that showed that a patient with schizophrenia and a predicted aripiprazole minimum concentration (C_{min}) of ≥ 95 ng/mL was 4.41 times less likely to relapse than a patient with a C_{min} <95 ng/mL.[Wang et al., 2022] Additionally, a value of 95 ng/mL is consistent with 94 ng/mL, which is the median steady-

state minimum aripiprazole plasma concentration ($C_{min,ss}$) for oral aripiprazole 10 mg (i.e., the lowest daily dose of oral aripiprazole considered effective for the treatment of adults with schizophrenia);[Salzman et al., 2017; Abilify Prescribing Information, 2020] it is also broadly similar to a therapeutic threshold of up to 100-120 ng/mL reported by other researchers.[Hiemke et al., 2018; Meyer & Stahl, 2021; Hart et al., 2022] A reference line indicating 534 ng/mL (the 75th percentile of simulated maximum concentration at steady state [$C_{max,ss}$] values following administration of once-daily oral aripiprazole 30 mg/day) was also included.

- [0136] Rich PK profiles were simulated by sampling concentrations every 2 hours post-dose for 24 hours following oral dosing and every 24 hours post-dose following AOM or Ari RTU LAI dosing.
- [0137] Software and Tools
- [0138] The popPK model was developed using non-linear mixed effects modeling software (NONMEM v7.4.2; Icon Development Solutions, Ellicott City, MD, USA). Estimation was performed by first-order conditional estimation with interaction; if satisfactory convergence could not be achieved, estimation was performed by stochastic approximation expectation-maximization followed by importance sampling for evaluating the MVOF. Data preparation, graphical analysis, model diagnostics, and statistical summaries were performed using R (v4.0.5 and above; R Foundation for Statistical Computing, Vienna, Austria) and RStudio (v1.2.5042 and above; RStudio, Inc.). All simulations were performed using Pumas (v2.0; Pumas-AI, Inc., Centreville, VA, USA).
- [0139] Results: Population Pharmacokinetic Model Development
- [0140] Base Model
- [0141] As a first step, external validation of the prior model (which characterized aripiprazole plasma concentrations following administration of oral aripiprazole or AOM) was undertaken using new AOM 400 data from Study 031-201-00181. The prior model was able to characterize the new data reasonably well, although a small degree of overprediction was observed at treatment initiation in the CWRES versus time panel and the CWRES versus population prediction panel (data not shown).
- [0142] After adding PK data for the Ari RTU LAI formulation to the input file, the model that best fit the data was a 3-compartment model with linear elimination and different absorption models for the oral, AOM, and Ari RTU LAI formulations (FIG. 1).
- [0143] In FIG. 1, $*V_c/F$ has a different numerical value for the Ari RTU LAI formulation. The following abbreviates are used in FIG. 1, AOM 400 is aripiprazole once-monthly 400 mg; Ari is aripiprazole; CL/F is apparent clearance; $F_{rel,AOM}$ is relative bioavailability of the AOM formulation; $F_{rel,LAI}$ is relative bioavailability of the Ari RTU LAI formulation; $K_{a,deltoid}$ is absorption rate constant for the AOM formulation at

the deltoid site; $K_{a, \text{gluteal}}$ is absorption rate constant for the AOM formulation at the gluteal site; $K_{a, \text{LAI}}$ is absorption rate constant for the Ari RTU LAI formulation; $K_{a, \text{oral}}$ is absorption rate constant for the oral formulation; LAI is long acting injectable; Q_1/F is apparent inter-compartmental clearance 1; Q_2/F is apparent inter-compartmental clearance 2; RTU is ready-to-use; V_c/F is apparent central volume; V_{p1}/F is apparent volume in peripheral compartment 1; and V_{p2}/F is apparent volume in peripheral compartment 2.

[0144] Absorption of the Ari RTU LAI formulation was modeled by a parallel zero-order and lagged first-order process that accounted for the complex absorption process inherent to LAIs. Absorption of the Ari RTU LAI formulation was parameterized by the fraction of total dose absorbed by the first-order process rather than the zero-order process (FRAC1), the duration of zero-order absorption (DUR0), the time lag for the start of the first-order process (LAG1), the absorption rate constant for the first-order process (K_a RTU), and bioavailability of the Ari RTU LAI formulation relative to the oral formulation ($F_{\text{relative RTU}}$). Except for apparent central volume (which is different for the RTU LAI formulation versus the other formulations of aripiprazole), all other disposition parameters (i.e., apparent clearances and peripheral volumes) were shared between the formulations and were held fixed to the values in the prior model.

[0145] Covariate Analysis (and Retained Covariates)

[0146] The effect of injection site on K_a RTU, gender on K_a RTU, and gender on FRAC1 were found to be statistically significant on univariate analysis and were carried forward. The effect of injection site on K_a RTU was dropped from the final covariate model, as only a minority of injections were administered at the deltoid site (the intended injection site for Ari 2MRTU 960 or Ari 2MRTU 720 is gluteal) and, in a sensitivity analysis, parameter estimates for the base model without the deltoid injection data were very similar to the base model with all data. As such, only the effects of gender on FRAC1 and on K_a RTU were retained in the final covariate model, with neither removed in a backwards elimination step.

[0147] Final Model

[0148] Parameter estimates for the final model are shown in Table 1; parameters that were not fixed were estimated with percent relative standard errors (% RSE) of <15%.

[0149] Table 1: Pharmacokinetic parameters for the final aripiprazole population pharmacokinetic model.

[Table 1]

Parameter	Description	Unit	Final parameter estimate		Inter-individual variability (% CV)			Residual variability (% CV or SD)		
			Estimate	% RSE	Estimate	% RSE	Shrinkage (%)	Estimate	% RSE	Shrinkage (%)
CL _E M	Apparent clearance for subjects who are not poor CYP2D6 metabolizers	L/h	3.71 Fixed	NA	0.155 (39.3)	4.7	8.4	NA	NA	NA
CL _P M	Apparent clearance for subjects who are poor CYP2D6 metabolizers	L/h	1.88 Fixed	NA				NA	NA	NA
2D6 _{CL}	Proportional change in apparent clearance in the presence of a strong CYP2D6 inhibitor	—	-0.511 Fixed	NA	NA	NA	NA	NA	NA	NA
3A4 _{CL}	Proportional change in apparent clearance in the presence of a strong CYP3A4 inhibitor	—	-0.237 Fixed	NA	NA	NA	NA	NA	NA	NA
VC	Apparent central volume of distribution for oral and AOM	L	93.4 Fixed	NA	1.87 (136.7)	6.2	33.3	NA	NA	NA
VCRT U	Apparent central volume of distribution for Ari RTU LAI	L	2035	0.02				NA	NA	NA
Q1	Apparent inter-compartment	L/h	0.591 Fixed	NA	NA	NA	NA	NA	NA	NA

	al clearance 1									
VP1	Apparent volume of distribution in peripheral compartment 1	L	118 Fixed	NA	NA	NA	NA	NA	NA	NA
Q2	Apparent inter- compartment al clearance 2	L/h	28.8 Fixed	NA	NA	NA	NA	NA	NA	NA
VP2	Apparent volume of distribution in peripheral compartment 2	L	134 Fixed	NA	NA	NA	NA	NA	NA	NA
R1	Rate of dose into oral absorption compartment	mg/h	9.33 Fixed	NA	NA	NA	NA	NA	NA	NA
KAP O	K _a absorption rate constant for oral	L/h	0.54 Fixed	NA	0.434 (65.9)	Fixed	62.4	NA	NA	NA
KAG LU	K _a for AOM (gluteal)	L/h	0.0009 04 Fixed	NA	0.359 (59.9)	Fixed	19.3	NA	NA	NA
KAD EL	K _a for AOM (deltoid)	L/h	0.0007 76 Fixed	NA	0.237 (48.7)	Fixed	17.7	NA	NA	NA
BMI_ KAG LU	Effect of BMI on AOM K _a (gluteal) and AOM K _a (deltoid): power for (BMI/28)	—	-0.975 Fixed	NA	NA	NA	NA	NA	NA	NA
SEX_ KAG LU	Proportional shift of K _a (gluteal) and K _a (deltoid) for males	—	0.346 Fixed	NA	NA	NA	NA	NA	NA	NA
DUR0	Duration of zero-order absorption	h	162	6.5	1.01 (100.7)	8.8	10.0	NA	NA	NA

	for Ari RTU LAI									
FRAC 1	Fraction of first-order absorption for Ari RTU LAI on transformed scale	—	3.82 (79.3 %)	6.3	0.634 (79.6)	13.2	19.2	NA	NA	NA
SEX FRAC 1	Proportional shift of FRAC1 for males	—	-0.556	7.8	NA	NA	NA	NA	NA	NA
KAR TU	K _a for Ari RTU LAI	L/h	0.0012 7	0.03	0.307 (55.4)	13.4	32.0	NA	NA	NA
SEX KAR TU	Proportional shift of K _a RTU for males	—	0.907	0.1	NA	NA	NA	NA	NA	NA
ALA GI	Lag-time of first-order absorption for Ari RTU LAI	h	419	0.7	NA	NA	NA	NA	NA	NA
FREL _AO M	Relative bioavailabilit y of AOM versus oral	—	1.48 Fixed	NA	NA	NA	NA	NA	NA	NA
FREL _RTU	Relative bioavailabilit y of Ari RTU LAI versus oral	—	1.58	1.9	NA	NA	NA	NA	NA	NA
PRO	Proportional error for oral and AOM	—	NA	NA	NA	NA	NA	0.0660 (25.7)	0.8	3.8
PRO PH3	Proportional error for oral and AOM in the Phase 3 study 31-07- 246	—	NA	NA	NA	NA	NA	0.0772 (27.8)	1.8	12.2
PRO _RTU	Proportion error for Ari RTU LAI	—	NA	NA	NA	NA	NA	0.0650 (25.5)	0.9	7.1
ADD _RTU	Additive error for Ari RTU LAI	—	NA	NA	NA	NA	NA	1.81 (1.35)	9.6	7.1

[0150] AOM, aripiprazole once-monthly; Ari, aripiprazole; BMI, body mass index; CV, co-efficient of variation; CYP, cytochrome P450; K_a, first-order absorption rate constant; LAI, long-acting injectable; NA, not applicable; RSE, relative standard error; RTU, ready-to-use; SD, standard deviation.

[0151] Per the final model, for typical individuals, the first peak in concentration occurred at 6.75 days (162.1 hours) post-dose for the Ari RTU LAI formulation. The fractions

absorbed by the first-order and zero-order processes were 79.3% and 20.7%, respectively, in females and 62.7% and 37.3%, respectively, in males. First-order absorption started after a lag of 17.5 days (419 hours). In females, the K_a was 0.00127 per hour, corresponding to an absorption half-life of 22.7 days. In males, the K_a was 0.00242 per hour, corresponding to an absorption half-life of 11.9 days. Following the first dose, the second peak occurred at 41 days post-dose in a typical female and at 32 days post-dose in a typical male. At steady-state, the second peak occurred at 33 days post-dose in a typical female and at 28 days post-dose in a typical male. F_{relative} of the Ari RTU LAI formulation was 1.58 versus the oral formulation and 1.06 versus the AOM formulation.

[0152] Impact of Covariates

[0153] Regarding retained covariates, K_a RTU (i.e., the absorption rate constant) was 90.7% higher in males versus females, while FRAC1 (i.e., the fraction of first-order absorption) was 56.0% lower in males versus females.

[0154] Typical PK profiles were simulated for covariate combinations of interest, with all other covariates fixed to their reference values and all random effects fixed to zero. These were plotted on the same graph for visual comparison over 48 weeks (i.e., 6 consecutive administrations of Ari 2MRTU 960 dosed 8 weeks apart), with average concentration at steady state ($C_{\text{avg,ss}}$), $C_{\text{max,ss}}$, and $C_{\text{min,ss}}$ compared across covariate categories. Since CYP2D6 metabolizer status was identified as a covariate on the CL/F of aripiprazole in the prior model, and was retained in the current analysis, simulations were performed separately for poor and normal metabolizers of CYP2D6. The results of simulations to demonstrate the effects of gender on aripiprazole exposure parameters ($C_{\text{avg,ss}}$, $C_{\text{max,ss}}$, and $C_{\text{min,ss}}$) according to CYP2D6 metabolizer status following repeated administrations of Ari 2MRTU 960 until steady state (20 doses) are shown in Table 2, while a graphical assessment of the effect of retained covariates is shown in FIG. 2. The following abbreviations are used in FIG. 2, Ari 2MRTU 960 is aripiprazole 2-month ready-to-use 960 mg; and CYP is cytochrome P450.

[0155] Although males had higher peak concentrations (12% higher in normal metabolizers and 6% higher in poor metabolizers) and lower trough concentrations (22% lower in normal metabolizers and 10% lower in poor metabolizers) of aripiprazole than females, no difference in $C_{\text{avg,ss}}$ was observed between the genders. As expected, simulated aripiprazole concentrations were higher in poor versus normal metabolizers of CYP2D6; based on simulated data (Table 2), $C_{\text{avg,ss}}$ in CYP2D6 poor metabolizers was approximately two times (97.4%) than that in normal metabolizers.

[0156] Table 2. Simulated typical aripiprazole exposure parameters at steady state according to CYP2D6 metabolizer status and gender following repeated administration of Ari 2MRTU 960.

[Table 2]

CYP2D6 metabolizer status	Gender	$C_{avg,ss}$ (ng/mL)	$C_{max,ss}$ (ng/mL)	$C_{min,ss}$ (ng/mL)
Normal	Male	303.4	395.1	211.4
	Female	303.4	351.6	257.2
Poor	Male	598.8	685.0	498.1
	Female	598.8	645.7	549.7

- [0157] Ari 2MRTU 960, aripiprazole 2-month ready-to-use 960 mg; $C_{avg,ss}$, average concentration at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; CYP, cytochrome P450.
- [0158] Standard goodness-of-fit diagnostic plots for the final model are shown in FIG. 3; overall, the final model was able to adequately describe aripiprazole concentrations following administration of the Ari RTU LAI formulation. The slight overprediction at treatment initiation that was noted in the external validation of the prior model with the AOM 400 data from Study 031-201-00181 was not present in the fit of the final model.
- [0159] In FIG. 3, circles represent observed data. Solid black lines in the figures in the upper panel represent a line of unity. Solid black lines in the figures in the lower panel indicate the zero intercept. Black dashed lines with conditional weighted residuals equal to ± 4 are provided as reference lines to check for potential outliers. Grey dashed lines represent a locally estimated scatterplot smoother. The abbreviation AOM is aripiprazole once-monthly; and Ari RTU LAI is aripiprazole ready-to-use long-acting injectable.
- [0160] The predictive performance of the model was considered adequate based on prediction-corrected VPC (pcVPC) and non-parametric VPC. Overall, the pcVPC showed good predictive performance of the final model (FIG. 4), as evidenced by distributions of the observed data that were comparable with the 90% prediction intervals for the individual predictions.
- [0161] In FIG. 4, dashed lines represent observed data (median; 5th and 95th percentile, black). Solid lines represent simulated data (median; 5th and 95th percentile, black). Shaded regions represent the 95% confidence interval of the simulated median and the 5th and 95th percentile. The abbreviation AOM is aripiprazole once-monthly and Ari RTU LAI is aripiprazole ready-to-use long-acting injectable.
- [0162] The final popPK model was used to simulate aripiprazole plasma concentration-time profiles as a means of exploring aspects of Ari 2MRTU dosing, reflecting various scenarios that might arise in clinical practice.

[0163] Treatment Initiation

[0164] Across multiple treatment initiation scenarios, Ari 2MRTU 960 resulted in plasma concentrations of aripiprazole that were comparable to AOM 400. This was the case for: initiation of Ari 2MRTU 960 following a switch from AOM 400 (FIG. 5A); initiation of Ari 2MRTU 960 plus 14 days of overlapping oral aripiprazole in patients previously stabilized on oral aripiprazole 10 or 20 mg/day (FIGs. 5B and 5C); initiation of Ari 2MRTU 960 plus 14 days of overlapping oral aripiprazole in patients not previously stabilized on oral aripiprazole (FIGs. 5D and 5E); initiation of Ari 2MRTU 960 on Day 28 following administration of AOM 400 on Day 0 plus 14 days of overlapping oral aripiprazole in patients previously stabilized on oral aripiprazole 20 mg/day (FIG. 5F); and initiation of Ari 2MRTU 960 on Day 28 following administration of AOM 400 on Day 0 plus 14 days of overlapping oral aripiprazole 20 mg/day in patients not previously stabilized on oral aripiprazole (FIG. 7). FIG. 7 is a graph of simulated median aripiprazole concentration-time profile for Ari 2MRTU 960 on Day 28 following AOM on Day 0 (with overlapping oral aripiprazole 20 mg in patients without prior oral aripiprazole stabilization). For comparative purposes, FIG. 7 includes a solid black line, representing simulation results for the same patients treated with AOM 400 on Days 28 and 56. Reference lines represent the plasma concentration identified as the lower efficacy threshold for the prevention of impending relapse (95 ng/mL), and 75th percentile of simulated $C_{\max,ss}$ following a daily dose of oral aripiprazole 30 mg (534 ng/mL).

[0165] In FIGs. 5A-5F, for comparative purposes, each figure includes a solid black line, representing simulation results for the same patients treated with AOM 400 (with the same oral overlap, where relevant). Reference lines represent the plasma concentration identified as the lower efficacy threshold for the prevention of impending relapse (95 ng/mL), and 75th percentile of simulated $C_{\max,ss}$ following a daily dose of oral aripiprazole 30 mg (534 ng/mL). The abbreviation for AOM 400 is aripiprazole once-monthly 400 mg; Ari 2MRTU 960 is aripiprazole 2-month ready-to-use 960 mg; and $C_{\max,ss}$ is maximum concentration at steady state.

[0166] Scenarios involving a two-injection start (i.e., Ari 2MRTU 960 plus AOM 400 at separate injection sites plus a single dose of oral aripiprazole 20 mg, all on the first day of treatment) resulted in more stable plasma concentrations of aripiprazole, compared with a single dose of Ari 2MRTU 960 plus 14 days of oral aripiprazole 10 mg/day or 20 mg/day. This was the case for: patients with prior stabilization on oral aripiprazole 10 mg/day (FIG. 8A), 20 mg/day (FIG. 8B), and 30 mg/day (FIG. 8C), and patients without prior stabilization on oral aripiprazole (FIG. 8D). In FIGs. 8A-8D, for comparative purposes, a red line, representing simulation results for the same patients treated with Ari 2MRTU 960 on Day 0 with overlapping oral aripiprazole 10 mg or 20

mg on Day 0-13. Figure 8D includes solid red and dotted green lines, representing simulation results for the same patients treated with Ari 2MRTU 960 on Day 0 with overlapping oral aripiprazole 10 mg or 20 mg, respectively, on Day 0-13. Reference lines represent the plasma concentration identified as the lower efficacy threshold for the prevention of impending relapse (95 ng/mL), and the 75th percentile of simulated $C_{\max,ss}$ following a daily dose of oral aripiprazole 30 mg (534 ng/mL). The abbreviations are AOM 400 is aripiprazole once-monthly 400 mg; Ari 2MRTU 960 is aripiprazole 2-month ready-to-use 960 mg; and $C_{\max,ss}$ is maximum concentration at steady state. Simulated median Aripiprazole concentration with a two-injection start in CYP2D6 poor metabolizers (i.e., Ari 2MRTU 720 plus AOM 300 at separate injection sites plus a single dose of oral aripiprazole 20 mg, all on the first day of treatment) with or without prior stabilization are shown in FIG.11 and FIG.12. Reference lines represent median $C_{\min,ss}$ following a daily dose of 10 mg oral aripiprazole (94.0 ng/mL), 75th percentile of $C_{\max,ss}$ following a daily dose of 30 mg oral aripiprazole (534 ng/mL), and 95th percentile of $C_{\max,ss}$ following a daily dose of 30 mg oral aripiprazole (741 ng/mL).

[0167] Missed / Delayed Doses

[0168] Missed/delayed doses were simulated to explore the impact of imperfect adherence with Ari 2MRTU 960 (FIG. 6). In scenarios in which Ari 2MRTU 960 dosing was delayed by 2, 4, 6, and 8 weeks, trough median plasma concentrations at the time of dosing were 191 ng/mL, 144 ng/mL, 110 ng/mL, and 80.1 ng/mL respectively. At 56 days after the delayed dose had been administered, trough median plasma concentrations had increased to 231 ng/mL, 217 ng/mL, 205 ng/mL, and 196 ng/mL, respectively (in the last case, the dose was given with 14 days of overlapping oral aripiprazole 10 mg/day).

[0169] In FIG. 6, reference lines represent the plasma concentration identified as the lower efficacy threshold for the prevention of impending relapse (95 ng/mL), [Wang et al., 2022] and 75th percentile of simulated $C_{\max,ss}$ following a daily dose of oral aripiprazole 30 mg (534 ng/mL). The abbreviation Ari 2MRTU 960 is aripiprazole 2-month ready-to-use 960 mg and $C_{\max,ss}$ is maximum concentration at steady state.

[0170] CYP2D6 Metabolizer Status

[0171] Ari 2MRTU 720 was simulated in CYP2D6 poor metabolizers, with results demonstrating non-inferior steady-state concentrations of aripiprazole versus AOM 300 (FIG. 9). In FIG. 9, for comparative purposes, the figure includes a solid black line, representing simulation results for the same patients treated with AOM 300. Reference lines represent the plasma concentration identified as the lower efficacy threshold for the prevention of impending relapse (95 ng/mL), and the 75th percentile of simulated $C_{\max,ss}$ following a daily dose of oral aripiprazole 30 mg (534 ng/mL). The abbreviations are AOM 300 is aripiprazole once-monthly 300 mg; Ari 2MRTU 720 is aripiprazole

2-month ready-to-use 720 mg; $C_{\max,ss}$ is maximum concentration at steady state; and CYP is cytochrome P450.

[0172] Concomitant Long-Term Use of a CYP2D6 or CYP3A4 Inhibitor

[0173] Ari 2MRTU 720 plus a concomitant CYP3A4 strong inhibitor resulted in median steady-state plasma concentrations that were comparable to Ari 2MRTU 960 without a concomitant CYP3A4 or CYP2D6 strong inhibitor. In contrast, administration of Ari 2MRTU 720 with a concomitant CYP2D6 strong inhibitor resulted in higher median steady-state plasma concentrations versus Ari 2MRTU 960 without a concomitant CYP3A4 or CYP2D6 strong inhibitor (FIG. 10). In FIG. 10, for comparative purposes, the figure includes a solid black line, representing simulation results for the same patients treated with Ari 2MRTU 960. Reference lines represent the plasma concentration identified as the lower efficacy threshold for the prevention of impending relapse (95 ng/mL), [Wang et al 2022] and the 75th percentile of simulated $C_{\max,ss}$ following a daily dose of oral aripiprazole 30 mg (534 ng/mL). The abbreviations are Ari 2MRTU 720 is aripiprazole 2-month ready-to-use 720 mg; Ari 2MRTU 960 is aripiprazole 2-month ready-to-use 960 mg; $C_{\max,ss}$ is maximum concentration at steady state; and CYP is cytochrome P450.

[0174] Scenario involving a reference two-injection start (i.e., Ari 2MRTU 960 plus Ari 2MRTU 960 at separate injection sites plus a single dose of oral aripiprazole 20 mg, all on the first day of treatment) resulted in a delayed time to reach exposures in the therapeutic range. In this reference two-injection start, therapeutic aripiprazole concentrations were not maintained following the first week of administration.

[0175] Discussion

[0176] PopPK analyses are a well-established quantitative means of explaining variability in drug concentrations among individuals, including as a result of intrinsic factors, extrinsic factors, differences in dosing, and routes of administration. Such analyses are frequently undertaken as part of the drug development process to inform dosing regimens to be tested in future clinical trials. PopPK models can also be used to simulate PK profiles for scenarios that are beyond those that have been clinically studied.

[0177] The development and use of a popPK model to characterize the PK of a novel RTU LAI formulation of aripiprazole that is administered every two months is described. Based on the current analysis, aripiprazole PK following administration of Ari RTU LAI was best characterized by a linear 3-compartment model with parallel zero- and lagged first-order absorption. In an analysis of potential extrinsic and intrinsic co-variables affecting the absorption characteristics of Ari RTU LAI, gender was identified as a statistically significant covariate; specifically, gender was found to affect the fraction of first-order absorption and the first-order K_a , with faster absorption observed

in males versus females. The finding of gender as a statistically significant covariate of Ari RTU LAI absorption was consistent with AOM absorption in an earlier model on which the current model was based; however, a direct comparison was not possible due to the different structures of the absorption models (i.e., first-order absorption for AOM versus parallel zero- and first-order absorption for Ari RTU LAI). Although gender was found to affect both the fraction of first- and zero-order absorption and the first-order K_a for Ari RTU LAI, it was not expected to be clinically relevant as a result of a combination of these effects. This was confirmed by simulations of typical PK profiles following repeated administration of Ari 2MRTU 960 that showed no difference in $C_{avg,ss}$ values in males versus females. The effect of CYP2D6 metabolizer status was retained as a covariate from the prior model, with simulated $C_{avg,ss}$ found to be approximately two-fold (97.4%) higher in poor versus normal CYP2D6 metabolizers.

[0178] The final popPK model was used to conduct simulations to evaluate dosing of Ari 2MRTU 960 and Ari 2MRTU 720 across multiple realistic clinical situations. Various treatment initiation scenarios were simulated, which accounted for different prior treatments (i.e., whether or not patients were stabilized on oral aripiprazole or AOM 400). The use of overlapping oral aripiprazole for 14 days, or a two-injection start with Ari 2MRTU 960 plus AOM and a single dose of oral aripiprazole, were also simulated as a means of more rapidly reaching exposures in the therapeutic range, given the very slow absorption of Ari 2MRTU 960. Simulations also accounted for Ari 2MRTU 720 mg in poor metabolizers of CYP2D6 and in long-term users of strong CYP2D6 and CYP3A4 inhibitors. This is important since CYP2D6 metabolizer status is known to influence the PK of aripiprazole and, per the label for AOM, a dose of 300 mg every four weeks is recommended in CYP2D6 poor metabolizers. Additionally, CYP2D6 and CYP3A4 are both involved in the elimination of aripiprazole. Two-injection start with Ari 2MRTU 720 plus AOM and a single dose of oral aripiprazole simulated as a means of more rapidly reaching exposures in the therapeutic range, given the very slow absorption of Ari 2MRTU 720. The simulation data showed that two-injection start allows rapid reach exposures in the therapeutic range, even though the concentration of Aripiprazole takes few days to reach 95 ng/mL with a single dose of 780 mg RTU or a single dose of 1200 mg RTU and the initiation speed does not change drastically when the dose is increased from 780 mg to 1200 mg as shown in FIG. 13. FIG. 13 is the results of the Phase 1, Open Label, Single Ascending Dose, Parallel Arm Trial to Determine the Pharmacokinetics, Safety, and Tolerability of Aripiprazole 2 Month Intramuscular Depot Administered Gluteally in Adult Subjects with Schizophrenia, as described in U.S. Patent Application Publication No. US 2022/0,160,621 A1, which is incorporated herein by reference in its entirety.

- [0179] Lastly, missed/delayed doses were simulated to assess the impact of imperfect adherence with a dosing interval of every two months. Collectively, the simulations showed that the PK exposure profile for Ari RTU LAI was comparable to AOM, with a longer dosing interval.
- [0180] The data presented here provide clinicians with useful information regarding a variety of dosing scenarios for a two-monthly RTU LAI formulation of aripiprazole. It is impractical/infeasible to include all potential dosing scenarios in efficacy and safety trials, but popPK modelling and simulation addresses this, by generating PK profiles for scenarios beyond those specifically studied as part of the clinical trial program. In this manner, modelling and simulations act as ‘virtual’ clinical trials, allowing more scenarios to be investigated than could be conducted in real-life clinical trials. Nonetheless, any simulations presented here must be viewed in context with the approved use of Ari 2MRTU 960 and Ari 2MRTU 720, according to patient type, prior treatment, and/or country/region.
- [0181] The popPK model was developed to characterize the PK of Ari 2MRTU 960, which was then used to perform model-based simulations exploring various aspects of dosing of this novel formulation. The final model was considered fit for purpose, adequately describing the PK of plasma aripiprazole concentrations following administration of Ari 2MRTU 960; the model also established estimates for key popPK parameters and identified sources of variability in drug exposure. Simulations across a variety of dosing regimens that could reasonably be encountered in clinical practice demonstrated a PK exposure profile that was comparable to AOM, with a longer dosing interval.
- [0182] All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference.
- [0183] Claims or descriptions that include “or” or “and/or” between at least one members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The disclosure includes embodiments in which more than one, or all the group members are present in, employed in, or otherwise relevant to a given product or process.
- [0184] Furthermore, the disclosure encompasses all variations, combinations, and permutations in which at least one limitation, element, clause, and descriptive term from at least one of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include at least one limitation found in any other claim that is dependent on the same base claim. Where

elements are presented as lists, e.g., in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the disclosure, or aspects of the disclosure, is/are referred to as comprising particular elements and/or features, embodiments of the disclosure or aspects of the disclosure consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth in haec verba herein. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub range within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0185] Those of ordinary skill in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the disclosure described herein. Such equivalents are intended to be encompassed by the following claims.

Claims

- [Claim 1] A method of dose initiation for an aripiprazole treatment to a patient in need thereof comprising:
administering two, separate injections of aripiprazole, wherein a first injection comprises 960 mg or 720 mg of aripiprazole in a first long-acting injectable (LAI) formulation, and a second injection comprises 400 mg or 300 mg of aripiprazole in a second LAI formulation, to the patient with an injection site chosen from a gluteal site, a deltoid site, and combinations thereof, and a single dose of oral aripiprazole, wherein the step of administering occurs on a first day of the aripiprazole LAI treatment.
- [Claim 2] The method according to claim 1, wherein the first LAI formulation is in the form of a gel when allowed to stand, and changes to a sol when subjected to an impact.
- [Claim 3] The method according to claim 1, wherein the second LAI formulation is a suspension prepared from lyophilized powder and water for injection.
- [Claim 4] The method according to any one of claims 1 to 3, wherein the first injection comprises 960 mg of aripiprazole.
- [Claim 5] The method according to any one of claims 1 to 4, further comprising after the first day of the aripiprazole LAI treatment, administering a maintenance dose of the first LAI formulation once in about two months.
- [Claim 6] The method according to claim 5, wherein the maintenance dose of the first LAI formulation is chosen from 960 mg and 720 mg of aripiprazole.
- [Claim 7] The method according to claim 6, wherein when the patient is a CYP2D6 poor metabolizer or is taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days, the maintenance dose of the first LAI formulation is 720 mg of aripiprazole.
- [Claim 8] The method according to any one of claims 1 to 7, wherein the two, separate injections of aripiprazole are administered at separate gluteal injection sites of the patient.
- [Claim 9] The method according to any one of claims 1 to 7, wherein the two, separate injections of aripiprazole are administered at gluteal and deltoid injection sites of the patient.
- [Claim 10] The method according to any one of claims 1 to 7, wherein the two,

- separate injections of aripiprazole are administered at separate deltoid injection sites of the patient.
- [Claim 11] The method according to any one of claims 1 to 10, wherein the patient has schizophrenia.
- [Claim 12] The method according to any one of claims 1 to 10, wherein the patient has bipolar I disorder.
- [Claim 13] The method according to any one of claims 1 to 12, wherein the dose of oral aripiprazole ranges from about 10 mg to about 20 mg of aripiprazole.
- [Claim 14] The method according to claim 13, wherein the dose of oral aripiprazole comprises about 20 mg of aripiprazole.
- [Claim 15] The method according to claim 13, wherein the dose of oral aripiprazole comprises about 10 mg of aripiprazole.
- [Claim 16] The method according to any one of claims 1 to 15, wherein the patient has not been previously stabilized on oral aripiprazole before the treatment.
- [Claim 17] The method according to claim 1, wherein the patient is a CYP2D6 poor metabolizer or is taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days, the first injection comprises 720 mg of aripiprazole, the second injection comprises 400 mg or 300 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 10 mg or about 20 mg of aripiprazole.
- [Claim 18] The method according to claim 17, wherein the patient is a CYP2D6 poor metabolizer or is taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days, the first injection comprises 720 mg of aripiprazole, the second injection comprises 300 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 20 mg of aripiprazole.
- [Claim 19] The method according to claim 1, wherein the first injection comprises 960 mg of aripiprazole, the second injection comprises 400 mg or 300 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 10 mg or about 20 mg of aripiprazole.
- [Claim 20] The method according to claim 19, wherein the first injection comprises 960 mg of aripiprazole, the second injection comprises 400 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 20 mg of aripiprazole.
- [Claim 21] A method of treating schizophrenia or bipolar I disorder in a patient in need thereof comprising:

administering two, separate injections of aripiprazole, wherein a first injection comprises 960 mg or 720 mg of aripiprazole in a first long-acting injectable (LAI) formulation, and a second injection comprises 400 mg or 300 mg of aripiprazole in a second LAI formulation, to the patient with an injection site chosen from a gluteal site, a deltoid site, and combinations thereof, and a single dose of oral aripiprazole, wherein the step of administering occurs on a first day of the aripiprazole LAI treatment and wherein the dose of oral aripiprazole ranges from about 10 mg to about 20 mg of aripiprazole; and continuing administering with a maintenance dose of the first LAI formulation comprising 960 mg or 720 mg of aripiprazole, wherein the maintenance dose is administered once in about two months after the first day of the aripiprazole LAI treatment.

- [Claim 22] The method according to claim 21, wherein the first injection comprises 960 mg of aripiprazole, the second injection comprises 400 mg or 300 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 10 mg or about 20 mg of aripiprazole.
- [Claim 23] The method according to claim 22, wherein the first injection comprises 960 mg of aripiprazole, the second injection comprises 400 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 20 mg of aripiprazole.
- [Claim 24] The method according to claim 21, wherein the first injection comprises 720 mg of aripiprazole, the second injection comprises 400 mg or 300 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 10 mg or about 20 mg of aripiprazole.
- [Claim 25] The method according to claim 24, wherein the first injection comprises 720 mg of aripiprazole, the second injection comprises 300 mg of aripiprazole, and the single dose of oral aripiprazole comprises about 20 mg of aripiprazole.
- [Claim 26] The method according to claim 21, wherein the dose of oral aripiprazole comprises about 20 mg of aripiprazole.
- [Claim 27] The method according to claim 21, wherein the about two months ranges from 54 days to 58 days.