CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216655Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA Resubmission
Application Number(s)	216655
Priority or Standard	Standard
Submit Date(s)	August 24, 2022; September 19, 2023
Received Date(s)	August 24, 2022; September 19, 2023
PDUFA Goal Date	July 19, 2024
Division/Office	Division of Psychiatry
Review Completion Date	July 19, 2024
Established/Proper Name	Aripiprazole
(Proposed) Trade Name	Opipza
Pharmacologic Class	Atypical antipsychotic
Code name	LP088
Applicant	Xiamen LP Pharmaceutical Co., Ltd.
Dosage form	Oral soluble film
Applicant proposed Dosing Regimen	<u>Starting dosage</u>: • Schizophrenia in adults: 10 to 15 mg/day; pediatric patients 13 years and older: 2 mg/day • Adjunctive treatment of major depressive disorder (MDD) in adults: 2 to 5 mg/day • Irritability associated with autistic disorder in pediatric patients 6 years and older: 2 mg/day • Treatment of Tourette's disorder in pediatric patients 6 years and older: <50 kg: 2 mg/day; ≥50 kg: 2 mg/day <u>Recommended dosage</u>: • Schizophrenia in adults: 10 to 15 mg/day; pediatric patients 13 years and older: 10 mg/day • Adjunctive treatment of MDD in adults: 5 to 10 mg/day • Irritability associated with autistic disorder in pediatric patients 6 years and older: 5 to 10 mg/day • Treatment of Tourette's disorder in pediatric patients 6 years and older: <50 kg: 5 mg/day; ≥50 kg: 10 mg/day <u>Maximum recommended dosage:</u> • Schizophrenia in adults: 30 mg/day; pediatric patients 13 years and older: 30 mg/day • Adjunctive treatment of MDD in adults: 15 mg/day • Irritability associated with autistic disorder in pediatric patients 6 years and older: 15 mg/day • Treatment of Tourette's disorder in pediatric patients 6 years and older: <50 kg: 10 mg/day; ≥50 kg: 20 mg/day

Applicant Proposed Indication(s)/Population(s)	• Schizophrenia • Adjunctive treatment of major depressive disorder • Irritability associated with autistic disorder • Treatment of Tourette's disorder
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Schizophrenia (disorder) 58214004 Major depressive disorder (disorder) 370143000 Autistic disorder (disorder) 408856003 Gilles de la Tourette's syndrome (disorder) 5158005
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	• Treatment of schizophrenia in patients ages 13 years and older • Adjunctive treatment of major depressive disorder in adults • Irritability associated with autistic disorder in pediatric patients 6 years and older • Treatment of Tourette's disorder in pediatric patients 6 years and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Schizophrenia (disorder) 58214004 Major depressive disorder (disorder) 370143000 Autistic disorder (disorder) 408856003 Gilles de la Tourette's syndrome (disorder) 5158005
Recommended Dosing Regimen	<u>Starting dosage</u>: • Schizophrenia in adults: 10 to 15 mg/day; pediatric patients 13 years and older: 2 mg/day • Adjunctive treatment of MDD in adults: 2 to 5 mg/day • Irritability associated with autistic disorder in pediatric patients 6 years and older: 2 mg/day • Treatment of Tourette's disorder in pediatric patients 6 years and older: <50 kg: 2 mg/day; ≥50 kg: 2 mg/day <u>Recommended dosage</u>: • Schizophrenia in adults: 10 to 15 mg/day; pediatric patients 13 years and older: 10 mg/day • Adjunctive treatment of MDD in adults: 5 to 10 mg/day • Irritability associated with autistic disorder in pediatric patients 6 years and older: 5 to 10 mg/day • Treatment of Tourette's disorder in pediatric patients 6 years and older: <50 kg: 5 mg/day; ≥50 kg: 10 mg/day <u>Maximum recommended dosage</u> • Schizophrenia in adults: 30 mg/day; pediatric patients 13 years and older: 30 mg/day • Adjunctive treatment of MDD in adults: 15 mg/day

	• Irritability associated with autistic disorder in pediatric patients 6 years and older: 15 mg/day • Treatment of Tourette's disorder in pediatric patients 6 years and older: <50 kg: 10 mg/day; ≥50 kg: 20 mg/day

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Shin-Ye (Sandy) Chang, PharmD
Nonclinical Reviewer	Sonia Tabacova, PhD
Nonclinical Team Leader	Amy Avila, PhD
Nonclinical Team Supervisor	Aisar Atrakchi, PhD
Office of Clinical Pharmacology Reviewer	Kofi A. Kumi, PhD
Office of Clinical Pharmacology Team Leader	Venkateswaran Chithambaram Pillai, PhD
Clinical Reviewer	Roberta Glass, MD
Clinical Team Leader	Martine Solages, MD
Cross-Disciplinary Team Leader	Venkateswaran Chithambaram Pillai, PhD
Division Director (OCP)	Mehul Mehta, PhD
Clinical Deputy Division Director (Signatory)	Bernard Fischer, MD

Additional Reviewers of Application

Office of Pharmaceutical Quality	ONDP BC - Julia Pinto, PhD SPQA / ATL - Valerie Amspacher, PharmD Drug Substance – Zhixing Shan/Katie Duncan Drug Product – Andrei Ponta, PhD Process and Facilities – Teng (Daisy) Xu and Jingbo Xiao Biopharmaceutics - Swapna Pamu/Okpo Eradiri RBPM – Teshara Bouie
Office of Prescription Drug Promotion	Lindsay McCann, PharmD, BCCCP
Division of Medical Policy Programs	Laurie Buonaccorsi, PharmD/Barbara Fuller,RN, MSN (Team Leader)
Office of Surveillance and Epidemiology (OSE)/ Division of Medication Error Prevention and Analysis	Loretta Holmes, BSN, PharmD/Yevgeniya (Jen) Kogan, PharmD, BCSCP (Team Leader)
OSE Project Manager	Phuong Nguyen, , GWCPM, CQIA
Division of Pediatrics and Maternal Health	Carla Epps, MD/Shetarra Walker, MD (Team Leader)
Associate Director of Labeling	Kimberly Updegraff, RPh, MHS, MS

Signatures

See archived signatory memos for each discipline.

Glossary

AE	adverse event
AR	adverse reaction
ASD	autism spectrum disorder
AUC	area under the plasma concentration-time curve
CMC	chemistry, manufacturing, and controls
ECG	electrocardiogram
eCRF	electronic case report form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
iPSP	initial pediatric study plan
LD	listed drug
MedDRA	Medical Dictionary for Regulatory Activities
MDD	major depressive disorder
NDA	new drug application
OCP	Office of Clinical Pharmacology
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSF	oral soluble film
OSIS	Office of Study Integrity and Surveillance
PK	pharmacokinetics
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
TEAE	treatment emergent adverse event
TD	Tourette's disorder

1 Executive Summary

1.1. Product Introduction

Aripiprazole is an atypical antipsychotic with partial agonism at D_2 and 5-HT_{1A} receptors and antagonism at 5-HT_{2A} receptors. The Applicant is proposing a new formulation of aripiprazole, aripiprazole oral soluble film (OSF) in strengths of 2 mg, 5mg, and 10 mg. This formulation may be helpful for patients with swallowing difficulties. The Applicant is pursuing a 505(b)(2) path with Abilify (aripiprazole, NDA 021436) as the listed drug (LD). The LD is available in tablets (2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg), orally disintegrating tablets (10 mg and 15 mg), oral solution (1 mg/mL), and injection (9.75 mg/1.3 mL single-dose vial). The indications for the LD include treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I, adjunctive treatment of major depressive disorder (MDD), irritability associated with autistic disorder, and treatment of Tourette's disorder. Because the data supporting the acute treatment of manic and mixed episodes associated with bipolar I is still under patent, the Applicant is not pursuing this indication, but is pursing all other indications of the LD. The Applicant conducted two pharmacokinetic bridging studies comparing aripiprazole OSF 10 mg to aripiprazole tablets 10 mg (one study was conducted under fasting conditions and the other was conducted under fed conditions).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for the proposed indications is provided by the Agency's previous findings of effectiveness for the LD and the establishment of a scientifically acceptable PK bridge between the LD and aripiprazole OSF. Product approval is recommended.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

This NDA relies on the Agency's previous findings of safety and effectiveness for the listed drug (LD, Abilify; NDA 021436) and the scientifically acceptable PK bridge that was established between the LD and aripiprazole OSF. Therefore, the effectiveness of aripiprazole OSF is expected to be similar to the LD. No new safety issues were identified from the Applicant's pharmacokinetic studies. The benefit-risk profile of aripiprazole OSF does not differ from the LD. This assessment supports the marketing approval of aripiprazole OSF for the treatment of schizophrenia, adjunctive treatment of MDD, irritability associated with autistic disorder, and treatment of Tourette's disorder. The approval of aripiprazole OSF gives additional options for treatment based on patients' needs and preferences.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The Applicant has proposed the following indications for aripiprazole OSF: treatment of schizophrenia, adjunctive treatment of MDD, irritability associated with autistic disorder, and treatment of Tourette's disorder. • These conditions are associated with impairment in social and occupational functioning, psychological distress, and a range of adverse outcomes including suicidal ideation and behavior.	Schizophrenia, MDD, autism, and Tourette's disorder have significant impacts on individual patients and on public health.
Current Treatment Options	• All the proposed indications are conditions for which chronic treatment is generally required and for which adherence to treatment can improve outcomes.	Availability of an oral soluble film may aid in adherence in patients for whom swallowing tablets is difficult, including some pediatric patients and patients with dysphagia related to co-occuring physical health conditions.
Benefit	• The Applicant proposes to rely on the findings of effectiveness for the listed drug (LD) aripiprazole (Abilify) tablets (NDA 021436). • The clinical pharmacology program in this submission consisted of two pivotal relative bioavailability studies (LP088-20-09 and LP088-2010) after single-dose administration to establish a pharmacokinetic (PK) bridge	The submitted bioavailability studies have established an adequate scientific bridge to the LD. The results of these studies, along with the Agency's findings of safety and effectiveness for the LD,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	between aripiprazole OSF and the LD under both fed and fasting conditions. • The Office of Clinical Pharmacology (OCP) determined that the exposures (peak plasma concentrations (Cmax) and the area under the plasma concentration-time curve (AUC)) from equal doses of aripiprazole OSF were comparable to that of the LD, Abilify tablets, after single-dose administration under both fasting and fed conditions.	provide substantial evidence of effectiveness to support approval of aripiprazole OSF.
Risk and Risk Management	• The most common treatment emergent adverse events (TEAEs) reported in both studies were blood pressure decrease and bradycardia; both are listed as adverse reactions in approved labeling for the LD. • Review of laboratory, vital sign, and electrocardiogram data did not reveal any new or unexpected safety signals. • No subjects reported clinically significant abnormal oral or tongue application site assessment findings.	Review of the completed bioavailability studies did not reveal any new or unexpected safety signals. The safety profile of aripiprazole OSF is expected to be consistent with that of the LD.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		N/A
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

The proposed indications for aripiprazole OSF are:

- Schizophrenia in adults and pediatric patients 13 years and older
- Adjunctive treatment of major depressive disorder (MDD) in adults
- Irritability associated with autistic disorder in pediatric patients 6 years and older
- Treatment of Tourette's disorder in pediatric patients 6 years and older

Schizophrenia

Schizophrenia is a serious condition characterized by a constellation of symptoms that may include delusions, hallucinations, disorganized speech, disorganized behavior, diminished emotional expression, and avolition (American Psychiatric Association 2022). Specific clinical features of schizophrenia are categorized as positive symptoms (e.g., hallucinations, delusions, disorganized thinking and behavior), negative symptoms (e.g., decreased expressiveness, apathy, avolition), cognitive impairment (e.g., decreased processing speed, attention, memory, reasoning, and social cognition), and other mood and anxiety symptoms. Schizophrenia is associated with significant impairments in social and occupational functioning and is the 18th leading cause of years lost to disability (YLD) globally (World Health Organization 2020). Schizophrenia is also a significant risk factor for suicide. Antipsychotics constitute the first-line medication treatment for schizophrenia.

Adjunctive Treatment of MDD

MDD is a debilitating and chronic illness. This disease is characterized by low mood, anhedonia, feelings of guilt and worthlessness, low energy, and other emotional and physical symptoms (American Psychiatric Association 2022). In severe cases, MDD can result in suicide. Partial response to pharmacologic treatment is common. In the National Institute of Mental Health (NIMH)-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, only 28% of patients achieved remission (defined as a score of ≤ 7 on the 17-item Hamilton Depression Rating Scale (HAM-D17)) during first-line treatment with a selective serotonin reuptake inhibitor (Trivedi et al. 2006). Depressive disorders are the second leading cause of YLD worldwide (World Health Organization 2020). To date, only three drugs have received an indication for the adjunctive treatment of MDD: aripiprazole, quetiapine extended-release, and brexpiprazole.

Autism

Autism Spectrum Disorder (ASD) is a neurodevelopment condition characterized by deficits in reciprocal social communication and restricted, repetitive behaviors. Symptoms initially present in early childhood and contribute to difficulties in developing, maintaining, and understanding

relationships. In addition to these core symptoms, pediatric patients with ASD often suffer from challenging behaviors, including symptoms of irritability, which may manifest as tantrums, self-injury, and aggressive behaviors. To date, there are no FDA-approved pharmacologic options for treatment of core symptoms of ASD. Aripiprazole and risperidone are the only products approved for the treatment of irritability associated with ASD.

Tourette Disorder

Tourette disorder (TD) is a neurodevelopmental disorder characterized by the presence of multiple motor tics and one or more vocal tics. TD has been associated with impaired social functioning, difficulties completing activities of daily living, physical pain, suicidal ideation, and significant caregiver burden (Robertson et al. 2017). Three medications are currently approved for the treatment of TD. Haloperidol is indicated for the treatment of tics and vocal utterances associated with TD in children and adults, though approved labeling notes that safety and efficacy in pediatric patients have not been established. Aripiprazole is approved for use in pediatric patients 6 to 18 years of age with TD. Pimozide is indicated for the suppression of vocal and motor tics associated with TD that fail to respond to standard treatments. Limited data on the safety and efficacy of pimozide in children younger than 12 years of age are available.

2.2. Analysis of Current Treatment Options

Risperidone and aripiprazole, which are approved for the treatment of schizophrenia and for the treatment of irritability associated with autistic disorder, are available as orally distentgrating tablets (Risperdal M-tab and Abilify Discmelt, respectively). Olanzapine, which is indicated for the treatment of schizophrenia, is also available as an orally disentegating tablet (Zyprexa Zydis). No other approved pharmacologic products are available in orally disintegrating formulations for the indications proposed in this application. All the proposed indications are serious conditions for which chronic treatment is generally required. Availability of additional orally disintegrating formulations may aid in adherence in patients for whom swallowing tablets is difficult, including some pediatric patients and patients with dysphagia related to co-occuring physical health conditions. Therefore, the availability of an aripiprazole oral soluble film in the treatment armamentarium would be a valuable option for these patients.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Aripiprazole oral soluble film (OSF) is not currently marketed in the United States or elsewhere.

3.2. Summary of Presubmission/Submission Regulatory Activity

The product was developed under IND 150931. The Applicant conducted both bioavailability studies in China. The Applicant originally submitted this new drug application (NDA) on August 24, 2022, but the Division issued a Refuse to File letter (dated October 21, 2022) because the Applicant did not submit an initial pediatric study plan (iPSP) prior to submitting the NDA and because the application did not fulfill the following chemistry requirements:

- Provide adequate information about composition and safety of the imprinting/marking ink solution with respect to the total daily intake

- Include acceptance criteria for the imprinting/marking on the film in the Appearance test of the proposed product specification

- Update the 356(h) and all relevant sections of the application to include the manufacturing facility(ies) responsible for imprinting. Ensure that all facilities remain ready for the commercial production and inspection.

- Manufacture a minimum of one batch for each strength (no less than 1/10 of the commercial scale) of imprinted/marked films using the commercial manufacturing process and control strategy and provide the following information:

    - The batch records in 3.2.R of the NDA as the representative of commercial batch production.

    - At least 6 months of long-term and accelerated stability data of the above mentioned batches of imprinted/marked films of each strength and commit to continue stability testing of these batches up to the proposed expiry and submit the remainder of the stability data in the annual reports.

- Data demonstrating that the imprinted/marked films meet the proposed drug product specification at release and on stability

- Data demonstrating that the imprinted/marked film has comparable drug release, film strength, and film integrity to the non-imprinted/non-marked film at release and on stability

The Applicant submitted an iPSP on August 9, 2023, and a revision on August 21, 2023. The Division issued an Agreed Initial Pediatric Study plan-Agreement letter on September 1, 2023. The Applicant resubmitted the NDA on September 19, 2023, and the Division issued a Filling communication-No Filing Review Issues Identified letter on November 29, 2023.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Study Integrity and Surveillance (OSIS)

The Office of Study Integrity and Surveillance (OSIS) was consulted for an inspection of the clinical site, Xiamen Lotus Hospital, Xiamen (Fujian, China) and bioanalytical site, (b) (4) (b) (4).

No objectionable conditions of the clinical site were observed following a remote regulatory assessment (RRA) of the clinical site. However, the RRA report notes that an external statistical company created a randomization sheet that identified the bottles that were subsequently retained as reserve samples by the clinical site. The finding is a protocol deviation because the protocol specified that the clinical site was supposed to randomly select reserve samples from investigation products (IP) supplied by Sponsor for the studies. Based on the review of RRA report and post-RRA correspondence received from the Office of Regulatory Affairs (ORA) investigator, OSIS concluded that the protocol deviation did not impact the clinical data from studies conducted at the clinical site because the study Sponsor was required to retain reserves in accordance with 21 CFR 312.57(d).

OSIS determined that an inspection of the bioanalytical sites was not needed due to the recent RRA for the same bioanalytical site in March 2023 for NDAs (b) (4) and (b) (4). OSIS concluded that the reviewed studies were reliable.

4.2. Product Quality

The Office of Product Quality (OPQ) recommends approval for this application based on drug substance, drug product, process/facilities and biopharmaceutics reviews.

Drug Substance: The chemistry, manufacturing, and control (CMC) information for the drug substance, aripiprazole, is cross-referenced to Type II DMF (b) (4). Aripiprazole is manufactured by the holder of the referenced DMF – (b) (4). The Applicant refers to the DMF and provides a brief description of the general properties, specification, impurities, analytical methods and validations, batch analyses, stability, etc. for the drug substance. All the information is adequate. The controls on the impurities in the aripiprazole drug substance are adequate. There are no concerns of potential genotoxic impurities and (b) (4) for the drug substance, including (b) (4) (b) (4). Based upon stability data in the DMF, the DMF Holder assigned an expiration date of (b) (4) years for aripiprazole stored (b) (4) (b) (4) in the proposed container closure system.

Drug Product: Aripiprazole OSF is a rectangular white film, which disintegrates rapidly when placed in the oral cavity. The three strengths are dose-proportional, with the film size (b) (4) (the 2 mg and 5 mg doses are (b) (4) and (b) (4)

respectively, that of the 10 mg dose). The drug product is packaged into individual (b) (4) pouches. The excipients are within the limits specified in the FDA inactive ingredient database for this route of administration calculated based on maximum daily dose. The Applicant has provided release results for 13 batches (four to five batches of each strength), which met the proposed specifications. The drug product may be granted a 36-month expiry when stored at controlled room temperature based on the long-term stability data provided. The Applicant is claiming categorical exclusion for submission of an environmental assessment based on 21 CFR Part 25.31(a) and has included a statement of no extraordinary circumstances, in accordance with 21 CFR 25.15. Based on the drug product control strategies, release data, and stability results, the proposed drug product is adequate.

Manufacturing: The manufacturing equipment for commercial batches is identical to that for the registration batches. Composition of all three strengths is same and dose proportional to each other. No active pharmaceutical ingredient (API) overage and no scale up has been proposed. The commercial batch sizes are the same as registration batch size for each corresponding strength. The drug product facility Xiamen LP Pharmaceutical has demonstrated experience manufacturing oral soluble film based on the pre-approval inspection (PAI) conducted April 15 to 19, 2024. Hence, this facility is deemed acceptable for the manufacturing operations of aripiprazole OSF.

Biopharmaceutics: The Applicant proposed in vitro dissolution method (USP apparatus (II Paddle) ; Speed: 75 RPM; Medium: pH 4.0 sodium acetate buffer; Volume/Temperature: 1000 mL/37 °C; Acceptance criteria: Q= (b) (4) % in 30 minutes) was acceptable. The proposed drug product has rapid dissolution profiles with at least 85% of the drug dissolved in 15 to 30 minutes. Based on proportional similarity in composition, acceptable dissolution characteristics, comparable pharmacokinetic characteristics between aripiprazole OSF 10 mg and the LD 10 mg and the linear pharmacokinetic characteristics of the LD, the Applicant's biowaiver request for lower strengths (2 mg and 5 mg) is granted. From a Biopharmaceutics perspectives, aripiprazole 2 mg, 5 mg, and 10 mg strengths are acceptable.

See the archived integrated quality assessment review from the OPQ for additional information.

4.3. Clinical Microbiology

There were no clinical microbiology data submitted with this application.

4.4. Devices and Companion Diagnostic Issues

There were no data related to devices or companion diagnostics submitted with this application.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

There was no nonclinical data in this submission. This aripiprazole OSF 505(b)(2) application relies on FDA's previous findings reported in the LD (Abilify tablets, NDA 21-436) for the nonclinical pharmacology and toxicology (including general, genetic, carcinogenicity, reproductive and developmental, and special toxicology studies).

5.2. Referenced NDA

Abilify Tablets (NDA 21-436).

6 Clinical Pharmacology

6.1. Executive Summary

Abilify (aripiprazole) oral tablets (NDA021436; 2 mg, 5 mg and 10 mg) is approved for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I, adjunctive treatment of major depressive disorder, irritability associated with autistic disorder and treatment of Tourette's disorder. The Applicant is seeking approval of aripiprazole oral soluble film (OSF) via the 505(b)(2) pathway for the same indications as the listed drug (LD), aripiprazole oral tablets except for acute treatment of manic and mixed episodes associated with bipolar I disorder. The Applicant believes that the OSF formulation would be useful for patients with difficulties swallowing or patients unwilling to swallow a tablet. The OSF should be placed on the tongue where it essentially disintegrates instantaneously. However, the active pharmaceutical ingredient (API) does not dissolve in the mouth and is swallowed with saliva to be absorbed in the gastrointestinal (GI) tract essentially same as the LD. (b) (4) (b) (4) This application relies on the Agency's previous findings of safety and effectiveness of the LD.

The clinical pharmacology program in this submission consisted of two pivotal relative bioavailability studies (LP088-20-09 and LP088-2010) after single-dose administration to establish a pharmacokinetic (PK) bridge between aripiprazole OSF and the LD under both fed and fasting conditions.

The Office of Clinical Pharmacology (OCP) reviewed the pivotal relative bioavailability studies submitted in this application and finds that the exposures (peak plasma concentrations (Cmax) and the area under the plasma concentration-time curve (AUC)) from equal doses of aripiprazole OSF were comparable to that of the LD, Abilify tablets, after single-dose administration under both fasting and fed conditions.

The PK bridging between the formulations is adequate and therefore the proposed product, aripiprazole OSF, can rely on the safety and effectiveness of the LD. Because the exposures after administration of aripiprazole are equivalent to that of the LD under both fed and fasting conditions, aripiprazole OSF can be administered without regard to meals, similar to the administration instructions for the LD.

Per recommendation from OSIS, data from the clinical and bioanalytical sites for the pivotal relative bioavailability studies (LP088-20-09 and LP088-20-10) are reliable.

OCP recommends the approval of aripiprazole OSF for the same indications as the LD except acute treatment of manic and mixed episodes associated with Bipolar I (which the Applicant has not requested).

6.2. Summary of Clinical Pharmacology Assessment

In a single-dose relative bioavailability study under fasting conditions, the pharmacokinetics (PK) of aripiprazole OSF and aripiprazole tablet, the LD was compared in healthy adult subjects. A single-center, randomized, open-label, single-dose, two-treatment, two-period study was conducted to assess the relative bioavailability of aripiprazole OSF compared to the LD. Each subject received either 10 mg aripiprazole OSF or aripiprazole tablet 10 mg in one period and the alternate treatment in the second period. There was a washout period of 28 days between treatments. The results indicated that the Cmax and AUCinf of the aripiprazole OSF were equivalent to the LD. The 90% confidence intervals (CIs) for the geometric mean ratio (GMR) of Cmax and AUCinf were contained within the acceptable range (80% to 125%) to conclude that the products are equivalent.

In another single-dose relative bioavailability study, the PK of Aripiprazole OSF was compared to the LD under fed conditions. This was a single-center, randomized, open-label, two-treatment, two-period crossover study. In Period 1 on Day 1, following an overnight fast of at least 10 hours, subjects consumed a high-fat and high-calorie breakfast beginning 30 minutes prior to dosing. Subjects then received a single oral dose of aripiprazole tablet 10 mg or aripiprazole OSF 10 mg. In Period 2, subjects were crossed over to the alternate treatment. There was a 28-day washout between each single-dose administration. Aripiprazole OSF 10 mg was placed on the tongue, subjects were instructed to close their mouth immediately and swallow normally without fluid ingestion. Subjects consumed 240 ± 2 mL drinking water 15 minutes post-dose for aripiprazole OSF. (b) (4) Subjects took the LD with water. The results indicated that the Cmax and AUCinf were equivalent. The 90% CIs for the GMR of Cmax and AUCinf were contained within the acceptable range (80% to 125%) to conclude that the products are equivalent.

The median time to reach Cmax (Tmax) for aripiprazole OSF and LD were delayed from 1.5 hours and 2 hours, respectively, under fasting conditions to 6 hours under fed conditions for both the formulations. Given that the proposed drug product is intended for chronic treatment, the delay in Tmax over approximately 4.5 hours is deemed clinically not meaningful.

6.2.1. Clinical Pharmacokinetics

Because the PK bridging between aripiprazole OSF and the LD is adequate—the proposed aripiprazole OSF formulation relies on the clinical PK information except absorption for the LD.

Absorption

In two pivotal relative bioavailability studies, the PK of aripiprazole OSF 10 mg and aripiprazole tablets 10 mg was compared under fasting and fed conditions in healthy subjects. The geometric mean ratios (OSF/tablet) of Cmax and AUCinf values under fasting conditions were about 115% and 106%, respectively. The geometric mean ratios for Cmax and AUCinf values

under fed conditions were about 91% and 95%, respectively. Following administration of aripiprazole OSF under fasting conditions, the median Tmax of aripiprazole is 1.5 hours.

Food: Aripiprazole OSF can be administered with or without food. No meaningful differences in exposures (Cmax and AUCinf) of aripiprazole were observed following administration of aripiprazole OSF 10 mg and aripiprazole tablet 10 mg under fasting and fed (high-fat meal, 800 to 1000 Kcal) conditions. Median Tmax of aripiprazole OSF and aripiprazole tablets was delayed from 1.5 hours and 2 hours, respectively under fasting conditions to 6 hours under fed conditions.

Distribution

The steady-state volume of distribution of aripiprazole following intravenous administration is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution.

At therapeutic concentrations, aripiprazole and its major metabolite, dehydro-aripiprazole are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 to 30 mg/day aripiprazole for 14 days, there was dose dependent D2 receptor occupancy indicating brain penetration of aripiprazole in humans.

Elimination

The mean elimination half-lives are about 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. For CYP2D6 poor metabolizers, the mean elimination half-life for aripiprazole is about 146 hours.

Metabolism

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.

Excretion

Following a single oral dose of [^{14}C]-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 approximately 18% of the oral dose was recovered unchanged in the feces.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Because the exposures (Cmax and AUCinf) of aripiprazole after administration of aripiprazole OSF compared to Abilify tablets are contained within the 80% to 125% bioequivalence limits of the LD under both fasting and fed conditions, the information relevant to dosing and therapeutic individualization of aripiprazole OSF can rely on the LD.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. Clinical Pharmacology Questions

Are the exposures of aripiprazole after aripiprazole OSF 10 mg similar to the LD, aripiprazole tablet after single dose administration under fasting conditions?

Yes, the exposures of aripiprazole after aripiprazole OSF are similar to the LD, aripiprazole tablet, after single dose administration under fasting conditions.

A single-center, randomized, open-label, single-dose, two-treatment, two-period, crossover study was conducted to assess the relative bioavailability of aripiprazole OSF 10 mg compared to the LD, aripiprazole tablet 10 mg, administered under fasting conditions in healthy adult human subjects. Each subject was randomized to one of two treatment sequences according to a randomization schedule. Randomized subjects were dosed on the same day of Period 1 and were crossed over to the alternate formulation and were dosed on the same day of Period 2. Following an overnight fast of at least 10 hours, subjects received a single oral dose of aripiprazole OSF 10 mg or aripiprazole tablet 10 mg.

The two treatments used in the study are:

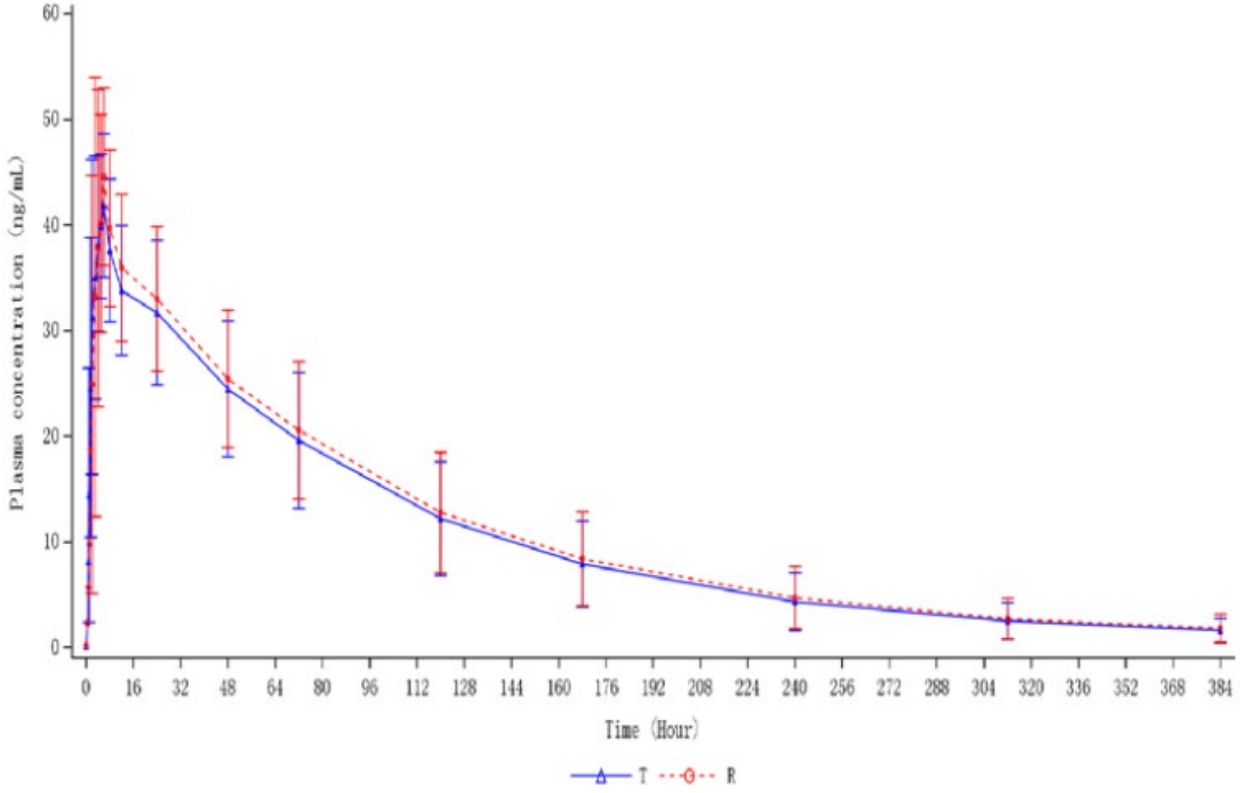
Test: Aripiprazole OSF 10 mg, manufactured and provided by Xiamen LP Pharmaceutical Co., Ltd. Aripiprazole OSF 10 mg was placed on the tongue, subjects were instructed to close their mouth immediately and swallow normally without fluid ingestion. Subjects consumed 240 ± 2 mL drinking water 15 minutes post dose.

Reference: Abilify tablets 10 mg (aripiprazole), manufactured by Otsuka America Pharmaceutical, Inc., Aripiprazole tablet 10 mg was taken with approximately 240 ± 2 mL drinking water.

The two study periods were separated by a washout period of 28 days.

The results are shown in the following figure and table.

Figure 1. Mean (SD) Plasma Aripiprazole Concentration-time Profile



Source: Study LP088-20-09 report, p. 52.

Table 1. Study LP088-20-09: Statistical Summary of the Comparative Bioavailability Results

	Geometric mean and its ratio					
PK parameter (unit)	Aripiprazole OSF N=45	Aripiprazole Tablets N=45	Aripiprazole OSF/Tablets (%)	90% CI(%)	Intra-subject CV (%)	Power (%)
C_{max} (ng/mL)	59.93	52.31	114.56	106.48, 123.24	20.84	63.6
AUC_{0-t} (hr*ng/mL)	3816.96	3591.04	106.29	102.05, 110.71	11.52	100.0
$AUC_{0-\infty}$ (hr*ng/mL)	4007.08	3773.04	106.20	101.95, 110.63	11.56	100.0

Source: Study LP088-20-09 report, p. 53.

The PK parameters (Cmax and AUCinf) are equivalent after administration of aripiprazole OSF and the LD under fasting conditions. The 90% CI for the GMR of Cmax and AUCinf are contained within the acceptable regulatory interval of 80% to 125%. The results suggest that the PK bridge between the formulations is adequate and aripiprazole OSF can rely on the Agency's previous findings of safety and effectiveness of the LD.

Are the exposures of aripiprazole comparable after administration of aripiprazole OSF and the LD under fed conditions? Does this product require specific dosing instruction regarding food?

There are no clinically meaningful differences in exposures when aripiprazole OSF and the LD were administered under fed conditions compared to fasting conditions. Aripiprazole OSF can be administered with or without food, similar to the LD.

A single-center, randomized, open-label, single-dose, two-treatment, two-period, crossover study was conducted under fed conditions. Following an overnight fast of at least 10 hours, subjects consumed a high fat and high calorie breakfast beginning 30 minutes prior to dosing. This meal contained approximately 150 protein calories, 250 carbohydrate calories, and 500 to 600 fat calories. Subjects then received a single oral dose of aripiprazole OSF 10 mg or aripiprazole tablet 10 mg (LD). Subjects were crossed over to the alternate aripiprazole tablets 10 mg or aripiprazole OSF 10 mg in the other period. There was a minimum of a 28-day washout period between each single dose administration.

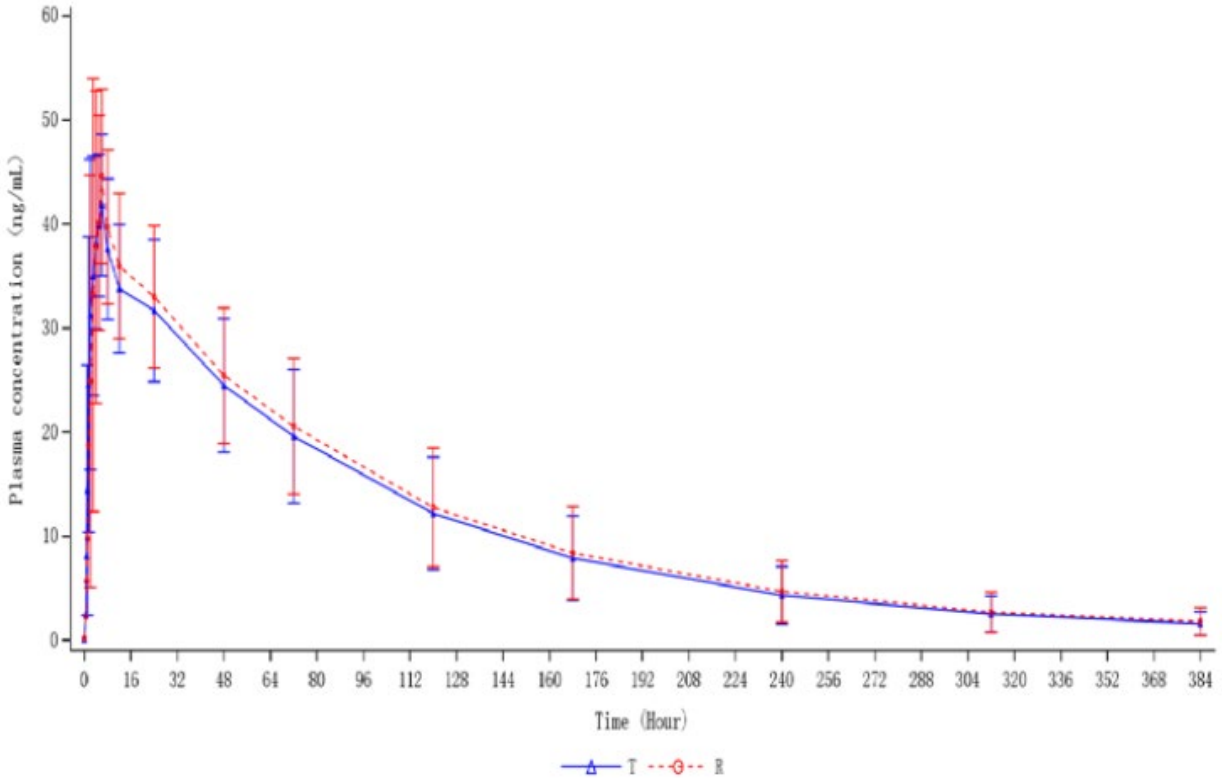
The two treatments used in the study are:

Test: Aripiprazole OSF 10 mg, manufactured and provided by Xiamen LP Pharmaceutical. Aripiprazole OSF 10 mg was placed on the tongue, subjects were instructed to close their mouth immediately and swallow normally without fluid ingestion. Subjects consumed 240 ± 2 mL drinking water 15 minutes post dose for aripiprazole (b) (4).

Reference: Aripiprazole tablets 10 mg manufactured by Otsuka America Pharmaceutical, Inc. Aripiprazole tablet 10 mg was taken with approximately 240 ± 2 mL drinking water.

The results are shown in the following figure and table.

Figure 2. Mean (SD) Plasma Aripiprazole Concentration-time Profile



Source: Study LP088-20-10 report, p. 58.

Table 2. Study LP088 20-10: Statistical Summary of the Comparative Bioavailability Results

PK parameter (unit)	Geometric Least Squares Means			90% CI (%)	Intra-subject CV (%)	Power (%)
	Aripiprazole OSF N=44	Aripiprazole Tablets N=44	Aripiprazole OSF/Tablets (%)			
C_{max} (ng/mL)	45.20	49.64	91.06	85.91, 96.51	16.33	98.1
AUC_{0-t} (hr*ng/mL)	3845.18	4037.20	95.24	92.46, 98.11	8.28	100.0
$AUC_{0-\infty}$ (hr*ng/mL)	4015.94	4232.14	94.89	92.07, 97.80	8.45	100.0

Source: Study LP088 20-10 report, p. 59.

The exposures (Cmax and AUCinf) are comparable when aripiprazole OSF and the LD were administered under fed conditions (Table 2). Given that the 90% CIs for the GMR (aripiprazole OSF/LD) of Cmax and AUCinf are contained within 80% to 125% acceptable limit, the Agency concluded that the the food effect on the PK of aripiprazole OSF is similar to that of the LD. Although median Tmax of aripiprazole was delayed from 1.5 hours and 2 hours, respectively under fasting conditions to 6 hours under fed conditions for both the formulations, the delay in

Tmax under fed conditions was deemed clinically not meaningful due to chronic treatment of aripiprazole OSF is required for the intended indications.
Because the food effect is similar between aripiprazole OSF and the LD and the Prescribing Information for the LD recommends that aripiprazole tablet can be administered with or without food, the proposed drug product, aripiprazole OSF can also be administered without regard to meals.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Sources of clinical data included bioavailability Studies LP088-20-10 and LP088-20-09. See Table 1 for a description of each study.

Table 3. Listing of Clinical Trials Relevant to NDA 216655

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route)	Subjects
Study LP088 -20-10	The objectives of this study are to assess the bioequivalence of Aripiprazole Oral Soluble Film 10 mg *versus* aripiprazole tablets 10 mg in healthy adult human subjects under fed conditions and to monitor the safety of the subjects.	Randomized, open-label, single-dose, two-treatment, two-period, crossover study	**Test Product-T:** Aripiprazole Oral Soluble Film, Dose: 10 mg Dosage Form: Film Route: Oral **Reference Product-R:** Abilify (aripiprazole) Tablets, Dose: 10 mg Dosage Form: Tablet Route: Oral	N = 46 (M-27/F-19) Age Mean: 45.7 ±6.63 Range: 35-64 N = 47 (M-27/F-20) Age Mean: 46.0 ±6.61 Range: 35-64
Study LP088 -20-09	The objectives of this study are to assess the bioequivalence of Aripiprazole Oral Soluble Film 10 mg *versus* aripiprazole tablets 10 mg in healthy adult human subjects under fasting conditions and to monitor the safety of the subjects.	Randomized, open-label, single-dose, two-treatment, two-period, crossover study	**Test Product-T:** Aripiprazole Oral Soluble Film, Dose: 10 mg Dosage Form: Film Route: Oral **Reference Product-R:** ABILIFY (aripiprazole) Tablets, Dose: 10 mg Dosage Form: Tablet Route: Oral Lot No.: ALS00219A	N = 48 (M-36/F-12) Age Mean: 45.8 ±7.46 Range: 35-62 N = 46 (M-34/F-12) Age Mean: 45.7 ±7.08 Range: 35-62

Source: Adapted from Applicant's Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 2, p. 5.

7.2. Review Strategy

Because this NDA was submitted under the 505(b)(2) pathway, much of the understanding of the safety and effectiveness of aripiprazole OSF relies on the Agency's previous findings for the LD, Abilify (aripiprazole) tablets (NDA 021436). The clinical review for this application focused on whether the safety data from the submitted pharmacokinetic studies were consistent with the available safety information for the LD. Many sections of the clinical review were abbreviated or were not applicable.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Studies LP088-20-09 and LP088-20-10

No clinical efficacy studies were submitted with this application. The Applicant submitted relative bioavailability studies to bridge to the findings of safety and effectiveness for the LD. See Section 6 for the clinical pharmacology evaluation of the biovailability studies.

Trial Design

The Applicant submitted the following bioavailability studies:

1. **LP088-20-09:** "A Randomized, Open-Label, Single-Dose, Two-Treatment, Two-Period, Crossover Study to Assess the Bioequivalence of Aripiprazole Tablets 10 mg and Aripiprazole Oral Soluble Film 10 mg Administered Under Fasting Conditions in Forty-five Healthy Adult Human Subjects." The study contained two arms: aripiprazole tablets (the LD) and aripiprazole OSF with a crossover to the other treatment arm.

2. **LP088-20-10:** "A Randomized, Open-Label, Single-Dose, Two-Treatment, Two-Period, Crossover Study to Assess the Bioequivalence of Aripiprazole Tablets 10 mg and Aripiprazole Oral Soluble Film 10 mg Administered Under Fed Conditions in Forty-Four Healthy Adult Human Subjects." The study contained two arms: aripiprazole tablets (the LD) and aripriprazole with a cross-over to the other treatment arm.

See Section 6 for full description of the study designs, endpoints, and analysis.

Study Endpoints

See Section 6.

Statistical Analysis Plan

See Section 6.

Protocol Amendments

The initial versions of both protocols were dated July 30, 2020. Version 2.0 for both protocols (dated September 22, 2020) included changes to the general information/title page and facilities as well as correction of typographical errors.

8.1.2. Study Results

See Section 6.

Compliance with Good Clinical Practices

The clinical study reports indicate that the studies were perfomed in accordance with applicable Good Clinical Practice and International Council on Harmonisation (ICH) guidelines regarding study conduct, record keeping, data collection, and regulatory submission.

Financial Disclosure

The Applicant has submitted FDA form 3454 and attested that it has not entered into any inappropriate financial arrangement with the listed clinical investigator.

Patient Disposition

A total of 48 subjects were enrolled in Study LP088-20-09; 45 subjects completed the study. A total of 48 subjects were enrolled in Study LP088-20-10; 44 subjects completed the study. See Table 2 and Table 3 for additional details about subject disposition.

Table 4. Study LP088-20-09: Subject Disposition

Disposition	No. Subjects
Total screened	**124**
Total screened but not enrolled	**76**
Did not meet Inclusion/Exclusion Criteria	64
Other reasons*	12
Total enrolled and randomized	**48**
Withdrawn prematurely	3
The subject requested to be withdrawn from the study	2
Experienced emesis prior to 2 times T_{max}	1
Total completed study	**45**

*Other reasons include withdrawal of consent and subjects who were eligible and admitted as alternates but not randomized.

Source: Applicant's Clinical Study Report, Table 10-1, p. 44.

Table 5. Study LP088-20-10: Subject Disposition

Disposition	No. of Subjects
Total screened	**97**
Total screened but not enrolled	**49**
Did not meet Inclusion/Exclusion Criteria	37
Other reasons*	12
Total enrolled and randomized	**48**
Withdrawn prematurely	4
Withdrawn due to AE	2
Experienced emesis prior to 2 times T_{max}	2
Total completed study	**44**

*Other reasons include withdrawal of consent and subjects who were eligible and admitted as alternates but not randomized.

Source: Applicant's Clinical Study Report, Table 10-1, p. 49.

Protocol Violations/Deviations

In Study LP088-20-09, nine subjects (18.8%) administered aripiprazole OSF and three subjects (6.5%) admistered aripiprazle tablets had protocol deviations in the following categories: blood sample collected late; blood collecton volume deviation; concomitant medication deviation; and vital signs collected late. In Study LP088-20-10, 23 subjects (50%) administered aripiprazole OSF and 24 subjects (51.1%) subjects administered aripiprazole tablets had protocol deviations in the following categories: blood sample collected outside of time window; high fat breakfast deviation; oral and tongue application site evaluation outside of window; plasma handling out of time window; serology tests deviation; and vital signs measurement outside of time window. These protocol deviations were minor and do not impact interpretation of study data.

Table of Demographic Characteristics

The studies enrolled adult subjects 18 to 64 years of age from a single site in China; 100% of subjects were Asian. Approximately 75% of subjects in Study LP088-20-09 were male; slightly more than half of subjects in Study LP088-20-10 were male. See Table 4 and Table 5 for additional information about demographic and baseline characteristics of subjects enrolled in the studies.

Table 6. Study LP088-20-09: Demographic and Baseline Characteristics

		Aripiprazole OSF N = 48	Aripiprazole Tablets N = 46	Total N=48
Age (years)	Mean ± SD	45.8 ± 7.46	45.7 ± 7.08	45.8 ± 7.46
	Range	35, 62	35, 62	35, 62
Age Groups n (%)	18-40	14 (29%)	13 (28%)	14 (29%)
	41-64	34 (71%)	33 (72%)	34 (71%)
	65-75	0	0	0
	>75	0	0	0
Sex n (%)	Male	36 (75%)	34 (74%)	36 (75%)
	Female	12 (25%)	12 (26%)	12 (25%)
Race n (%)	Asian	48 (100%)	46 (100%)	48 (100%)
	Other race	0	0	0
BMI (kg/m2)	Mean ± SD	23.3 ± 2.03	23.2 ± 2.03	23.3 ± 2.039
	Range	19.6, 26.0	19.6, 26.0	19.6, 26.0
Other Factors		N/A	N/A	N/A

N is the number of subjects who are included in FAS and have taken the corresponding drugs in the treatment group.

BMI=body mass index

Source: Applicant's Clinical Study Report, Table 11-2, p. 49.

Table 7. Study LP088-20-10: Demographic and Baseline Characteristics

		Aripiprazole OSF N = 46	Aripiprazole Tablets N = 47	Total N=48
Age (years)	Mean ± SD	45.7 ± 6.63	46.0 ± 6.61	45.8 ± 6.70
	Range	35, 64	35, 64	35, 64
Age Groups n (%)	18-40	11 (24%)	11 (23%)	12 (25%)
	41-64	35 (76%)	36 (77%)	36 (75%)
	65-75	0	0	0
	>75	0	0	0
Sex n (%)	Male	27 (59%)	27 (57%)	27 (56%)
	Female	19 (41%)	20 (43%)	21 (44%)
Race n (%)	Asian	46 (100%)	47 (100%)	48 (100%)
	Other race	0	0	0
BMI (kg/m^2)	Mean ± SD	23.1 ± 1.92	23.0 ± 1.89	23.1 ± 1.92
	Range	19.4, 26.0	19.4, 26.0	19.4, 26.0
Other Factors		N/A	N/A	N/A

N is the number of subjects who are included in FAS and have taken the corresponding drugs in the treatment group.

BMI=body mass index

Source: Applicant's Clinical Study Report, Table 11-2, p. 55.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

There were no notable medical or surgical history findings in the studies. See Table 4 and Table 5 for additional information about baseline body mass index (BMI), which ranged from 19.6 to 26 kg/m^2 for all subjects.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Subjects were 100% compliant with respect to study treatment in each period except for the discontinued subjects. Study drug administration was performed under supervision by examination of the oral cavity of the subjects by trained study personnel. One subject in Study LP088-20-09 had protocol deviations related to concomitant medications (zopiclone and estazolam) on non-dosing days. No prior or concomitant medication use was reported during Study LP088-20-10.

Efficacy Results – Primary Endpoint

Data Quality and Integrity

The data were of sufficient quality for review.

Efficacy Results – Secondary and other relevant endpoints

Not applicable.

Dose/Dose Response

Not applicable.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Not applicable.

Additional Analyses Conducted on the Individual Trial

Not applicable.

8.1.3. Assessment of Efficacy Across Trials

Not applicable.

Primary Endpoints

Not applicable.

Secondary and Other Endpoints

Not applicable.

Subpopulations

Not applicable.

Additional Efficacy Considerations

Not applicable.

8.1.4. Integrated Assessment of Effectiveness

No clinical efficacy data were submitted in this application. The submitted relative bioavailability studies have established an adequate scientific bridge to the LD. See Section 6.

8.2. Review of Safety

8.2.1. Safety Review Approach

The Applicant proposes to rely on the Agency's prior findings of safety for the LD by establishing an acceptable scientific bridge to ariprazole OSF. The safety review for this application included an analysis of adverse event, vital sign, laboratory assessment, and electrocardiogram (ECG) data from the submitted bioavailability studies.

8.2.2. Review of the Safety Database

Overall Exposure

The submitted PK studies enrolled a total of 96 healthy volunteers, of whom 94 were exposed to aripiprazole OSF.

Adequacy of the safety database:

The safety information relevant to this product includes the Agency's findings of safety for the LD and the submitted safety data from the completed aripiprazole OSF bioavailability studies; the safety population included all subjects who received a dose of study drug. These studies

included assessment of route-specific adverse events related to oral application of the product. Overall, the application included adequate data to assess the safety of aripiprazole OSF.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data quality was acceptable for review.

Categorization of Adverse Events

The Applicant used the following categorization of adverse events:

> Any adverse event (clinical sign, symptom, or disease) temporal associated with the use of the investigational agent, whether or not considered related to the investigational product, was documented on the electronic case report form (eCRF). All adverse events (AEs) reported by the subject or observed by the Principal Investigator were individually listed. The signs and symptoms, time of onset (24-hour clock), duration, action taken and follow-up procedures were reported. All AEs occurring during the study, including during the washout interval, were documented on the eCRF. The definitions regarding AE in this current study are listed as follows:
>
> **Adverse Event:** Any untoward medical occurrence in a clinical investigation subject administered a drug and does not necessarily have a causal relationship with this treatment. An AE can therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporal associated with the use of an investigational product, whether or not related to the investigational product.
>
> **Serious Adverse Event (SAE):** Any experience that is fatal or life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability / incapacity, or is a congenital anomaly or birth defect.
>
> **Unexpected Adverse Event:** Any adverse event that is not identified in nature, severity, or frequency in the Abilify (aripiprazole) Tablets 10 mg Product Labeling.
>
> The Investigator evaluated all AEs according to the following criteria:
>
> Seriousness: whether or not the AE is fatal or life threatening, persistent or permanently disabling, requires or prolongs inpatient hospitalization, or is a congenital anomaly.
>
> Intensity: to be graded as mild, moderate and severe.

The Applicant's categorization of adverse events was acceptable.

Routine Clinical Tests

Routine clinical tests included physical examination, laboratory assessments (hematology, biochemistry, and urinalysis), vital signs (blood pressure, heart rate, temperature), electrocardiograms, and application site assessments.

8.2.4. Safety Results

Deaths

No deaths occurred in the submitted studies.

Serious Adverse Events

No serious adverse events were reported in the submitted studies.

Dropouts and/or Discontinuations Due to Adverse Effects

Study LP088-20-09

- Subject (b) (6) had vomiting approximately 1 hours and 47 minutes after administration of aripiprazole OSF and withdrew from the study.
- Subjects (b) (6) and (b) (6) both withdrew from the study after Period 1; no reasons were recorded in the study report or case report forms. The reason for discontinuation was listed as subject choice.

Study LP088-20-10

- Subject (b) (6) experienced syncope after receiving aripiprazole tablet in Period 1. She was withdrawn from the study; her syncope resolved before checkout from the clinical site.
- Subject (b) (6) reported emesis in Period 1 after receiving aripiprazole OSF. She was withdrawn from the study; the emesis was resolved before checkout from the clinical site.
- Subject (b) (6) reported emesis in Period 2 after receiving aripiprazole tablet. He was withdrawn from the study; the emesis resolved before checkout from the clinical site.
- Subject (b) (6) reported right humeral fracture in Period 1 after receiving aripiprazole tablet. She was withdrawn from the study.

In summary, the adverse event of vomiting led to study discontinuation for two subjects after treatment with aripiprazole OSF and one subject who received aripiprazole tablet. No other adverse events led to discontinuation after administration of aripiprazole OSF. Vomiting is a labeled adverse reaction of the LD.

Severe Adverse Events

In Study LP088-20-09, one subject (Subject (b) (6)) experienced insomnia after administration of aripiprazole OSF and anxiety after administration of aripiprazole tablets. The subject did not withdraw from the study. Insomnia is a labeled adverse reaction for the LD.

Treatment Emergent Adverse Events and Adverse Reactions

The most common treatment emergent adverse events (TEAEs) reported in both studies were blood pressure decrease and bradycardia.

In Study LP088-20-09, blood pressure decrease was reported by 7 subjects (15%) after administration of aripiprazole OSF and 13 subjects (28%) after administration of aripiprazole tablets. Bradycardia was reported by four subjects (8%) after administration of aripiprazole OSF and six subjects (13%) after administration of aripiprazole tablets.

In Study LP088-20-10, blood pressure decrease was reported by 18 subjects (38%) after administration of aripiprazole OSF and 16 subjects (34%) after administration of aripiprazole tablets. Bradycardia was reported by 8 subjects (17.4%) after administration of aripiprazole OSF and 10 subjects (21.3%) after administration of aripiprazole tablets.

All TEAEs resolved without intervention. Blood pressure decrease and bradycardia are listed as adverse reactions in approved labeling for the LD.

Application site assessment was performed prior to dosing and at 0.5, 2, 24, and 72 hours in each period after administration of the aripiprazole oral soluble film. No subjects reported clinically significant abnormal oral or tongue application site assessment findings.

Laboratory Findings

In both studies, hematology, biochemistry, and urine analysis were collected for all enrolled subjects at Screening and at the end of the study. Abnormal laboratory values reported in Studies LP088-20-09 and LP088-20-10 were just outside the reference range and shifts from Baseline were generally not clinically meaningful. There was no observable pattern of laboratory changes suggesting an unexpected safety signal.

Vital Signs

In both studies, vital signs (including blood pressure, heart rate, and temperature) were assessed at Screening; Period 1 and Period 2 check-in; pre-dose and 0.5, 1.5, 2.5, 3.5, 4, 5, 6, 7, 8, 10, 12, 24, 36, 48, and 72 hours in each period after post-dose; and at end of the study. Abnormal vital sign measurements were just outside the reference range and shifts from Baseline were generally small. There was no observable pattern of vital sign changes suggesting an unexpected safety signal.

Electrocardiograms (ECGs)

In both studies, ECGs were performed at Screening, 4, 10, 24, 72 hours in each period after post-dose, and at the end of study. An abnormal ECG was reported as an adverse event if the investigator determined that it was clinically significant. In Study LP088-20-09, a higher proportion of subjects (20%) reported ECG-related TEAEs after administration of aripiprazole tablets compared with aripiprazole OSF (8%). In Study LP088-20-10, a similar proportion of subjects reported ECG-related TEAEs in the aripiprazole OSF and aripiprazole tablet groups (20% and 23%, respectively).

QT

There were no TEAEs related to QT prolongation.

Immunogenicity

No hypersensitivity reactions or other safety signals potentially related to immunogenicity occurred in the studies.

8.2.5. Analysis of Submission-Specific Safety Issues

There were no specific safety issues explored in this application.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

There were no clinical outcome assessment analyses informing safety and tolerability.

8.2.7. Safety Analyses by Demographic Subgroups

The make-up of the study population was homogenous with respect to age and race. The size of subgroups relevant to sex was too small for useful analysis.

8.2.8. Specific Safety Studies/Clinical Trials

No specific safety studies or clinical trials were submitted with this application.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

There were no data related to human carcinogenicity or tumor development.

Human Reproduction and Pregnancy

There were no data related to human reproduction or pregnancy in this application.

Pediatrics and Assessment of Effects on Growth

See Section 10. No additional pediatric data were submitted with this application. This product will rely on the findings of safety and effectiveness for the LD for the pediatric indications.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No additional information regarding drug abuse, potential, withdrawal, or rebound were included in this application.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable.

Expectations on Safety in the Postmarket Setting

The safety profile of this product is expected to be similar to that of the LD.

8.2.11. Integrated Assessment of Safety

Review of the completed bioavailability studies did not reveal any new or unexpected safety signals. The most frequently reported TEAEs, blood pressure decrease and bradycardia, are listed as adverse reactions in the labeling for the LD. The safety profile of aripiprazole OSF appears to be consistent with that of the LD.

8.3. Statistical Issues

Not applicable.

8.4. Conclusions and Recommendations

The Applicant has established an adequate scientific bridge to the LD and can rely on the findings of safety and effectiveness for the LD. From a clinical perspective, there are no objections to approval of aripiprazole OSF for the following indications:

- Treatment of schizophrenia in patients ages 13 years and older
- Adjunctive treatment of major depressive disorder (MDD) in adults
- Irritability associated with autistic disorder in pediatric patients 6 years and older
- Treatment of Tourette's disorder in pediatric patients 6 years and older

The LD is also approved for the treatment of acute treatment of manic and mixed episodes associated with bipolar I; however, the Applicant did not pursue approval for this indication.

9 Advisory Committee Meeting and Other External Consultations

The Agency did not refer this marketing application to an advisory committee for review. This drug is not first in its class. Evaluation of the data did not raise significant, unexpected safety or efficacy issues. Therefore, the Agency concluded that outside expertise was not necessary.

10 Pediatrics

The Applicant has proposed to include pediatric patients in the indicated population for three conditions (to mirror the approved populations for the LD):

- Treatment of schizophrenia in patients 13 years of age and older
- Irritability associated with autistic disorder in pediatric patients 6 years of age and older
- Treatment of Tourette's disorder in pediatric patients 6 years of age and older

The Applicant submitted an iPSP on August 9, 2023, and a revision August 21, 2023. An Agreed Initial Pediatric Study plan-Agreement letter was issued on September 1, 2023. The iPSP includes a plan to request a waiver in the following populations:

- Pediatric patients ages 0 to 13 years of age with schizophrenia
- Pediatric patients ages 0 to 6 years of age with irritability associated with autistic disorder
- Pediatric patients ages 0 to 6 years of age with Tourette's disorder

Because the Applicant is relying on the findings of safety and effectiveness for the LD in pediatric patients and because there are no clinically meaningful differences in efficacy or safety between aripiprazole OSF and the LD, no additional studies were required in the pediatric populations for which the LD is indicated.

The LD is only approved for adjunctive treatment of major depressive disorder (MDD) in adults. This indication is included on the FDA list of adult-related conditions that qualify for a waiver because they rarely or never occur in pediatrics.

The LD is approved for acute treatment of manic and mixed episodes associated with bipolar I in pediatric patients ages 10 to 17 years. The Applicant did not pursue approval for this indication.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

The Applicant submitted draft labeling that generally aligned with approved labeling for the LD. The label was revised to use product-specific language where appropriate and to include the following:

GENERAL

The Applicant proposed a (b) (4) (b) (4)

HIGHLIGHTS

The age range of the approved populations was added to the indication statements. The boxed warning regarding increased mortality in elderly patients with dementia-related psychosis and suicidal thoughts and behavior was revised to align with the most current class language.

2 DOSAGE AND ADMINISTRATION

Language proposed by the Applicant in Section 2.6 about (b) (4) (b) (4) was removed because no data were submitted to support inclusion of this information in labeling.

Revised the title of the "(b) (4)" section to "Important Administration Information" and included additional information (also shared in the separate Instructions for Use document) specific to the oral film. A sentence was also added to address how to administer multiples of the oral film if/when necessary.

5 WARNINGS AND PRECAUTIONS

In general, the Warnings and Precautions section was revised to align with recent class labeling language where applicable. Section (b) (4) was removed because (b) (4) (b) (4).

7 DRUG INTERACTIONS

The table of clinically important drug interactions and the information regarding drugs that have no clinically important interactions with aripiprazole were revised to align with current labeling practice.

8 USE IN SPECIFIC POPULATIONS

As discussed, the proposed (b) (4) was removed from the label, including Section 8.4 (Pediatric Use):

(b) (4)

12 CLINICAL PHARMACOLOGY

Section 12.3 Pharmacokinetics was revised to include relevant PK measures and parameters that are important for the safe and effective use of aripiprazole OSF, as per current labeling guidance.

17 PATIENT COUNSELING INFORMATION

This section was revised to better align with the other sections of the Prescribing Information and with current class labeling language.

Other Prescription Drug Labeling

The Applicant submitted a Medication Guide (MG) and Instructions for Use (IFU). The IFU was revised to make clear that patients should let the film dissolve in the mouth before swallowing. In addition, the IFU was modified to indicate that if more than one film is needed to reach the prescribed dose, patients should wait until the previous film has dissolved before taking another. The IFU was also revised to include specific instructions to explain what patients should do if the film tears or dissolves in the hand before administration.

12 Risk Evaluation and Mitigation Strategies (REMS)

The review team did not identify a need for a risk evaluation and mitigation strategy (REMS) for this product.

13 Postmarketing Requirements and Commitment

No postmarketing requirements or commitments are recommended.

14 Clinical Deputy Division Director Comments (Signatory)

This review reflects my edits and feedback. I agree with the findings as described by the review team and concur with the approval recommendation.

15 Appendices

15.1. References

1. American Psychiatric Association. (2022). Diagnostic and statistical manual of mental disorders (5th ed., text rev.). https://doi.org/10.1176/appi.books.9780890425787.

2. Global Health Estimates 2020: Disease burden by Cause, Age, Sex, by Country and by Region, 2000-2019. Geneva, World Health Organization; 2020.

3. Trivedi MH, AJ Rush, SR Wisniewski, et al., Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice. Am J Psychiatry. 2006;163:28–40.

4. Robertson MM, V Eapen, HS Singer, et al., Gilles de la Tourette Syndrome (2017), Nat Rev Dis Primers, doi: 10.1038/nrdp.2016.97.

15.2. Financial Disclosure

The Applicant has submitted FDA form 3454 and attested that it has not entered into any inappropriate financial arrangement with the listed clinical investigator.

Covered Clinical Study (Name and/or Number): LP088-20-09 and LP088-20-10

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

15.3. Clinical Pharmacology

Clinical Study Report

Study Report #: LP088-20-09 Study Period: 12/26/20 – 2/9/21

Study Site: Phase I Clinical Trial Center, Xiamen Lotus Hospital, Xiamen, Fujian, China

Principal Investigator: Zhiqing Huang, MD, PhD

Analytical Site: (b) (4)

Principal Scientist: Lu Zhang

EDR: \\cdsesub1\evsprod\nda216655\0001\m5

Title: A Randomized, Open-Label, Single-Dose, Two-Treatment, Two-Period, Crossover Study to Assess the Bioequivalence of Aripiprazole Tablets 10 mg and Aripiprazole Oral Soluble Film (OSF) 10 mg Administered Under Fasting Conditions in Healthy Adult Human Subjects

Objectives: To assess the bioequivalence of aripiprazole OSF 10 mg versus aripiprazole tablets 10 mg in healthy adult human subjects under fasting conditions and to monitor the safety of the subjects.

Study Design: Single-center, randomized, open-label, single-dose, two-treatment, two-period, crossover study to assess the bioequivalence of aripiprazole OSF 10 mg versus aripiprazole tablets 10 mg administered under fasting conditions in healthy adult human subjects, between 35 to 65 years of age (both inclusive). Up to 48 healthy male and female volunteers were enrolled. Each subject was randomized to one of two treatment sequences according to a randomization schedule prepared prior to the start of the study. Randomized subjects were dosed on the same day of Period 1 and were crossed over to the alternate formulation and were dosed on the same day of Period 2.

In Period 1 on Day 1, following an overnight fast of at least 10 hours, subjects received a single oral dose of aripiprazole tablet 10 mg or aripiprazole OSF 10 mg in sitting posture at approximately 0800 hours (± 2 hour). Aripiprazole tablet 10 mg was taken with approximately 240 ± 2 mL drinking water. Aripiprazole OSF 10 mg was placed on the tongue, subjects were instructed to close their mouth immediately and swallow normally without fluid ingestion. Subjects consumed 240 ± 2 mL drinking water 15 minutes post-dose for aripiprazole OSF.

Treatment:
Reference: Abilify 10 mg tablets (aripiprazole), manufactured by Otsuka America Pharmaceutical, Inc., Lot No.: ALS00219A.
Test: Aripiprazole OSF 10 mg, in boxes of 10 pouches per box (1 film per pouch), manufactured and provided by Xiamen LP Pharmaceutical Co., Ltd. Lot Number S201001.

A minimum of a 28-day washout occurred between each single-dose administration. Subjects refrained from drinking water for 1 hour after dosing in each period except for the 240 ± 2 mL of water during the aripiprazole tablets dosing and 240 ± 2 mL of water following 15 minutes post dose for aripiprazole OSF.

Pharmacokinetic Sampling: Serial blood samples for determination of aripiprazole plasma concentration and pharmacokinetic (PK) analysis were obtained at pre-dose (0 hour) and 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12, 24, 48, 72, 120, 168, 240, 312, and 384 hours following drug administration in each period.

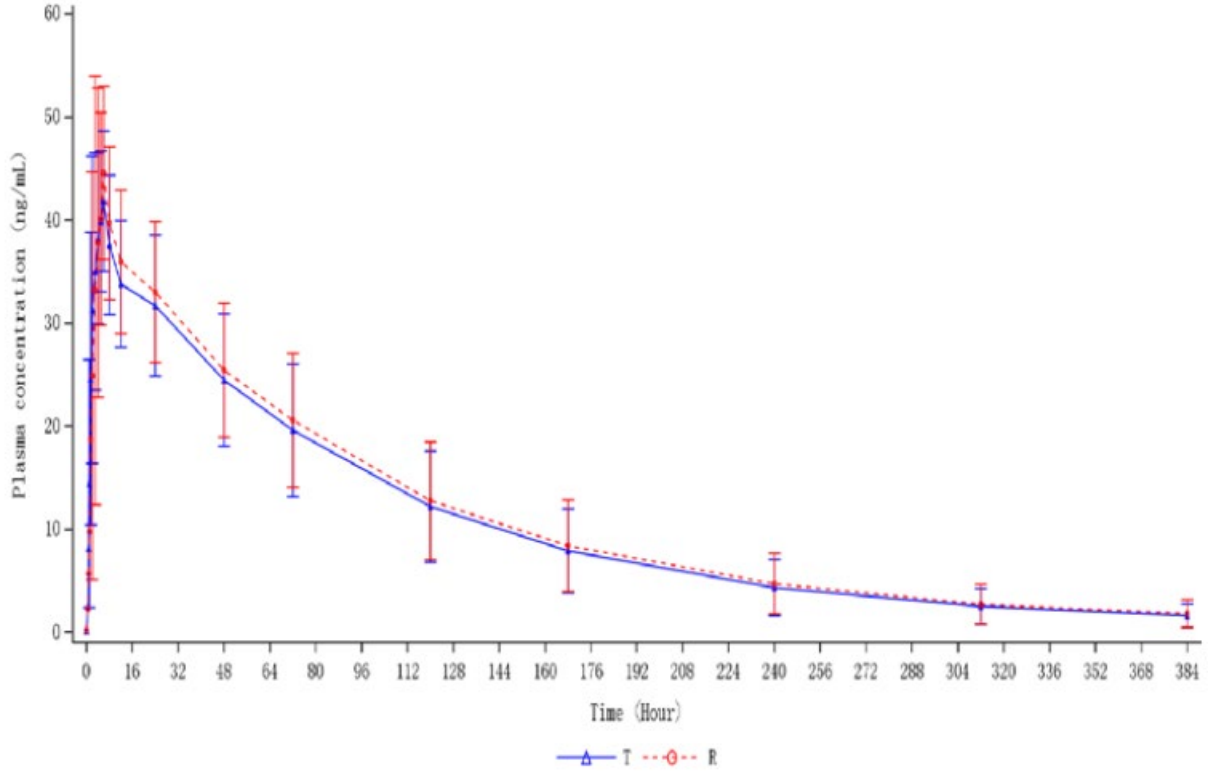
Bioanalysis: Plasma samples were extracted and analyzed for plasma aripiprazole concentrations using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method. Calibration curves with concentrations ranging from 0.2000 ng/mL to 100.000 ng/mL were used to determine the concentrations of aripiprazole.

Results:
Subject Disposition

Randomized/Completed/Discontinued due to AE	48/45/1
Mean (± SD) Overall Age (Median (range)) years	45.8 ± 7.46 (45 (35,62))
Male/Female	36/12
Race (White/Black/Asian)	0/0/48
Overall Weight (± SD) kg	63.3 ± 9.68

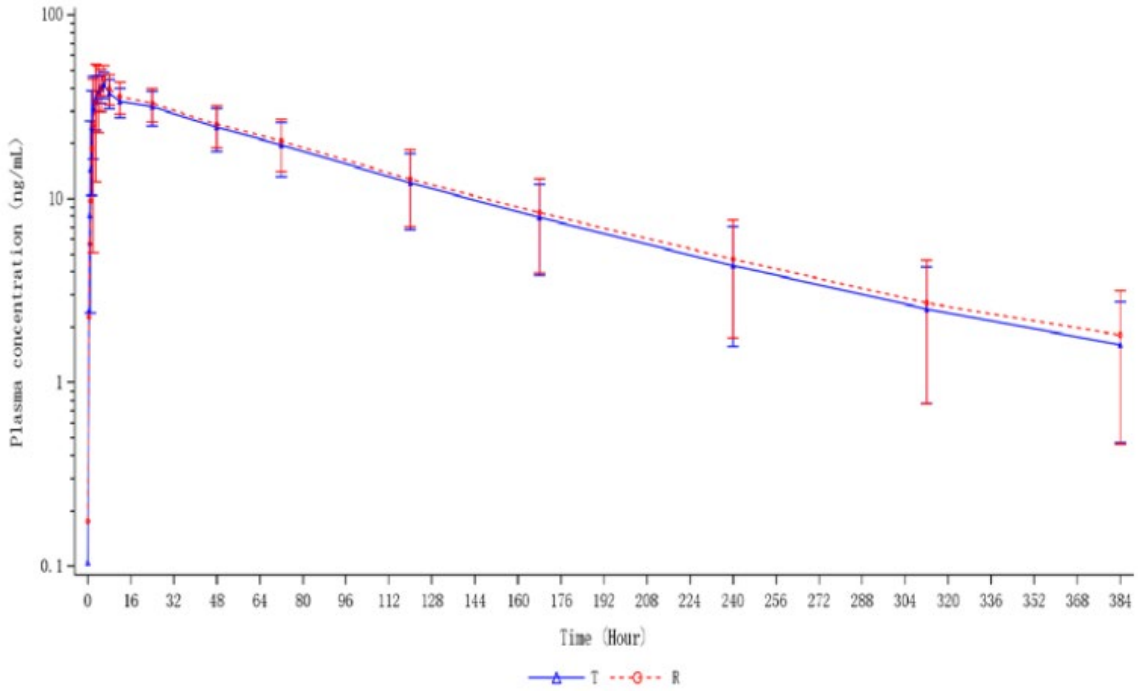
The Sponsor stated that aripiprazole OSF dissolve quickly after dosing and disintegrated within 30 secs after being placed on the tongue. The range of dissolution time of aripiprazole OSF was 1 to 6 mins and the mean ±SD of dissolution time was 2.3 ± 1.34 min.

Figure 3. Mean (SD) Plasma Aripiprazole Concentration-time Profile (Linear Scale)



T: Aripiprazole OSF
R: Aripiprazole tablets
Source: Figure 11-1, LP-088-20-09 Clinical study report, p. 52.

Figure 4. Mean (SD) Plasma Aripiprazole Concentration-time Profile (Semi-log Scale)



T: Aripiprazole OSF
R: Aripiprazole tablets
Source: Figure 11-2, LP-088-20-09 Clinical study report, p. 52.

Table 8. Summary Statistics of Pharmacokinetic Parameters

Parameter (unit)	Statistic	Aripiprazole OSF N=45	Aripiprazole Tablets N=45
C_{max} (ng/mL)	Mean (SD)	61.620 (15.2819)	55.111 (17.4926)
AUC_{0-t} (hr*ng/mL)	Mean (SD)	4027.287 (1354.5620)	3798.972 (1294.9846)
$AUC_{0-\infty}$ (hr*ng/mL)	Mean (SD)	4261.154 (1537.8357)	4027.560 (1489.0697)
T_{max}^* (h)	Median (Range)	1.500 (1, 6)	2.000 (1, 6)
$t_{1/2}$ (hr)	Mean (SD)	88.534 (19.6672)	89.388 (19.5789)
$AUC_{\%Extrap\_obs}$ (%)	Mean (SD)	4.709 (2.8977)	4.769 (3.1467)
λ_z (1/hr)	Mean (SD)	0.010 (0.0015)	0.010 (0.0015)
R^2_{adj}	Mean (SD)	0.997 (0.0052)	0.998 (0.0040)
T_{lag}^* (hr)	Median (Range)	0.000 (0-0.28)	0.000 (0-0.75)

Data Source: Table 14.2.2.3

*: T_{max} and T_{lag} are displayed by median (minimum, maximum).

N: the number of subjects who are included in PKPS.

Source: Study 20-09 report, p. 51.

Table 9. Statistical Summary of the Comparative Bioavailability Results

	Geometric mean and its ratio					
PK parameter (unit)	Aripiprazole OSF N=45	Aripiprazole Tablets N=45	Aripiprazole OSF/Tablets (%)	90% CI(%)	Intra-subject CV (%)	Power (%)
C_{max} (ng/mL)	59.93	52.31	114.56	106.48, 123.24	20.84	63.6
AUC_{0-t} (hr*ng/mL)	3816.96	3591.04	106.29	102.05, 110.71	11.52	100.0
$AUC_{0-\infty}$ (hr*ng/mL)	4007.08	3773.04	106.20	101.95, 110.63	11.56	100.0

Source: Study 20-09 report, p. 54.

The reviewer was able to reproduce the Applicant's analyses and therefore the statistical analyses of PK results are deemed acceptable.

Pharmacokinetic Summary: Total exposure (AUCs) to aripiprazole after administration of OSF and oral tablet appeared to be similar and Tmax was 0.5 hour shorter after administration of OSF compared to the oral tablet.

The exposures of aripiprazole OSF were contained within the 80% to 125% regulatory criteria for bioequivalence. Therefore, the PK bridge between the formulations is considered adequate.

Clinical Pharmacology Reviewer Comments: The PK bridging between aripiprazole OSF 10 mg and aripiprazole 10-mg tablet is adequately established under fasting conditions. Therefore, the proposed product, aripiprazole OSF can rely on the Agency's previous findings of safety and effectiveness of the LD, aripiprazole tablet.

Clinical Study Report

Study Report #: LP088-20-10	Study Period: 12/13/20 – 1/10/21
Study Site:	Phase I Clinical Trial Center, Xiamen Lotus Hospital Xiamen, Fujian, China
Principal Investigator:	Zhiqing Huang, MD, PhD
Analytical Site:	(b) (4)
Principal Scientist:	Lu Zhang
EDR:	\\cdsesub1\evsprod\nda216655\0001\m5

Title: A Randomized, Open-Label, Single-Dose, Two-Treatment, Two-Period, Crossover Study to Assess the Bioequivalence of Aripiprazole Tablets 10 mg and Aripiprazole Oral Soluble Film 10 mg Administered Under Fed Conditions in Healthy Adult Human Subjects.

Objectives: To assess the bioequivalence of aripiprazole OSF 10 mg versus aripiprazole tablets 10 mg in healthy adult human subjects under fed conditions and to monitor the safety of the subjects.

Study Design: Single-center, randomized, open-label, single-dose, two-treatment, two-period, crossover study. In Period 1 on Day 1, following an overnight fast of at least 10 hours, subjects consumed a high fat and high calorie breakfast beginning 30 minutes prior to dosing. This meal contained approximately 150 protein calories, 250 carbohydrate calories, and 500 to 600 fat calories. Subjects consumed a high fat and high calorie breakfast within 30 minutes. Subjects then received a single oral dose of aripiprazole tablet 10 mg or aripiprazole OSF 10 mg in sitting posture at approximately 0800 hours (± 2 hour). In Period 2 on Day 29 or later, subjects were crossed over to the alternate aripiprazole tablets 10 mg or aripiprazole OSF 10 mg and the same procedures were performed at the same time points as for Period 1. There was a minimum of a 28-day washout between each single-dose administration.

Aripiprazole tablet 10 mg was taken with approximately 240 ± 2 mL drinking water. Aripiprazole OSF 10 mg was placed on the tongue, subjects were instructed to close their mouth

immediately and swallow normally without fluid ingestion. Subjects consumed 240 ± 2 mL drinking water 15 minutes post-dose for aripiprazole OSF.

Inhibitors or inducers of CYP3A4 and CYP2D6, such as carbamazepine, ketoconazole, quinidine, fluoxetine or paroxetine were prohibited from 14 days prior to dosing and during the study and the washout interval.

Treatment:
Reference: Aripiprazole (Abilify) 10 mg tablets manufactured by Otsuka America Pharmaceutical, Inc., (Lot Number ALS00219A).
Test: Aripiprazole 10 mg OSF, manufactured and provided by Xiamen LP Pharmaceutical Co., Ltd. (Lot Number S201001).

Bioanalysis: Plasma samples were analyzed for aripiprazole concentrations using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method. Calibration curves with concentrations ranging from 0.2000 ng/mL to 100.000 ng/mL, were used to determine the concentrations of aripiprazole.

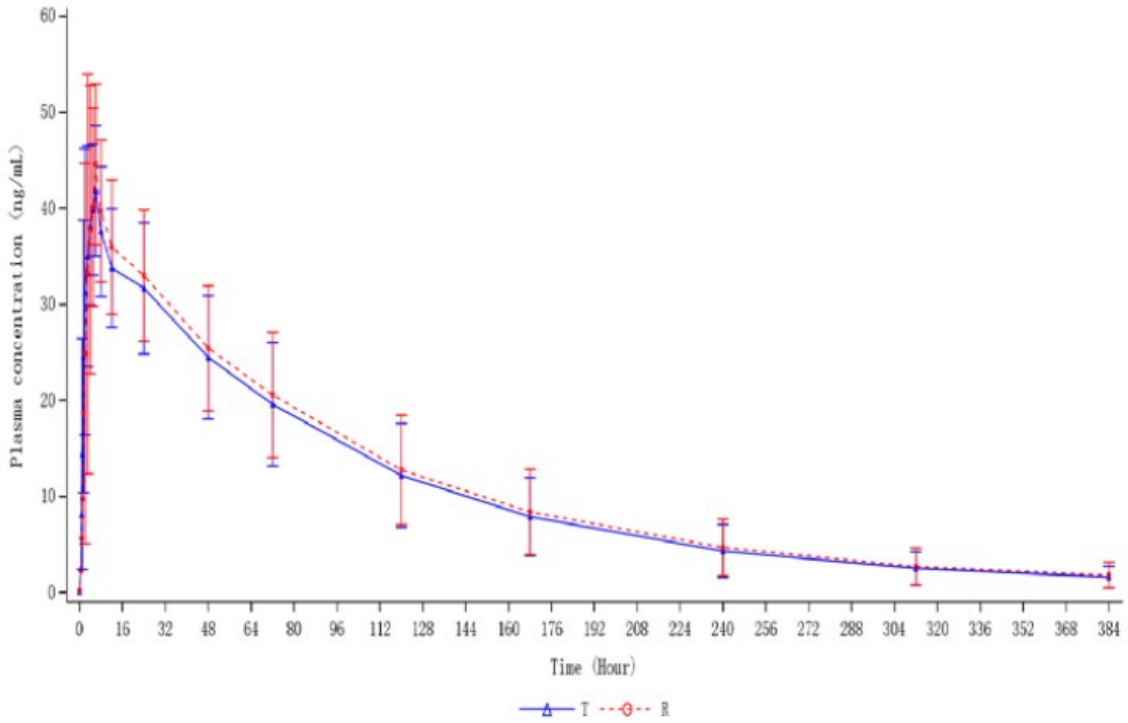
Pharmacokinetic Sampling: Serial blood samples for determination of aripiprazole plasma concentrations were obtained pre-dose (0 hour) and 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 120, 168, 240, 312, and 384 hours post-dose.

Results:
Subject Disposition

Randomized/Completed/Discontinued due to AE	48/44/2
Mean (± SD) Overall Age (range) years	45.8 ± 6.70 (35, 64)
Male/Female	27/21
Race (Caucasian/Black/Asian)	0/0/48
Overall Weight (± SD) kg	61.5 ± 8.38

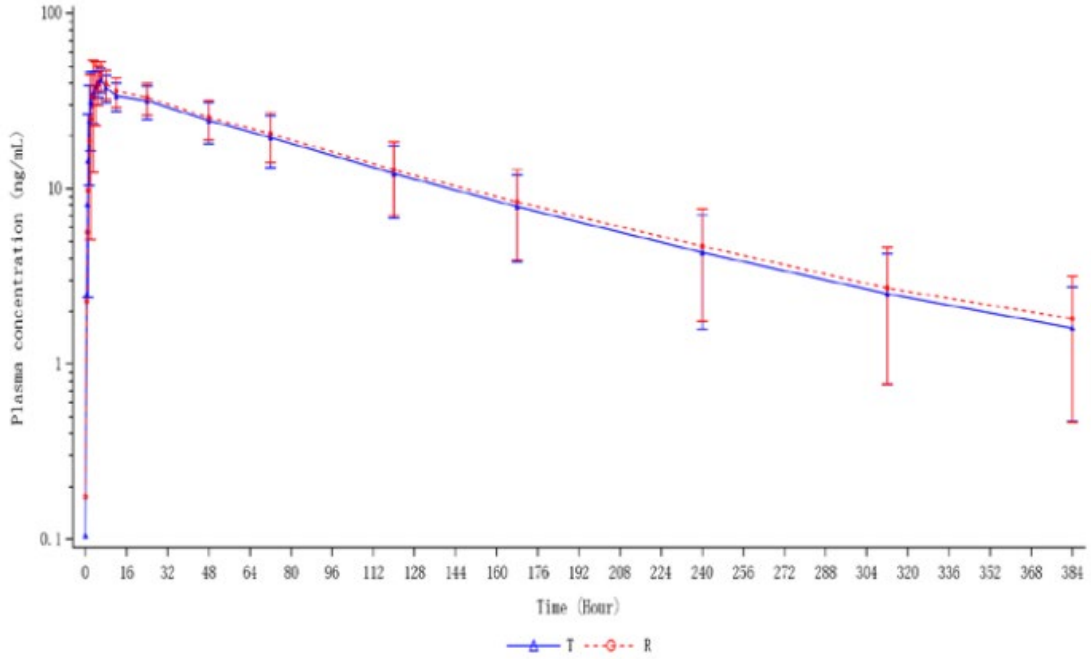
The Sponsor reported that the range of dissolution time of aripiprazole OSF was 1 to 10 min and the mean ± SD of dissolution time was 2.9 ± 2.04 min.

Figure 5. Mean (SD) Plasma Aripiprazole Concentration-time Profile (Linear Scale)



T: Aripiprazole OSF
R: Aripiprazole tablets
Source: Figure 11-1, LP-088-20-10 Clinical study report, p. 58.

Figure 6. Mean (SD) Plasma Aripiprazole Concentration-time Profile (Semi-log Scale)



T: Aripiprazole OSF
R: Aripiprazole tablets
Source: Figure 11-1, LP-088-20-10 report, p. 58.

Table 10. Summary Statistics of Pharmacokinetic Parameters

Parameter (unit)	Statistic	Aripiprazole OSF N=44	Aripiprazole Tablets N=44
C_{max} (ng/mL)	Mean (SD)	45.902 (8.3640)	50.845 (11.8925)
AUC_{0-t} (hr*ng/mL)	Mean (SD)	4077.311 (1371.2266)	4290.364 (1458.6569)
$AUC_{0-\infty}$ (hr*ng/mL)	Mean (SD)	4289.650 (1535.4209)	4538.354 (1660.5951)
T_{max}^{*} (hr)	Median (Range)	6.00 (1.5-12)	6.00 (1.5-24.03)
$t_{1/2}$ (hr)	Mean (SD)	84.732 (15.9410)	86.090 (17.3457)
$AUC_{\%Extrap\_obs}$ (%)	Mean (SD)	4.217 (2.6049)	4.558 (3.0484)
λ_z (1/hr)	Mean (SD)	0.010 (0.0000)	0.010 (0.0000)
R^2_{adj}	Mean (SD)	0.996 (0.0058)	0.997 (0.0059)
T_{lag}^{*} (hr)	Median (Range)	0.000 (0-0.52)	0.000 (0-2.02)

Source: LP088-20-10 p. 57.

Table 11. Statistical Summary of the Comparative Bioavailability Results

PK parameter (unit)	Geometric Least Squares Means: Aripiprazole OSF N=44	Aripiprazole Tablets N=44	Aripiprazole OSF/Tablets (%)	90% CI (%)	Intra-subject CV (%)	Power (%)
C_{max} (ng/mL)	45.20	49.64	91.06	85.91, 96.51	16.33	98.1
AUC_{0-t} (hr*ng/mL)	3845.18	4037.20	95.24	92.46, 98.11	8.28	100.0
$AUC_{0-\infty}$ (hr*ng/mL)	4015.94	4232.14	94.89	92.07, 97.80	8.45	100.0

Source: Protocol LP088-20-10 report, p. 59.

The reviewer was able to reproduce the Applicant's analyses and therefore the statistical analyses of PK results are deemed acceptable.

The 90% CIs for Cmax, AUCt, and AUCinf were within 80% to 125% of the regulatory criteria for bioequivalence. The results suggest that the PK bridging between the formulations is adequate.

Pharmacokinetic Summary: The 90% CI for the geometric mean ratio of PK parameters, Cmax and AUCinf for aripiprazole OSF to aripiprazole oral tablet was contained within 80% to 125% bioequivalence limit.

Therefore, aripiprazole OSF is considered equivalent to aripiprazole oral tablets. The median (range) Tmax of plasma aripiprazole following administration of aripiprazole OSF and aripiprazole tablets was 6.00 (1.5 to 12) and 6.00 (1.5 to 24.03) hours, respectively.

Clinical Pharmacology Reviewer Comments: The PK bridging between aripiprazole OSF 10 mg and aripiprazole 10-mg tablet is adequately established under fed conditions. This suggests that the food effect is similar between aripiprazole OSF and aripiprazole tablet. Therefore, similar to the administration instructions for the LD, the proposed product, aripiprazole OSF, can be administered with or without food.

Bioanalysis

The following table contains a summary of the bioanalytical method validation.

Bioanalytical Method Validation

Information requested	**Data**
Bioanalytical method validation report location	Appendix 16.5.3
Analyte	Aripiprazole
Internal standard (IS)	Aripiprazole -d8

Method description	Plasma concentrations of aripiprazole in the samples were determined by a validated LC-MS/MS method, using aripiprazole-d8 as an internal standard (IS). Aripiprazole and IS were extracted from plasma by liquid-liquid extraction. Gradient elution was carried out with the mobile phase A: 0.2% formic acid in 10 mM ammonium formate and mobile phase B: 0.2% formic acid in acetonitrile, with a total flow rate of 1.00 mL/min. Reversed-phase HPLC separation was achieved with a Thermo, Betasil Silica, 50×3mm column. MS/MS detection was set at mass transitions of m/z 448.2→285.2 for aripiprazole and m/z 456.3→293.3 for aripiprazole –d8 (ISTD). The aripiprazole and IS was monitored in the positive ion mode using the MRM transitions in ESI mode.
Limit of quantitation (units/mL)	0.200 ng/mL
Average recovery of drug (%)	89.2% (LQC: 92.3%, MQC: 89.4%, HQC: 85.8%)
Average recovery of IS (%)	91.4%
Standard curve concentrations (units/mL)	0.200 ng/mL to 100 ng/mL
QC concentrations (Units/mL)	0.200 ng/mL, 0.600 ng/mL, 5.00 ng/mL, 40.0 ng/mL, 80.0 ng/mL and 800 ng/mL
QC intraday precision range (%)	1.4 % to 7.1%
QC intraday accuracy range (%)	94.0% to 105.0%
QC interday precision range (%)	2.4 % to 7.5%
QC interday accuracy range (%)	98.5% to 99.6%
Bench-top stability (hrs)	24.0 hours (at room temperature)
Stock stability (days)	24.0 hours (at room temperature) (stock solution and dilution stability of drug & ISTD, spiking solution stability of drug at the lowest and highest level) 44 days (within 2 to 8°C) (for drug stock, & ISTD stock) 43 days (within 2 to 8°C) (stock dilution stability of drug, spiking solution stability of drug at the lowest and highest level)
Processed stability (hrs)	143.0 hours (within 2 to 8°C)

Freeze-thaw stability (cycles)	5 cycles (at -20 ± 10°C) 5 cycles (at -70 ± 10°C)
Long-term storage stability (days)	175 days at -70 ± 10°C & -20 ± 10°C
Dilution integrity	800 ng/mL diluted up to 20-fold
Selectivity	No significant interference at the retention times and transitions of analyte and internal standard

Source: Applicant biopharmaceutic summary, p. 7.

Clinical Pharmacology Reviewer Comments: The method validation met the acceptance criteria set a priori and is acceptable.

Summary of Bioanalysis for study LP088-20-09

Clinical trial number	LP088-20-09	
Validation report number	8376-574	
Sample analysis analytical plan number	8459-844	
Validated method	ARPPHPC	
Equipment	Manufacture	Model
1)HPLC	Shimadzu	Prominence, 20 Series
2)Ion source	Applied Biosystem	Turbo V™
3)Detector	Applied Biosystem	Sciex API 4000
		(b) (4)
Data collection/Management software	Nautilus: Sample tracking / Laboratory Information Management System (LIMS) Watson: Laboratory Information Management System (LIMS), data regression and reporting Analyst: Data collection and chromatographic interpretation E-WorkBook: Laboratory execution software (LES) system Veeva QMS: Quality Issues Management System	
Analytical matrix	Human plasma	
Anticoagulant	K_2EDTA	
Sample tube material	2 mL polypropylene cryotube	
Internal standard (ISTD)	Aripiprazole-d8	
Sample extraction type	Liquid-liquid extraction	
Injection volume	3.0 µL	
Calibration model, weighting factor	Linear regression, $1/x^2$	
Calibration curve range(ng/mL)	0.200 to 100	
Quantitation method	Peak area ratio	
Quality Control (QC) levels (ng/mL)	LQC	0.600
	LMQC	5.00
	MQC	40.0
	HQC	80.0
	DQC	800
Analytical method performance (Analytical Runs)		
	Precision(%CV) maximum	RE% (range)
QC	4.2%	0.2 %~ 2.6% (inter-run)
Calibration standards LLOQ	4.3%	-0.5%
Calibration standards except LLOQ	5.0%	-0.7% ~ 1.0% (inter-run)
Analytical runs (not included of CAL and QC Qualification run)	Accepted runs	Rejected runs
	18	1
Bioanalytical experimental start date	19 Feb 2021	
Total number of subjects analyzed	48	
Total number of samples analyzed	1860	
Bioanalytical experimental completion date	02 Mar 2021	
Sample storage duration (from sample collection to extraction completion)	64 days (Collection Date of the first sample: 27 Dec 2020; Extraction Completion Date: 01 Mar 2021)	

Matrix frozen stability and storage conditions	175 days at -10 to -30°C and -60 to -80°C
Stock solution preparation accuracy comparison	RE -1.6%

Source: Bioanalytical Report-fasted, p. 12.

Incurred Sample Reanalysis (ISR): There were 152 samples reanalyzed to test the aripiprazole reproducibility of the method. It was observed that 100.0% of the repeat results and original results were within ±20% of the mean of the two values, which was within the acceptance criteria.

Clinical Pharmacology Reviewer Comments: The bioanalysis of samples for study LP088-20-09 and ISR are reasonable and acceptable.

Summary of Bioanalysis for Study LP088-20-10

Clinical trial number	LP088-20-10	
Validation report number	8376-574	
Sample analysis analytical plan number	8459-845	
Validated method	ARPPHPC	
Equipment	Manufacture	Model
1)HPLC	Shimadzu	Prominence, 20 Series
2)Ion source	Applied Biosystem	Turbo V™
3)Detector	Applied Biosystem	Sciex API 4000
		(b) (4)
Data collection/Management software	Nautilus: Sample tracking / Laboratory Information Management System (LIMS) Watson: Laboratory Information Management System (LIMS), data regression and reporting Analyst: Data collection and chromatographic interpretation E-WorkBook: Laboratory execution software (LES) system Veeva QMS: Quality Issues Management System	
Analytical matrix	Human plasma	
Anticoagulant	K_2EDTA	
Sample tube material	2 mL polypropylene cryotube	
Internal standard (ISTD)	Aripiprazole-d8	
Sample extraction type	Liquid-liquid extraction	
Injection volume	3.0 µL	
Calibration model, weighting factor	Linear regression, $1/x^2$	
Calibration curve range(ng/mL)	0.200 to 100	
Quantitation method	Peak area ratio	
Quality Control (QC) levels (ng/mL)	LLOQ	0.200
	LQC	0.600
	LMQC	5.00
	MQC	40.0
	HQC	80.0
	DQC	800
Analytical method performance (Analytical Runs)		
	Precision(%CV) maximum	RE% (range)
QC	4.1%	-0.2 %~ 1.3% (inter-run)
Calibration standards LLOQ	3.6%	0.5%
Calibration standards except LLOQ	4.0%	-0.8% ~ 1.0% (inter-run)
Analytical runs (not included of CAL and QC Qualification run)	Accepted runs	Rejected runs
	17	0
Bioanalytical experimental start date	29 Jan 2021	
Total number of subjects analyzed	48	
Total number of samples analyzed	1825	
Bioanalytical experimental completion date	08 Feb 2021	
Sample storage duration (from sample	56 days (Collection Date of the first sample: 14	

Clinical trial number	LP088-20-10	
Validation report number	8376-574	
Sample analysis analytical plan number	8459-845	
Validated method	ARPPHPC	
Equipment	Manufacture	Model
1)HPLC	Shimadzu	Prominence, 20 Series
2)Ion source	Applied Biosystem	Turbo V™
3)Detector	Applied Biosystem	Sciex API 4000
		(b) (4)
Data collection/Management software	Nautilus: Sample tracking / Laboratory Information Management System (LIMS) Watson: Laboratory Information Management System (LIMS), data regression and reporting Analyst: Data collection and chromatographic interpretation E-WorkBook: Laboratory execution software (LES) system Veeva QMS: Quality Issues Management System	
Analytical matrix	Human plasma	
Anticoagulant	K_2EDTA	
Sample tube material	2 mL polypropylene cryotube	
Internal standard (ISTD)	Aripiprazole-d8	
Sample extraction type	Liquid-liquid extraction	
Injection volume	3.0 µL	
Calibration model, weighting factor	Linear regression, $1/x^2$	
Calibration curve range(ng/mL)	0.200 to 100	
Quantitation method	Peak area ratio	
Quality Control (QC) levels (ng/mL)	LLOQ	0.200
	LQC	0.600
	LMQC	5.00
	MQC	40.0
	HQC	80.0
	DQC	800
Analytical method performance (Analytical Runs)		
	Precision(%CV) maximum	RE% (range)
QC	4.1%	-0.2 %~ 1.3% (inter-run)
Calibration standards LLOQ	3.6%	0.5%
Calibration standards except LLOQ	4.0%	-0.8% ~ 1.0% (inter-run)
Analytical runs (not included of CAL and QC Qualification run)	Accepted runs	Rejected runs
	17	0
Bioanalytical experimental start date	29 Jan 2021	
Total number of subjects analyzed	48	
Total number of samples analyzed	1825	
Bioanalytical experimental completion date	08 Feb 2021	
Sample storage duration (from sample collection to extraction completion)	56 days (Collection Date of the first sample: 14 Dec 2020; Extraction Completion Date: 08 Feb 2021)	
Matrix frozen stability and storage conditions	175 days at -10 to -30°C and -60 to -80°C	
Stock solution preparation accuracy comparison	RE -1.6%	

Source: Bioanalytical Report for LP088-20-10, p. 11.

ISR: There were 150 samples reanalyzed to test the aripiprazole reproducibility of the method. It was observed that 100.0% of the repeat results and original results were within ±20% of the mean of the two values, which was within the acceptance criteria.

Clinical Pharmacology Reviewer Comments: The analytical method, its validation and the bioanalysis of the samples are reasonable and acceptable.

15.4. Additional Clinical Outcome Assessment Analyses

No additional clinical outcome assessment analyses were submitted with this application.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BERNARD A FISCHER
07/19/2024 12:41:48 PM