Clinical and Translational Science

ARTICLE OPEN ACCESS

Bioequivalence of Aripiprazole Oral Soluble Films and Orally Disintegrating Tablets in Healthy Participants: A Crossover Study

Ruoming Li[1] | Shaojie Yang[1] | Guigang Yang[1] | Xingli Gu[2] | Zuokai Zhang[2] | Taixin Wang[2] | Yunlong Tan[1] | Song Chen[1]

[1]Peking University HuiLongGuan Clinical Medical School, Beijing HuiLongGuan Hospital, Beijing, China | [2]Qilu Pharmaceutical Co. Ltd., Jinan, China

Correspondence: Song Chen (asongsi@163.com)

Received: 26 October 2024 | **Revised:** 8 January 2025 | **Accepted:** 10 January 2025

Funding: The authors received no specific funding for this work.

Keywords: bioequivalence | pharmacokinetics | psychiatric | schizophrenia

ABSTRACT

Schizophrenia is a serious mental disorder with high disability rates, and antipsychotics, especially second-generation ones like aripiprazole, are the cornerstone of treatment. As a novel formulation, oral soluble films (OSF) offer an alternative to tablets or capsules, improving patient compliance. This study aimed to assess the bioequivalence, pharmacokinetic (PK) properties, and safety of aripiprazole OSF and aripiprazole orally disintegrating tablets (ODT) in healthy Chinese participants. A single-dose, randomized, open-label, and crossover study was conducted. Participants received 10 mg of test aripiprazole OSF (Qilu Pharmaceutical) and reference aripiprazole ODT (Otsuka Pharmaceutical) under fasting and fed states. The fasting trial comprised a three-sequence, three-period design, while the fed trial comprised a two-sequence, two-period design. In the fasting trial, after single oral dosing of aripiprazole OSF (with water), aripiprazole OSF (without water), and aripiprazole ODT, C_{max} were 55 ± 10 ng/mL, 54 ± 10 ng/mL, and 48 ± 13 ng/mL, respectively; the $AUC_{0\text{-}72h}$ were 1857 ± 377 h·ng/mL, 1823 ± 350 h·ng/mL, and 1745 ± 405 h·ng/mL, respectively. In the fed trial, after single oral dosing of aripiprazole OSF and ODT with water, the C_{max} were 43 ± 9 ng/mL and 43 ± 10 ng/mL, respectively; $AUC_{0\text{-}72h}$ were 2024 ± 387 h·ng/mL and 1994 ± 426 h·ng/mL, respectively. In terms of bioequivalence evaluation, the 90% confidence intervals of the geometric mean ratio of the main PK parameters of aripiprazole OSF and ODT in the fasting and fed states were all within the acceptable equivalence range (80%–125%). Both formulations were well-tolerated. In conclusion, aripiprazole OSF and ODT reached bioequivalence, and aripiprazole OSF demonstrates significant potential for application in the treatment of psychiatric disorders.

JEL Classification: Integrity Check

1 | Introduction

Schizophrenia is a serious mental disorder characterized by cognitive and behavioral dysfunction [1], ranking among the top 20 most disabling diseases. The age-standardized point prevalence is approximately 0.28%, with an estimated 21 million patients worldwide [2]. From 1990 to 2019, its prevalence, incidence, and disability-adjusted life-years increased by 65%, 37%, and 65% [3], respectively, posing significant economic and social burdens [4]. Therefore, it is crucial to implement appropriate and effective interventions.

Antipsychotics are the cornerstone of schizophrenia treatment [5]. Second-generation antipsychotics (SGAs), represented by aripiprazole, are recommended as first-line therapy [6, 7]. However, patients with schizophrenia often exhibit partial compliance with medication, which can lead to worsening of symptoms, relapse, re-admission, and even suicide [8]. Various

Summary

- What is the current knowledge on the topic?
  - Aripiprazole, a second-generation antipsychotic, is a cornerstone for schizophrenia treatment.
  - Traditional formulations like tablets face challenges with medication adherence.
- What question did this study address?
  - This study addressed the bioequivalence, pharmacokinetic properties, and safety of aripiprazole oral soluble films (OSF) compared to orally disintegrating tablets (ODT) in healthy Chinese participants.
- What does this study add to our knowledge?
  - This study is the first to report the PK data of aripiprazole OSF and demonstrates its bioequivalence to aripiprazole ODT in healthy Chinese participants.
  - Additionally, it highlights the potential of OSF as an alternative formulation to improve patient acceptance due to its rapid dissolution and ease of administration.
- How might this change clinical pharmacology or translational science?
  - This study introduces a new treatment option for schizophrenia that addresses medication nonadherence by validating an alternative drug formulation.
  - By taking patients' needs and preferences into account, this patient-centered strategy has the potential to improve therapeutic outcomes.

methods, such as phone calls and text messages, are employed to remind patients to take their medication, but effectively monitoring adherence remains challenging [9].

Oral soluble films (OSF), also known as oral films or odispersible films, can be used as alternatives to tablets or capsules. OSFs dissolve rapidly and release medication in the saliva [10], reducing the chances of patients spitting them out. Therefore, compared to other traditional oral formulations such as tablets, they can help improve patient compliance. This form of medication is more convenient for populations at high risk, including the elderly, children, and patients with schizophrenia, etc [11, 12]. However, it's important to consider individual patient preferences, as well as the specific medication's taste and formulation, which may influence acceptance and adherence.

Qilu Pharmaceutical Co. Ltd. (Shandong, China) developed an aripiprazole OSF formulation in order to better accommodate clinical requirements. This was a single-dose, randomized, open-label, crossover bioequivalence trial. By determining the plasma concentration of aripiprazole in healthy participants after oral administration of aripiprazole OSF and aripiprazole orally disintegrating tablets (ODT), the pharmacokinetic (PK) parameters of aripiprazole in healthy Chinese participants were estimated, and the bioequivalence of the two formulations under both fasting and fed states were evaluated. Herein, we present the following content in accordance with the CONSORT Reporting Checklist for randomized crossover trials [13].

2 | Methods

2.1 | Study Design

The study was conducted in accordance with the Good Clinical Practice Guidelines of the International Council for Harmonization (ICH), the principles articulated in the Declaration of Helsinki, and the regulations of the China National Medical Products Administration (NMPA). This single-center study was conducted at the Phase I Clinical Research Center of Beijing HuiLongGuan Hospital (Beijing, China) and was approved by the independent Ethics Committee of Beijing HuiLongGuan Hospital following a comprehensive review of the study protocol and informed consent forms. Informed consent was obtained from all participants prior to enrollment. The studies were officially registered with the identification codes CTR20192111 and CTR20192119 (http://www.chinadrugtrials.org.cn/index.html#).

The bioequivalence study consisted of two independent trials: a randomized, open-label, single-dose, three-sequence, three-period crossover trial conducted under fasting conditions and a randomized, open-label, single-dose, two-sequence, two-period crossover trial conducted under fed conditions. This study design also aligns with the bioequivalence research conducted on ondansetron OSF (Zuplenz) and montelukast OSF [14, 15]. The mean plasma elimination half-life ($t_{1/2}$) of aripiprazole oral tablets is approximately 70–80 h [16]. The European Medicines Agency (EMA) stipulates a washout period of at least five elimination half-lives [17], while the NMPA mandates a washout period of no less than seven elimination half-lives [18, 19]. To ensure the complete metabolism of aripiprazole prior to the subsequent dosage cycle, a washout period of 28 days was implemented between each administration. Blocked randomization was performed by professional statisticians according to random number tables generated using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

Research physicians generated the allocation sequence, enrolled participants, and assigned participants to different formulations. Following EMA guidelines [17], which highlight fasting conditions as optimal for detecting formulation differences, our fasting trial evaluated the impact of water intake on drug absorption. Participants were randomized to receive a single dose of the test formulation (aripiprazole OSF, 10 mg) with or without 240 mL of water. The reference formulation (aripiprazole ODT, 10 mg) was administered with water. In the fed trial, all participants received a single dose of aripiprazole OSF or ODT with 240 mL of water. Figure 1 illustrates the study design and research process. The treatment sequence was selected to ensure that each treatment was balanced across all periods and sequences, enhancing the reliability of the results.

2.2 | Participants

Healthy participants of either sex aged from 45 to 65 years with a body mass index (BMI) between 18 and 28 kg/m [2] were considered eligible for recruitment. Participants with any significant abnormalities in their medical history, laboratory examinations, chest CT scans, electrocardiograms, vital signs, or

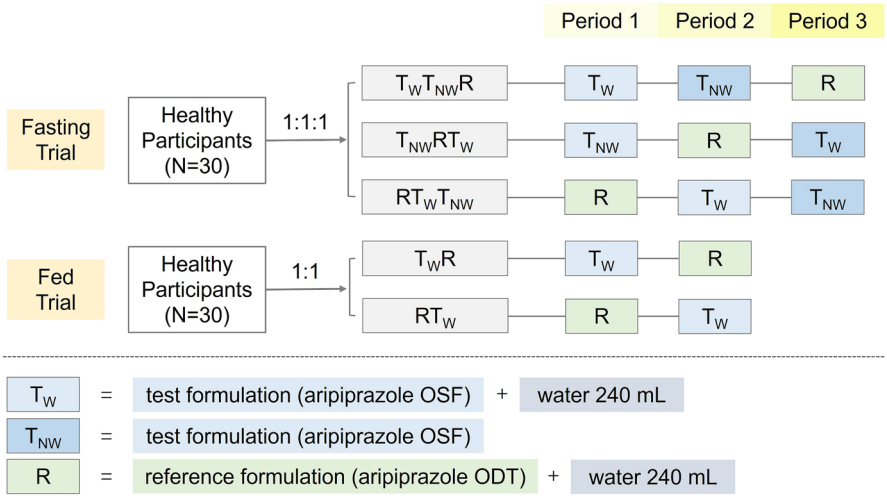

FIGURE 1 | Flow diagram of the study design. ODT, orally disintegrating tablets; OSF, oral soluble film; R, reference formulation (aripiprazole ODT, 10 mg) with 240 mL of water; T_{NW}, test formulation (aripiprazole OSF) without water; T_W, test formulation (aripiprazole OSF, 10 mg) with 240 mL of water.

physical examinations were excluded. Other primary exclusions were as follows: smoking more than five cigarettes per day in the 3 months prior to receiving the study drug; allergic history of aripiprazole, diphenhydramine, dimenhydrinate, benztropine, or excipients (such as hydroxypropyl methylcellulose, polyvinyl alcohol, or lactose); exposure to any antipsychotic drug within 2 months or any prescription; and functional vitamins or herbal medicine products within 14 days prior to the administration.

Regarding the sample size calculation, in a bioequivalence study evaluating aripiprazole ODT from Caduceus Pharma Limited against aripiprazole ODT (Abilify) from Otsuka Pharmaceutical under fasting conditions, the intra-individual coefficient of variation (CV) for C_{max} and the area under the concentration-time curve from time zero to 72 h ($AUC_{0\text{-}72h}$) were reported as 18.59% and 10.73%, respectively [20]. Bioequivalence was evaluated according to the NMPA criteria, which stipulate a geometric mean ratio (GMR) range of 80.00%–125.00%, with a significance level (α) of 0.05, a target GMR range of 0.95–1.05, and 0.9 statistical power. Based on these parameters and prior research findings, the initial estimated sample size was determined to be 24 participants, allocated as 8 participants per group for the fasting trial and 12 participants per group for the fed trial [21]. To account for potential dropouts, the final sample size was adjusted to be 30 participants per trial.

2.3 | Formulations and Administration

The test aripiprazole OSF (10 mg) was manufactured by Qilu Pharmaceutical Co. Ltd. (Shandong, China). The reference aripiprazole ODT, Abilify (10 mg), was manufactured by Otsuka Pharmaceutical Co. Ltd. (Hiroshima, Japan). After fasting overnight for at least 10 h on the day before administration, the participants were administered a single dose of aripiprazole OSF or ODT according to a random table in the fasting or fed states. During the fed trial, participants consumed a standardized, high-fat, high-calorie breakfast (totaling 956.88 kcal), composed of 25% carbohydrates (238.88 kcal), 17% protein (162.88 kcal), and 58% fat (555.12 kcal). To minimize the occurrence of adverse events, such as nausea and dizziness, and to ensure the safety of the healthy participants, they were required to assume a supine position within 15 min following administration and to maintain this position for 8 h.

2.4 | Blood Sampling

Venous blood samples were collected for PK analysis, and 4 mL of blood was collected at 20 time points (0 h within 1 h before dosing; 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 10.0, 12.0, 24.0, 48.0, and 72.0 h after dosing). Blood samples were collected using vacuum tubes that contained an Ethylene Diamine Tetraacetic Acid- K_2 (EDTA-K_2) as an anticoagulant. After centrifugation (1700 × g, 10 min, 4°C) of the blood samples, the plasma samples were pipetted into tubes and stored in an ultra-low temperature refrigerator (temperature range ≤ −60°C) for PK evaluation.

2.5 | Pharmacokinetic (PK) Assay

An aripiprazole assay was performed using high-performance liquid chromatography (HPLC)-tandem mass spectrometry (MS/MS). HPLC was conducted with LC-30 AD (Shimadzu, Kyoto, Japan), and MS detection was carried out with a TRIPLE QUAD 6500^+ mass spectrometer (Applied Biosystems/Sciex, MA, USA). The method was developed and fully validated for linearity, selectivity, sensitivity, stability, accuracy, and precision by Shanghai Xihua Scientific Co. Ltd. (Shanghai, China). The determination of aripiprazole and method validation section can be found in the Supporting Informations.

2.6 | Tolerability

The research physicians closely monitored, identified, and documented adverse events (AEs) throughout the trial. All AEs

(clinical symptoms, signs, or diseases) that occurred after the first dose (including the washout period) were recorded in the source files. Detailed records were maintained regarding the signs and symptoms of AEs, including the date and time of occurrence, duration, interventions undertaken, and any follow-up visits. For the fasting trial, laboratory tests were performed during the screening period (D-7 to D-1), the second cycle (D-1), the third cycle (D-1), and the third cycle (D4, end of trial). For the fed trial, laboratory tests were performed during the screening period (D-7 to D-1), the second cycle (D-1), and the second cycle (D4, end of trial). The severity of AEs was assessed according to the Common Terminology Criteria for Adverse Events Version 5.0. Participants who experienced AEs were monitored regularly until symptoms subsided, any abnormal laboratory values returned to normal or baseline levels, irreversible changes were observed, or the observed changes were appropriately explained.

2.7 | Outcome Measures and Statistical Analysis

SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) was used to conduct PK non-compartmental analysis and validation, bioequivalence evaluation, and statistical safety analysis.

The average plasma drug concentration–time curve was drawn from trial data. PK parameters of aripiprazole, including C_{max}, time to maximum plasma concentration (T_{max}), and $AUC_{0\text{-}72h}$, were calculated using the non-compartmental analysis method. Aripiprazole exhibits a prolonged half-life ($t_{1/2}$), with an average elimination $t_{1/2}$ ranging from approximately 58.0–78.6 h for the parent compound and 94 h for its active metabolite [22, 23]. The CV for C_{max} is approximately 10.1%–18.6%, and for AUC it is approximately 6.1%–10.73% [16, 20]. Based on the specified characteristics, and in alignment with the guidelines established by the ICH, FDA, and NMPA [18, 24, 25], it was chosen to use $AUC_{0\text{-}72h}$ instead of $AUC_{0\text{-}t}$ or $AUC_{0\text{-}\infty}$, because 72 h is sufficient for the drug's gastrointestinal transit and absorption. Additionally, the FDA's "Draft Guidance on Aripiprazole" also recommends the use of $AUC_{0\text{-}72h}$ for BE statistical analysis [26].

The primary PK parameters of aripiprazole, the C_{max} and $AUC_{0\text{-}72h}$, were used to evaluate the bioequivalence. These values were both estimated using an analysis of variance (ANOVA) model after logarithmic transformation with sequence, period, and formulation as fixed effects, and individual (nested sequence) as random effects. Bioequivalence was confirmed when the confidence interval (CI) of the GMR for C_{max} and $AUC_{0\text{-}72h}$ fell within the 80.00%–125.00% equivalent interval. The difference in T_{max} between the formulations was evaluated using the Wilcoxon signed-rank test.

3 | Results

3.1 | Study Population

In September 2019, 96 participants were screened in the fed trial and 30 were successfully enrolled. In March 2020, 115 participants were screened in the fasting trial and 30 were enrolled. All 60 participants enrolled completed the entire study, and in the fasting trial, one participant's data from the second period was excluded from the calculation of PK parameters and bioequivalence analysis due to the aripiprazole concentration prior to administration exceeding 5% of the C_{max}. A flow diagram of the participants is shown in Figure 2. The demographic characteristics of the participants are summarized in Table 1.

3.2 | Pharmacokinetics

In the fasting trial, after single oral dosing of aripiprazole OSF (10 mg, with water), aripiprazole OSF (10 mg, without water), and aripiprazole ODT (10 mg), the mean ± SD of plasma aripiprazole C_{max} were 55 ± 10 ng/mL, 54 ± 10 ng/mL, and 48 ± 13 ng/mL, respectively; the $AUC_{0\text{-}72h}$ were 1857 ± 377 h·ng/mL, 1823 ± 350 h·ng/mL, and 1745 ± 405 h·ng/mL, respectively; the median (range) of T_{max} were 2 (1–4) h, 2 (1–5) h, and 3 (1–6) h, respectively. For the fed trial, after single oral dosing of aripiprazole OSF (10 mg) and aripiprazole ODT (10 mg) with water, the C_{max} were 43 ± 9 ng/mL and 43 ± 10 ng/mL; the $AUC_{0\text{-}72h}$ were 2024 ± 387 h·ng/mL and 1994 ± 426 h·ng/mL; the T_{max} were 5 (2–24) h and 5 (2–24) h, respectively. Figure 3 illustrates the plasma concentration-time profiles.

3.3 | Bioequivalence Evaluation

In the fasting trial, the bioequivalence evaluation of the primary PK parameters between OSF (with water) and ODT (with water) showed that the GMR for C_{max} and $AUC_{0\text{-}72h}$ were 116.73% and 107.23%, respectively. For OSF (without water) vs. ODT (with water), the C_{max} and $AUC_{0\text{–}72h}$ were 115.30% and 105.12%. The GMR of C_{max} and $AUC_{0\text{-}72h}$ in the fed trial were 100.51% and 101.95%. The intra-individual CV was low (< 20%) for both the OSF and ODT. As summarized in Table 2. The results indicated that the aripiprazole OSF and aripiprazole ODT were bioequivalent.

3.4 | Tolerability

In both trials, all participants who received at least one dose of the test or reference formulation were included in the tolerability analysis. During the fasting trial, 72 AEs were observed among 26 participants, representing an incidence of 86.7%. Of these events, one was classified as a moderate AE, while the remaining AEs were considered mild. During the fed trial, 69 AEs were reported among 30 participants, and the incidence of AEs was 100.0%. Twelve events in 9 cases were identified as moderate AEs, with the rest being mild. Detailed information on tolerability is presented in Table 3.

4 | Discussion

To better provide appropriate pharmacotherapy for patients with schizophrenia, we conducted a single-dose, randomized, open-label, and crossover study, and reported the pharmacokinetic properties of aripiprazole OSF for the first time. The findings of this study demonstrated that, following a single oral administration, the pharmacokinetic profiles of the test aripiprazole OSF and the reference aripiprazole ODT were comparable in

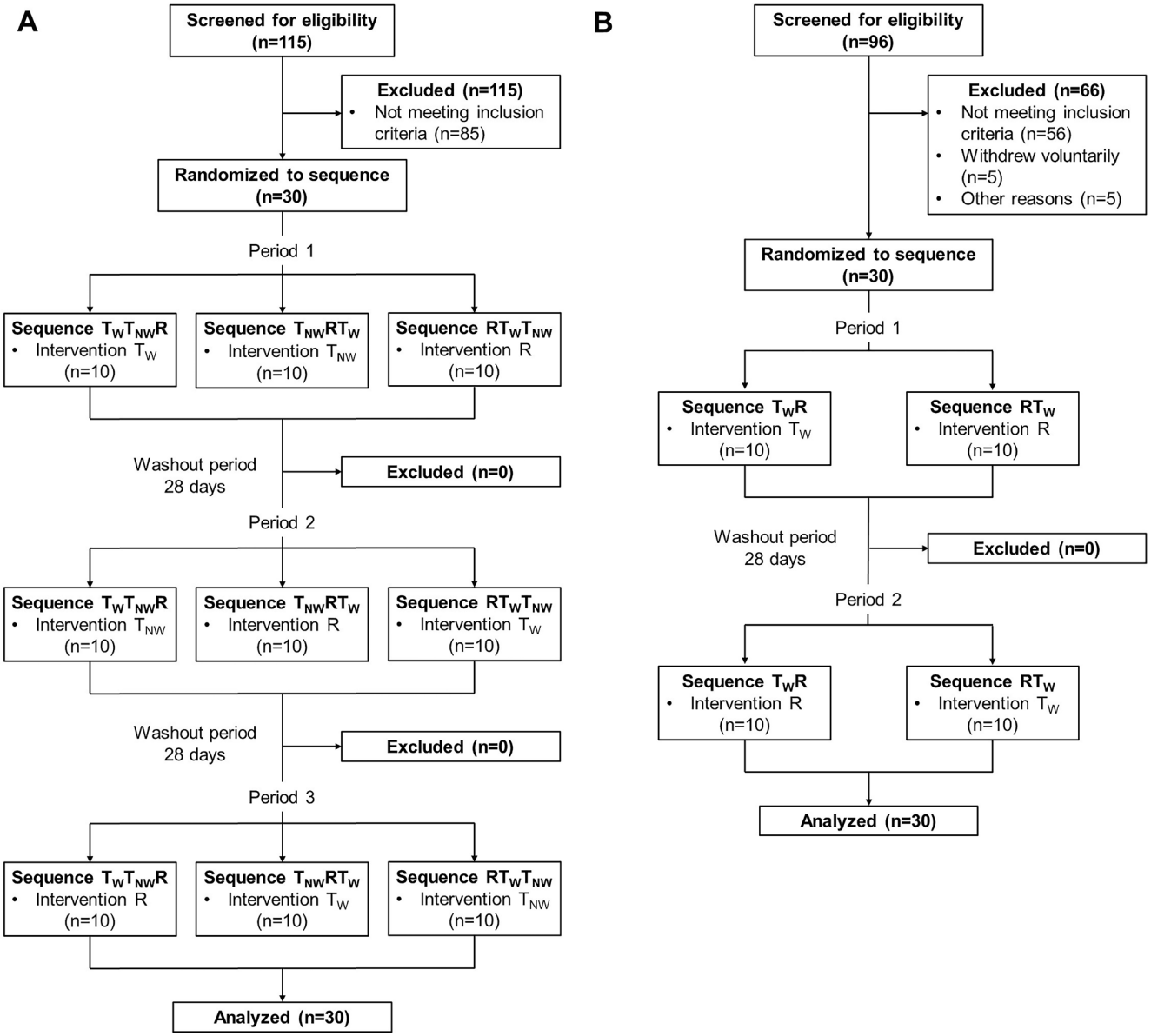

FIGURE 2 | Study participants under (A) fasting and (B) fed states.

TABLE 1 | Demographic characteristics of participants in the fasting and fed trials.

Variables	The fasting trial ($n=30$)	The fed trial ($n=30$)
Age (years)	48 ± 3	51 ± 3
Sex		
Male	21 (70.0%)	17 (56.7%)
Female	9 (30.0%)	13 (43.3%)
Weight (kg)	64.3 ± 7.2	63.4 ± 7.5
Height (cm)	164.9 ± 6.9	162.0 ± 6.7
BMI (kg/m^2)	23.7 ± 2.1	24.1 ± 2.0

Note: Data are presented as mean ± SD or number [%]; BMI = weight (kg)/[height (m)].
Abbreviations: BMI, body mass index; SD, standard deviation.

healthy Chinese participants, meeting the criteria for bioequivalence. Furthermore, both formulations were well-tolerated by the participants.

Continued antipsychotic treatment is crucial for ameliorating the symptoms of schizophrenia [5]. Nonetheless, there is an urgent need for further optimization of these treatment strategies. Cognitive impairments frequently associated with schizophrenia can hinder patients' comprehension of the treatment's significance, thereby adversely affecting adherence to prescribed medication regimens [27, 28]. This often leads to suboptimal medication compliance. It is estimated that the discontinuation rate of oral antipsychotics in patients with schizophrenia ranges from 26% to 44%, with up to 66% of patients exhibiting at least partial nonadherent [29].

To better address the previously discussed challenges, a range of pharmacological formulations is available for the treatment

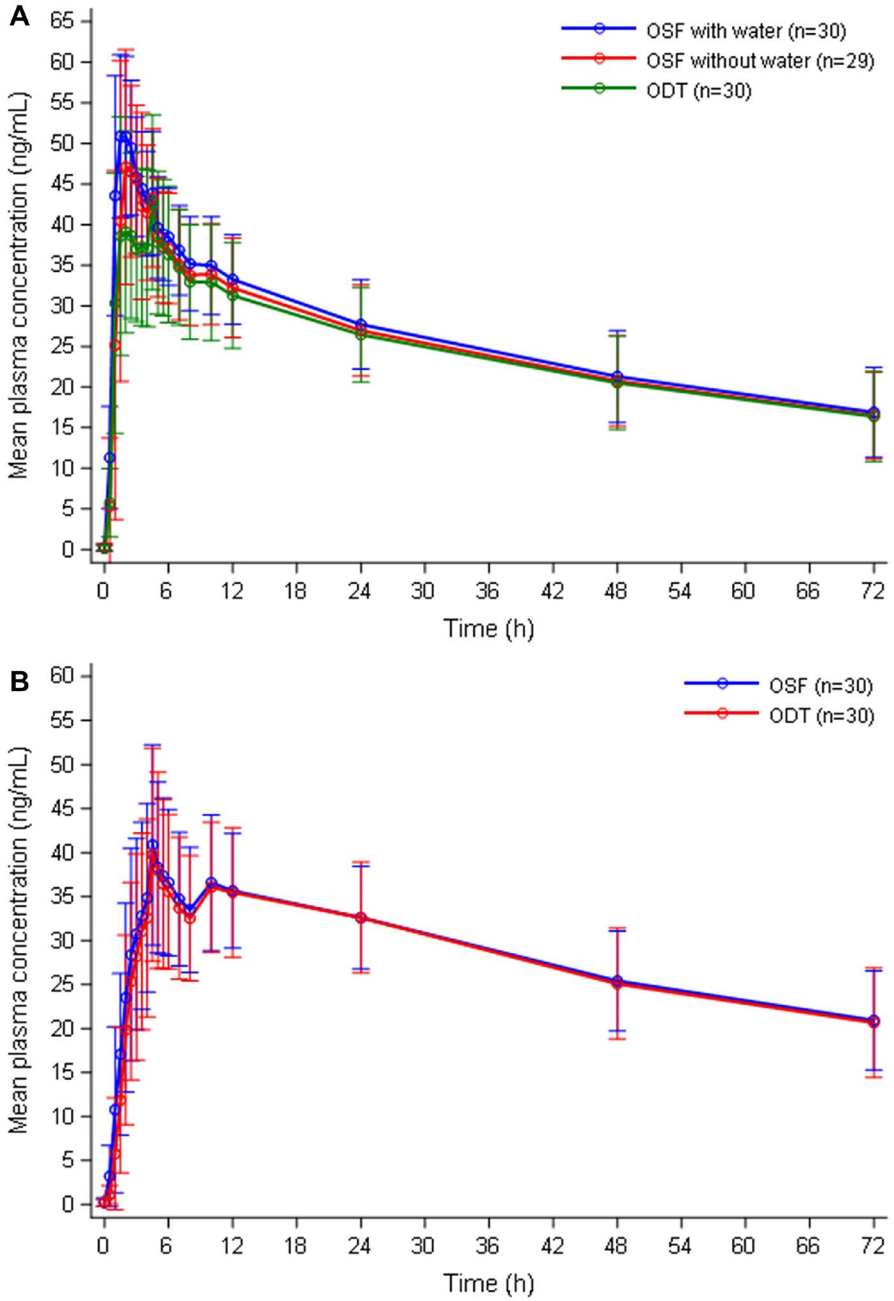

FIGURE 3 | Mean plasma concentration-time profiles of aripiprazole under fasting (A) and fed (B) states. Data were presented as Mean ± SD.

of schizophrenia. These include injectable and long-acting injectable options, which can be administered intramuscularly or subcutaneously. Injections can better maintain relatively stable plasma drug concentrations, reducing the risk of adverse events, and can decrease dosing frequency, thereby improving patient compliance [30]. However, oral formulations continue to be the preferred choice for patients due to their convenience, non-invasiveness, and ease of administration [31]. Although ODT and sublingual tablets exhibit rapid faster absorption and avoid first-pass metabolism, issues such as patients spitting out or hiding the medication remain a challenge [32]. Consequently, there is a clinical imperative to develop novel drug formulations that simplify administration, and improve patient adherence.

The novel formulation, OSF, presents a promising solution in terms of patient acceptance and compliance. Its active ingredients can be quickly dissolved and absorbed, reducing metabolism by enzymes in the intestinal wall and liver, and thereby enhancing the bioavailability of the drug [33, 34]. However, OSF present certain limitations, such as the physicochemical properties of the product may not be suitable for drugs requiring higher doses; due to the unpleasant taste and odor of the drugs, taste-masking is required in OSF; and OSF have more stringent storage requirements [12, 34, 35]. Several OSF formulations targeting various indications have received marketing approval from regulatory authorities, including the FDA, NMPA, and EMA. Currently, available OSF products include olanzapine, risperidone, ondansetron, and clobazam [34].

TABLE 2 | Bioequivalence analysis of main PK parameters of aripiprazole under fasting and fed states.

Parameters	GM		GMR (%)		Intra-Individual CV (%)	Power (%)
	OSF	ODT	OSF/ODT	90% CIs		
OSF with water versus ODT under fasting state						
	$n=30$	$n=30$				
C_{max} (ng/mL)	54.00	46.26	116.73	(109.13, 124.86)	15.69	50.56
AUC_{0-72h} (h·ng/mL)	1822.37	1699.54	107.23	(103.68, 110.90)	7.81	100.00
T_{max} (h)[a]	2 (1–4)	3 (1–6)	—	—	—	—
OSF without water vs. ODT under fasting state						
	$n=29$	$n=30$				
C_{max} (ng/mL)	53.34	46.26	115.30	(107.70, 123.43)	15.69	60.96
AUC_{0-72h} (h·ng/mL)	1786.60	1699.54	105.12	(101.59, 108.77)	7.81	100.00
T_{max} (h)[a]	2 (1–5)	3 (1–6)	—	—	—	—
OSF vs. OCT under fed state						
	$n=30$	$n=30$				
C_{max} (ng/mL)	42.18	41.97	100.51	(95.77, 105.48)	11.02	100.00
AUC_{0-72h} (h·ng/mL)	1986.14	1948.13	101.95	(99.29, 104.69)	6.03	100.00
T_{max} (h)[a]	5 (2–24)	5 (2–24)	—	—	—	—

Abbreviations: AUC_{0-72h}, area under the concentration–time curve from time 0 to the last measurable concentration; C_{max}, maximum plasma concentration; GM, geometric mean; GMR, geometric mean ratio; ODT, orally disintegrating tablet; OSF, oral soluble film; T_{max}, time to maximum plasma concentration.
[a]Values were presented as median (range).

In both the OSF and ODT, compared with the fasting state, the T_{max} of aripiprazole under the fed state were prolonged, and the C_{max} was decreased, indicating that food may decelerate the absorption rate of aripiprazole, which is consistent with previous research [16]. It has been reported that a high-fat meal slightly decreases the AUC_{0-216h} and $AUC_{0-\infty}$ of aripiprazole, but this study did not observe a similar trend, potentially due to the application of AUC_{0-72h} only. The influence of food on oral bioavailability is related to complex interactions between drugs, formulations, food components, and physiological processes in the stomach and intestine [36]. More research is needed to explore the impact of food on the in vivo process of aripiprazole.

Aripiprazole is primarily metabolized by cytochrome P450 (CYP) isoenzymes, most importantly CYP2D6 and CYP3A4 [23]. Research indicates that the levels of various CYP enzymes are elevated in Western populations compared to Japanese populations [37]. The phenotype of poor CYP2D6 metabolism is highest among Europeans (5.4%) and lower among East Asians (0.4%) [38]. Furthermore, 50%–100% of East Asian patients exhibit higher plasma concentrations per daily dose of aripiprazole than Western patients [39], indicating slower metabolism of aripiprazole in East Asians [40]. Consistent with this hypothesis, a BE study of aripiprazole ODT in western participants reported a mean C_{max} of aripiprazole was approximately 42 ng/mL. The GM of AUC_{0-72h} for the test and the reference formulations of aripiprazole were 1300.41 and 1261.55 h·ng/mL, respectively [20]. These values were lower than the results obtained in our study.

According to the literature, the most common adverse reactions of aripiprazole include headache, agitation, anxiety, insomnia, somnolence, nausea, vomiting, etc [41]. In our study, the AEs with an incidence of exceeding 10% included somnolence, sinus bradycardia, orthostatic hypotension, increase in heart rate, bradycardia, hypotension, increase in triglycerides, hypertriglyceridemia, decrease in diastolic pressure, increase in serum cholesterol, which were similar to the results reported in previous literature. According to the FDA's "Draft Guidance on Aripiprazole" [26], adults under the age of 35 are more prone to dystonia induced by antipsychotics. The low incidence of dystonia observed in this study may be attributed to the inclusion of participants aged 45–65 years.

The present study introduced a new treatment option for schizophrenia patients, potentially enhancing adherence and outcomes. However, there are several limitations in the present study. First, the participants included were all healthy adults aged 45–65 years old and received a single dose of medication, which is inconsistent with the patient population in clinical practice. Second, regarding the effect of food on the PK of aripiprazole and the bioequivalence of the two formulations, we only studied the effects of a high-fat diet. In summary, the variability in sample size, diet, and physiological status between healthy participants and patients, single-dose studies have difficulty

TABLE 3 | Adverse events after administration of aripiprazole OSF and ODT in the fasting and fed states.

Preferred Terminology	OSF with water m, *n* (%)	OSF without water m, *n* (%)	ODT m, *n* (%)	Total m, *n* (%)
Under fasting state				
Alanine aminotransferase increased	1, 1 (3.33)	0, 0 (0.00)	0, 0 (0.00)	1, 1 (3.33)
Blood pressure diastolic decreased	1, 1 (3.33)	1, 1 (3.33)	1, 1 (3.33)	3, 3 (10.00)
Blood pressure increased	1, 1 (3.33)	0, 0 (0.00)	0, 0 (0.00)	1, 1 (3.33)
Blood urea nitrogen increased	0, 0 (0.00)	0, 0 (0.00)	1, 1 (3.33)	1, 1 (3.33)
Cholesterol serum elevated	0, 0 (0.00)	2, 2 (6.67)	1, 1 (3.33)	3, 3 (10.00)
Electrocardiogram T wave abnormal	2, 1 (3.33)	1, 1 (3.33)	1, 1 (3.33)	4, 2 (6.67)
Extrasystole ventricular	1, 1 (3.33)	1, 1 (3.33)	2, 2 (6.67)	4, 2 (6.67)
Gamma-glutamyltransferase increased	1, 1 (3.33)	0, 0 (0.00)	0, 0 (0.00)	1, 1 (3.33)
Hemoglobin decreased	0, 0 (0.00)	0, 0 (0.00)	1, 1 (3.33)	1, 1 (3.33)
Heart rate increased	2, 2 (6.67)	4, 4 (13.33)	4, 4 (13.33)	10, 7 (23.33)
Hypotension orthostatic	4, 4 (13.33)	6, 6 (20.00)	4, 4 (13.33)	14, 9 (30.00)
Nausea	2, 2 (6.67)	2, 2 (6.67)	0, 0 (0.00)	4, 3 (10.00)
Sinus bradycardia	6, 6 (20.00)	6, 6 (20.00)	7, 7 (23.33)	19, 13 (43.33)
Total bile acid increased	0, 0 (0.00)	2, 2 (6.67)	0, 0 (0.00)	2, 2 (6.67)
Triglycerides increased	1, 1 (3.33)	1, 1 (3.33)	2, 2 (6.67)	4, 4 (13.33)
Under fed state				
Amylase increased	1, 1 (3.33)	—	0, 0 (0.00)	1, 1 (3.33)
Blood pressure increased	1, 1 (3.33)	—	3, 3 (10.00)	4, 3 (10.00)
Bradycardia	3, 3 (10.00)	—	4, 4 (13.33)	7, 6 (20.00)
Creatine phosphokinase increased	0, 0 (0.00)	—	1, 1 (3.33)	1, 1 (3.33)
Diarrhea	1, 1 (3.33)	—	0, 0 (0.00)	1, 1 (3.33)
Electrocardiogram T wave abnormal	2, 2 (6.67)	—	1, 1 (3.33)	3, 3 (10.00)
Hypertriglyceridaemia	1, 1 (3.33)	—	4, 3 (10.00)	5, 4 (13.33)
Hypotension	1, 1 (3.33)	—	4, 4 (13.33)	5, 5 (16.67)
Hypotension orthostatic	6, 6 (20.00)	—	5, 5 (16.67)	11, 8 (26.67)
Nausea	1, 1 (3.33)	—	0, 0 (0.00)	1, 1 (3.33)
Sinus bradycardia	2, 2 (6.67)	—	2, 2 (6.67)	4, 4 (13.33)
Somnolence	13, 12 (40.00)	—	13, 13 (43.33)	26, 15 (50.00)

Abbreviations: m, number of events; n, number of cases; ODT, orally disintegrating tablets; OSF, oral soluble films.

reflecting the actual situation of long-term medication. The PK characteristics, safety, and efficacy of aripiprazole OSF in patients require further investigation.

Author Contributions

R.L. and S.C. wrote the manuscript; Y.T. and X.G. designed the research; S.Y. G.Y., and S.C. performed the research; R.L., Z.Z., and T.W. analyzed the data.

Acknowledgments

We extend our sincere thanks to the Research Department of Qilu Pharmaceutical Co. Ltd. (Shandong, China) for their invaluable support in conducting this study. We also acknowledge with appreciation the Beijing Municipal Health Commission for providing the "Beijing Research Ward Excellence Program (BRWEP)" platform. Lastly, we would like to express our deepest gratitude to all the participants in the study, whose contributions were essential to the success of our research. Additional supporting information may be found in the online version of the article at the publisher's website.

Conflicts of Interest

This study investigates aripiprazole oral soluble films, a product manufactured by Qilu Pharmaceutical Co. Ltd. The research was funded by Qilu Pharmaceutical Co. Ltd., and three authors (Xingli Gu, Zuokai Zhang, and Taixin Wang) are employees of the company. These authors have declared their potential conflicts of interest. The other authors have no relevant financial or professional relationships with Qilu Pharmaceutical Co. Ltd. or the study subject to disclose.

References

1. M. J. Owen, A. Sawa, and P. B. Mortensen, "Schizophrenia," *Lancet* 388, no. 10039 (2016): 86–97.

2. GBD-Mental-Disorders-Collaborators, "Global, Regional, and National Burden of 12 Mental Disorders in 204 Countries and Territories, 1990–2019: A Systematic Analysis for the Global Burden of Disease Study 2019," *Lancet Psychiatry* 9, no. 2 (2022): 137–150.

3. F. J. Charlson, A. J. Ferrari, D. F. Santomauro, et al., "Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016," *Schizophrenia Bulletin* 44, no. 6 (2018): 1195–1203.

4. H. Jin and I. Mosweu, "The Societal Cost of Schizophrenia: A Systematic Review," *PharmacoEconomics* 35, no. 1 (2017): 25–42.

5. M. Lähteenvuo and J. Tiihonen, "Antipsychotic Polypharmacy for the Management of Schizophrenia: Evidence and Recommendations," *Drugs* 81, no. 11 (2021): 1273–1284.

6. H. Sakurai, N. Yasui-Furukori, T. Suzuki, et al., "Pharmacological Treatment of Schizophrenia: Japanese Expert Consensus," *Pharmacopsychiatry* 54, no. 2 (2021): 60–67.

7. G. A. Keepers, L. J. Fochtmann, J. M. Anzia, et al., "The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia," *American Journal of Psychiatry* 177, no. 9 (2020): 868–872.

8. P. M. Llorca, "Partial Compliance in Schizophrenia and the Impact on Patient Outcomes," *Psychiatry Research* 161, no. 2 (2008): 235–247.

9. T. Wu, X. Xiao, S. Yan, et al., "Digital Health Interventions to Improve Adherence to Oral Antipsychotics Among Patients With Schizophrenia: A Scoping Review," *BMJ Open* 13, no. 11 (2023): e071984.

10. B. Morath, S. Sauer, M. Zaradzki, and A. H. Wagner, "Orodispersible Films—Recent Developments and New Applications in Drug Delivery and Therapy," *Biochemical Pharmacology* 200 (2022): 115036.

11. J. Ferlak, W. Guzenda, and T. Osmałek, "Orodispersible Films-Current State of the Art, Limitations, Advances and Future Perspectives," *Pharmaceutics* 15, no. 2 (2023): 361.

12. P. Batista, M. Pintado, and P. Oliveira-Silva, "Overview About Oral Films in Mental Disorders," *Pharmaceuticals* 16, no. 8 (2023): 1063.

13. K. Dwan, T. Li, D. G. Altman, and D. Elbourne, "CONSORT 2010 Statement: Extension to Randomised Crossover Trials," *BMJ* 366 (2019): l4378.

14. Research FCFDEA, "Clinical Pharmacology Andbiopharmaceutics Review(s) for 022524ORIG1S000," 2024.

15. G. Zhu, L. Wang, S. Han, et al., "Pharmacokinetics and Bioequivalence Study of Montelukast Sodium Oral Soluble Film and Chewable Tablet in Healthy Chinese Volunteers: Randomized Trials Under Fasting and Fed Conditions," *Annals of Translational Medicine* 11, no. 2 (2023): 93.

16. J. Xiang, N. Xu, X. Wang, et al., "Bioequivalence of 2 Aripiprazole Orally Disintegrating Tablets in Healthy Chinese Volunteers Under Fasting and Fed Conditions," *Clinical Pharmacology in Drug Development* 10, no. 8 (2021): 840–849.

17. EMA, "Guideline on the Investigation of Bioequivalence," 2010, http://www.ema.europa.eu.

18. NMPA, "Guidance Principles for Bioequivalence Studies of Generic Chemical Drugs in Humans Using Pharmacokinetic Parameters as Endpoint Evaluation Indicators (Issued by NMPA)," 2016, https://www.nmpa.gov.cn/index.html.

19. Administration(NMPA) NMP, "Guidance Principles for Bioequivalence Studies of Generic Chemical Drugs in Humans Using Pharmacokinetic Parameters as Endpoint Evaluation Indicators (Issued by NMPA)," 2016, https://www.nmpa.gov.cn/index.html.

20. MHRA, "Public Assessment Report: Aripiprazole 10 mg Orodispersible Tablets (UK Licence No: PL 24668/0273–276)," 2015, https://products.mhra.gov.uk.

21. S. A. Julious, "Sample Sizes for Clinical Trials With Normal Data," *Statistics in Medicine* 23, no. 12 (2004): 1921–1986.

22. S. Mallikaarjun, D. E. Salazar, and S. L. Bramer, "Pharmacokinetics, Tolerability, and Safety of Aripiprazole Following Multiple Oral Dosing in Normal Healthy Volunteers," *Journal of Clinical Pharmacology* 44, no. 2 (2004): 179–187.

23. W. A. Kinghorn and J. P. McEvoy, "Aripiprazole: Pharmacology, Efficacy, Safety and Tolerability," *Expert Review of Neurotherapeutics* 5, no. 3 (2005): 297–307.

24. FDA, "Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application," 2021, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioequivalence-studies-pharmacokinetic-endpoints-drugs-submitted-under-abbreviated-new-drug.

25. ICH, "M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms," 2024, https://www.fda.gov/.

26. FDA, "Draft Guidance on Aripiprazole," 2021, http://www.accessdata.fda.gov/scripts/cder/dissolution/.

27. J. P. Lacro, L. B. Dunn, C. R. Dolder, S. G. Leckband, and D. V. Jeste, "Prevalence of and Risk Factors for Medication Nonadherence in Patients With Schizophrenia: A Comprehensive Review of Recent Literature," *Journal of Clinical Psychiatry* 63, no. 10 (2002): 892–909.

28. X. Zhu, M. Wen, Y. He, J. Feng, X. Xu, and J. Liu, "The Relationship Between Level of Education, Cognitive Function and Medication Adherence in Patients With Schizophrenia," *Neuropsychiatric Disease and Treatment* 19 (2023): 2439–2450.

29. G. Kaplan, J. Casoy, and J. Zummo, "Impact of Long-Acting Injectable Antipsychotics on Medication Adherence and Clinical, Functional, and Economic Outcomes of Schizophrenia," *Patient Preference and Adherence* 7 (2013): 1171–1180.

30. C. U. Correll, E. Kim, J. K. Sliwa, et al., "Pharmacokinetic Characteristics of Long-Acting Injectable Antipsychotics for Schizophrenia: An Overview," *CNS Drugs* 35, no. 1 (2021): 39–59.

31. I. E. Cupone, A. Sansone, F. Marra, A. M. Giori, and E. A. Jannini, "Orodispersible Film (ODF) Platform Based on Maltodextrin for Therapeutical Applications," *Pharmaceutics* 14, no. 10 (2022): 2011.

32. K. Nordstrom and M. H. Allen, "Alternative Delivery Systems for Agents to Treat Acute Agitation: Progress to Date," *Drugs* 73, no. 16 (2013): 1783–1792.

33. R. Sevinç Özakar and E. Özakar, "Current Overview of Oral Thin Films," *Turkish Journal of Pharmaceutical Sciences* 18, no. 1 (2021): 111–121.

34. S. Jacob, S. H. S. Boddu, R. Bhandare, S. S. Ahmad, and A. B. Nair, "Orodispersible Films: Current Innovations and Emerging Trends," *Pharmaceutics* 15, no. 12 (2023): 2753.

35. M. He, L. Zhu, N. Yang, H. Li, and Q. Yang, "Recent Advances of Oral Film as Platform for Drug Delivery," *International Journal of Pharmaceutics* 604 (2021): 120759.

36. M. Koziolek, S. Alcaro, P. Augustijns, et al., "The Mechanisms of Pharmacokinetic Food-Drug Interactions—A Perspective From the

UNGAP Group," *European Journal of Pharmaceutical Sciences* 134 (2019): 31–59.

37. T. Shimada, H. Yamazaki, M. Mimura, Y. Inui, and F. P. Guengerich, "Interindividual Variations in Human Liver Cytochrome P-450 Enzymes Involved in the Oxidation of Drugs, Carcinogens and Toxic Chemicals: Studies With Liver Microsomes of 30 Japanese and 30 Caucasians," *Journal of Pharmacology and Experimental Therapeutics* 270, no. 1 (1994): 414–423.

38. A. Gaedigk, K. Sangkuhl, M. Whirl-Carrillo, T. Klein, and J. S. Leeder, "Prediction of CYP2D6 Phenotype From Genotype Across World Populations," *Genetics in Medicine* 19, no. 1 (2017): 69–76.

39. S. K. Lin, "Racial/Ethnic Differences in the Pharmacokinetics of Antipsychotics: Focusing on East Asians," *Journal of Personalized Medicine* 12, no. 9 (2022): 1362.

40. C. Hiemke, N. Bergemann, H. W. Clement, et al., "Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017," *Pharmacopsychiatry* 51, no. 1–2 (2018): 9–62.

41. A. Preda and B. B. Shapiro, "A Safety Evaluation of Aripiprazole in the Treatment of Schizophrenia," *Expert Opinion on Drug Safety* 19, no. 12 (2020): 1529–1538.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.