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APPLICATION NUMBER:

217006Orig1s000

MULTI-DISCIPLINE REVIEW
Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation
NDA 217006
Abilify Asimtufii (aripiprazole) injection

NDA217006 Multi-Disciplinary Review and Evaluation

Application Type	Original NDA
Application Number(s)	217006
Priority or Standard	Standard
Submit Date(s)	6/27/2022
Received Date(s)	6/27/2022
PDUFA Goal Date	4/27/2023
Division/Office	Office of Neuroscience/Division of Psychiatry
Review Completion Date	4/27/2023
Established/Proper Name	Aripiprazole monohydrate
(Proposed) Trade Name	Abilify Asimtufii
Pharmacologic Class	Atypical Antipsychotic
Code name	OPC-14597, LU AF41155, Aripiprazole 2M RTU
Applicant	Otsuka Pharmaceutical Company, Ltd.
Dosage form	Injection
Applicant proposed Dosing Regimen	Every 2 months
Applicant Proposed Indication(s)/Population(s)	Treatment of schizophrenia and as a maintenance monotherapy treatment of bipolar I disorder
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	58214004 |Schizophrenia (disorder)| 371596008 |Bipolar I disorder (disorder)|
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Schizophrenia Bipolar Disorder
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	58214004 |Schizophrenia (disorder)| 371596008 |Bipolar I disorder (disorder)|
Recommended Dosing Regimen	960 mg administered once every two months as a single injection; dose can be reduced to 720 mg in patients with adverse reactions

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OPQ=Office of Pharmaceutical Quality;
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
HF= Human Factors
DPV= Division of Pharmacovigilance
DMPP= Division of Medical Policy Programs
PLT= Patient Labeling Team
DPMH = Division of Pediatric and Maternal Health

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Signatures

See archived signatory memos for each discipline.

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Glossary

2M	2-month
APA	American Psychiatric Association
AE	adverse event
AESI	Adverse events of special interest
AIMS	Abnormal Involuntary Movement Scale
AR	adverse reaction
AUC_{0-56}	Area under the concentration-time curve of aripiprazole from time zero to 56 days postdose
AUC_{0-28}	Area under the concentration-time curve of aripiprazole from time zero to 28 days postdose
BARS	Barnes Akathisia Rating Scale
BD-I	Bipolar disorder type I
BP	Blood pressure
C7	Plasma concentration of aripiprazole 7 days postdose
C14	Plasma concentration of aripiprazole 14 days postdose
C28	Plasma concentration of aripiprazole 28 days postdose
C56	Plasma concentration of aripiprazole 56 days postdose
CGI-BP	Clinical Global Impression - Bipolar Version
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression – Severity
CPK	Creatine phosphokinase
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DRESS	drug reaction with eosinophilia and systemic symptoms
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCTD	electronic common technical document
EPS	extrapyramidal symptoms
ET	Early termination
GCP	good clinical practice
ICF	informed consent form
ICH	International Conference on Harmonization
IM	intramuscular
IMP	investigational medicinal product
iPSP	initial Pediatric Study Plan
IR	information request
IRB	institutional review board
LAI	long-acting injectable
LD	listed drug

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MADRS	Montgomery-Åsberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
PANSS	Positive and Negative Syndrome Scale
PeRC	Pediatric Review Committee
PK	pharmacokinetics
PREA	Pediatric Research Equity Act
PT	Preferred Term
PTF%	Peak-to-trough percent fluctuation
RTU	Ready-to-use
SAEs	serious adverse events
SAS	Simpson-Angus Neurologic Rating Scale
sc	subcutaneous
SCZ	schizophrenia
SWN-S	Subjective Well-being under Neuroleptic Treatment-Short Form
TEAE	treatment emergent adverse event
ULN	upper limit of the normal range
VAS	Visual Analog Scale
YMRS	Young Mania Rating Scale

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1. Executive Summary

1.1. Product Introduction

Aripiprazole 2-month (2M) ready-to-use (RTU) injectable suspension is an extended-release formulation of aripiprazole administered every 8 weeks via gluteal intramuscular injection by a healthcare professional. It is available as sterile aqueous injectable suspension of 960 mg/3.2 mL and 720 mg/2.4 mL single-dose, pre-filled syringes.

Otsuka Pharmaceuticals' once monthly intramuscular injection of aripiprazole (Abilify Maintena) was approved by FDA in 2013 for the treatment of schizophrenia in adults and maintenance monotherapy treatment of bipolar I disorder in adults. The same Applicant is now seeking approval of aripiprazole 2M RTU injection via a 505(b)(1) application. This application relies on the Agency's previous findings of safety and efficacy of the listed drug (LD), Abilify Maintena (NDA 202971).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for the treatment of schizophrenia in adults and maintenance monotherapy treatment of bipolar I disorder in adults is provided by the Agency's previous findings of effectiveness for Abilify Maintena (NDA202971) and the establishment of pharmacokinetic (PK) bridge between Abilify Maintena and aripiprazole 2M RTU.

The pivotal PK bridging study (031-201-00181) demonstrated that steady-state exposures of aripiprazole following administration of 960 mg aripiprazole 2M RTU were similar to those of 400 mg Abilify Maintena Q1M in subjects with schizophrenia or bipolar I disorder (see Section 6). The PK bridging between aripiprazole 2M RTU and Abilify Maintena is adequate; therefore, substantial evidence of effectiveness is established for product approval.

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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 LD, Abilify Maintena (NDA202971), and the PK bridge that was established between the LD and aripiprazole 2M RTU. Therefore, the effectiveness of aripiprazole 2M RTU 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 2M RTU does not differ from the LD. Aripiprazole 2M RTU offers additional dosing options for patients. Accordingly, aripiprazole 2M RTU will be approved for the treatment of schizophrenia and as a maintenance monotherapy treatment of bipolar I disorder.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	**Schizophrenia** • Schizophrenia is a serious mental illness characterized by chronic or recurrent psychosis (e.g., delusions, hallucinations, and thought disorganization). • Schizophrenia is also frequently associated with negative symptoms (e.g., social withdrawal, avolition, blunted affect) and cognitive deficits (e.g., attention, executive function, working memory, and social cognition). • Individuals with schizophrenia experience significant impairments in social and occupational functioning and, on average, have a life expectancy around 15 years less than individuals without schizophrenia. • Approximately 50% of individuals with schizophrenia experience a relapse/exacerbation in psychotic symptoms within one year after their last episode; most relapses occur in the context of medication nonadherence. • The worldwide prevalence of schizophrenia is approximately 0.5	Schizophrenia and bipolar I disorder are serious conditions, associated with significant disability and a shortened life expectancy. Evidence informing the analysis of the conditions is from published literature and psychiatric textbooks, as well as clinical experience with these populations.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	to 1%, and schizophrenia is one of the leading causes of years lost due to disability worldwide. <u>Bipolar I Disorder</u> • Bipolar I disorder is a severe and persistent mental illness characterized by episode(s) of mania and, in the majority of cases, episodes of major depression. • Individuals with bipolar I disorder demonstrate severe impairment in occupational functioning approximately 30% of the time, and individuals with bipolar I disorder attain lower levels of socioeconomic status than members of the general population with equivalent educational levels. • After one manic episode, greater than 90% of individuals have recurrent mood episodes, and suicide risk is estimated to be at least 15 times the general population risk. • Aggregate lifetime prevalence estimates for bipolar I disorder range from 0.6 to 1%.	
[Current Treatment Options](#)	<u>Schizophrenia</u> • Antipsychotics are the first-line medication therapy for schizophrenia; current practice guidelines recommend that antipsychotics should be initiated as soon as possible in an acute schizophrenia exacerbation and continued indefinitely to reduce the risk of relapse. • Antipsychotics have been shown to be effective for reducing positive symptoms of schizophrenia (e.g., delusions, hallucinations, disorganized thinking and behavior). Negative symptoms and cognitive deficits of schizophrenia generally show little to no improvement from antipsychotic treatment.	Antipsychotics reduce the severity of positive symptoms of schizophrenia and the risk of psychosis exacerbations. Antipsychotics also reduce the severity and risk of recurrence of manic and mixed episodes in bipolar I disorder. Nonadherence to daily oral antipsychotics is common in individuals with schizophrenia and bipolar I disorder and can lead to psychiatric hospitalization and other adverse outcomes. Long-acting injectable antipsychotics may

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Antipsychotics are broadly categorized as first-generation/typical antipsychotics (e.g., chlorpromazine, fluphenazine, haloperidol, etc.) and second-generation/atypical antipsychotics (e.g., clozapine, risperidone, olanzapine, quetiapine, and aripiprazole). In general, first-generation antipsychotics have a higher risk for causing extrapyramidal side effects than second-generation antipsychotics. • Adverse reactions from antipsychotics vary between drugs but may include weight gain, extrapyramidal side effects, increased prolactin, sedation, and QT prolongation. • Nonadherence to daily oral antipsychotic treatment is very common in individuals with schizophrenia. The consequences of medication nonadherence can include acute psychosis exacerbation, occupational and social problems, danger to self or others, and psychiatric hospitalization. • Long-acting injectable antipsychotic medications maintain therapeutic blood levels of antipsychotics for extended periods (weeks to months) and may reduce the risk of schizophrenia exacerbation in patients who are nonadherent to oral antipsychotics. • In addition to antipsychotic medications, patients with schizophrenia are frequently treated with adjunctive medications to target depression, anxiety, obsessions and compulsions, and side effects of antipsychotics (e.g., dystonia, parkinsonism, tardive dyskinesia, and akathisia). • When integrated with pharmacotherapy, psychosocial interventions have been shown to improve the course of	reduce the risk of exacerbations in patients who are nonadherent to oral antipsychotics. Patients may also prefer long-acting medications over taking oral medications daily. The dosing schedule for Abilify Asimtufi (aripiprazole) injection (every 2 months) offers an additional choice for patients and providers.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	schizophrenia. These interventions include cognitive behavioral therapy, assertive community treatment, supported employment, and social skills therapy. Bipolar I Disorder • Second generation antipsychotics are part of various treatment guidelines for bipolar I disorder, and multiple studies have demonstrated their effectiveness in acute mania/mixed episodes and to prevent recurrence of mania/mixed episodes.	
Benefit	• The Applicant submitted Study 031-201-00181, an open-label, randomized, multicenter, PK bridging study, which evaluated the safety, tolerability, and steady-state exposures of aripiprazole comparing administration of 960 mg aripiprazole 2M RTU to those of 400 mg Abilify Maintena Q1M in subjects with schizophrenia or bipolar I disorder (N=266). • An adequate scientific bridge was established between aripiprazole 2M RTU LAI and the LD Abilify Maintena. • The effectiveness of aripiprazole 2M RTU LAI is based on the findings of effectiveness for the LD, Abilify Maintena.	Aripiprazole 2M RTU LAI is anticipated to be as effective as the LD, Abilify Maintena. It is anticipated that this product will fit into the therapeutic armamentarium as a long-acting injectable antipsychotic option that requires less frequent injections than the other aripiprazole product on the market. This fact is anticipated to be appreciated by patients as well as caregivers.
Risk and Risk Management	• The primary safety variables for Study 031-201-00181 included reported AEs, vital signs, ECG, clinical laboratory monitoring (serum chemistry, hematology, and urinalysis), physical examinations, extrapyramidal symptoms (the Simpson-Angus Neurologic Rating Scale, Abnormal Involuntary Movement Scale, and Barnes Akathisia Rating Scale), Visual Analog Scale scores for pain perception, investigator's assessment of most recent injection site, and the Columbia-Suicide Severity Rating Scale. The primary safety endpoints were adequate to address the	In Study 031-201-00181, the Applicant has demonstrated that the safety profile of aripiprazole 2M RTU LAI and Abilify Maintena are similar. The assessment of safety findings from the aripiprazole 2M RTU LAI development program did not reveal any unexpected safety signals when compared to other formulations of

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	study's objectives. • Analyses of safety data did not show any significant clinical difference between the safety profile of aripiprazole 2M RTU LAI and the safety profile of Abilify Maintena, except for higher frequency of TEAEs related to injection site reactions, which were mild. • Aripiprazole 2M RTU LAI was associated with weight gain, extrapyramidal symptoms, insomnia, anxiety, headache, and hyperglycemia—showing a similar safety profile to Abilify Maintena. • Nineteen percent of subjects on aripiprazole 2M RTU LAI had injection site reactions, mainly pain (18%). However, all events occurred within 2 days of the injection and lasted less than 5 days in all but two subjects. The majority of injection site pain events occurred with the first injection, were mild and did not lead to drug discontinuation.	aripiprazole. Formulation-specific injection site reactions were mild overall. Potential risks related to administration of this product will be described in labeling. Labeling will include language instructing prescribers not to administer more than one dose of Aripiprazole 2M RTU LAI per dosing interval. There were no safety issues that would preclude approval of this NDA.

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1.4. Patient Experience Data

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

X	**The patient experience data that were submitted as part of the application include:**			Section of clinical study report where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	CSR 031-201-00181, Sections 11.4.1.2 and 12.5.5 CSR 031-201-00104, Section 12.5.5, CSR 031-201-00279, Sections 11.5.1 and 12.5.5
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	CSR 031-201-00181, Sections 11.4.1.2 and 12.5.5, CSR 031-201-00104, Section 12.5.5, CSR 031-201-00279, Sections 11.5.1, and 12.5.5
		☐	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:**			
	☐	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.**			

Source: 031-201-00181 CSR, 031-201-00104 CSR, 031-201-00279 CSR
CSR = clinical study report

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2. Therapeutic Context

2.1. Analysis of Condition

Schizophrenia

Schizophrenia is a serious psychiatric disorder affecting approximately 1% of the population worldwide. Schizophrenia is a severe, chronic condition with significant morbidity and mortality. Per *the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), the disorder is characterized by a constellation of symptoms that may include delusions, hallucinations, disorganized speech, grossly disorganized behavior, diminished emotional expression, and avolition (American Psychiatric Association (APA), 2013). Although cognitive symptoms are not included in the diagnostic criteria of schizophrenia, impairments in processing speed, attention, working memory, and social cognition are frequent and disabling manifestations. Mood and anxiety symptoms are also common in individuals with schizophrenia.

The pathogenesis of schizophrenia is poorly understood. Schizophrenia is a heterogeneous syndrome likely caused by a complex group of diseases resulting from interactions between genes and environment. Rare cases arise from an abnormality in a single genetic locus (e.g., 22q11 deletion syndrome). However, for most people with schizophrenia, multiple genes are involved, each contributing a small amount to the overall condition. Environmental risk factors associated with schizophrenia are equally diverse and include prenatal maternal infections, nutritional deficiencies, obstetrical complications, adverse childhood events, and urbanicity (Wahbeh and Avramopoulos, 2021). The underlying neurobiology of schizophrenia has not been clearly established; there is no recognized central pathophysiology or disease mechanism (Rasetti and Weinberger, 2011). Hypothetical neurochemical models of schizophrenia include excessive mesolimbic dopaminergic activity, hypoactivity of N-methyl-D-aspartate (NMDA) glutamate receptors, and dysfunctional gamma-amino-butyric acid (GABA)-mediated modulation of pyramidal neurons (Birnbaum and Weinberger, 2017).

The onset of schizophrenia is typically in early adulthood, occurring 5 to 7 years later in women than in men. The course of illness is heterogeneous, with many experiencing multiple acute symptom exacerbations and remissions within a chronic and disabling illness. On average, women tend to have better premorbid functioning and less prominent negative symptoms (e.g., affective flattening, alogia, anhedonia, and avolition) and a higher severity of affective symptoms (Giordano et al., 2021).

Schizophrenia is associated with significant impairments in social and occupational functioning and is among the 20 leading causes of disability worldwide (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Individuals with schizophrenia experience premature mortality compared with the general population, with an average of 14.5 years of

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potential life lost (Hjorthøj et al., 2017). About 4% to 10% of people with schizophrenia die by suicide, with rates that are highest among males in the early course of the disorder (Sher and Kahn, 2019). Overall, schizophrenia is a serious condition, associated with significant disability and a shortened life expectancy.

Bipolar I disorder

Bipolar I disorder is a severe and persistent psychiatric disorder characterized by episode(s) of mania, and, in most cases, episodes of hypomania or major depression. To be diagnosed with bipolar disorder, a person must have experienced at least one episode of mania or hypomania. Per the DSM-5, to be considered mania, the elevated, expansive, or irritable mood must last for at least 1 week and be present most of the day, nearly every day (APA, 2013).

The mean age of onset for the first mood episode is approximately 18 years of age (Merikangas et al., 2007). First onset of bipolar disorder later in life has been described, but onset of manic symptoms in late mid-life or late-life may indicate the presence of a co-occurring medical condition such as a frontotemporal neurocognitive disorder or the effects of substance use. Suicide risk is a major concern for individuals with bipolar I disorder; suicide risk is estimated to be at least 15 times the general population risk (Marangell et al., 2006). Functional impairment is also significant; individuals with bipolar I disorder demonstrate severe impairment in occupational functioning approximately 30% of the time (Judd et al., 2008), and individuals with bipolar I disorder attain lower levels of socioeconomic status than members of the general population with equivalent educational levels (Schoeyen et al., 2011). Aggregate lifetime prevalence estimates for bipolar I disorder range from 0.6 to 1% (Merikangas et al., 2011).

2.2. Analysis of Current Treatment Options

Schizophrenia

The most recent APA practice guideline for the treatment of schizophrenia recommends that patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects (Keepers et al, 2020). Antipsychotic treatment should be initiated in an acute schizophrenia exacerbation to reduce acute symptoms, with the aim of returning the individual to his or her baseline level of functioning. Later, maintenance treatment will aim to prevent recurrence of symptoms and maximize functioning and quality of life.

The mechanism by which antipsychotics improve psychotic symptoms is not completely understood but may involve antagonism of dopamine D2 receptors and/or serotonin 5-HT2A receptors. Binding to other neurotransmitter receptors (e.g., α1-adrenergic, muscarinic, and histaminergic receptors) generally corresponds to the adverse reaction (AR) profile for a given drug (Correll and Kane, 2014). First-generation or typical antipsychotics are antagonist at the dopamine receptor(s) and second-generation or atypical antipsychotics are also antagonists at the 5-HT2A receptor. Some of the relevant class-based safety issues for antipsychotics include

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extrapyramidal symptoms (EPS) and tardive dyskinesia, neuroleptic malignant syndrome, hyperprolactinemia, orthostatic hypotension, metabolic effects including dyslipidemia, hyperglycemia, and weight gain, QT interval prolongation, seizures, blood dyscrasias, sedation, and an increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis. In general, second-generation antipsychotics have been associated with more weight gain, hyperglycemia, and hyperlipidemia compared to the first-generation antipsychotics.

Several antipsychotics are available in long-acting injectable (LAI) formulations (Table 1). The primary clinical benefit of LAIs is that they maintain therapeutic blood levels of antipsychotics for extended periods (weeks to months) and may reduce the risk of schizophrenia exacerbation in patients who are nonadherent to oral medications (Kishimoto et al. 2018). Potential disadvantages of LAIs include a longer time to achieve steady state blood levels, delayed resolution of adverse reactions (AR), injection site reactions, and more frequent appointments for drug administration (Brissos et al. 2014).

Although there are a number of approved treatments for schizophrenia, an individual patient may require several trials with different antipsychotic drugs before an effective and reasonably tolerated treatment is identified. Additionally, most available medications predominantly affect positive symptoms but do not appear to meaningfully impact negative symptoms or cognitive impairment.

Table 1: Representative Long-Acting Injectable Antipsychotics Currently Available in the United States

Product Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Important Differentiating Safety and Tolerability Issues	Other Comments
Aripiprazole monohydrate (Abilify Maintena)	Schizophrenia in adults. Maintenance treatment as monotherapy of bipolar I disorder in adults.	2013	IM in deltoid or gluteal, monthly	N/A	In conjunction with first dose, need to continue oral antipsychotic for 14 days
Aripiprazole lauroxil (Aristada)	Schizophrenia in adults.	2015	IM in deltoid or gluteal, every 1 or 2 months, or every 6 weeks	N/A	In conjunction with first dose, need to continue oral aripiprazole for 3 weeks

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Aripiprazole lauroxil (Aristada Initio)	Schizophrenia in adults.	2018	IM deltoid or gluteal, one-time injection	N/A	To be used as one-time loading dose with a one-time oral aripiprazole loading dose at time of Aristada initiation
Fluphenazine decanoate	Schizophrenia in adults.	1972	IM or SC, every 2 to 4 weeks	First generation antipsychotic – higher EPS liability	Need to continue oral fluphenazine until effective decanoate dosage is established
Haloperidol decanoate	Schizophrenia in adults.	1986	IM, monthly	First generation antipsychotic – higher EPS liability	Depending on initiation dose, may need to continue oral haloperidol for up to 3 months.
Olanzapine pamoate (Zyprexa Relprevv)	Schizophrenia in adults.	2009	IM in gluteal muscle, every 2 or 4 weeks	Risk of post injection delirium/sedation syndrome; risk evaluation and mitigation strategy requires 3 hours monitoring post-injection in a certified facility.	No overlap period needed with oral antipsychotic
Paliperidone palmitate (Invega Sustenna)	Schizophrenia in adults. Treatment of schizoaffective disorder.	2009	IM in deltoid or gluteal muscle; monthly after loading doses (two loading doses 1 week apart)	N/A	No overlap period needed with oral paliperidone
Paliperidone palmitate (Invega Trinza)	Schizophrenia in adults.	2015	IM in deltoid or gluteal muscle; every 3 months	N/A	Can only be used if patient has received monthly injections of Invega Sustenna for ≥4 months

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Paliperidone palmitate (Invega Hafyera)	Schizophrenia in adults.	2021	IM in gluteal muscle; every 6 months	N/A	Can only be used if patient has received monthly injections of Invega Sustenna for ≥4 months or Invega Trinza for ≥1 three month cycle
Risperidone microspheres (Risperdal Consta)	Schizophrenia in adults. Maintenance treatment as monotherapy or adjunctive with lithium or valproate of bipolar I disorder in adults.	2003	IM in deltoid or gluteal muscle, every 2 weeks	N/A	In conjunction with first dose, need to continue oral antipsychotic for 3 weeks
Risperidone for extended-release injectable suspension (Perseris)	Schizophrenia in adults.	2018	SC injection in abdomen every 4 weeks	N/A	No overlap period needed with oral risperidone
Risperidone for extended-release injectable suspension (Rykindo)	Schizophrenia in adults. Maintenance treatment as monotherapy or adjunctive with lithium or valproate of bipolar I disorder in adults.	2023	IM in gluteal muscle, every 2 weeks	N/A	In conjunction with first dose, need to continue oral risperidone for 1 week

Source: Clinical reviewer-generated

Abbreviations: EPS = extrapyramidal symptoms; IM = intramuscular; N/A = not applicable; SC = subcutaneous

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Bipolar I disorder
Pharmacological treatment is the cornerstone of current therapeutics for bipolar disorder which includes lithium, mood-stabilizing anticonvulsants (notably carbamazepine, lamotrigine, and valproate) and second-generation antipsychotics. The LAI antipsychotics approved for the treatment of bipolar I disorder are Risperdal Consta (approved for maintenance treatment as monotherapy or adjunctive with lithium or valproate in adults), Abilify Maintena (approved for maintenance treatment as monotherapy in adults), and recently Rykindo (approved for maintenance treatment as monotherapy or adjunctive with lithium or valproate in adults).

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3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Abilify Asimtufii (aripiprazole 2M LAI) has not been approved or marketed in the United States. Abilify Maintena (NDA 202971), the LD, has been approved and marketed since 2013. The Applicant has conducted a pivotal pharmacokinetic (PK) study to bridge to the LD, and is relying on the Agency's findings of safety and effectiveness of the LD. Because the Applicant has right of reference to the LD, the path for approval is via 505(b)(1).

3.2. Summary of Presubmission/Submission Regulatory Activity

Otsuka Pharmaceutical Co., Ltd. developed aripiprazole 2M LAI, an investigational drug product of aripiprazole extended release, for gluteal intramuscular injection for the treatment of schizophrenia and as a maintenance monotherapy treatment of bipolar I disorder, under investigational new drug (IND) application 134612.

On April 19, 2017, the Applicant submitted IND 134612. The Division determined that the IND-opening protocol was safe to proceed and issued a May Proceed letter on May 19, 2017.

On May 25, 2018, the Applicant requested a Type C meeting to discuss the overall clinical development and acceptability of the proposed multiple dose trial design and statistical analysis plan. Preliminary comments were issued on August 1, 2018. Upon receipt of the preliminary comments, the meeting was cancelled by the Applicant. Within the preliminary comments, the Division agreed that the Applicant's PK bridging approach was acceptable, but the adequacy of the multiple-dose trial would be a matter of review once the NDA was submitted. The Division advised the Sponsor to assess safety and tolerability in addition to conducting a PK evaluation and agreed with their approach to use PK simulation data to support labeling language for patients switching from other aripiprazole formulations. The Division also recommended that the Applicant obtain data regarding influence of stress factors on the in vitro and in vivo drug release profiles.

The Applicant submitted an initial Pediatric Study Plan (iPSP) on April 2, 2019, detailing their plan to request a full waiver for children and adolescents 0 to 17 years of age for the treatment of schizophrenia because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric patients (section 505B(a)(4)(A)(iii) of the Pediatric Research Equity Act (PREA)). The Applicant also included plans to request a full waiver for children 0 to 9 years of age for the maintenance monotherapy treatment of bipolar I disorder because necessary studies are impossible or highly impracticable (section 505B(a)(4)(B)(i) of PREA) and a full waiver for children and adolescents 10 to 17 years of age because the drug does not represent a meaningful benefit over existing therapies for pediatric patients and is not likely to be used in a

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substantial number of patients 10 to 17 years of age (section 505B(a)(4)(A)(iii) of PREA). The Division issued a written response on June 26, 2019, requesting revisions to clarify the basis for the waiver request and background information. The Applicant submitted an agreed iPSP on September 10, 2019, wherein they accepted all the revisions by the Division. An initial agreement letter was sent to the Applicant from the Division on September 30, 2019.

The Applicant requested a Type C written response only meeting on January 24, 2020, to discuss the development of a _____ (b) (4) ready-to-use (RTU) formulation. Within the written responses, the Division informed the Sponsor that we did not agree with their proposed _____ (b) (4) trial to establish safety and efficacy of aripiprazole _____ (b) (4) compared to Abilify Maintena or their proposed statistical methods and PK endpoints. The Division stated that appropriate bridging is needed between aripiprazole _____ (b) (4) and Abilify Maintena to support NDA filing. The Division also reiterated the need for data regarding the influence of stress factors and to consider studying the effect of immune/inflammatory response modulators on the in vivo drug release profile. Additionally, the Division expressed concerns for unexpected dose dumping or drug release.

On December 9, 2020, the Applicant requested a Type C teleconference to discuss CMC development plans and proposed data to support an NDA for the 2M RTU aripiprazole formulation. The Applicant cancelled the meeting upon receipt of preliminary comments that were issued on December 4, 2020.

On December 2, 2020, the Applicant requested a Type C written response only meeting to discuss the nonclinical study design planned to address the concerns of immune/inflammatory response modulator and stress factors studies. The Division informed the Applicant that we had no objections to their proposed protocol, but that the adequacy of the studies would be a matter of review.

The Applicant submitted a Human Factors validation protocol, Use-Related Risk Analysis, draft Human Factors Engineering/Usability Engineering report and Instructions for Use on November 4, 2021. The Human Factors protocol was found acceptable upon review. Identified issues were communicated to the Applicant in a December 28, 2021, information request.

A Type B Pre-NDA meeting was requested on December 10, 2021, and occurred via teleconference on March 9, 2022. During the meeting, the Division informed the Applicant that a 120-day safety update was not needed if there was no additional data to report at that time. The Division agreed that the nonclinical studies appeared acceptable to address potential impacts of the release profile, but that the final determination would be a matter of review. The Division informed the Applicant that datasets should be submitted for all supportive clinical trials that include safety monitoring and the recommended analyses should be included in their submission. The Division agreed with the Applicant's proposal to incorporate PK information from 031-201-00181 trial in the USPI, but that the acceptability of the proposed USPI language would be a matter of review. The Division also agreed with the Applicant's proposal to

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summarize demonstrated comparability between the aripiprazole 2M LAI formulation and Abilify Maintena in the USPI based on bridging and/or popPK studies while retaining relevant data from the current Abilify Maintena USPI but stated that the overall acceptability would be a matter of review.

The Applicant submitted a proprietary name request on January 26, 2022, for   (b) (4). The name was later withdrawn by the Applicant on November 14, 2022, due to concerns from the Office of Surveillance and Epidemiology (OSE). The Applicant submitted a second proprietary name request for the name   (b) (4) on August 16, 2022. The name was withdrawn by the Applicant on November 9, 2022, due to concerns from the OSE. A third proprietary name request was submitted on November 9, 2022, for the name Abilify Asimtufii and was approved on February 7, 2023.

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

4.1. Office of Study Integrity and Surveillance (OSIS)

OSIS was consulted to inspect the bioanalytical and clinical sites of the pivotal study, 031-201-00181. Because a recent inspection in ⬛⬛⬛⬛ (b) (4) revealed no concerns, OSIS determined that an inspection was not needed for the bioanalytical site (Bioequivalence Establishment Inspection Report Review archived on January 18, 2023). Also, it was concluded that data from the clinical sites are reliable (Bioequivalence Establishment Inspection Report Review archived on February 22, 2023).

4.2. Product Quality

During the review, the Office of Product Quality (OPQ) noted ⬛⬛⬛⬛⬛⬛⬛ (b) (4)

⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛ (b) (4)

⬛⬛⬛⬛ (b) (4) setting appropriate particle size specifications especially critical. In this NDA submission, there was only one batch of drug product used in the PK bridging clinical trial, 18C95A300. This was the only batch available to use in setting particle size specifications. A dialog with the Applicant (including information requests and a teleconference on March 9, 2023) allowed OPQ and the Applicant to agree to tighter particle size specifications to align with the particle size of the single drug product batch used in the clinical study performed and prevent possible changes to drug PK parameters (see Section 6, Clinical Pharmacology, p. 61, for a description of concerns).

Refer to the OPQ Integrated Quality Assessment and the incorporated OPQ discipline reviews for details about their evaluations. OPQ recommends approval of this application based on reviews from the drug substance, drug product, manufacturing (process and facilities), biopharmaceutics, and microbiology disciplines.

4.3. Clinical Microbiology

Based on the OPQ Integrated Quality Assessment, the microbiology assessment is adequate, and approval is recommended.

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4.4. Devices and Companion Diagnostic Issues

The OPQ Integrated Quality Assessment suggests that the device (pre-filled syringe) functionality is adequate, and approval is recommended.

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5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The aripiprazole 2M RTU LAI formulation is intended for IM administration every 2 months and is a suspension with higher aripiprazole concentrations (300 mg/mL) compared to the approved aripiprazole IM depot formulation, Abilify Maintena (NDA 202971). In support of this NDA, the Applicant relied, in part, on the Agency's previous findings of nonclinical safety of the Applicant's approved aripiprazole drug products Abilify (aripiprazole oral tablets, NDA 21436) and Abilify Maintena (IM depot formulation, NDA 202971), in addition to conducting nonclinical studies with the aripiprazole 2M RTU LAI formulation.

The nonclinical pharmacokinetic (PK) and irritation toxicity studies conducted with aripiprazole 2M RTU LAI did not show any new or unexpected treatment-related toxicities as compared to those previously identified with the IM depot formulation of aripiprazole. In repeat-dose irritation studies in beagle dogs, aripiprazole 2M RTU LAI IM administration was well tolerated without clinical signs of discomfort or significant local irritation after 52-weeks of intermittent IM monthly doses up to 420 mg/animal. A foreign-body type of localized granulomatous inflammatory reaction to deposited drug was observed at the injection site, but there was no evidence of local muscle injury and the changes at the injection sites were reversible after a 26-week recovery period. There were no changes in other parameters including clinical chemistry indicative of muscle injury (aspartate aminotransferase and creatine kinase). Histopathology examination at the injection site showed a foreign-body granulomatous inflammation consisting of macrophages with vacuoles or foamy cytoplasm. The inflammatory foci contained crystal-like material representing deposited drug. The severity of inflammatory response decreased with time and there was no microscopic evidence of muscle necrosis at the injection sites.

Application of exercise, heat, pressure, and administration of an anti-inflammatory agent (diclofenac) to rats administered 2M RTU LAI had minimal effects on the PK of aripiprazole. Single IM administration of 50 mg/kg 2M RTU LAI along with stress factors in six conditions (control, anesthesia control, physical stimulation, exercise stimulation, whole body heat stimulation, and local heat stimulation) resulted in less than 2-fold changes in C_{max} or AUC after stress challenge, while mean residence time and t_{max} values were similar across all groups. After a single aripiprazole 2M RTU LAI IM dose of 50 mg/kg in parallel with repeated oral administration of diclofenac sodium at 5 mg/kg/day for 7 days to assess the effect of inflammatory response modulators, exposure to aripiprazole (C_{max} only) was minimally decreased and t_{max} was prolonged by 2.8 days.

These challenges are not likely to cause clinically significant changes in aripiprazole exposure in patients administered aripiprazole 2M RTU LAI because the conditions in these nonclinical

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studies represent a worse-case scenario and the changes in PK parameters of aripiprazole observed in rats were minimal.
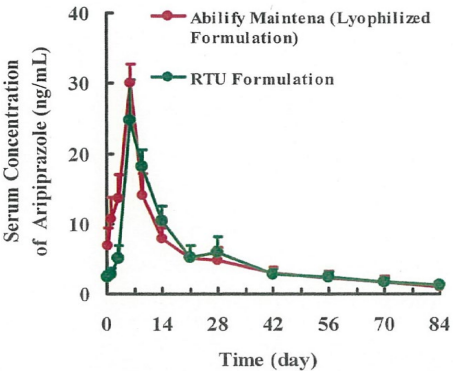
5.2. Referenced NDAs, BLAs, DMFs

NDA 021436 Abilify (oral aripiprazole approved in in 2002) and NDA 202971 Abilify Maintena (IM depot formulation of aripiprazole approved in 2013)

5.3. Pharmacology

No pharmacology studies were conducted with aripiprazole 2M RTU LAI formulation. The pharmacology studies are referenced from previously approved aripiprazole NDAs (021436 and 202971).

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Single-dose PK study in rats: Study Title: PK Study for Aripiprazole IM Depot RTU Injection (Report No.14075) Rats (6/group) received a single IM dose (50 mg/kg) of either aripiprazole RTU formulation (300 mg/mL) or aripiprazole IM depot formulation (Abilify Maintena, 200 mg/mL). Blood samples were collected periodically over 84 days.	Serum aripiprazole concentrations were similar between aripiprazole RTU formulation and aripiprazole IM depot formulation and there were no meaningful differences in the PK parameters between the 2 injectable formulations, as shown in the Sponsor's table and figure below: **Serum Concentrations of Aripiprazole Following IM Injection at a dose of 50 mg/kg in Male Rats** *(Source: Toxicology Written Summary)* Mean PK Parameters |	Aripiprazole IM Depot[a]	Aripiprazole RTU Formulation
---	---	---
AUC_{0-84d} (ng.d/mL)	433.38	431.10
C_{max} (ng/mL)	30.00	25.38
T_{max} (day)	6.0	6.5	 [a]Abilify Maintena

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Type of Study	Major Findings
	Particle Size Distributions of Abilify Maintena (Lyophilized Formulation) and RTU Formulation | Formulation	Lot No.	Measurement Condition	Mean Particle Size (um)	10%D	50%D	90%D
---	---	---	---	---	---	---
Abilify Maintena (Lyophilized Formulation)	12K73A400	-				(b) (4)
RTU Formulation	13H80A300	Condition 2 Condition 1					 *Condition 1: Secondary particle size; Condition 2: Primary particle size *Source: Study Report No.14075*
Study Title: Effect of Applied Stress on the Plasma Concentration-time Profile of Aripiprazole (OPC-31) after Intra-muscular Injection of OPC-31 2M RTU LAI Formulation to Rats (Report No. 036018)	Application of stress stimuli [physical stimulation (repeated application of pressure (approximately 200 g) and release at intervals of approximately 5 seconds for 10 minutes), exercise stimulation (treadmill, 30 m/min for 15 min), whole body heat stimulation (40°C for 20 min), and local heat stimulation (47° C, 3 sec)] for 21 days in rats, starting in parallel with a single IM administration of OPC-31 2M RTU LAI formulation at a dose of 50 mg/kg, had minimal effect on aripiprazole systemic exposure as compared to control (drug but no stress) and anesthesia control group (drug and inhalation anesthesia for 10 min by 2% isoflurane). C_{max} or AUC changes were less than 2-fold after the application of stress factors, and mean residence time and t_{max} values were similar across all test and control groups. **Effect of Applied Stress on Plasma Concentration-time Profile of OPC-31 After IM Injection of OPC-31 2M RTU LAI* to Rats** *(Source: PK Tabulated Summary* 	Condition (Dose: 50 mg/kg)	C_{max} (ng/mL)	t_{max} (day)	AUC_t (ng·day/mL)	AUC_∞ (ng·day/mL)	MRT_∞ (day)
---	---	---	---	---	---
Control	26.22 ± 5.12	7.2 ± 1.8	267.7 ± 54.3	349.3 ± 70.7	16.62 ± 5.99
Exercise stimulation	25.36 ± 2.20	6.8 ± 1.1	273.3 ± 37.6	325.8 ± 42.1	13.32 ± 1.04
Anesthesia control	19.26 ± 3.80	7.2 ± 1.8	203.0 ± 18.0	309.2 ± 116.5	19.29 ± 9.75
Physical stimulation	28.00 ± 4.41	6.0 ± 0.0	274.9 ± 30.3	328.1 ± 35.1	13.16 ± 2.25
Whole body heat stimulation	23.66 ± 2.46	6.8 ± 1.8	235.1 ± 20.8	300.0 ± 83.8	15.18 ± 6.44
Local heat stimulation	25.42 ± 8.26	6.8 ± 1.1	230.2 ± 68.0	302.3 ± 67.3	18.36 ± 13.52	 Mean ± SD (n=5). These values were determined from 5 animals. *Lot # 18C95A300
Study Title: Effect of Anti-Inflammatory Agent on the Plasma Concentration-time Profile of Aripiprazole (OPC-31) after Intramuscular Injection of OPC-31 2M RTU LAI Formulation to Rats (Report No. 036019)	Repeated oral administration of anti-inflammatory agent diclofenac sodium to rats at doses of 2 and 5 mg/kg for 7 days, starting in parallel with a single IM administration of OPC-31 2M RTU LAI formulation at a dose of 50 mg/kg, resulted in a 30% decrease in exposure to aripiprazole (C_{max} only) and in 40% increase in t_{max} at diclofenac HD of 5 mg/kg. Only a slight decrease in AUC of 14% was observed. **Effect of an Anti-Inflammatory Agent on the Plasma Concentration-time Profile of Aripiprazole After IM injection of OPC-31 2M RTU LAI* to rats** *(Source: PK Tabulated Summary)*

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Type of Study	Major Findings						

Dose (mg/kg)		C_{max} (ng/mL)	t_{max} (day)	AUC_t (ng·day/mL)	AUC_∞ (ng·day/mL)	MRT_∞ (day)
50/0	Mean ±SD	31.53 ± 2.68	6.8 ± 1.1	320.6 ± 30.0	402.2 ± 33.9	14.47 ± 1.01
	Ratio	1.0	1.0	1.0	1.0	1.0
50/2	Mean ±SD	32.14 ± 5.51	7.2 ± 1.1	327.7 ± 49.6	403.7 ± 51.7	14.20 ± 3.09
	Ratio	1.0	1.1	1.0	1.0	1.0
50/5	Mean ±SD	21.79 ± 5.00	9.6 ± 2.2	274.2 ± 35.3	372.2 ± 92.0	16.37 ± 2.37
	Ratio	0.7	1.4	0.9	0.9	1.1

*Lot # 18C95A300

Type of Study	Major Findings
Distribution, Metabolism and Excretion	No distribution, biotransformation, and excretion studies were performed for aripiprazole 2M RTU LAI. Previous in vitro and in vivo studies on distribution, biotransformation, and excretion of aripiprazole to support clinical development of the 2M RTU LAI formulation are referenced in the oral Abilify NDA 21436 and aripiprazole IM depot formulation NDA 202971.

TK data from toxicology studies

Type of Study	Major Findings
Single Intramuscular Dose Irritation Study of OPC-14597 Suspension for Depot Injection (New Component) in Beagle Dogs. Report No. 029243	**Toxicokinetic Parameters of OPC-14597** (*Source: Study Report No. 029243, p.22*)

Toxicokinetic Parameters of OPC-14597

Dose Level* (mg/body)	T_{max} (day)	C_{max} (ng/mL)	AUC_{28d} (ng·d/mL)	AUC_{56d} (ng·d/mL)
400	16	28.99	515.4	898.9

*Each treated animal was given 1.4 mL of 300 mg/mL OPC-14597 suspension for injection

Changes of the Mean Plasma Concentrations of OPC-14597

Dose Level* (mg/body)	Concentration (ng/mL) Day after administration (day)								
	0.25	1	3	7	10	14	21	28	56
400	2.090	6.215	7.021	12.43	22.97	25.57	23.90	15.14	7.470

*Each treated animal was given 1.4 mL of 300 mg/mL OPC-14597 suspension for injection

Mean plasma concentrations gradually increased during the first 2 weeks after administration, with a decline afterwards. At 56 days after administration, the mean plasma concentration was half of that at 28 d after administration.

Type of Study	Major Findings
52-week Intermittent IM Dose Irritation Study of OPC-14597 Suspension for Depot Injection in Beagle Dogs with 26-week Recovery Test. Report No. 030649	TK analysis not performed

5.5. General Toxicology

General toxicology studies were not performed with aripiprazole 2-month ready-to-use long-acting injectable. Nonclinical studies characterizing general toxicology profile of aripiprazole referred to oral aripiprazole (NDA 021436) and aripiprazole IM depot formulation (NDA 202971).

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5.6. Local Tolerance

Single- and repeat-dose local irritation studies in dogs were conducted to support the present application.

On March 27, 2023, the Applicant provided a response to an information request asking for the quantitative composition of the OPC-14597 aqueous solution for injection that was used as vehicle control in the single dose and 52-week irritation studies. The Applicant responded that the OPC-14597 aqueous solution for injection (vehicle control) composition used in these studies is identical to the aripiprazole RTU composition found in Module 3.2.P.1, except for the removal of aripiprazole (as shown in the following Sponsor's table):

3.2.P.1 Description and Composition of the Drug Product (Aripiprazole, 2M RTU LAI)

Table 3.2.P.1-1	Composition of Aripiprazole 2M RTU LAI				
Component	Reference Standard	Function	Quantity (mg/mL)	Quantity (mg) 720-mg/syringe	Quantity (mg) 960-mg/syringe (b) (4)
Sterile Aripiprazole Monohydrate	In-house	Active	300.0[a]		
Carboxymethylcellulose Sodium	USP	(b) (4)	5.0		
Povidone[b]	USP		4.0		
Polyethylene Glycol 400	NF		1.0		
Sodium Phosphate, Monobasic, Monohydrate	USP		0.74		
Sodium Chloride	USP		6.1		
Sodium Hydroxide	NF	pH Adjusting Agent	q.s. to pH (b) (4)	q.s. to pH (b) (4)	q.s. to pH (b) (4)
Water for Injection	USP	(b) (4)	q.s.	q.s. to (b) (4) mL[c]	q.s. to (b) (4) mL[c]

NF = National Formulary; USP = United States Pharmacopeia; q.s. = quantum sufficit (as much as suffices)

[a]As anhydrous aripiprazole.

(b) (4)

Study title/ number: Single Intramuscular Dose Irritation Study of OPC-14597 Suspension for Depot Injection (New Component) in Beagle Dogs/ 029243

Noteworthy findings:
- No clinical signs of pain or changes in clinical chemistry indicative of muscle injury.

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- Macroscopically, white foci in the injection site muscle with histopathology of granulomatous inflammation consistent with a foreign-body reaction (accumulation of macrophages with vacuoles or foamy cytoplasm around eosinophilic material representing the deposited drug).

- Severity of inflammation decreased but did not completely resolve after 8 weeks. There was no evidence of drug-related skeletal muscle injury.

Conducting laboratory and location: Otsuka Tokushima Research Institute, Japan
GLP compliance: Yes

Methods

Drug: OPC-14597, Lot No. 12K88A300
     Particle size distribution *(Source: Certificate of Analysis, Study Report No. 029243, Appendix 1)*

Condition- 1*	Mean particle size (b) (4)	
	10%D (b) (4) 50%D (b) (4), 90%D (b) (4)	
Condition-2*	Mean particle size (b) (4)	
	10%D (b) (4) 50%D (b) (4), 90%D (b) (4)	

*Condition 1: Secondary particle size; Condition 2: Primary particle size

Dose and frequency of dosing:	0 (saline), 0 (vehicle), 420 mg (300 mg/mL, 1.4 mL/animal)
	Note: The dose volume of 1.4 mL was selected based on the "expected" maximal clinical dose of 400 mg.
	Single dose
Route of administration:	IM
Formulation/Vehicle:	OPC-14597 aqueous solution for injection Lot No. 13A91P300
Species/Strain:	Dog/Beagle
Number/Sex/Group:	9/ M
Age:	6 months
Satellite groups/ unique design:	• Both Vehicle and Saline control groups included • Plasma samples for evaluation of systemic exposure to OPC-14597 collected at 0.25, 1, 3 and 7, 10, 14, 21, 28 and 56 days after administration

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- Injection sites examined at scheduled necropsies on Days 8, 29 and 57 in 3 dogs/group/time point

Deviation from study protocol
affecting interpretation of results: None

Observations and Results: changes from control

Parameters	Major findings
Mortality	No
Clinical Signs	No clinical signs associated with pain
Body Weights	No changes
Hematology	Transient increase in white blood cells (up to 60% vs. vehicle control) on Day 2 (a result of acute inflammation at injection site) in the drug-treated animals. The change reversed on Day 8.
Clinical Chemistry	No changes in analyzed parameters (AST and Creatine Kinase)
Gross Pathology	White foci in the injection site muscle of all drug treated dogs sacrificed on Days 8, 29 and 57. The size of the foci gradually decreased over time.
Histopathology (Local tissues examined only)	White foci microscopic characteristics: granulomatous inflammation (accumulation of macrophages with vacuoles or foamy cytoplasm around eosinophilic deposits interpreted as drug). Inflammation severity decreased by Day 57. No evidence of muscle necrosis at the injection sites.

Histopathological Findings – Summary
(Source: Study Report 029243, p. 42)

Dose		A0			B0			B300		
Stage		Day 8	Day 29	Day 57	Day 8	Day 29	Day 57	Day 8	Day 29	Day 57
No. of Animals		3	3	3	3	3	3	3	3	3
Injection site	Examined	3	3	3	3	3	3	3	3	3
Granulomatous inflammation	-	3	3	3	3	3	3	0	0	0
	±	0	0	0	0	0	0	0	0	2
	+	0	0	0	0	0	0	3	3	1

- : No changes , ± : Very slight , + : Slight
A0 : 0mg/mL (Saline)   B0 : 0 mg/mL OPC-14597   B300 : 300 mg/mL OPC-14597

Study title/ number: Fifty-two-week Intermittent Intramuscular Dose Irritation Study of OPC-14597 Suspension for Depot Injection (New Component) in Beagle Dogs with 26-week Recovery Test/ 030649

Noteworthy findings:
- No clinical signs of pain or changes in clinical chemistry indicative of muscle injury.

- Macroscopically, white foci in the injection site muscles of all treated animals, with histopathology of granulomatous inflammation consistent with a foreign-body reaction (accumulation of macrophages with vacuoles or foamy cytoplasm around eosinophilic material representing deposited drug).

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- Severity of inflammation and size of foci decreased after recovery period. There were no lesions in the regional lymph nodes (popliteal and medial iliac) at any time point.

- Safety margin: 1.6x vs. the proposed maximal clinical dose of 960 mg, based on mg/m2 body surface.

Conducting laboratory and location: Otsuka Tokushima Research Institute, Japan
GLP compliance: Yes

Methods
Drug: OPC-14597, Lot No. 12K88A300-0206

Particle size distribution (*Source: Certificate of Analysis, Study Report No. 030649, Appendix 1*)

Measurement Condition	Mean Particle Size (um)	10%D	50%D	90%D
Condition-1*				(b) (4)
Condition-2*				

*Condition 1: Secondary particle size; Condition 2: Primary particle size

Dose and frequency of dosing:	0 (saline), 0 (vehicle), 420 mg (300 mg/mL, 1.4 mL/animal) *Note:* The dose volume of 1.4 mL was selected based on the "expected" maximal clinical dose of 400 mg Monthly (Every 4 weeks up to week 49)
Route of administration:	IM
Formulation/Vehicle:	OPC-14597 aqueous solution for injection Lot No. 13B74P300
Species/Strain:	Dog/Beagle
Number/Sex/Group:	3/M
Age:	6 months
Satellite groups/ unique design:	- No satellite groups - PK not assessed - Vehicle and saline control groups included - Administration alternately into the right and left hindlimbs (biceps femoris muscle) once every 4 weeks - Necropsy at the end of the 24- and 52-week of treatment and after the 26-week recovery period
Deviation from study protocol affecting interpretation of results:	None

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Observations and Results: changes from control

Parameters	Major findings
Mortality	No drug-related mortality. One animal died due to spontaneous acute heart failure unrelated to treatment during recovery period (Week 20)
Clinical Signs	No clinical signs associated with pain, and no significant injection site changes, except for erythema around the injection site (20 × 20 mm) transiently noted in one treated animal on the following day of the 8th administration (Day 198).
Body Weights	No statistically significant changes in body weight or body weight gain in treated group vs. controls, except for a transient lower body weight gain at Week 41
Hematology	No drug-related abnormalities
Clinical Chemistry	No increase in AST or Creatine Kinase suggesting muscular damage
Gross Pathology	White foci in the muscles of bilateral injection sites of all aripiprazole-treated animals, without changes in popliteal and medial iliac lymph nodes. At the end of the 26-week recovery period, the white foci still existed but were obviously smaller in size.
Histopathology (Local tissues examined only)	The white foci were characterized microscopically by localized granulomatous inflammation (accumulation of macrophages with vacuoles or foamy cytoplasm) around eosinophilic crystal-like deposits, interpreted as accumulated drug. Foreign body giant cells, lymphocytes, neutrophils, capillary proliferation and fibroblast proliferation were occasionally present within the areas of granulomatous inflammation. At the end of the 26-week recovery period, the severity of granulomatous inflammation was decreased and drug deposition at the injection site was reduced vs. that at the end of the dosing period. **Histopathological Findings - Summary** *(Source: Study Report No. 030649 p. 79)* See table below

Histopathological Findings - Summary
(Source: Study Report No. 030649 p. 79)

Stage		Week 24			Week 52			Recovery Week 26		
Dose		A0	B0	B300	A0	B0	B300	A0	B0	B300
No. of Animals		3	3	3	3	3	3	3	3	2
Injection site, right	Examined	3	3	3	3	3	3	3	3	2
Granulomatous inflammation	NAD	3	3	0	3	3	0	3	3	0
	±	0	0	0	0	0	0	0	0	2
	+	0	0	3	0	0	3	0	0	0
Injection site, left	Examined	3	3	3	3	3	3	3	3	2
Granulomatous inflammation	NAD	3	3	0	3	3	0	3	3	0
	±	0	0	0	0	0	0	0	0	2
	+	0	0	3	0	0	3	0	0	0

A0 : 0mg/mL (Saline) B0 : 0 mg/mL OPC-14597 B300 : 300 mg/mL OPC-14597
NAD: No abnormalities detected ±: Very slight +: Slight ++: Moderate +++: Severe

5.7. Genetic Toxicology

No genotoxicity studies were conducted as part of this application (referenced to NDA 202971).

5.8. Carcinogenicity

No carcinogenicity studies were conducted as part of this application (referenced to NDA 202971).

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5.9.   Reproductive and Developmental Toxicology

No reproductive and developmental toxicity studies were conducted as part of this application (referenced to NDA 202971).

5.10. Other Toxicology Studies

No other studies were performed for aripiprazole 2M RTU LAI.

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6. Clinical Pharmacology

6.1. Executive Summary

Aripiprazole 2M RTU is a new formulation of aripiprazole that does not require reconstitution and is intended for dosing every 2 months via IM injection in the gluteal muscle.

Aripiprazole 2M RTU has a higher aripiprazole concentration (300 mg/mL) compared to the listed drug (LD) Abilify Maintena (200 mg/mL after reconstitution). Abilify Maintena (NDA 202971, aripiprazole Q1M IM depot), also owned by Otsuka, is a lyophilized cake of aripiprazole monohydrate. It is reconstituted to an aqueous suspension prior to administration and is intended for once-monthly injection.

No clinical efficacy trial of aripiprazole 2M RTU has been conducted in the development program. The Applicant used an exposure-matching (PK-bridging) approach together with safety data to support their application. There is a total of three phase 1 clinical studies that have been included in this application:

- Study 031-201-00181: A pivotal open-label, multiple-dose, randomized, parallel-arm, multicenter trial designed to assess the safety, tolerability, and PK of multiple doses of either aripiprazole 2M RTU LAI 960 mg or aripiprazole 1M depot 400 mg over 8 months in adult subjects with schizophrenia or bipolar I disorder.

- Study 031-201-00104: A phase 1, open-label, single ascending dose, parallel-arm, multicenter trial designed to determine the safety, tolerability, and PK of a single dose of either 780 mg or 1200 mg of aripiprazole 2M RTU LAI (as 2.6 mL and 4 mL of 300 mg/mL of aripiprazole LAI RTU, respectively) injected into the gluteal muscle in adult subjects with schizophrenia.

- Study 031-201-00279: A phase 1, two-part, open-label, single- and multiple-dose, multicenter trial designed to assess the PK, safety, and tolerability of 420 mg aripiprazole 1M RTU LAI (1.4 mL of 300 mg/mL aripiprazole RTU LAI injected into the deltoid or gluteal muscle sites in adult subjects with schizophrenia or bipolar I disorder.

In addition, a population PK model was developed, and PK simulations have been performed to inform aripiprazole 2M RTU dosing for initiation, a lower dose (720 mg) for CYP2D6 poor metabolizers, drug-drug interactions, early or missed doses, and theoretical dose dumping.

The Office of Clinical Pharmacology (OCP) reviewed the studies submitted in this application and finds that 90% confidence interval (CI) of the geometric mean ratio of the PK parameters, area under the plasma-concentration time curve (AUC_{ss}) and minimum plasma concentration ($C_{min,ss}$) were within 80 to 125% and ≥80% limits, respectively, following administration of 960

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mg aripiprazole 2M RTU and 400 mg LD at steady state over the least common time interval (i.e., 56 days). In addition, aripiprazole $C_{max, ss}$ was comparable between the products.

OCP's major findings and recommendation are summarized as follows:

1. An adequate bridging of aripiprazole 2M RTU to the LD has been conducted through a relative bioavailability study.

2. Efficacy of aripiprazole 2M RTU can be extrapolated based on similar exposure to the LD after multiple dose administration.

3. When switching from oral antipsychotics to aripiprazole 2M RTU 960 mg, the first injection should be accompanied by 14 consecutive days of concurrent oral aripiprazole (10 mg to 20 mg) or current oral antipsychotic.

4. When switching patients from aripiprazole Q1M IM depot to aripiprazole 2M RTU 960 mg (once every 2 months injection), aripiprazole 2M RTU should be administered in place of the next scheduled injection of aripiprazole Q1M IM depot. Aripiprazole 2M RTU 960 mg should then be dosed once every 2 months (every 56 days). The first aripiprazole 2M injection may be administered in place of the second, or later injection of aripiprazole Q1M IM depot.

5. Based on modeling and simulation, for subjects who are known CYP2D6 poor metabolizers and patients taking concomitant CYP2D6 inhibitors, 3A4 inhibitors, and/or CYP3A4 inducers for longer than 14 days, dosage adjustment is recommended (see Table 2).

Table 2: Dose Adjustments of Aripiprazole 2M RTU in Patients Who Are Known CYP2D6 Poor Metabolizers and Patients Taking Concomitant CYP2D6 Inhibitors, CYP3A4 Inhibitors, and/or CYP3A4 Inducers for Longer than 14 days

Factors	Adjusted Dose
CYP2D6 Poor Metabolizers	
Known CYP2D6 Poor Metabolizers	720 mg
Known CYP2D6 Poor Metabolizers taking concomitant CYP3A4 inhibitors	Avoid use
Patients Taking 960 mg Aripiprazole 2M RTU	
Strong CYP2D6 <u>or</u> CYP3A4 inhibitors	720 mg
CYP2D6 <u>and</u> CYP3A4 inhibitors	Avoid use
CYP3A4 inducers	Avoid use

6. If a patient misses a dose and less than 14 weeks have elapsed since the last injection, administer the next dose of aripiprazole 2M RTU as soon as possible. If more than 14 weeks

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have elapsed since the last injection, re-start concomitant oral aripiprazole for 14 days with the next administered injection of aripiprazole 2M RTU.

6.2. Summary of Clinical Pharmacology Assessment

Clinical Pharmacokinetics

Aripiprazole 2M RTU is intended to deliver aripiprazole over a 2-month period. Pooled analysis from different studies suggest that approximately linear PK was demonstrated for aripiprazole in the dose range of 420 mg to 1200 mg after single-dose administration of aripiprazole 2M RTU to the gluteal muscle.

Absorption: After a single dose administration of aripiprazole 2M RTU, median time to reach maximal plasma concentration of aripiprazole (T_{max}) was about 25 to 41 days post dose. Aripiprazole steady state appears to be reached by the fourth dose of 960 mg aripiprazole 2M RTU administered every 56 days. Median T_{max} was about 28 days following the fourth dose administration.
Following the fourth dose administration of 960 mg aripiprazole 2M RTU every 56 days or the eighth dose administration of 400 mg aripiprazole Q1M IM depot every 28 days in patients with schizophrenia or bipolar I disorder:
- The mean peak plasma concentration (C_{max}) of aripiprazole was 342 ng/mL and 344 ng/mL, respectively.
- The mean area under concentration curve (AUC) of aripiprazole was 14700 day*ng/mL ($AUC_{0-56 \ days}$) and 7840 day*ng/mL ($AUC_{0-28 \ days}$), respectively.
- The mean minimal plasma concentration (C_{min}) of aripiprazole was 250 ng/mL ($C_{56 \ days}$) and 257 ng/mL ($C_{28 \ days}$), respectively.

Distribution: Aripiprazole is distributed throughout the body with an apparent volume of distribution of 4.9 L/kg. At therapeutic concentrations, aripiprazole and dehydro-aripiprazole are greater than 99% bound to serum proteins, binding primarily to albumin   (b) (4).

Elimination: Following single dose administration of aripiprazole 2M RTU, the terminal elimination half-life of aripiprazole was about 21 days.

Metabolism: Based on in vitro studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4 (from LD label). Aripiprazole is the predominant drug moiety in the systemic circulation. Following multiple dose administration of 960 mg aripiprazole 2M RTU, dehydro-aripiprazole, the active metabolite, represents approximately 31% of aripiprazole exposure in plasma.

Excretion: Following a single oral dose of [14C]-labeled aripiprazole, approximately 25% and 55% of the administered radioactivity was recovered in the urine and feces, respectively. Less

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than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the feces ▆▆▆▆▆ (b) (4)

General Dosing and Therapeutic Individualization

General Dosing: Aripiprazole 2M RTU 960 mg should then be dosed once every 2 months (every 56 days) as gluteal intramuscular injection by a healthcare professional.

- When switching from oral antipsychotics to aripiprazole 2M RTU 960 mg, the first injection should be accompanied by 14 consecutive days of concurrent oral aripiprazole (10 mg to 20 mg) or current oral antipsychotic.

- When switching patients from aripiprazole Q1M IM depot to aripiprazole 2M RTU 960 mg (once every 2 months injection), aripiprazole 2M RTU should be administered in place of the next scheduled injection of aripiprazole Q1M IM depot. Aripiprazole 2M RTU 960 mg should then be dosed once every 2 months (every 56 days). The first aripiprazole 2M RTU injection may be administered in place of the second, or later injection of aripiprazole Q1M IM depot.

Therapeutic Individualization: Based on modeling and simulation, dose adjustment is recommended for subjects who are known CYP2D6 poor metabolizers and patients taking concomitant CYP2D6 inhibitors, 3A4 inhibitors, and/or CYP3A4 inducers for longer than 14 days (see Table 2).

Outstanding Issues: None.

6.3. Comprehensive Clinical Pharmacology Review

Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant did not conduct a dedicated efficacy and safety study with aripiprazole 2M RTU to support this application. The supportive evidence of effectiveness comes from a pivotal study, 031-201-00181: a multiple dose PK study to bridge aripiprazole 2M RTU to the LD. The study provided a direct comparison of steady state exposures during a least common dosing interval between aripiprazole 2M RTU 960 mg and the LD (400 mg Q1M IM depot) in subjects with schizophrenia or bipolar I disorder.

The 90% confidence interval (CI) of the geometric mean ratio of the PK parameters, AUC_{ss} and $C_{min,ss}$ of aripiprazole were within 80 to 125% and ≥80% limits, respectively, following administration of 960 mg aripiprazole 2M RTU and 400 mg LD at steady state over the least common time interval (i.e., 56 days). In addition, aripiprazole $C_{max,ss}$ was also comparable.

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Appropriate bridging and similarity are considered established between the two products, which supports the effectiveness claim for aripiprazole 2M RTU.

Table 3: Statistical Analysis of Aripiprazole Pharmacokinetic Parameters Following the Fourth Administration of Aripiprazole 2M RTU 960 mg or the Seventh and Eighth Administration of Aripiprazole IM Depot 400 mg

	PK Parameter	GMR (T/R)	90% CI
Aripiprazole 2M 960 mg (T) Versus LD 400 mg (R)	AUC_{0-56}*	1.006	0.851 - 1.190
	C_{56}/C_{28}†	1.011	0.893 - 1.145
	C_{max}†	1.071	0.903 - 1.270

*AUC_{0-56} following the 4th dose of aripiprazole 2M RTU 960 mg administered every 56 days or the sum of AUC_{0-28} following the 7th and 8th administration of LD 400 mg administered every 28 days.

†Aripiprazole plasma concentrations following the fourth administration of *Aripiprazole 2M* 960 mg (C_{56}) or the eighth administration of the LD 400 mg (C_{28}).

‡ Aripiprazole 2M RTU 960 mg (n=34), LD 400 mg (n=32)

§ Aripiprazole 2M RTU 960 mg (n=96), LD 400 mg (n=82).

Source: Tables 11.5.2.4-1 of CSR

Is the proposed dosing regimen of aripiprazole 2M RTU appropriate for the general patient population for which the indication is being sought?

Yes. The Applicant proposes gluteal muscle injections of 960 mg of aripiprazole 2M RTU every 56 days for maintenance treatment of patients with schizophrenia or bipolar I disorder. This dosing regimen is acceptable for the following reasons:

- Comparison of steady state aripiprazole exposure of aripiprazole 2M RTU versus the LD: The LD is approved for the treatment of schizophrenia and bipolar I disorder in adults. Study 031-201-00181 was conducted to evaluate steady-state PK of aripiprazole 2M RTU versus the LD. It provided the PK bridging between aripiprazole 2M RTU and the LD. The comparison of steady-state aripiprazole exposure demonstrated that aripiprazole 2M RTU after the 4th injection was similar to the LD after the 7th and 8th injection. This suggests that the proposed dosing regimen for aripiprazole 2M RTU is appropriate.

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Table 4: Mean (SD) Aripiprazole Pharmacokinetic Parameters following Fourth Administration of Aripiprazole 2M RTU 960 mg or Seventh and Eighth Administration of Aripiprazole IM Depot 400 mg

PK Parameter	Aripiprazole 2M LAI 960 mg Fourth Dose	Aripiprazole IM Depot 400 mg Seventh Dose	Aripiprazole IM Depot 400 mg Eighth Dose
C_{max} (ng/mL)	342 (157)[b]	339 (168)[d]	344 (212)[f]
t_{max} (day)[a]	28.0 (0.930 - 49.0)[b]	6.97 (1.05 - 28.0)[d]	4.07 (0.00 - 28.0)[f]
AUC_{0-56} (ng·day/mL)	14700 (7460)[b]	ND	ND
AUC_{0-28} (ng·day/mL)	7190 (3470)[b]	7760 (4300)[d]	7840 (5170)[f]
AUC_{29-56} (ng·day/mL)	7500 (4200)[b]	ND	ND
PTF%	63.4 (25.1)[b]	ND	48.3 (19.0)[f]
C_{28} (ng/mL)	ND	255 (137)[e]	257 (162)[g]
C_{56} (ng/mL)	250 (128)[c]	ND	ND

[a]Median (min - max). [b]n = 34. [c]n = 96. [d]n = 33. [e]n = 88. [f]n = 32. [g]n = 82.
Source: Table 11.5.2.3.2.2-1 of CSR 031-201-00181

- Comparison of steady state exposure of 960 mg aripiprazole 2M RTU versus oral aripiprazole: The recommended daily dose range of oral aripiprazole is 10/15 mg/day to 30 mg/day for the treatment of schizophrenia and bipolar I disorder in adults. Among these doses, there was no evidence that the higher-dose groups offered any advantage over the lowest-dose group in terms of efficacy (aripiprazole label). The comparison of the steady state exposure of aripiprazole 2M RTU versus oral aripiprazole demonstrates that the range of exposures (C_{min} to C_{max}) achieved by aripiprazole 2M RTU 960 mg at steady state are bracketed by the exposure range of oral aripiprazole in the recommended dose range (see Figure 1). Additionally, both the products (aripiprazole 2M RTU and the oral aripiprazole) are from the same company, Otsuka.

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Figure 1: Mean (SD) Aripiprazole Plasma Concentration versus Time Profiles following Fourth Administration of Aripiprazole 2M RTU LAI 960 mg (Black; n = 102) or Seventh and Eighth Administration of Aripiprazole IM Depot 400 mg Red; n = 93)
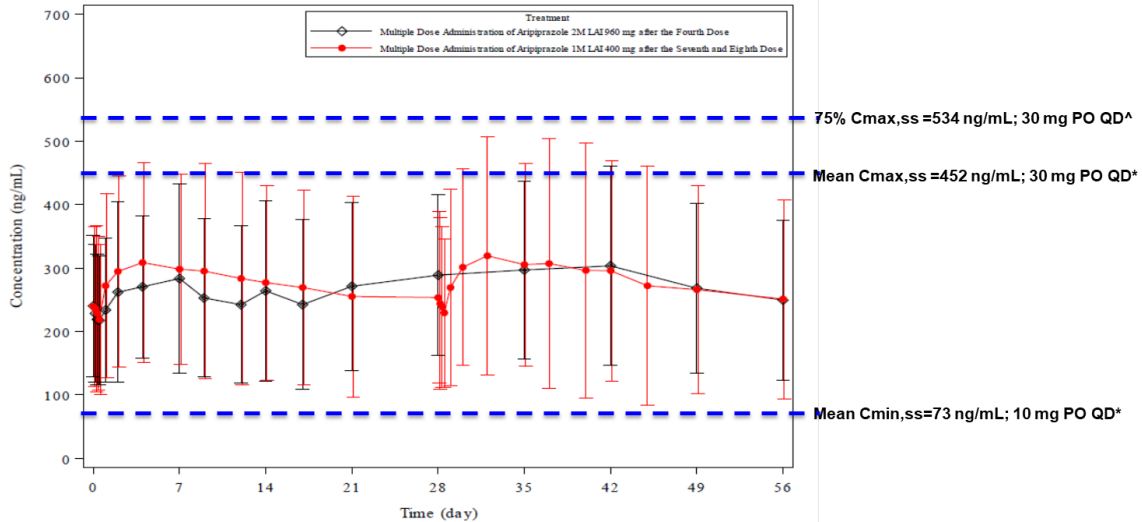
Note: Reference lines represent mean $C_{min,ss}$ following a daily dose of 10 mg oral aripiprazole (73 ng/mL), mean $C_{max,ss}$ at 30 mg daily oral aripiprazole (452 ng/mL), 75th percentile of $C_{max,ss}$ following a daily dose of 30 mg oral aripiprazole (534 ng/mL).
Source: * NDA21436 oral aripiprazole OCP review archived on August 06, 2002
^ Figure 4.1-1, 31-21-202 study report
Figure 11.5.2.3.1.2.1-2, 031-201-00181 study report

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

<u>CYP2D6 Poor Metabolizer</u>
The LD label recommends dose reductions for patients who are known CYP2D6 poor metabolizers. The Applicant has utilized PK simulations to assess the effect of the CYP2D6 poor metabolizer status. Based on the PK simulations, the Applicant recommends the low dose of 720 mg aripiprazole 2M RTU. The figure below represents the simulated steady-state PK profiles of aripiprazole following administration of the proposed 720 mg aripiprazole 2M RTU and 300 mg aripiprazole Q1M IM depot in CYP2D6 poor metabolizers.

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Figure 2: Simulated Median Steady-State Aripiprazole Plasma Concentration Time Profile following Administration of 300 mg Q4W Aripiprazole IM Depot or 720 mg Q8W Aripiprazole RTU LAI in CYP2D6 Poor Metabolizers
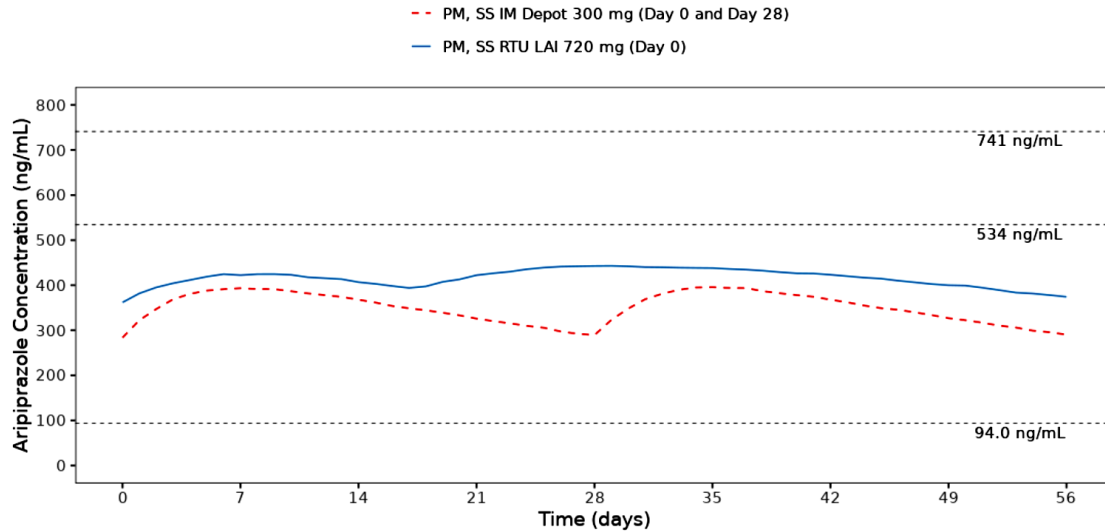
Group	Parameter	Mean	SD	5th	25th	Median	75th	95th
PM, SS IM Depot 300 mg (Day 0 and Day 28)	C56 (ng/mL)	310	143	126	211	290	387	563
PM, SS IM Depot 300 mg (Day 0 and Day 28)	Cavg (ng/mL)	378	148	182	275	346	453	637
PM, SS IM Depot 300 mg (Day 0 and Day 28)	Cmax (ng/mL)	425	158	217	317	396	510	689
PM, SS IM Depot 300 mg (Day 0 and Day 28)	AUC0-56 (ng·day/mL)	21194	8289	10195	15420	19395	25369	35659
PM, SS RTU LAI 720 mg (Day 0)	C56 (ng/mL)	393	159	163	282	374	479	696
PM, SS RTU LAI 720 mg (Day 0)	Cavg (ng/mL)	443	158	231	330	420	534	742
PM, SS RTU LAI 720 mg (Day 0)	Cmax (ng/mL)	508	205	256	375	467	600	827
PM, SS RTU LAI 720 mg (Day 0)	AUC0-56 (ng·day/mL)	24818	8871	12928	18459	23523	29925	41542

Reference lines represent median Cmin,ss following a daily dose of 10 mg oral aripiprazole (94.0 mg/mL), 75th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (534 mg/mL), and 95th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (741 mg/mL). This scenario does not include any drug interactions.
Source: CSR 31-21-202 Figure 4.2-1.

Overall, the Applicant's dose adjustment strategy for aripiprazole 2M RTU in subjects with CYP2D6 poor metabolizer status is similar to that for the LD. The PK simulations support the Applicant's proposal to administer the low dose level, 720 mg aripiprazole 2M RTU in subjects with CYP2D6 poor metabolizer status.

Are there clinically-relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Aripiprazole 2M RTU is a long-acting IM injection and is not expected to have any effect on drug release or drug PK based on food.

For aripiprazole 2M RTU LAI, no drug-drug interactions studies were conducted. Simulations based on the results of the population PK (PPK) analyses of aripiprazole 2M RTU LAI were performed to assess dose adjustment strategies for various drug-drug interaction scenarios.

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CYP2D6 inhibitors

The Applicant conducted PK simulations using the PPK model for aripiprazole 2M RTU LAI to assess the effect of concomitant use of CYP2D6 inhibitors or 3A4 inhibitors. The figure below shows the simulated PK profile when transitioning from SS oral 10 mg aripiprazole to aripiprazole 2M RTU LAI 960 mg with no concomitant medications, aripiprazole 2M RTU LAI 720 mg with a CYP3A4 inhibitor, or aripiprazole 2M RTU LAI 720 mg with a CYP2D6 inhibitor.

Figure 3: Simulated Median Aripiprazole Concentration Time Profile following Administration of 960 mg Aripiprazole RTU LAI (Day 0) in Subjects without CYP3A4 or CYP2D6 Strong Inhibitors or 720 mg Aripiprazole RTU LAI (Day 0) in Subjects with CYP3A4 or CYP2D6 Strong Inhibitors with 14 Days of 10 mg Oral Aripiprazole (Day 0 to Day 13) in Subjects Already Stabilized on 10 mg Oral Aripiprazole
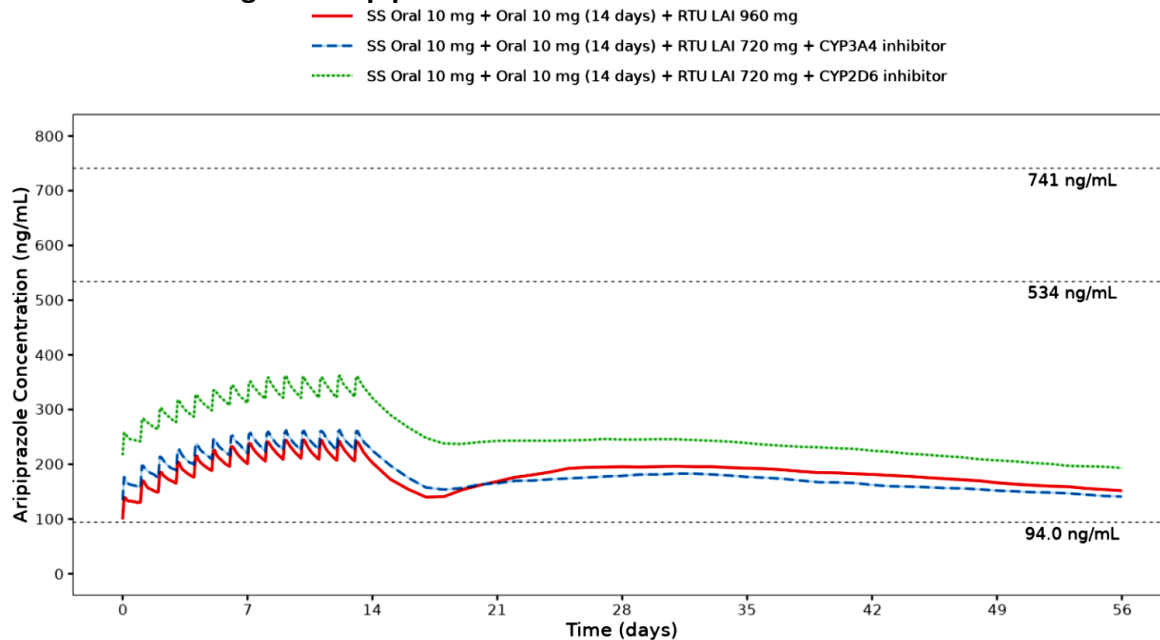
Group	Parameter	Mean	SD	5th	25th	Median	75th	95th
SS Oral 10 mg + Oral 10 mg (14 days) + RTU LAI 960 mg	C56 (ng/mL)	162	78.0	62.2	111	152	199	300
SS Oral 10 mg + Oral 10 mg (14 days) + RTU LAI 960 mg	Cmax (ng/mL)	322	227	127	201	273	377	627
SS Oral 10 mg + Oral 10 mg (14 days) + RTU LAI 960 mg	AUC0-56 (ng·day/mL)	11432	5130	4968	7868	10479	13948	20089
SS Oral 10 mg + Oral 10 mg (14 days) + RTU LAI 720 mg + CYP3A4 inhibitor	C56 (ng/mL)	152	71.7	63.0	101	141	184	284
SS Oral 10 mg + Oral 10 mg (14 days) + RTU LAI 720 mg + CYP3A4 inhibitor	Cmax (ng/mL)	321	192	140	211	284	374	598
SS Oral 10 mg + Oral 10 mg (14 days) + RTU LAI 720 mg + CYP3A4 inhibitor	AUC0-56 (ng·day/mL)	11238	4981	4866	7814	10343	13489	19843
SS Oral 10 mg + Oral 10 mg (14 days) + RTU LAI 720 mg + CYP2D6 inhibitor	C56 (ng/mL)	213	100	88.5	144	193	259	397
SS Oral 10 mg + Oral 10 mg (14 days) + RTU LAI 720 mg + CYP2D6 inhibitor	Cmax (ng/mL)	423	223	197	288	377	503	761
SS Oral 10 mg + Oral 10 mg (14 days) + RTU LAI 720 mg + CYP2D6 inhibitor	AUC0-56 (ng·day/mL)	15731	7041	6780	10912	14439	19316	27558

Reference lines represent median Cmin,ss following a daily dose of 10 mg oral aripiprazole (94.0 mg/mL), 75th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (534 mg/mL), and 95th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (741 mg/mL).
Source: CSR 31-21-202 Figure 8.2.2-1.

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The figure below shows the simulated PK profile at steady-state for aripiprazole 2M RTU LAI 960 mg with no concomitant medications, aripiprazole 2M RTU LAI 720 mg with a CYP3A4 inhibitor, and aripiprazole 2M RTU LAI 720 mg q2m with a CYP2D6 inhibitor.

Figure 4: Simulated Median Steady-State Aripiprazole Concentration Time Profile following Administration of 960 mg Q8W Aripiprazole RTU LAI in Subjects without CYP3A4 or CYP2D6 Strong Inhibitors or 720 mg Q8W Aripiprazole RTU LAI in Subjects with CYP3A4 or CYP2D6 Strong Inhibitors
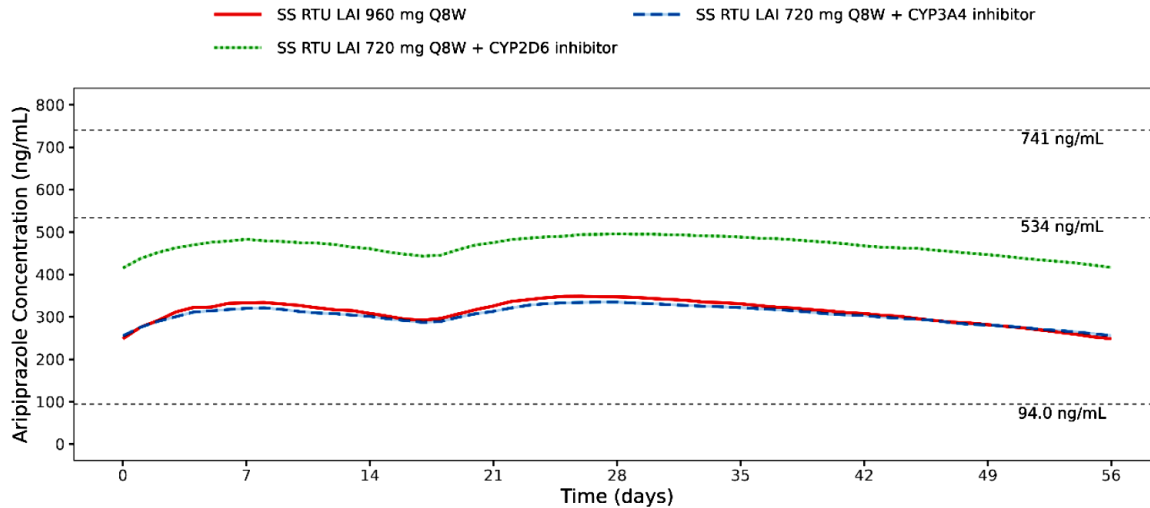
Group	Parameter	Mean	SD	5th	25th	Median	75th	95th
SS RTU LAI 960 mg Q8W	C56 (ng/mL)	278	153	76.7	173	249	357	542
SS RTU LAI 960 mg Q8W	Cmax (ng/mL)	430	210	202	306	386	517	700
SS RTU LAI 960 mg Q8W	AUC0-56 (ng·day/mL)	19259	8302	8804	13559	17158	23475	33091
SS RTU LAI 720 mg Q8W + CYP3A4 inhibitor	C56 (ng/mL)	283	147	89.7	185	256	364	534
SS RTU LAI 720 mg Q8W + CYP3A4 inhibitor	Cmax (ng/mL)	401	183	192	287	361	487	655
SS RTU LAI 720 mg Q8W + CYP3A4 inhibitor	AUC0-56 (ng·day/mL)	18795	8001	8654	13328	16842	23071	31960
SS RTU LAI 720 mg Q8W + CYP2D6 inhibitor	C56 (ng/mL)	457	217	171	311	417	585	820
SS RTU LAI 720 mg Q8W + CYP2D6 inhibitor	Cmax (ng/mL)	577	245	287	415	522	686	958
SS RTU LAI 720 mg Q8W + CYP2D6 inhibitor	AUC0-56 (ng·day/mL)	28684	11934	13503	20621	25855	35124	48320

Reference lines represent median Cmin,ss following a daily dose of 10 mg oral aripiprazole (94.0 mg/mL), 75th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (534 mg/mL), and 95th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (741 mg/mL).
Source: CSR 31-21-202 Figure 8.2.2-2.

The proposal to administer 720 mg aripiprazole 2M RTU when used concomitantly with CYP2D6 inhibitors is supported by the PK simulations and is acceptable to OCP.

CYP3A4 inhibitors
The two figures in the "CYP2D6 inhibitors" section also include the simulated PK profile for the proposed 720-mg dose level for aripiprazole 2M TRU LAI when used concomitantly with CYP2D6 inhibitors. The Applicant's proposal to administer 720 mg aripiprazole 2M RTU when used concomitantly with CYP3A4 inhibitors is supported by the PK simulations and is acceptable to OCP.

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Dual inhibitors

The Applicant did not conduct simulations for a scenario of aripiprazole 2M TRU LAI used concomitantly with both 2D6 inhibitors and 3A4 inhibitors. The Applicant proposes that aripiprazole 2M RTU LAI use is not recommended for subjects taking long-term concomitant administration of both CYP3A4 and CYP2D6 inhibitors. This is acceptable to OCP.

CYP3A4 inducers

The Applicant did not conduct simulations for aripiprazole 2M TRU LAI used concomitantly with CYP3A4 inducers. Similar to the aripiprazole IM depot product label, the Applicant proposes that use of aripiprazole 2M TRU LAI with concomitant CYP3A4 inducers is not recommended. This is acceptable to OCP.

What are the PK properties of aripiprazole 2M RTU?

Results from studies 031-201-00104 and 031-201-00279 were compiled and mean aripiprazole PK parameters following a single dose administration of aripiprazole 2M RTU to the gluteal muscle is summarized in Table 5.

After administration of a single dose of aripiprazole 2M RTU, median aripiprazole Tmax was about 25 to 41 days post-dose. Two different peak levels were observed. This could be possibly due to primary and secondary particles in the formulation. Refer to the CMC review for additional information. Terminal elimination half-life ($T_{1/2}$) of aripiprazole was about 20 to 22 days across the evaluated three dose levels. Less than dose proportional increase in C_{max} and approximately dose-proportional increase in AUC were observed over the range of 420 mg to 1200 mg. PK linearity following multiple dose administration cannot be evaluated because the multiple-dose study at the intended dosing interval of every 56 days was only conducted at one dose level (960 mg) of aripiprazole 2M RTU.

Table 5: PK Linearity Assessment after a Single-Dose Administration of Aripiprazole 2M RTU to Subjects with Schizophrenia or Bipolar I Disorder in the Gluteal Muscle

Parameters	Aripiprazole 2M RTU			Ratios using 420 mg as reference		
Dose (mg)	420	780	1200	1	1.9	2.9
Tmax (day)	39.1	25.1	41	-	-	-
C_{max} (ng/mL)	196	271	391	1	1.4	2.0
AUC_{inf} (ng/mL)	8400	13400	24700	1	1.6	2.9
AUC_t (ng/mL)	7820	12600	23800	1	1.6	3.0

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$C_{56\ day}$ (ng/mL)	79.5	123	261	1	1.5	3.3
$C_{28\ day}$ (ng/mL)	86.8	176	276	1	2.0	3.2
$T_{1/2}$ (day)	21.4	22	20	1	1.0	0.9

Data is presented as arithmetic mean expected T_{max} as median
Source: Table 11.5.2.3.3-1CSR 031-201-00104; Table 11.4.2.4.1.1-1 CSR 031-201-00279.

Following of multiple dose administration of aripiprazole 2M RTU 960 mg every 56 days, dehydro-aripiprazole, the active metabolite, represents approximately 31% of aripiprazole exposure in plasma, similar to that observed with aripiprazole Q1M IM depot injection.

Table 6: Dehydro-Aripiprazole Exposure (Mean) following the Fourth Dose Administration of Aripiprazole 2M RTU 960 mg or the Eighth Administration of Aripiprazole IM Depot 400 mg

Moiety/Ratio	PK Parameter	Aripiprazole 2M RTU 960 mg	Aripiprazole IM Depot 400 mg
Aripiprazole	C_{max} (ng/mL)	342	344
	AUC_{tau}* (day*ng/mL)	14700	7840
Dehydro-aripiprazole	C_{max} (ng/mL)	105	105
	AUC_{tau}* (day*ng/mL)	4590	2440
Ratio (Dehydro-aripiprazole /aripiprazole)	C_{max}	0.307	0.305
	AUC_{tau}*	0.312	0.311

*AUC_{tau}: $AUC_{0-56\ days,ss}$ for aripiprazole 2M RTU 960 mg; $AUC_{0-28\ days,ss}$ for aripiprazole Q1M IM depot 400 mg.
Source: Tables 11.5.2.3.2.2-1 and 11.5.2.3.2.2-2 CSR 031-201-00181.

What is the optimal strategy for switching subjects from oral Aripiprazole or other antipsychotics to aripiprazole 2M RTU LAI?

When switching from oral antipsychotics to Aripiprazole 2M RTU 960 mg, the first injection should be accompanied by 14 consecutive days of concurrent oral aripiprazole (10 mg to 20 mg) or current oral antipsychotic. The recommendation is based on the simulations shown below. These simulations showed that administration of aripiprazole 2M RTU 960 mg together with 14 days of 10 mg or 20 mg oral aripiprazole to subjects receiving oral antipsychotics other than aripiprazole, results in median aripiprazole concentrations within the exposure ranges achieved from approved oral aripiprazole doses (10 to 30 mg) by Day 3. It is comparable to aripiprazole IM depot 400 mg together with 14 days of concomitant 10 mg or 20 mg oral aripiprazole. Furthermore, regardless of what oral aripiprazole dose is administered following the first IM depot administration, median aripiprazole concentrations are predicted to remain above the lower end of the exposure ranges achieved from approved oral aripiprazole doses for the entire dosing interval.

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Figure 5: Simulated Median Aripiprazole Concentration-time Profile following Administration of 400 mg Aripiprazole IM Depot (Day 0 and Day 28) or 960 mg Aripiprazole 2M RTU LAI (Day 0) with 14 days 10 mg Oral Aripiprazole (Day 0 to Day 13) in Subjects without Prior Oral Aripiprazole Stabilization
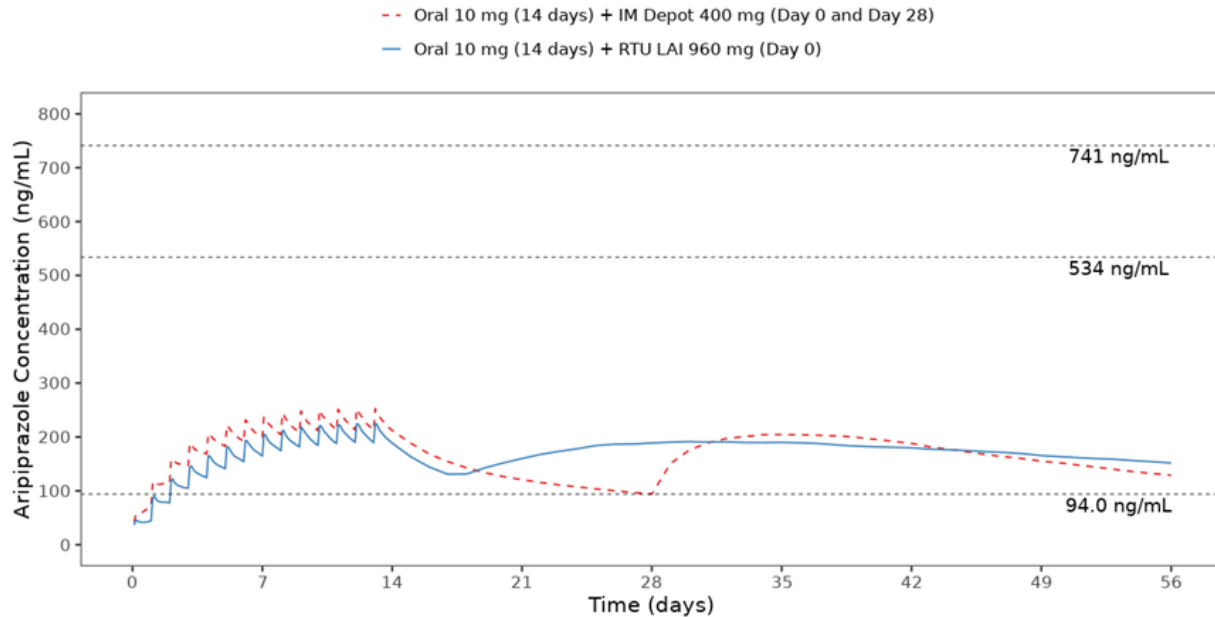
Group	Parameter	Mean	SD	5th	25th	Median	75th	95th
Oral 10 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	C56 (ng/mL)	147	80.1	62.0	90.0	129	182	283
Oral 10 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	Cmax (ng/mL)	283	123	133	198	261	343	493
Oral 10 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	AUC0-56 (ng·day/mL)	10467	5073	4476	6948	9609	12904	19074
Oral 10 mg (14 days) + RTU LAI 960 mg (Day 0)	C56 (ng/mL)	161	77.6	62.5	110	152	199	300
Oral 10 mg (14 days) + RTU LAI 960 mg (Day 0)	Cmax (ng/mL)	303	226	119	179	252	355	614
Oral 10 mg (14 days) + RTU LAI 960 mg (Day 0)	AUC0-56 (ng·day/mL)	10689	4915	4587	7290	9770	13092	19329

Note: Reference lines represent median Cmin,ss following a daily dose of 10 mg oral aripiprazole (94.0 mg/mL), 75th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (534 mg/mL), and 95th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (741 mg/mL).
Source: CSR 31-21-202 Figure 4.1-1.

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Figure 6: Simulated Median Aripiprazole Concentration-time Profile following Administration of 400 mg Aripiprazole IM Depot (Day 0 and Day 28) or 960 mg Aripiprazole 2M RTU LAI (Day 0) with 14 days <u>20 mg</u> Oral Aripiprazole (Day 0 to Day 13) in Subjects without Prior Oral Aripiprazole Stabilization
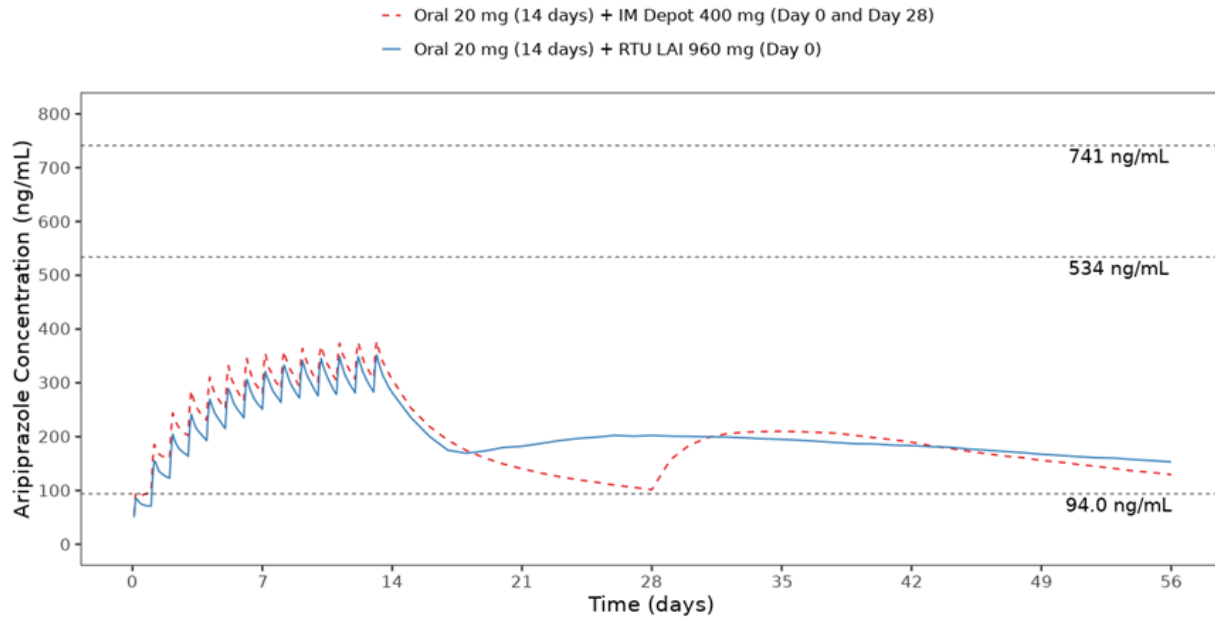
Group	Parameter	Mean	SD	5th	25th	Median	75th	95th
Oral 20 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	C56 (ng/mL)	148	82.1	62.1	90.2	129	183	285
Oral 20 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	Cmax (ng/mL)	412	157	208	301	386	501	673
Oral 20 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	AUC0-56 (ng·day/mL)	12245	5730	5401	8328	11240	15071	22143
Oral 20 mg (14 days) + RTU LAI 960 mg (Day 0)	C56 (ng/mL)	162	78.3	62.7	111	153	199	302
Oral 20 mg (14 days) + RTU LAI 960 mg (Day 0)	Cmax (ng/mL)	417	238	191	287	367	484	748
Oral 20 mg (14 days) + RTU LAI 960 mg (Day 0)	AUC0-56 (ng·day/mL)	12467	5363	5617	8875	11465	15089	21668

Note: Reference lines represent median Cmin,ss following a daily dose of 10 mg oral aripiprazole (94.0 mg/mL), 75th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (534 mg/mL), and 95th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (741 mg/mL).
Source: CSR 31-21-202 Figure 4.1-2.

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Figure 7: Simulated Median Aripiprazole Concentration-time Profile following Administration of 400 mg Aripiprazole IM Depot (Day 0 and Day 28) or 960 mg Aripiprazole 2M RTU LAI (Day 0) with 14 Days of 10 mg Oral Aripiprazole (Day 0 to Day 13) in Subjects Stabilized on 20 mg Oral Aripiprazole
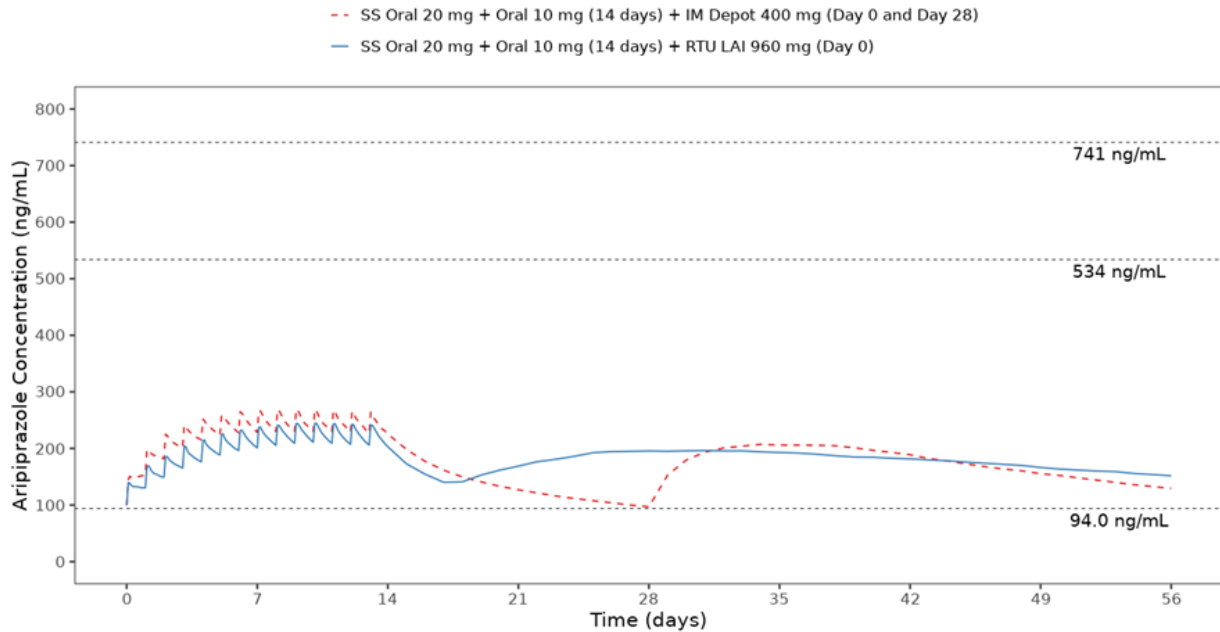
Group	Parameter	Mean	SD	5th	25th	Median	75th	95th
SS Oral 20 mg + Oral 10 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	C56 (ng/mL)	148	82.0	62.1	90.1	129	182	284
SS Oral 20 mg + Oral 10 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	Cmax (ng/mL)	304	138	141	208	277	375	532
SS Oral 20 mg + Oral 10 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	AUC0-56 (ng·day/mL)	11246	5712	4640	7390	10148	13823	21213
SS Oral 20 mg + Oral 10 mg (14 days) + RTU LAI 960 mg (Day 0)	C56 (ng/mL)	162	78.0	62.2	111	152	199	300
SS Oral 20 mg + Oral 10 mg (14 days) + RTU LAI 960 mg (Day 0)	Cmax (ng/mL)	322	227	127	201	273	377	627
SS Oral 20 mg + Oral 10 mg (14 days) + RTU LAI 960 mg (Day 0)	AUC0-56 (ng·day/mL)	11432	5130	4968	7868	10479	13948	20089

Note: Reference lines represent median Cmin,ss following a daily dose of 10 mg oral aripiprazole (94.0 mg/mL), 75th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (534 mg/mL), and 95th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (741 mg/mL).
Source: CSR 31-21-202 Figure 4.1-3.

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Figure 8: Simulated Median Aripiprazole Concentration-time Profile following Administration of 400 mg Aripiprazole IM Depot (Day 0 and Day 28) or 960 mg Aripiprazole 2M RTU LAI (Day 0) with 14 Days of 30 mg Oral Aripiprazole (Day 0 to Day 13) in Subjects Stabilized on 30 mg Oral Aripiprazole
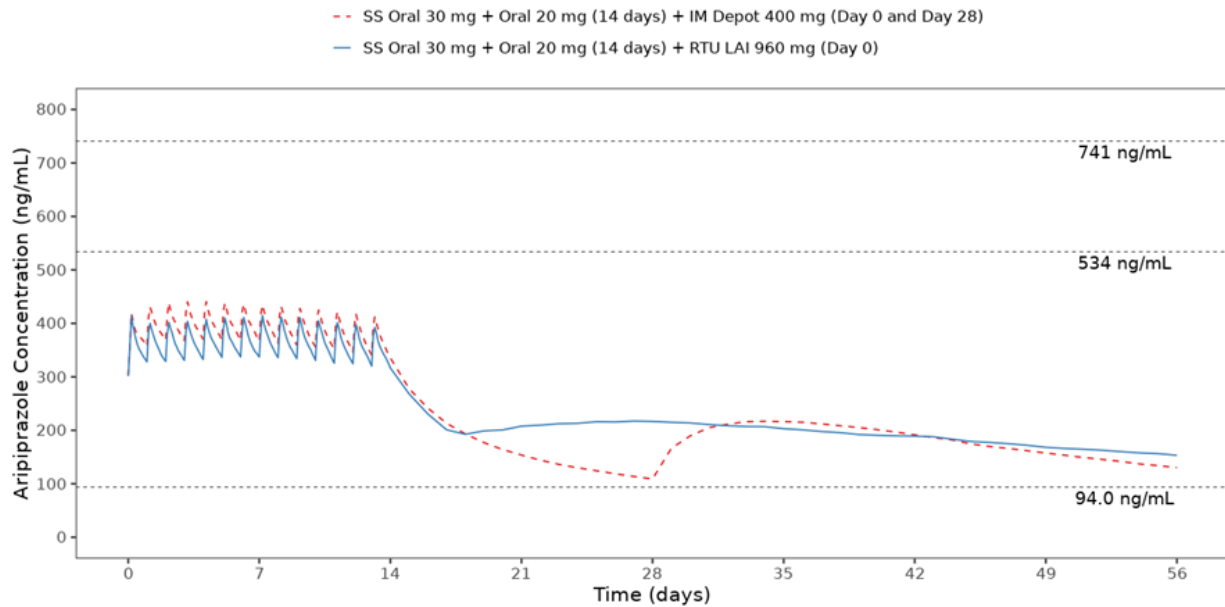
Group	Parameter	Mean	SD	5th	25th	Median	75th	95th
SS Oral 30 mg + Oral 20 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	C56 (ng/mL)	151	88.3	62.2	90.4	130	184	291
SS Oral 30 mg + Oral 20 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	Cmax (ng/mL)	500	208	240	360	458	606	861
SS Oral 30 mg + Oral 20 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	AUC0-56 (ng·day/mL)	14723	7909	5897	9492	13199	17855	28214
SS Oral 30 mg + Oral 20 mg (14 days) + RTU LAI 960 mg (Day 0)	C56 (ng/mL)	164	79.9	63.3	112	153	205	302
SS Oral 30 mg + Oral 20 mg (14 days) + RTU LAI 960 mg (Day 0)	Cmax (ng/mL)	519	261	243	365	459	628	881
SS Oral 30 mg + Oral 20 mg (14 days) + RTU LAI 960 mg (Day 0)	AUC0-56 (ng·day/mL)	14838	6634	6572	10267	13584	18056	25918

Note: Reference lines represent median Cmin,ss following a daily dose of 10 mg oral aripiprazole (94.0 mg/mL), 75th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (534 mg/mL), and 95th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (741 mg/mL).
Source: CSR 31-21-202 Figure 8.2.1-1.

What is the optimal strategy for switching subjects from the LD to aripiprazole 2M RTU?

When switching patients from aripiprazole Q1M IM depot (once per month injection) to aripiprazole 2M RTU 960 mg (once every 2 months injection), aripiprazole 2M RTU should be administered in place of the next scheduled injection of Abilify Maintena. Aripiprazole 2M RTU 960 mg should then be dosed once every 2 months (every 56 days). The first Aripiprazole 2M RTU injection may be administered in place of the second, or later injection of Aripiprazole Q1M IM depot. The recommendation is based on the following simulation, which shows that when 960 mg aripiprazole 2M RTU LAI is administered in place of the next scheduled dose to subjects stabilized on 400 mg aripiprazole IM depot, median aripiprazole plasma concentrations remain above the lower end of the exposure ranges achieved from approved oral aripiprazole doses (10 to 30 mg) throughout the dosing interval, without the need for 14 days of concurrent oral aripiprazole.

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Figure 9: Simulated Median Aripiprazole Concentration-time Profile following Administration of 400 mg Aripiprazole IM Depot (Day 0 and Day 28) or 960 mg Aripiprazole 2M RTU LAI (Day 0) in Subjects already Stabilized on 400 mg Aripiprazole IM Depot
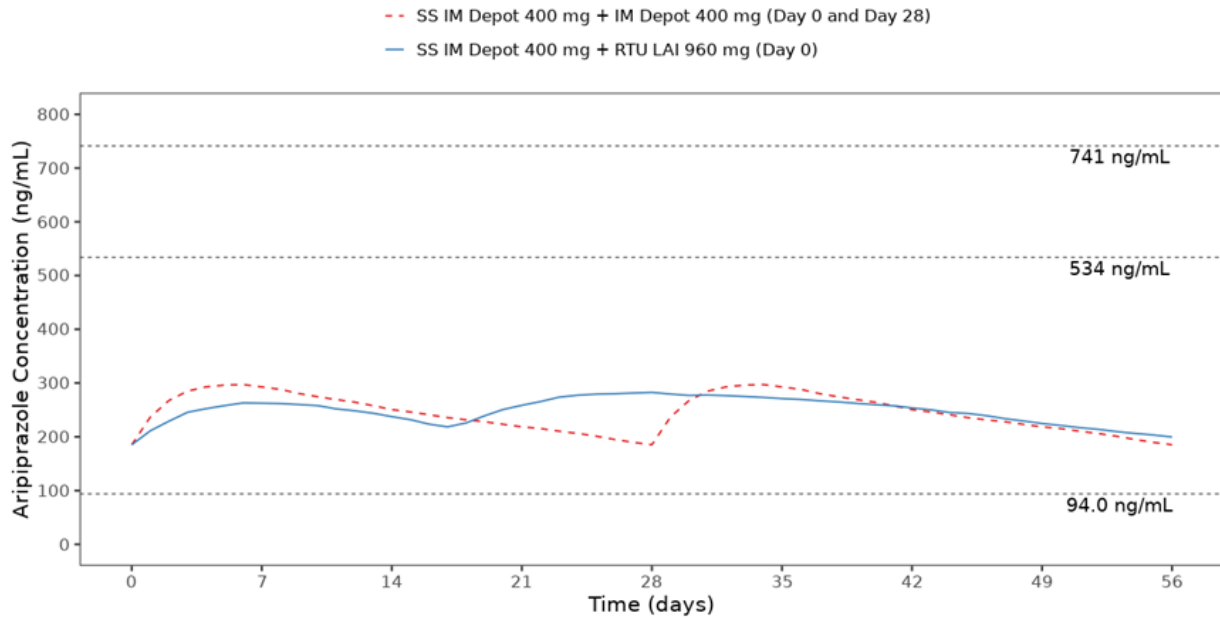
Group	Parameter	Mean	SD	5th	25th	Median	75th	95th
SS IM Depot 400 mg + IM Depot 400 mg (Day 0 and Day 28)	C56 (ng/mL)	206	108	74.8	132	185	259	408
SS IM Depot 400 mg + IM Depot 400 mg (Day 0 and Day 28)	Cmax (ng/mL)	322	136	155	231	299	390	556
SS IM Depot 400 mg + IM Depot 400 mg (Day 0 and Day 28)	AUC0-56 (ng·day/mL)	15198	6713	6891	10611	13428	18917	26359
SS IM Depot 400 mg + RTU LAI 960 mg (Day 0)	C56 (ng/mL)	220	105	89.5	147	200	277	411
SS IM Depot 400 mg + RTU LAI 960 mg (Day 0)	Cmax (ng/mL)	370	218	154	248	321	441	703
SS IM Depot 400 mg + RTU LAI 960 mg (Day 0)	AUC0-56 (ng·day/mL)	15419	6721	6875	10617	13909	18810	27781

Note: Reference lines represent median Cmin,ss following a daily dose of 10 mg oral aripiprazole (94.0 mg/mL), 75th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (534 mg/mL), and 95th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (741 mg/mL).
Source: CSR 31-21-202 Figure 4.1-5.

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Can aripiprazole 2M RTU be administered sooner or later than the scheduled dosing interval?
Following the initial injection of aripiprazole 2M RTU 960 mg, the dosing interval is once every
2 months (56 days after the previous injection). Patients may be given the aripiprazole 2M RTU
injection up to 2 weeks before the scheduled timepoint. This claim is supported by the
simulations presented in the figure below.

**Figure 10: Simulated Median Aripiprazole Concentration-time Profile following Administration of
960 mg Aripiprazole 2M RTU LAI as Scheduled (Day 0 and Day 56) or 14 Days Early (Day 0 and Day
42) in Subjects already Stabilized on 960 mg Aripiprazole 2M RTU LAI**
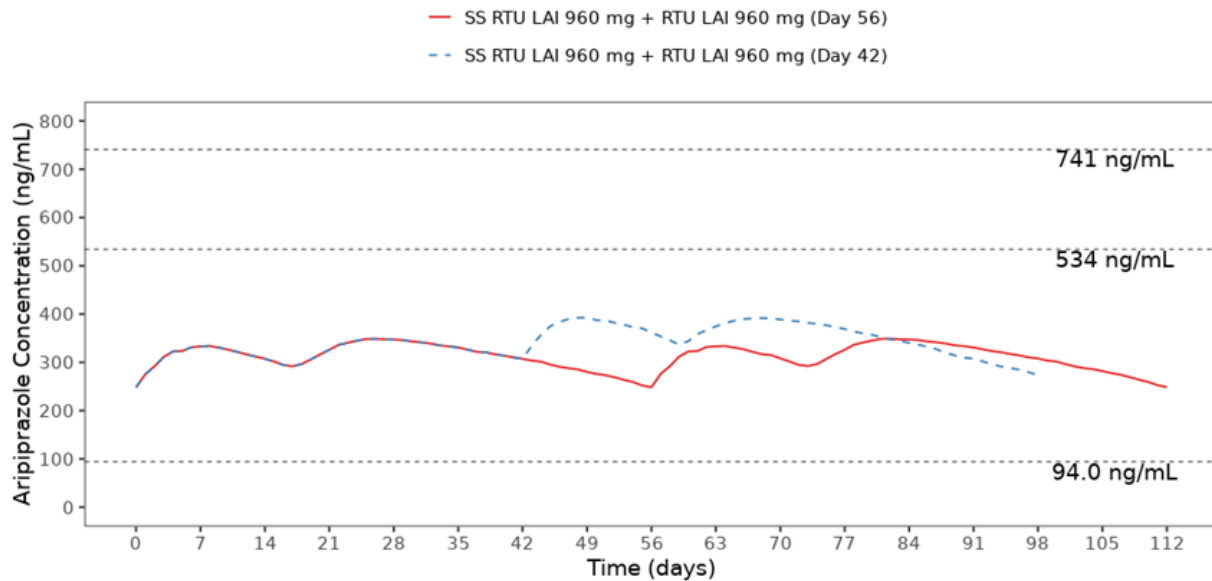
Group	Parameter	Mean	SD	5th	25th	Median	75th	95th
SS RTU LAI 960 mg + RTU LAI 960 mg (Day 56)	C112 (ng/mL)	278	153	76.7	173	249	357	542
SS RTU LAI 960 mg + RTU LAI 960 mg (Day 56)	Cmax (ng/mL)	430	210	202	306	386	517	700
SS RTU LAI 960 mg + RTU LAI 960 mg (Day 42)	C98 (ng/mL)	304	167	81.9	189	273	391	589
SS RTU LAI 960 mg + RTU LAI 960 mg (Day 42)	Cmax (ng/mL)	481	226	230	345	433	583	794

Note: Reference lines represent median Cmin,ss following a daily dose of 10 mg oral aripiprazole (94.0 mg/mL),
75th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (534 mg/mL), and 95th percentile of
Cmax,ss following a daily dose of 30 mg oral aripiprazole (741 mg/mL). Steady-state assumes Q8W dosing for
aripiprazole 2M RTU LAI.
Source: CSR 31-21-202 Figure 8.2.4-2.

If less than 14 weeks have elapsed since the last injection, administer the next dose of
aripiprazole 2M RTU as soon as possible. The once every 2 month schedule should be resumed.
If more than 14 weeks have elapsed since the last injection, restart concomitant oral
aripiprazole for 14 days with the next administered injection of aripiprazole 2M RTU. The
recommendation is based on the following simulation results.

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Figure 11: Simulated Median Aripiprazole Concentration-time Profile following Administration of 960 mg Aripiprazole 2M RTU LAI as Scheduled (Day 0 and Day 56) or Delayed by 2 Weeks (Day 0 and Day 70), 4 Weeks (Day 0 and Day 84), 6 Weeks (Day 0 and Day 98), or 8 Weeks (Day 0 and Day 112) with 14 Days of 10 mg Oral Aripiprazole (Day 112 to Day 125), in Subjects already Stabilized on 960 mg Aripiprazole 2M RTU LAI
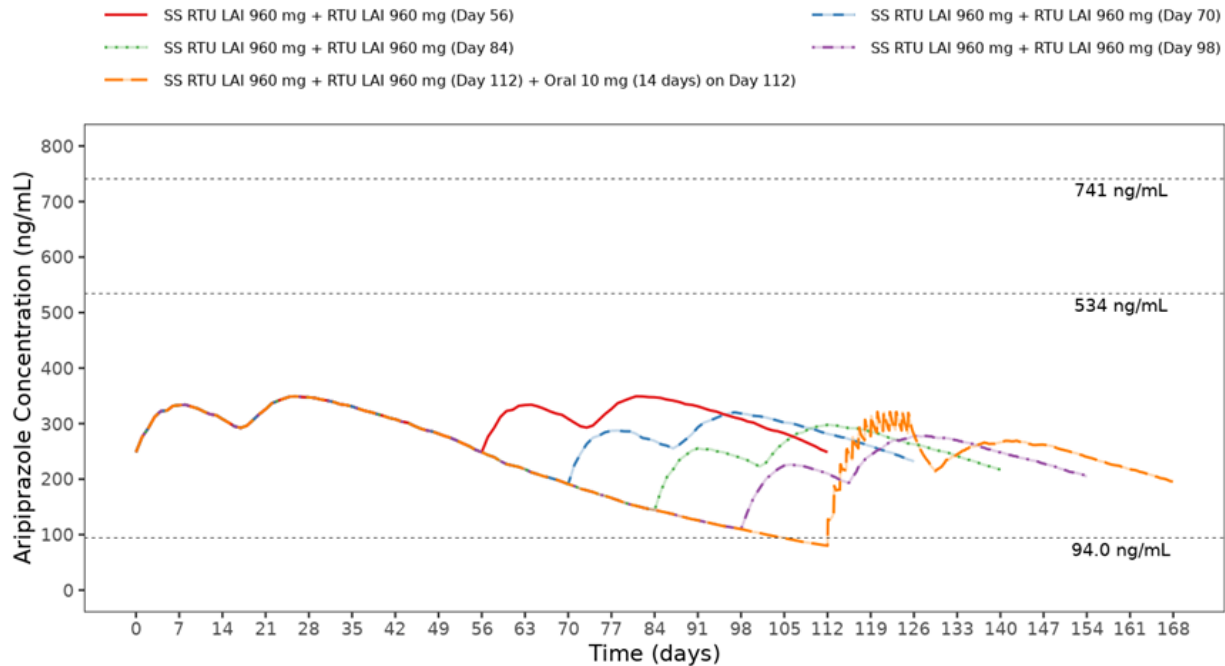
Group	Parameter	Mean	SD	5th	25th	Median	75th	95th
SS RTU LAI 960 mg + RTU LAI 960 mg (Day 56)	C56 (ng/mL)	278	153	76.7	173	249	357	542
SS RTU LAI 960 mg + RTU LAI 960 mg (Day 70)	C70 (ng/mL)	223	147	39.7	117	191	295	486
SS RTU LAI 960 mg + RTU LAI 960 mg (Day 84)	C84 (ng/mL)	179	139	17.3	74.0	144	250	443
SS RTU LAI 960 mg + RTU LAI 960 mg (Day 98)	C98 (ng/mL)	145	130	8.18	45.8	110	208	396
SS RTU LAI 960 mg + RTU LAI 960 mg (Day 112) + Oral 10 mg (14 days) on Day 112	C112 (ng/mL)	118	120	3.57	30.7	80.1	174	351
SS RTU LAI 960 mg + RTU LAI 960 mg (Day 56)	C112 (ng/mL)	278	154	76.7	173	249	359	547
SS RTU LAI 960 mg + RTU LAI 960 mg (Day 70)	C126 (ng/mL)	258	142	74.1	160	231	337	508
SS RTU LAI 960 mg + RTU LAI 960 mg (Day 84)	C140 (ng/mL)	242	132	72.8	153	217	311	469
SS RTU LAI 960 mg + RTU LAI 960 mg (Day 98)	C154 (ng/mL)	229	123	72.3	147	205	293	439
SS RTU LAI 960 mg + RTU LAI 960 mg (Day 112) + Oral 10 mg (14 days) on Day 112	C168 (ng/mL)	220	117	71.8	142	196	275	422

Note: Reference lines represent median Cmin,ss following a daily dose of 10 mg oral aripiprazole (94.0 mg/mL), 75th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (534 mg/mL), and 95th percentile of Cmax,ss following a daily dose of 30 mg oral aripiprazole (741 mg/mL). Steady-state assumes Q8W dosing for aripiprazole 2M RTU LAI.
Source: CSR 31-21-202 Figure 8.2.5-1.

Was the final to-be marketed formulation used in the pivotal PK study (Study 031-201-00181)?

No. The final to-be-marketed presentation was not used in the pivotal PK bridging study. The commercial presentation of aripiprazole 2M RTU is a prefilled syringe (PFS), while in the pivotal PK study (031-201-00181), a clinical product-glass vial filled with 5.4 mL of drug suspension (1620-mg/vial) was used. As per Applicant, although the dose strength and the container

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closure system are different for the commercial presentation (PFS), the composition of the drug suspension remains unchanged.

However, for aripiprazole 2M RTU LAI formulation, ████████████████ (b) (4)

██ (b) (4)

████████████ (b) (4). There were more physical manipulations (i.e., suspension pushed through the syringe multiple times before a needle was attached for dose administration) when product was presented in a vial form (in the clinical study) than will be in the final to-be-marketed PFS. This raises the concern that the manipulation/preparation difference between the two presentations would cause difference in particle size distribution, drug release and PK profile, which could alter the efficacy and safety profiles of the commercial PFS configuration. See Section 4.2, Product Quality, for a brief summary and the separate CMC reviews for this NDA submission for more detailed information regarding this potential problem and its resolution.

What studies (in vitro, animal, clinical) were conducted to assess the effect of stress factors on the release rate of drug from Aripiprazole 2M RTU?

Studies in rats were conducted to determine the effect of heat, pressure, exercise, and an anti-inflammatory agent on the PK profile of aripiprazole when aripiprazole 2M RTU was administered. Results from these nonclinical studies showed that the application of exercise, heat, and pressure, and the administration of an anti-inflammatory agent (diclofenac) had minimal effects on the PK of aripiprazole 2M RTU LAI after IM administration in rats (see Section 5 of this review for more information).

Was there any evidence of dose dumping observed with Aripiprazole 2M RTU in the clinical trials?

There was no evidence of dose dumping observed in the clinical development program for aripiprazole 2M RTU.

Can Aripiprazole 2M RTU be administered at both sites- gluteal muscle and deltoid muscle?

No. Aripiprazole 2M RTU was administered to the gluteal muscle in all the clinical PK studies, and none of the injections were administered into the deltoid muscle. Because currently there is no information available to inform the switchability between the gluteal muscle and other potential administration sites, aripiprazole 2M RTU is only to be administered into the gluteal muscle.

Was a validated bioanalytical method used for analysis of the drug moieties in the PK samples?

Yes, a validated LC-MS/MS method was applied to determine the concentrations of aripiprazole and dehydro-aripiprazole in human plasma. See Section 15 for additional information.

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7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 7: Listing of Clinical Trials for Aripiprazole 2M RTU LAI

Trial Identity	NCT no.	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
031-201-00181	NCT04030143	Phase 1b, open-label, multiple-dose, randomized, parallel-arm trial	Aripiprazole 2M RTU LAI 960 mg (test); 2-month gluteal intramuscular injection (total of four injections) administered every 56 days (± 2 days) over the course of 32 weeks Aripiprazole IM depot 400 mg (reference); 1-month gluteal intramuscular injection (total of eight injections) administered every 28 days (± 2 days) over the course of 32 weeks	Primary: Safety and tolerability based on reported AEs, vital signs, ECGs, clinical laboratory monitoring (serum chemistry, hematology, and urinalysis), physical examinations, EPS (SAS, AIMS, and BARS), VAS scores for pain perception, Investigator's assessment of most recent injection site, and the C-SSRS.	2-month injection (total of 4 injections); up to 28 days screening period 1-month injection (total of 8 injections); up to 28 days screening period	Aripiprazole 2M RTU LAI 960 mg (test): 132 Aripiprazole IM depot 400 mg (reference): 134 Total enrolled: 266	Male and female subjects ages 18 to 64 years, inclusive, with a diagnosis of schizophrenia or bipolar I disorder	16 sites in the United States.

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				C_{56} for aripiprazole 2M RTU LAI 960 mg after the fourth dose; C_{28} of aripiprazole IM depot 400 mg after the eighth dose; over the course of 32 weeks. AUC$_{0-56}$ for aripiprazole 2M RTU LAI 960 mg after the fourth dose; AUC$_{0-28}$ for aripiprazole IM depot 400 mg after the seventh and eighth doses; over the course of 32 weeks (robust sampling subjects).	Total (maximum) study duration: 225 days			

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Trial Identity	NCT no.	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies to Support Safety								
N/A								

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Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
031-201-00104	NCT03150771	Phase 1, open label, single ascending dose, parallel arm trial of aripiprazole 2-month intramuscular depot.	Cohort 1: 780 mg aripiprazole intramuscular injection (gluteal) Single dose on Day 1 Cohort 2: 1200 mg aripiprazole intramuscular injection (gluteal) Single dose on Day 1	Primary: Safety and tolerability were assessed based on reported AEs, clinical laboratory tests, physical examinations, ECGs, vital signs, suicidality via the Columbia-Suicide Severity Rating Scale (C-SSRS), EPS rating scales, VAS scores for pain perception, Investigator's assessment of injection site	Single dose on Day 1 and then followed for 183 days or until plasma concentrations were below the limits of quantification; up to 30-day screening period Total (maximum) study duration: Approximately 8 months	Cohort 1: 18 Cohort 2: 18 Total enrolled: 36	Male and female subjects between 18 to 64 years of age, inclusive, with a diagnosis of schizophrenia	Three sites in the United States.

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Trial Identity	NCT no.	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
031-201-00279	NCT03854409	An Open-label, Single- and Multiple-dose, Pharmacokinetic, Safety, and Tolerability Trial of Aripiprazole Long-acting Injectable Administered in the Deltoid or Gluteal Muscle in Adult Subjects with Schizophrenia or Bipolar I Disorder	420 mg aripiprazole 1M RTU LAI as: Part A: • Single dose IM injection (deltoid) • Single dose IM injection (gluteal) • Multiple doses IM injection (deltoid) • Multiple doses IM injection (gluteal) Part B: • Single dose IM (gluteal) within 3 seconds • Single dose IM injection (gluteal) within 7 to 8 seconds	Primary: For subjects in Part A (single-dose group) and in Part B, the following PK parameters were assessed for plasma aripiprazole and its major metabolite, dehydro- aripiprazole (OPC-14857): Maximum (peak) plasma concentration of the drug (C_{max}) C_{28}, AUC_{0-28} Time to maximum (peak) plasma concentration (t_{max}) Area under the concentration-time curve from time zero to infinity (AUC_∞)	Part A (Single): Single Deltoid administration on Day 1; 30-day screening period Part A (Multiple): 5 administrations separated by 28 days (Deltoid or Gluteal); 30-day screening period Part B: Single Gluteal administration on Day 1; 30-day screening period Total (maximum) study duration: Part A (Single): 156 days Part A (Multiple): 199 days Part B: 87 days	Part A (Single): 24 Subjects Part A (Multiple): 28 Subjects Part B: 20 Subjects Total enrolled: 72	Male and female subjects between 18 to 64 years of age, inclusive, with a diagnosis of schizophrenia or bipolar I disorder	Four sites in the United States.

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Trial Identity	NCT no.	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
				Terminal phase elimination half-life ($t_{1/2}$)				
				Apparent clearance of the drug from plasma after extravascular administration (CL/F) (for aripiprazole only)				
				For subjects in the multiple-dose group in Part A:				
				C_{max}, t_{max}				
				C_{28} (following the first dose and fifth dose)				
				AUC_{0-28}; $t_{1/2}$				
				CL/F (for aripiprazole only)				
				Ratio of dehydro-aripiprazole to aripiprazole C_{28} (following the first dose and fifth dose) and AUC_{0-28}.				

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2M = 2-month; AEs = adverse events; AIMS = Abnormal Involuntary Movement Scale; AUC 0-56 = Area under the concentration-time curve from time zero to 56 days post-dose; AUC 0-28 = AUC from time zero to 28 days post-dose; BARS = Barnes Akathisia Rating Scale; C 56 = plasma concentration of aripiprazole 56 days post-dose; C 28 = C 28 days post-dose; CGI-BP = Clinical Global Impression - Bipolar Version; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; C-SRSS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EPS = extrapyramidal symptoms; IM = intramuscular; IMP = investigational medicinal product; LAI = long-acting injectable; MADRS = Montgomery-Åsberg Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale; PK = pharmacokinetics; PTF% = Peak-to-trough percent fluctuation; RTU = ready-to-use; SAS = Simpson-Angus Neurologic Rating Scale; VAS = Visual Analog Scale; YMRS = Young Mania Rating Scale
Source: Applicant's response to Division's Information request (NDA 217006, SDN 10, November 14, 2022).

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7.2. Review Strategy

The Applicant relies on the Agency's previous findings of safety and effectiveness for the LD, Abilify Maintena (NDA 202971). The application includes one pivotal PK bridging and safety study (Study 031-201-00181), and two small, supporting PK and safety studies (Study 031-201-00104 and Study 031-201-00279). All studies have an open-label design (Table 7). The Applicant did not conduct any efficacy studies. Efficacy secondary endpoints from Study 031-201-00181 are briefly discussed, acknowledging the limits of the open-label design.

The safety review examined deaths, non-fatal serious adverse events (SAEs), and discontinuations due to adverse events (AEs) using data from all three studies. Safety analyses of changes in laboratory parameters, vital signs, and electrocardiogram (ECG) measures were based on Study 031-201-00181, the only study which allowed a comparison to the LD.

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8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

Study 031-201-00181

Overview and Objectives

Study Title: "A Phase 1b, Open-label, Multiple-dose, Randomized, Parallel-arm, Safety, Tolerability, and Pharmacokinetic Trial of Aripiprazole Intramuscular Depot Administered in the Gluteal Muscle in Adult Subjects with Schizophrenia or Bipolar I Disorder"

Primary Objectives
- To determine the safety and tolerability of multiple-dose administrations of aripiprazole in adult subjects with schizophrenia or bipolar I disorder

- To establish the similarity of aripiprazole concentrations on the last day of the dosing interval following the final administration of aripiprazole into the gluteal muscle site in adult subjects with schizophrenia or bipolar I disorder

- To establish the similarity of aripiprazole exposure over the dosing interval following the administration of aripiprazole into the gluteal muscle site in adult subjects with schizophrenia or bipolar I disorder

Secondary Objectives
- To determine the PK of aripiprazole

- To determine aripiprazole concentrations 7 days (C7) and 14 days (C14) after the first dose of aripiprazole for subjects enrolled to the robust sampling schedule

- To obtain information on the efficacy of aripiprazole over the course of 32 weeks

Trial Design

This study was an open-label, multiple-dose, randomized, parallel-arm, multicenter study in adult subjects with schizophrenia or bipolar I disorder, to evaluate the safety and tolerability of a new formulation of aripiprazole, aripiprazole 2M RTU LAI, and to establish the similarity of aripiprazole 2M RTU LAI exposure and concentrations with the LD (Abilify Maintena).

The study consisted of a Screening/Washout Period, a Treatment Phase, and a Follow-up Phase (Figure 12).

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Figure 12: Study Schema
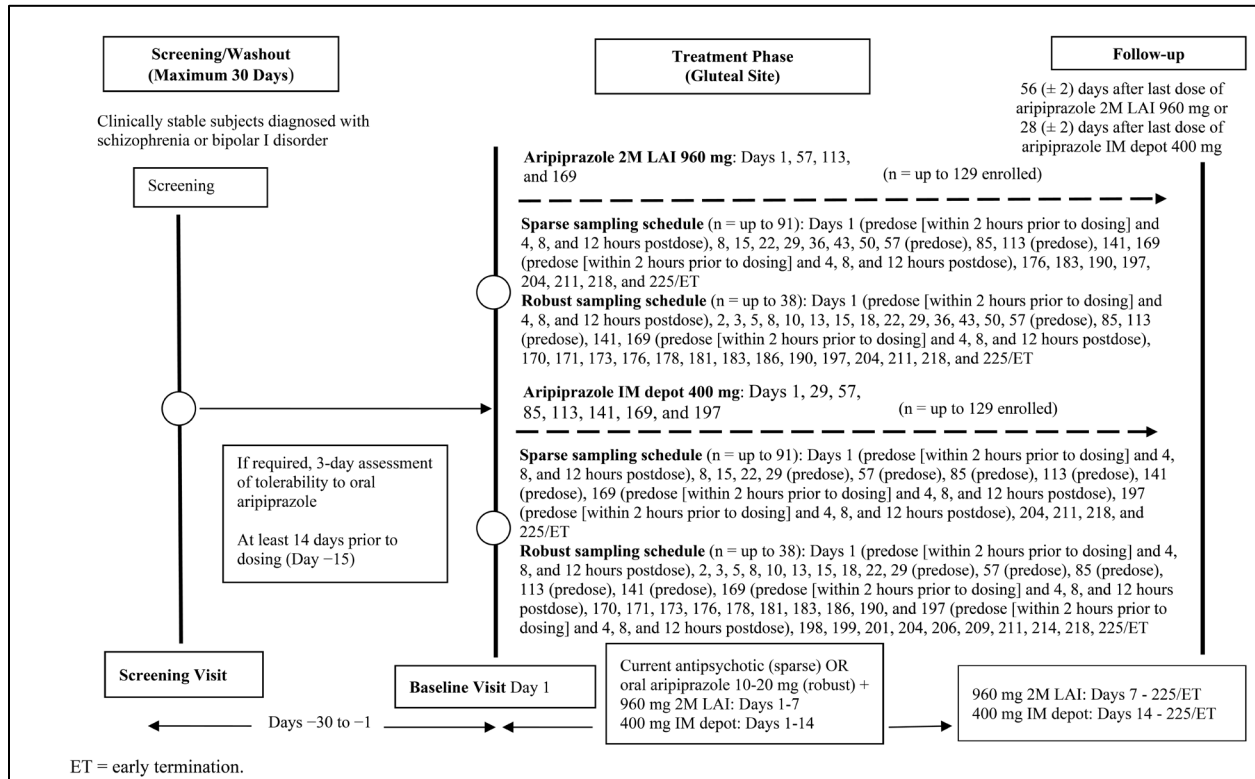
2M = 2-month; IM = intramuscular; LAI = long-acting injectable; ET = early termination
Source: Applicant's Clinical Study Report for Study 031-201-00181, Figure 9.1-1, p. 36.

After a screening period of up to 30 days, eligible subjects were randomized (1:1) to receive multiple doses of either aripiprazole 2M RTU LAI (four injections) or Abilify Maintena (eight injections) over the course of 32 weeks. Aripiprazole 2M RTU LAI was administered at 56-day (± 2 days) intervals and Abilify Maintena was administered at 28-day (± 2 days) intervals. A final visit occurred 56 (± 2) days after the last dose of aripiprazole 2M RTU LAI or 28 (± 2) days after the last dose of Abilify Maintena. Subjects who did not have a history of tolerating aripiprazole underwent testing to determine tolerability prior to enrollment. Testing consisted in receiving three single-doses of oral aripiprazole 10 mg on 3 consecutive days (total of 30 mg) in addition to their oral antipsychotic, mood stabilizer, and antidepressant at least 14 days prior to the first administration of aripiprazole 2M RTU LAI or Abilify Maintena.

Sparse versus Robust Sampling
Randomization to the two trial treatments were stratified by the PK sampling schedule (robust or sparse) and disease type (schizophrenia or bipolar I disorder). Four to six trial sites were designated as Robust Sampling Trial Sites; all other trial sites were designated as Sparse Sampling Trial Sites.

Subjects enrolled to the sparse sampling schedule were outpatients for administration of all doses of aripiprazole 2M RTU LAI or Abilify Maintena.

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Subjects enrolled into the robust sampling schedule, who were randomized to aripiprazole 2M RTU LAI, were housed in the clinical trial unit for 21 days after the first and fourth doses of the investigational medicinal product (IMP) and were outpatients for the rest of the trial. Subjects enrolled into the robust sampling schedule, who were randomized to Abilify Maintena stayed in the unit for 21 days after administration of the first, seventh, and eighth dose of Abilify Maintena.

Clinical Reviewer's Comment: The study design is appropriate for the study objectives. The study design supports the use of the product as described in the product label including the 3-day tolerability testing.

Overlap period

A schema of the different overlap options is represented in Table 8.

Table 8: Scenarios for Initiation of Oral Aripiprazole Overlap During the First 2 Weeks After the Initiation of IMP

Treatment	PK Sampling Schedule	Current Antipsychotic Medication		
		Abilify Maintena	**Oral Aripiprazole**	**Non-aripiprazole Oral Antipsychotics**
Aripiprazole 2M RTU LAI	Sparse	No oral overlap	7-day oral overlap with adjusted dose	Continue current antipsychotic for 7 days
	Robust	Not applicable	Not applicable	(Switch to) Oral aripiprazole 10 to 20 mg: 7-day oral overlap
Abilify Maintena	Sparse	No oral overlap	14-day oral overlap with adjusted dose	Continue current antipsychotic for 14 days
	Robust	Not applicable	Not applicable	(Switch to) Oral aripiprazole 10 to 20 mg: 14-day oral overlap

2M = 2-month; RTU = ready-to-use; LAI = long-acting injectable
Source: Clinical Reviewer adapted from Applicant's Clinical Study Protocol for Study 031-201-00181, Table 3.2.3-1, p. 37.

Subjects stabilized on a non-aripiprazole oral antipsychotic, who were enrolled in a sparse sampling schedule, continued on their medication, and subjects who were enrolled into a robust sampling schedule, switched to oral aripiprazole 10 to 20 mg (dose determined by the investigator's clinical judgment). Subjects took their oral antipsychotic medications concurrently with the IMP for 7 days after the first administration of aripiprazole 2M RTU LAI or 14 days after the first administration of Abilify Maintena. The oral antipsychotic was discontinued after 7 days of administration of aripiprazole 2M RTU LAI and after 14 days of administration of Abilify Maintena.

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For subjects who were stabilized on oral aripiprazole at a dose of 10 to 20 mg/day, the recommended supplemental oral aripiprazole dose was reduced to 10 mg/day with the first dose of IMP. For subjects who were stabilized on oral aripiprazole at a dose of > 20 to 30 mg/day, the recommended supplemental oral aripiprazole dose was reduced to 15 mg/day with the first dose of IMP.

There was no overlap for subjects who were already taking Abilify Maintena at baseline. Subjects who were on Abilify Maintena at baseline were enrolled at their next scheduled dose, and they could not receive IMP any earlier than 26 days after the last Abilify Maintena injection, as per Abilify Maintena labeling.

Clinical Reviewer's Comment: Despite using 7 days overlap with oral antipsychotics (including aripiprazole) as oral supplementation in the pivotal study, the product label for aripiprazole 2M RTU LAI labeling reports 14 days oral supplementation with oral antipsychotics. The 14-day oral supplementation was discussed with the clinical pharmacology reviewer as it does not derive from empirical data, but it is based on modeling and simulation. See Section 6, Clinical Pharmacology, for a review on the adequacy of the Applicant's proposal.

Dose adjustment

A one-time dose adjustment (reduction) was permitted in the trial due to safety and tolerability issues. Only one subject in the aripiprazole 2M RTU LAI 960 mg group had their dose decreased to 660 mg (per protocol) at the second injection.

Clinical Reviewer's Comment: The aripiprazole 2M RTU LAI labeling proposes dose adjustment to 720 mg for adverse reactions, or in subjects that are poor CYP2D6 metabolizers or in subjects on concomitant treatment with strong CYP2D6 or CYP3A4 inhibitors. The proposed dose adjustment in the aripiprazole 2M RTU LAI labeling does not derive from empirical data, but it is based on modeling and simulation. See Section 6, Clinical Pharmacology, for details.

Concurrent Treatment

Subjects could resume treatment on their previous oral non-aripiprazole antipsychotic medication after Day 28 if there was evidence of clinical deterioration based on the judgment of the investigator.

Subjects with a diagnosis of bipolar I disorder, who were taking a mood stabilizer (lithium, valproate, lamotrigine), were permitted to stay on their mood stabilizer and antidepressant (citalopram, escitalopram, sertraline) over the course of the trial, unless the medication was prohibited during the trial (e.g., fluoxetine, fluoxetine/olanzapine).

Clinical Reviewer's Comment: Use of concomitant medications was allowed by the protocol;

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however, the distribution across treatment arms is balanced and it did not affect the observation of safety events. The use of concomitant medications is described in Table 10.

Key inclusion criteria

- Male and female subjects between 18 and 64 years of age, inclusive

- A current diagnosis of schizophrenia or bipolar I disorder, as defined by DSM-5 criteria.

- Body mass index of 18 to 35 kg/m^2

- Good physical health as determined by no clinically significant deviation from normal, in the opinion of the investigator, in medical history, clinical laboratory determination, ECGs, or physical examinations.

- Prior history of tolerating aripiprazole and/or Abilify Maintena per the investigator's judgment.

- If the subject did not establish tolerability, then assessment of oral aripiprazole tolerability was completed within the screening period at least 14 days prior to the first administration of IMP (oral aripiprazole 10 mg/day for 3 consecutive days prior to Day −15).

- Subjects must be clinically stable for at least 2 months prior to screening AND

  o On a stable dose of one of the following oral atypical antipsychotic medications for at least 2 months prior to screening: aripiprazole (sparse only), brexpiprazole, risperidone, olanzapine, quetiapine, paliperidone, cariprazine, lurasidone, ziprasidone, or asenapine; or Abilify Maintena (sparse only). Additionally, subjects with bipolar I disorder who were stabilized on their current medications for at least 2 months prior to screening could continue their mood stabilizer (lithium, valproic acid, lamotrigine) and antidepressant (citalopram, escitalopram, sertraline).

  o Other oral non-aripiprazole, antipsychotic medications could be allowed if approved by the medical monitor and sponsor; however, clozapine was not allowed. (Subjects intended to enroll to the robust sites could not be taking oral aripiprazole or Abilify Maintena as their current atypical antipsychotic)

- Able to understand the nature of trial and follow protocol requirements and procedures.

Key exclusion criteria

- Sexually active males who did not commit to utilizing two of the approved birth control

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methods or who did not remain abstinent during the trial and for 180 days following the last dose of study drug, or had not had an orchiectomy, or sexually active women of child-bearing potential who did not commit to utilizing two of the approved birth control methods or who did not remain abstinent during the trial and for 150 days following the last dose of study drug. Abstinence was permitted if confirmed and documented at every trial visit.

- Subjects met DSM-5 criteria for substance use disorder within the past 180 days

- Positive drug screen for drugs of abuse (excluding nicotine, alcohol, and marijuana)

- Use of any CYP2D6 and CYP3A4 inhibitors, or CYP3A4 inducers, within 14 days (fluoxetine or fluoxetine/olanzapine within 28 days) prior to dosing, for the duration of the trial, and 30 days after the last dose of study drug

- Subjects could not receive varenicline beyond screening

- Subjects enrolled to the robust sampling schedule must not have taken oral aripiprazole for 30 days or Abilify Maintena for 1 year, prior to screening.

- Females who were pregnant, breast-feeding, lactating, and/or had a positive pregnancy test result prior to receiving study drug

- Any major surgery within 30 days prior to enrollment or scheduled/elective surgery during the trial

- Evidence of organ dysfunction or any clinically significant deviation from normal in the physical, electrocardiographic, or clinical laboratory examinations

- Significant risk of committing suicide based on history, routine psychiatric status examination, investigator's judgment, or subject who had an answer of "yes" on questions 4 or 5 (current or over the last 6 months) on the baseline version of the C-SSRS.

- In an acute relapse of schizophrenia

- Subjects with a current DSM-5 diagnosis other than schizophrenia or bipolar I disorder, including schizoaffective disorder, major depressive disorder, delirium, dementia, amnestic, or other cognitive disorders, borderline, paranoid, histrionic, or antisocial personality disorder

- Treatment-resistant to an atypical antipsychotic medication (subjects needed to have shown a previous response to an antipsychotic medication other than clozapine).

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- History of neuroleptic malignant syndrome or clinically significant tardive dyskinesia as assessed by the investigator

- History of or current hepatitis or acquired immunodeficiency syndrome or carriers of HBsAg or anti-HCV, and/or HIV antibodies

- Electroconvulsive therapy within 2 months of administration of IMP

- The following laboratory test, vital sign, and ECG results were exclusionary:
  - Platelets ≤ 75,000/mm3
  - Hemoglobin ≤ 9 g/dL
  - Neutrophils, absolute ≤ 1000/mm3
  - AST > 3x upper limit of normal
  - ALT > 3x upper limit of normal
  - Creatinine ≥ 2 mg/dL
  - Diastolic blood pressure > 105 mmHg
  - QTcF ≥ 450 msec in males or ≥ 470 msec in females, on two of three time points of triplicate ECGs performed

Clinical Reviewer's Comment: The study eligibility criteria are appropriate for the objectives of this phase 1 study.

Study Assessment

The safety of aripiprazole 2M RTU LAI was evaluated according to the schedule of assessments (Table 9 and Table 10).

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Table 9: Schedule of Assessments: Sparse Sampling

	Screening	Check-in[a]	Days ± 2											
	Day −30 to −1	Day 1	8 15 22	29	36[b] 43[b] 50[b]	57	85	113	141	169	176[b] 183[b] 190[b]	197	204 211 218	225/ET
Informed consent	X													
Confirmation of current diagnosis of schizophrenia or bipolar I disorder by DSM-5	X													
Inclusion/exclusion criteria	X	X												
Demographic information	X													
Medical and psychiatric history	X	X												
Discontinue prohibited medication/taper off restricted medication	X													
Document birth control methods	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer IMP tolerability dose	X													
Admit to trial site clinic	X[a,c]	X[d]												
Discharge from trial site clinic	X[c]	X[d]												
Outpatient visits to trial site clinic	X			X	X	X	X	X	X	X		X	X	X
Serum hepatitis and HIV screen	X													
Urine drug screen and urine or breath alcohol screen	X	X												
Urine pregnancy test[e]	X	X		X		X	X	X	X			X		X
FSH[f]	X													
Hematology, clinical chemistry, and urinalysis	X	X		X										X
Serum prolactin assessment	X	X		X										
Physical examination	X	X	X Day 15	X				X						X
Weight	X	X		X		X	X	X	X	X		X		X

	Screening	Check-in[a]	Days ± 2											
	Day −30 to −1	Day 1	8 15 22	29	36[b] 43[b] 50[b]	57	85	113	141	169	176[b] 183[b] 190[b]	197	204 211 218	225/ET
Height and BMI	X													
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	X Day 15	X		X		X						X
C-SSRS[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EPS assessments (SAS, AIMS, and BARS)	X	X	X	X		X	X	X	X	X		X		X
PANSS (schizophrenia subjects only), CGI-S, and SWN-S[j]	X	X		X		X		X				X		X
CGI-I						X								X
MADRS, YMRS, and CGI-BP (all 3 are in bipolar subjects only)[j]	X	X		X		X		X				X		X
Randomization		X												
Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy		X	X	X	X	X	X	X	X	X	X	X	X	X
VAS (perceived pain at injection site)[k]		X		X[i]		X	X[i]	X	X[i]	X		X[i]		
Investigator's assessment of injection site[k]		X		X[i]		X	X[i]	X	X[i]	X		X[i]		
Administer IMP: aripiprazole 2M LAI 960 mg		X				X		X		X				
Administer IMP: aripiprazole IM depot 400 mg		X		X		X	X	X	X	X		X		
PK blood draw		X[l,m]	X[n]	X[b,n] X[i,l,m]	X[n]	X[l,m]	X[b,n] X[i,l,m]	X[l,m]	X[b,n] X[i,l,m]	X[l,m]	X[n]	X[b,n] X[i,l,m]	X[n]	X[n]
CYP2D6 pharmacogenomics blood draw		X												

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	Screening	Check-in[a]	Days ± 2											
	Day −30 to −1	Day 1	8 15 22	29	36[b] 43[b] 50[b]	57	85	113	141	169	176[b] 183[b] 190[b]	197	204 211 218	225/ ET
FBR sample blood draw (optional)		X												
Assess and record AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Source: Applicant's Clinical Study Protocol for Study 031-201-00181, Table 3.7-1, page 46-49.

Table 10: Schedule of Assessments: Robust Sampling

	Screening	Check-in[a]	Days (Clinical Unit)					Days ± 2 (Outpatient)								Days (Clinical Unit) Days ± 2 (Outpatient)				Day ± 2
	Day −30 to −1	Day 1	2 3 5	8	10 13	15	18	22	29	36[b] 43[b] 50[b]	57	85	113	141	169	170 171 173 176 178 181 183 186 190	197	198[c] 199[c] 201[c] 206[c] 209[c] 214[c]	204 211 218	225/ ET
Informed consent	X																			
Confirmation of current diagnosis of schizophrenia or bipolar I disorder by DSM-5	X																			
Inclusion/exclusion criteria	X	X																		
Demographic information	X																			
Medical and psychiatric history	X	X																		
Discontinue prohibited medication/taper off restricted medication	X																			
Document birth control methods	X	X						X	X	X	X	X	X	X	X	X Day 190	X	X	X	X
Administer IMP tolerability dose	X																			
Admit to trial site clinic	X[a,d]	X													X		X[c]			
Discharge from trial site clinic	X[d]							X								X Day 190			X[c] Day 218	
Outpatient visits to trial site clinic	X							X	X	X	X	X	X	X			X[b]		X[b]	X

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	Screening	Check-in[a]	Days (Clinical Unit)					Days ± 2 (Outpatient)							Days (Clinical Unit) / Days ± 2 (Outpatient)					Day ± 2
	Day −30 to −1	Day 1	2/3/5	8	10/13	15	18	22	29	36[b]/43[b]/50[b]	57	85	113	141	169	170/171/173/176/178/181/183/186/190	197	198[c]/199[c]/201[c]/206[c]/209[c]/214[c]	204/211/218	225/ET
Serum hepatitis and HIV screen	X																			
Urine drug screen and urine or breath alcohol screen	X	X																		
Urine pregnancy test[e]	X	X							X		X	X	X	X	X		X			X
FSH[f]	X																			
Hematology, clinical chemistry, and urinalysis	X	X							X											X
Serum prolactin assessment	X	X							X											
Physical examination	X	X				X			X			X								X
Weight	X	X							X		X	X	X	X	X		X			X
Height and BMI	X																			
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X				X			X		X		X							X
C-SSRS[h]	X	X						X	X	X	X	X	X	X	X	X[b] Day 190	X		X Days 204[b], 211[b], 218[b,c]	X

	Screening	Check-in[a]	Days (Clinical Unit)					Days ± 2 (Outpatient)							Days (Clinical Unit) / Days ± 2 (Outpatient)					Day ± 2
	Day −30 to −1	Day 1	2/3/5	8	10/13	15	18	22	29	36[b]/43[b]/50[b]	57	85	113	141	169	170/171/173/176/178/181/183/186/190	197	198[c]/199[c]/201[c]/206[c]/209[c]/214[c]	204/211/218	225/ET
EPS assessments (SAS, AIMS, and BARS)	X	X		X		X		X	X		X	X	X	X	X		X			X
PANSS (schizophrenia subjects only), CGI-S, and SWN-S[i]	X	X							X		X		X		X		X			X
CGI-I											X									X
MADRS, YMRS, and CGI-BP (bipolar subjects only)[i]	X	X							X		X		X		X		X			X
Randomization		X																		
Record adjusted current oral antipsychotic, mood stabilizer, or antidepressant therapy		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VAS (perceived pain at injection site)[j]		X							X[c]		X	X[c]	X	X[c]	X		X[c]			
Investigator's assessment of injection site[j]		X							X[c]		X	X[c]	X	X[c]	X		X[c]			
Administer IMP: aripiprazole 2M LAI 960 mg		X									X		X		X					

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	Screening	Check-in[a]	Days (Clinical Unit)					Days ± 2 (Outpatient)								Days (Clinical Unit) / Days ± 2 (Outpatient)				Day ± 2
	Day −30 to −1	Day 1	2 3 5	8	10 13	15	18	22	29	36[b] 43[b] 50[b]	57	85	113	141	169	170 171 173 176 178 181 183 186 190	197	198[c] 199[c] 201[c] 206[c] 209[c] 214[c]	204 211 218	225/ ET
Administer IMP: aripiprazole IM depot 400 mg		X							X		X	X	X	X	X		X			
PK blood draw		$X^{k,l}$	X^m	X^m	X^m	X^m	X^m	X^m	$X^{b,m}$ $X^{c,k}$	$X^{b,m}$ $X^{c,k}$	X^k	$X^{b,m}$ $X^{c,k}$	X^k	$X^{b,m}$ $X^{c,k}$	$X^{k,l}$	X^m	$X^{b,m}$ $X^{c,k,l}$	$X^{c,m}$	X^m	X^m
CYP2D6 pharmacogenomics blood draw		X																		
FBR sample blood draw (optional)		X																		
Assess and record AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Record prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Source: Applicant's Clinical Study Protocol for Study 031-201-00181, Table 3.7-2, page 50-53.

Study Endpoints

Primary endpoints
Primary endpoints included safety and pharmacokinetic endpoints.

Safety endpoints included reported AEs, vital signs, ECG, clinical laboratory monitoring (serum chemistry, hematology, and urinalysis), physical examinations, EPS (the Simpson-Angus Neurologic Rating Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS)), Visual Analog Scale (VAS) scores for pain perception, investigator's assessment of most recent injection site, and the Columbia-Suicide Severity Rating Scale (C-SSRS).

Pharmacokinetic endpoints included:
- Plasma concentration of aripiprazole 56 days post-dose (C56) for aripiprazole 2M RTU LAI after the fourth dose or plasma concentration of aripiprazole 28 days post-dose (C28) for Abilify Maintena after the eighth dose over the course of 32 weeks

- The area under the concentration-time curve of aripiprazole from time zero to 56 days post-dose (AUC_{0-56}) for aripiprazole 2M RTU LAI after the fourth dose or the area under the concentration-time curve of aripiprazole from time zero to 28 days post-dose (AUC_{0-28}) for Abilify Maintena after the seventh and eighth doses over the course of 32 weeks, based on the PK data from subjects enrolled to the robust sampling schedule

Secondary endpoints
In addition to PK parameters described in Section 6, the Applicant included efficacy measures as secondary endpoints. Efficacy was assessed by the Positive and Negative Syndrome Scale (PANSS; schizophrenia subjects only), Clinical Global Impression - Severity (CGI-S; schizophrenia subjects only), Clinical Global Impression - Improvement (CGI-I), Subjective Well-being under

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Neuroleptic Treatment-Short Form (SWN-S), Montgomery-Åsberg Depression Rating Scale (MADRS; bipolar subjects only), Young Mania Rating Scale (YMRS; bipolar subjects only), and Clinical Global Impression - Bipolar Version (CGI-BP; bipolar subjects only).

Clinical Reviewer's Comment: The primary and secondary endpoints are adequate to address the study's objectives. The pharmacokinetic endpoints are discussed in Section 6, Clinical Pharmacology. Efficacy of aripiprazole 2M RTU LAI is compared to the LD using descriptive statistics, acknowledging the limitations of an open-label design.

Datasets for analyses

- The safety population includes all randomized subjects who received at least one dose of aripiprazole injection, regardless of any protocol violation

- The efficacy population includes all randomized subjects who received at least one dose of aripiprazole injection and have at least one efficacy assessment

- Baseline was defined as the last evaluable assessment prior to aripiprazole IMP injection

- Last visit was defined as the last evaluable assessment upon completion or early termination (ET) of treatment phase

- Only subjects who received at least one dose of aripiprazole 2M RTU LAI or LD and had assessment at both baseline and at least one post-baseline visit were included in the analyses of change from baseline (secondary endpoint).

Please refer to Section 6 for discussion of PK methodology.

Protocol Amendments

There were two amendments to the protocol for Study 031-201-00181:

Amendment 01 (dated May 31, 2019) was finalized at the time of the Study 031-201-0081 submission and was submitted along with the original study on June 3, 2019. The primary reason for this amendment was to allow an additional dose of Abilify Maintena (eighth dose) to better align the treatment duration with aripiprazole 2M RTU LAI and to compare PK parameters between Abilify Maintena and aripiprazole 2M RTU LAI over the last 8 weeks of treatment.

Amendment 02 (dated July 31, 2019) was finalized upon Agency's recommendation based on the review of Amendment 01. The primary reason for Amendment 02 was to include Agency's recommendation to include C-SSRS assessment at every outpatient visit. The amended protocol also clarified that subjects enrolled to the robust sampling schedule who were randomized to

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aripiprazole 2M RTU LAI and who were not able to accommodate the scheduled stay of 21 days in the clinical unit, were permitted to have some visits as outpatients with approval from the medical monitor. In addition, the amended protocol clarified that the trial would have taken place from Day −30 to Day 225/ET for both treatment arms.

Clinical Reviewer's comment: The amendments were made prior to patient enrollment and do not impact data integrity.

Results of Study 031-201-00181

Compliance with Good Clinical Practices

The Applicant states that the study was conducted in full accordance with the International Council for Harmonization (ICH) Good Clinical Practice (GCP) Consolidated Guideline and the applicable local laws and regulatory requirements of the country in which the trial was conducted.

The Applicant states that copies of the protocol, any amendments, and the informed consent form were reviewed and approved by the governing institutional review board (IRB) for each investigational site, as appropriate, prior to trial start or prior to implementation of the protocol or protocol amendment, if any, at that site. An attestation was included in Section 5 of the CSR.

Financial Disclosure

This trial was conducted in 266 enrolled/randomized subjects at 20 sites in the United States. Four sites did not enroll subjects. There were 21 disclosures received for 21 principal investigators from 20 institutions (a principal investigator left one site and was substituted by another principal investigator). No investigators had financial interest information to disclose for this study (see Section 15.2, Financial Disclosures).

Patient Disposition

The study screened 394 subjects and enrolled, randomized and treated 266 subjects. A total of 132 subjects in the aripiprazole 2M RTU LAI group, and 134 subjects in the Abilify Maintena group were randomized and received at least one dose the study drug. Safety and efficacy analyses included all subjects in each treatment group.

Of the 132 subjects in the aripiprazole 2M RTU LAI group, 102 subjects (77.3%) completed the trial and 30 subjects (22.7%) discontinued from the trial. Of the 134 subjects in the Abilify Maintena group, 92 subjects (68.7%) completed the trial and 42 subjects (31.3%) discontinued from the trial (Table 11).

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Table 11: Disposition of Subjects

	Abilify Maintena			Aripiprazole 2M RTU LAI		
	SCZ (N=93) n (%)	BD-I (N=41) n (%)	Total (N=134) n (%)	SCZ (N=92) n (%)	BD-I (N=40) n (%)	Total (N=132) n (%)
Randomized	93 (100)	41 (100)	134 (100)	92 (100)	40 (100)	132 (100)
Completed[a]	63 (68)	29 (71)	92 (69)	73 (79)	29 (72)	102 (77)
Discontinued	30 (32)	12 (29)	42 (31)	19 (21)	11 (28)	30 (23)
Adverse event	7 (8)	3 (7)	10 (8)	4[b] (4)	1 (2.5)	5 (4)
Lost to follow-up	5 (5)	2 (5)	7 (5)	2 (2)	1 (2.5)	3 (3)
Protocol deviation	2 (2)	0 (0)	2 (1.5)	1 (1)	1 (2.5)	2 (1.5)
Withdrawal by subject	11 (12)	7 (17)	18 (13)	8 (9)	8 (20)	16 (12)
Physician decision	1 (1)	0	1 (1)	1 (1)	0	1 (1)
Other due to covid-19[c]	3 (3)	0	3 (2)	2 (2)	0	2 (1.5)
Other not due to covid-19	1 (1)	0	1 (1)	1 (1)	0	1 (1)

BD-I = Bipolar disorder type I; SCZ = schizophrenia
[a]Subjects completed the Day 225 visit
[b]Includes one subject who discontinued from the trial primarily due to a treatment emergent adverse event (TEAE) of cardiac arrest with a fatal outcome.
[c]Discontinuation due to local, regional, or national COVID-19 restrictions, not due to COVID-19 infection or adverse events.
Source: Table 10.1.-1 of Applicant's Clinical Study Report of Study 031-201-00181 and Clinical Reviewer's Summary using Subject-Level Analysis Dataset (ADSL.xpt) of Study 031-201-00181.

Clinical Reviewer's Comment: There is a slight imbalance of patients with schizophrenia who discontinued treatment in the Abilify Maintena group compared to the aripiprazole 2M RTU LAI group (32% versus 21%, respectively). The reasons for higher discontinuation in the Abilify Maintena group appear to be non-specific, including AEs, lost to follow-up, and withdrawal by subject. Overall, this imbalance does not seem clinically significant.

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Protocol Violations/Deviations

A total of 113 subjects in Study 031-201-00181 had a protocol deviation; 68 (51.5%) in the aripiprazole 2M RTU LAI group, and 45 (33.6%) were in the LD group. Most protocol deviations were related to procedural deviations due to COVID-19 (N=58, 43.9% subjects in the aripiprazole 2M RTU LAI group and N=30, 22.4% subjects in the LD group). Three subjects in the aripiprazole 2M RTU LAI group and two subjects in the LD group had deviations related to prohibited concomitant medications. Two subjects in the aripiprazole 2M RTU LAI group and one subject in the LD group had deviation related to inclusion/exclusion criteria. Two protocol deviations in each treatment group led to discontinuation from the study (positive urine drug screen in three subjects and one non-compliance for illicit drug use in one subject). No subject was excluded from the study analyses due to protocol deviations.

In study 031-201-00104, 11 protocol deviations occurred (six procedural deviations, and five prohibited concomitant medications). In Study 031-201-00279, all protocol deviations (two subjects in part A and two subjects in part B) were procedural.

Clinical Reviewer's Comment: In Study 031-201-00181, cases with protocol deviations related to entry criteria and prohibited concomitant medications were equally distributed between the two treatment groups. The procedural deviations due to COVID-19 were more frequent in the aripiprazole 2M RTU LAI group compared to the Abilify Maintena group. Most of them resulted in visits performed remotely over the phone; however, they did not affect the overall safety evaluation nor impacted the integrity of the study. In conclusion, all protocol deviations were reviewed for clinical relevance and none of the deviations seem to have had an impact on the overall clinical assessment or study outcome.

Table of Demographic Characteristics

Demographic characteristics were generally balanced among the two treatment groups (Table 12). Overall, there were more male subjects (66%) than female subjects, there were more black or African Americans subjects (73%) than other races, and most subjects (91%) were non-Hispanics. The mean age of subjects enrolled in the study was approximately 47 years old.

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Table 12: Demographic Characteristics of the Randomized Sample - Study 031-201-00181

Demographic Parameters	Abilify Maintena			Aripiprazole 2M RTU LAI		
	SCZ (N=93) n (%)	BD-I (N=41) n (%)	Total (N=134) n (%)	SCZ (N=92) n (%)	BD-I (N=40) n (%)	Total (N=132) n (%)
Sex						
Male	67 (72)	19 (46)	86 (64)	65 (71)	25 (63)	90 (68)
Female	26 (28)	22 (54)	48 (36)	27 (29)	15 (37)	42 (32)
Age						
Mean years (SD)	48 (12)	45 (11)	47 (12)	48 (10)	47 (12)	48 (11)
Median (years)	51	48	50	50.5	51.5	51
Min, max (years)	19, 64	18, 64	18, 64	21, 64	20, 62	20, 64
Age Group						
< 45 years	30 (32)	16 (39)	46 (34)	27 (29)	14 (35)	41 (31)
≥ 45 years	63 (68)	25 (61)	88 (66)	65 (71)	26 (65)	91 (69)
≥ 65 years	0	0	0	0	0	0
Race						
Black or African American	77 (83)	18 (44)	95 (71)	80 (87)	19 (47)	99 (75)
White	12 (13)	21 (51)	33 (25)	11 (12)	18 (45)	29 (22)
Asian	2 (2)	2 (5)	4 (3)	0	3 (8)	3 (2)
Other	2 (2)	0	2 (1)	1 (1)	0	1 (1)
Ethnicity						
Not Hispanic or Latino	88 (95)	34 (83)	122 (91)	87 (95)	32 (80)	119 (90)
Hispanic or Latino	4 (4)	7 (17)	11 (8)	4 (4)	8 (20)	12 (9)
Unknown	1 (1)	0 (0)	1 (1)	1 (1)	0	1 (1)
Region						
United States	93 (100)	41 (100)	134 (100)	92 (100)	40 (100)	132 (100)
Rest of the World	0	0	0	0	0	0
PK sampling						
Robust	31 (33)	11 (27)	42 (31)	31 (34)	11 (28)	42 (32)
Sparse	62 (67)	30 (73)	92 (69)	61 (66)	29 (72)	90 (68)

BD-I = bipolar disorder type I; SCZ = schizophrenia; SD = standard deviation
Source: Table 11.2-1, pg. 58, and Summary 11.2 of Applicant's Clinical Study Report of Study 031-201-00181 and Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) of Study 031-201-00181.

Baseline disease characteristics were generally balanced among the two treatment groups (Table 13).

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Table 13: Baseline Disease Characteristics of The Randomized Sample - Study 031-201-00181

Baseline Disease Characteristics		Abilify Maintena N=134		Aripiprazole 2M RTU LAI N=132	
		SCZ n=93	BD-I n=41	SCZ n=92	BD-I n=40
PANSS total score	Mean (SD)	61.8 (13.5)		62.0 (13.5)	
	Min, Max	36, 103		34, 103	
PANSS positive subscale score	Mean (SD)	15.2 (4.5)		15.7 (4.6)	
	Min, Max	7, 25		7, 27	
PANSS negative subscale score	Mean (SD)	17.1 (4.2)		17.6 (4.3)	
	Min, Max	9, 29		9, 28	
CGI - S score	Mean (SD)	3.1 (0.9)		3.3 (0.9)	
	Min, Max	1, 5		1, 5	
CGI-BP severity for mania	Mean (SD)		2.3 (1.2)		1.8 (1.0)
	Min, Max		1, 5		1, 5
CGI-BP severity for depression	Mean (SD)		2.5 (1.1)		2.2 (1.2)
	Min, Max		1, 5		1, 4
CGI-BP severity for overall bipolar illness	Mean (SD)		2.8 (1.2)		2.4 (1.1)
	Min, Max		1, 5		1, 4
MADRS total score	Mean (SD)		13.5 (9.7)		10.9 (9.4)
	Min, Max		0, 41		0, 29
YMRS total score	Mean (SD)		9.4 (8.2)		6.7 (7.3)
	Min, Max		0, 35		0, 30

BD-I = bipolar disorder type I; CGI-BP = Clinical Global Impression - Bipolar Version; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; MADRS = Montgomery-Åsberg Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale; SCZ = schizophrenia; SD = standard deviation; YMRS = Young Mania Rating Scale
Source: Table 11.2-2, pg. 59-60, and Summary 11.2 of Applicant's Clinical Study Report of Study 031-201-00181 and Clinical Reviewer's Summary based on PANSS Analysis Dataset (PANSS.xpt), MADRS Analysis Dataset (ADMADRS.xpt), CGI Analysis Dataset (ADCGI.xpt), and YMRS Analysis Dataset (ADYMRS.xpt) of Study 031-201-00181.

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

The treatment groups were also comparable in their use of prior medications. All patients in each treatment group received medications prior to study entry. Antipsychotics were the most frequently reported medications being taken prior to the start of IMP and were taken by all subjects. The oral antipsychotics taken prior to the start of IMP were generally balanced between the two treatment groups (Table 14).

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Table 14: Antipsychotic Medications and Mood Stabilizers Taken Prior to the Start of the Trial Treatment Phase, by Disease Type (Safety Sample)

Medication	Abilify Maintena			Aripiprazole 2M RTU LAI		
	SCZ (n=93) n (%)	BD-I (n=41) n (%)	Total (N=134) n (%)	SCZ (n=92) n (%)	BD-I (n=40) n (%)	Total (N=132) n (%)
Antipsychotics						
Oral Aripiprazole	22 (23.7)	13 (31.7)	35 (26.1)	28 (30.4)	17 (42.5)	45 (34.1)
IM Depot Aripiprazole	3 (3.2)	0	3 (2.2)	5 (5.4)	1 (2.5)	6 (4.5)
Asenapine	1 (1.1)	0	1 (0.7)	0	0	0
Asenapine Maleate	0	0	0	1 (1.1)	0	1 (0.8)
Brexpiprazole	1 (1.1)	1 (2.4)	2 (1.5)	1 (1.1)	2 (5.0)	3 (2.3)
Cariprazine	0	0	0	1 (1.1)	0	1 (0.8)
Cariprazine Hydrochloride	1 (1.1)	0	1 (0.7)	1 (1.1)	1 (2.5)	2 (1.5)
Chlorpromazine	0 (0.0)	1 (2.4)	1 (0.7)	0	0	0
Haloperidol	3 (3.2)	0	3 (2.2)	0	0	0
Lurasidone Hydrochloride	1 (1.1)	3 (7.3)	4 (3.0)	2 (2.2)	1 (2.5)	3 (2.3)
Olanzapine	14 (15.1)	4 (9.8)	18 (13.4)	9 (9.8)	3 (7.5)	12 (9.1)
Paliperidone	6 (6.5)	1 (2.4)	7 (5.2)	1 (1.1)	0	1 (0.8)
Quetiapine	6 (6.5)	5 (12.2)	11 (8.2)	7 (7.6)	5 (12.5)	12 (9.1)
Quetiapine Fumarate	21 (22.6)	13 (31.7)	34 (25.4)	23 (25.0)	11 (27.5)	34 (25.8)
Risperidone	27 (29.0)	5 (12.2)	32 (23.9)	29 (31.5)	9 (22.5)	38 (28.8)
Ziprasidone	2 (2.2)	0	2 (1.5)	2 (2.2)	2 (5.0)	4 (3.0)
Mood Stabilizers						
Carbamazepine	0	1 (2.4)	1 (0.7)	0	0	0
Lithium	0	1 (2.4)	1 (0.7)	1 (1.1)	2 (5.0)	3 (2.3)
Lithium Carbonate	0	1 (2.4)	1 (0.7)	0	1 (2.5)	1 (0.8)
Valproate Semisodium	1 (1.1)	6 (14.6)	7 (5.2)	0	8 (20.0)	8 (6.1)
Valproic Acid	1 (1.1)	1 (2.4)	2 (1.5)	0	0	0

BD-I = bipolar disorder type I; IM = intramuscular; SCZ = schizophrenia
Source: Table 11.2-3, pg. 62, and Summary 11.2 of Applicant's Clinical Study Report of Study 031-201-00181 and Clinical Reviewer's Summary based on Concomitant Medication Analysis Dataset (ADCM.xpt) of Study 031-201-00181.

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Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment noncompliance was defined as having less than 54 days between injections for aripiprazole 2M RTU LAI and < 26 days between injections for Abilify Maintena. A total of 130 subjects out of 132 (98.5%) who received aripiprazole 2M RTU LAI and 118 out of 134 (88.1%) who received Abilify Maintena achieved treatment compliance.

The treatment groups were comparable in their concomitant use of antipsychotics, mood stabilizers and benzodiazepines/benzodiazepine related medications, as summarized in the table below (Table 15). A slightly higher percentage of participants took risperidone in the aripiprazole 2M RTU LAI group compared to the Abilify Maintena group.

Table 15: Antipsychotics and Mood Stabilizers Taken during the Treatment Phase of Study 031-201-00181

Standardized Medication Name	Abilify Maintena N= 134 n (%)	Aripiprazole 2M RTU LAI N=132 n (%)
Antipsychotics		
aripiprazole	9 (7)	9 (7)
asenapine	1 (<1)	0
asenapine maleate	1 (<1)	1 (<1)
brexpiprazole	2 (1)	2 (1)
cariprazine	0	1 (<1)
haloperidol	1 (<1)	0
lurasidone hydrochloride	4 (3)	1 (<1)
olanzapine	16 (12)	11 (8)
paliperidone	3 (2)	1 (<1)
quetiapine	38 (28)	37 (28)
risperidone	14 (10)	23 (17)
ziprasidone	2 (1)	3 (2)
Mood Stabilizers		
lithium	2 (1)	2 (1)
valproic acid	8 (6)	8 (6)
Benzodiazepines or Benzodiazepine-related Drugs		
alprazolam	1 (<1)	0
diazepam	2 (1)	0
eszopiclone	2 (1)	1 (<1)
lorazepam	50 (37)	55 (42)
temazepam	1 (<1)	2 (1)
zaleplon	2 (1)	2 (1)
zolpidem	34 (25)	38 (29)

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Source: Clinical Reviewer's Summary based on Concomitant Medication Analysis Dataset (ADCM.xpt) of Study 031-201-00181. Similar to data on antipsychotics, mood stabilizers, and benzodiazepines reported in supporting Clinical Table CT4.2, page 196-197 of Summary of Applicant's Clinical Study Report of Study 031-201-00181, with the following modifications: quetiapine and quetiapine fumarate have been combined together in the Clinical Reviewer's table; valproate semisodium and valproic acid have been combined together in the Clinical Reviewer's table; lithium and lithium carbonate have been combined together in the Clinical Reviewer's table; zolpidem and zolpidem tartrate have been combined together in the Clinical Reviewer's table.

There were no differences between treatment group in the use of concomitant antidepressants or other non-CNS medications.

Efficacy Results – Primary Endpoint

Study 031-201-00181 was intended to establish PK bridge between aripiprazole 2M RTU LAI and Abilify Maintena. The primary endpoints were safety and pharmacokinetic to establish a bridge to the LD. See Sections 8., Statistical and Clinical Evaluation, and 6., Clinical Pharmacology, for more information.

Data Quality and Integrity

The submission contains all required components of the electronic common technical document (eCTD). The overall quality and integrity of the datasets was reviewed by the DF-core Data-fitness Service and appeared acceptable.

Requests for additional information from the Applicant throughout the review process were addressed in a timely fashion.

Efficacy Results – Secondary and other relevant endpoints

The Applicant conducted efficacy measurements using PANSS, CGI-S, CGI-I for schizophrenia, and CGI-S, CGI-I, MADRS, and YMRS for bipolar disorder type I comparing the two treatment arms, despite being an open-label study.

A summary of efficacy analyses is reported in Table 16 for patients with schizophrenia, and in Table 17 for patients with bipolar disorder I.

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Table 16: Efficacy Sample – Patients with Schizophrenia

Scales	Abilify Maintena n Mean (SD)	Aripiprazole 2M RTU LAI n Mean (SD)
PANSS Total Score Last Visit – change from baseline	85 -1.7 (8.5)	89 -2.6 (11.7)
CGI-Severity last visit – change from baseline	85 -0.1 (0.7)	89 -0.3 (0.6)
CGI-Improvement last visit	82 3.6 (0.9)	88 3.5 (1.0)

CGI = Clinical Global Impression; PANSS = Positive and Negative Syndrome Scale; SD = Standard Deviation
Source: Clinical Reviewer's Summary based on CGI Analysis Dataset (adcgi.xpt), and PANSS Analysis Dataset (adpanss.xpt) of Study 031-201-00181. Similar to data reported in Table 11.4.1.2.1-1 (page 64), Table 11.4.1.2.2-1 (page 65), and Table 11.4.1.2.6-1 (page 69) of Summary of Applicant's Clinical Study Report of Study 031-201-00181 but with less details.

Table 17: Efficacy Sample – Patients with Bipolar Disorder I

Scales	Abilify Maintena n Mean (SD)	Aripiprazole 2M RTU LAI n Mean (SD)
MADRS last visit - change from baseline	40 -3.3 (12.5)	39 -3.5 (9.1)
YMRS - last visit - change from baseline	40 -4.7 (7.7)	39 -1.9 (7.1)
CGI-BP Severity last visit - change from baseline	40 -0.6 (1.2)	39 -0.2 (1.0)
CGI-Improvement last visit	35 3.2 (1.5)	35 3.1 (1.2)

CGI = Clinical Global Impression; MADRS = Montgomery-Asberg Depression Rating Scale; SD = Standard Deviation; YMRS = Young Mania Rating Scale
Source: Clinical Reviewer's Summary based on CGI Analysis Dataset (adcgi.xpt), MADRS Analysis Dataset (admadrs.xpt), and YMRS Analysis Dataset (adymrs.xpt) of Study 031-201-00181. Similar to data reported in Table 11.4.1.2.3-1 (page 66), Table 11.4.1.2.4-1 (page 67), Table 11.4.1.2.5-1 (page 68), and Table 11.4.1.2.6-1 (page 69) of Summary of Applicant's Clinical Study Report of Study 031-201-00181 but with less details.

Clinical Reviewer's Comment: The study was not designed to compare effectiveness of aripiprazole 2M RTU LAI to Abilify Maintena, but the Applicant presented analyses of change from baseline to end-of-treatment for each treatment arm in the two patient populations. Efficacy of aripiprazole 2M RTU LAI in reducing psychotic symptoms as measured by the PANSS total score and the CGI-S, in patients with schizophrenia appears similar to that of the LD Abilify Maintena. In patients with bipolar disorder, efficacy of aripiprazole 2M RTU LAI appears comparable to that of the LD on multiple clinical measures as described in Table 17.

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Dose/Dose Response

N/A

Durability of Response

N/A

Persistence of Effect

N/A

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

N/A

Additional Analyses Conducted on the Individual Trial

N/A

Integrated Review of Effectiveness

N/A

Other Supportive Studies

Study 031-201-00104

Study Title: "A Phase 1, Open-label, Single Ascending Dose, Parallel-arm Trial to Determine the Pharmacokinetics, Safety, and Tolerability of Aripiprazole 2 Month Intramuscular Depot Administered Gluteally in Adult Subjects with Schizophrenia"

This was an open-label, single ascending dose, parallel-arm, multicenter trial designed to determine the safety, PK, and tolerability of single-dose administrations of 780 mg (Cohort 1) and 1200 mg (Cohort 2) of aripiprazole LAI formulation administered in the gluteal muscle in 36 adult subjects with schizophrenia. Concomitant with the aripiprazole LAI formulation and for the duration of the trial, subjects continued to receive their current oral antipsychotic medication. The duration of the treatment for each subject, including screening, in-clinic periods, a single-dose injection, and outpatient visits, was approximately 8 months.

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Study 031-201-00279

Study Title: "An Open-label, Single- and Multiple-dose, Pharmacokinetic, Safety, and Tolerability Trial of Aripiprazole Long-acting Injectable Administered in the Deltoid or Gluteal Muscle in Adult Subjects with Schizophrenia or Bipolar I Disorder"

This was a two-part, open-label, single- and multiple-dose, multicenter trial designed to assess the PK, safety, and tolerability of 420 mg aripiprazole 1M LAI RTU in subjects with schizophrenia or bipolar I disorder. Subjects were randomized to receive aripiprazole 1M LAI RTU as single or multiple doses in the deltoid or gluteal muscle sites according to the randomization schedule. In Part A, for subjects in the single-dose group (N=24), a single dose of 420 mg aripiprazole 1M LAI RTU was administered either in the deltoid or gluteal muscle sites (1:1 randomization). Eligible subjects were stabilized on an atypical oral antipsychotic or mood stabilizer(s) medication other than aripiprazole. Subjects continued their current non-aripiprazole antipsychotic or mood stabilizer(s) medication to maintain clinical stability of the subjects for the duration of the trial. After the administration of aripiprazole 1M LAI RTU, subjects were followed for 18 weeks (126 days) for PK and safety assessments. In Part A, for subjects in the multiple-dose group (N=28), multiple doses of 420 mg aripiprazole 1M LAI RTU were administered at monthly, 28-day (± 2 days) intervals. The first aripiprazole 1M LAI RTU administration was either in the deltoid or gluteal muscle (1:1 randomization) followed by four additional monthly administrations in the same injection site as the first dose (for a total of five monthly administrations for each subject). Part B comprised of a single group of 20 subjects who were randomized to an injection duration according to a 1:1 randomization schedule prior to dosing on Day 1. Subjects received a single dose of 420 mg aripiprazole 1M LAI RTU in the gluteal muscle site. After the administration of aripiprazole 1M LAI RTU, subjects in Part B were followed for 57 days for PK and safety assessments.

Assessment of Efficacy Across Trials

N/A

The clinical studies submitted with this new drug application (NDA) were intended to establish PK bridge between aripiprazole 2M RTU LAI and Abilify Maintena. The Applicant did not conduct efficacy studies.

Integrated Assessment of Effectiveness

N/A

The studies submitted to this NDA were not designed to assess the effectiveness of aripiprazole 2M RTU LAI, which relies on the Agency's findings of Abilify Maintena and from trials with the oral aripiprazole formulation.

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8.2. Review of Safety

Safety Review Approach

The safety review included evaluation of adverse events occurring under all treatment conditions as well as an assessment of changes in vital sign parameters and laboratory assessments following exposure to the drug.

This safety review is primarily based on data from Study 031-201-00181, because it provides a direct comparison between 2M RTU LAI aripiprazole and the LD. Safety narratives for deaths and AEs were also reviewed for the two supportive phase 1 studies (Study 031-201-00104 and Study 031-201-00279).

The safety of Abilify Maintena is well characterized. As per product label, warnings and precautions include cerebrovascular adverse reactions in elderly patients with dementia, neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, orthostatic hypotension, leukopenia, neutropenia, agranulocytosis, seizures, potential for cognitive and motor impairment. The Abilify Maintena safety profile is similar to that of the Abilify oral tablets, with the exception of injection site reactions, which is an IM depot-specific AE. The Applicant provided pharmacokinetic data to support reliance on the systemic safety of Abilify Maintena. Because 2M RTU LAI aripiprazole is an extended-release formulation intended for dosing every 2 months, and the dose needed to support the extension of the dosing interval is higher than the LD (960 mg), this safety review has a particular focus on local site reactions and severity and timing of systemic adverse reactions (ARs).

The following events were assessed in the three studies:
- Deaths
- Serious AEs
- Discontinuation rate due to AEs

In addition, the following events were assessed only in the pivotal study (Study 031-201-00181)
- AEs
- Adverse Events of Special Interest (AESI):
  - EPS-related AEs
  - suicidality-related AEs
  - injection-site-related AEs
  - glucose-related AEs
  - QT interval-related AEs
  - prolactin-related AEs
  - white blood cell abnormality-related AEs
  - orthostasis-related-AEs
  - lipid-related AEs
  - weight-related AEs

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- Vital signs
- ECGs
- Clinical laboratory monitoring (serum chemistry, hematology, and urinalysis)
- Physical examinations
- EPS as measured by the SAS, AIMS, and BARS, frequency and time to EPS
- VAS scores for pain perception
- Investigator's Assessment of Most Recent Injection Site
- Suicidality via the C-SSRS
- Concomitant medication usage

Review of the Safety Database

Overall Exposure

Per the Applicant, all three studies (Study 031-201-00181, Study 031-201-00104, and Study 031-201-00279) are completed and there are no ongoing studies for this program. This review focuses on all available data and no further data were submitted by the Applicant at the 120-day update. The composition of the safety population is described in Table 18.

Table 18: Safety Population for Aripiprazole 2M RTU LAI Development

Clinical Trial Groups	Aripiprazole 2M RTU LAI (n=240)	Abilify Maintena (n= 134)
Primary safety study 031-201-00181	132	134
Phase 1 Study 031-201-00104	36	0
Phase 1 Study 031-201-00279	72	0
Controlled trials conducted for other indications	0	0

Source: Applicant's Tabular Listing of Clinical Studies and Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) of the Clinical Study Report of Study 031-201-00181.

Adequacy of the safety database

The safety analysis set includes all patients who received at least one dose of 2M RTU LAI aripiprazole or Abilify Maintena. In Study 031-201-00181, 108 subjects were exposed to three injections of aripiprazole 2M RTU LAI; and 104 subjects were exposed to four injections (Table 14). One subject required one time dose reduction due to EPS-related treatment emergent adverse events (TEAE; adverse events starting only during the active treatment period with the IMP). Exposure data from the single ascending dose study (031-201-00104) and in the single- and multiple-dose study (031-201-00279) are also reported in Table 19.

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Table 19: Exposure to aripiprazole 2M RTU LAI and aripiprazole 1M RTU LAI

Study 031-201-00181	2M RTU LAI aripiprazole n (dose)
1st injection (8 weeks 2M LAI)	132 (960 mg)
2nd injection (16 weeks 2M LAI)	114[a] (960 mg)
3rd injection (24 weeks 2 M LAI)	108 (960 mg)
4th injection (32 weeks 2M LAI)	104 (960 mg)
Study 031-201-00104	**2M RTU LAI aripiprazole n (dose)**
1 injection (8 weeks 2M LAI)	18 (780 mg)
1 injection (8 weeks 2M LAI)	18 (1200 mg)
Study 031-201-00279	**1M RTU LAI aripiprazole n (dose)**
Part A SD 1 injection (4 weeks 1M LAI)	24 (420 mg)
Part A MD 1st injection (4 weeks 1M LAI)	28 (420 mg)
2nd injection (8 weeks 1M LAI)	28 (420 mg)
3rd injection (12 weeks 1M LAI)	26 (420 mg)
4th injection (16 weeks 1M LAI)	26 (420 mg)
5th injection (20 weeks 1M LAI)	26 (420 mg)
Part B MD 1st injection (4 weeks 1M LAI)	20 (420 mg)

Aripiprazole 2M RTU LAI = aripiprazole 2-months ready-to-use long-acting-injection
Aripiprazole 1M RTU LAI = aripiprazole 1-month ready-to-use long-acting-injection
SD = single dose; MD = multiple doses
[a]One subject received a one-time dose of 600 mg instead than 960 mg of aripiprazole 2M RTU LAI
Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) of the Clinical Study Report of Study 031-201-00181, Study 201-00104, and Study 201-00279.

Clinical Reviewer's Comment: The size of the safety database appears adequate to draw meaningful conclusions from the study results. The open-label design and use of concomitant antipsychotic medications in Study 031-201-00181 limit the interpretability of the safety data; however, aripiprazole is a currently marketed drug with a known safety profile.

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Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

This submission contains all required components of the electronic common technical document (eCTD). The overall quality and integrity of the datasets was reviewed by the DF-core Data-fitness Service and appeared acceptable. The Office of Study Integrity and Surveillance (OSIS) conducted inspections of sites of Study 031-201-00181 and concluded the data from audited study are reliable.

There were unreported AEs for three subjects (subject ⬛ (b) (6), rash; subject ⬛ (b) (6), neck stiffness, upper respiratory infection; subject ⬛ (b) (6), right shoulder strain) and one unreported medication (subject ⬛ (b) (6), diphenhydramine). There were changes in dates for medications that could potentially affect eligibility of subjects ⬛ (b) (6) and ⬛ (b) (6)

Clinical Reviewer's Comment: A review of these deviations did not raise concerns and did not affect safety conclusions.

Categorization of Adverse Events

The Applicant categorized adverse events using Medical Dictionary for Regulatory Activities (MedDRA) versions 23.0. AEs were recorded at each study visit for all studies, and the Applicant used standard methods for severity coding. Verbatim and preferred terms (PTs) were inspected and most of the Applicant's mapping were acceptable. Clinical judgment was used to review available data and narratives for AE adjudication apart from those the Applicant included. As a result, the clinical review includes some AE analysis adjustment which deviates from the Applicant's analyses for tables in Section 8 (Applicant AE data tables were used for the other sections; refer to the source under each table, as needed).

The following terms were grouped together:

EPS: Akathisia, bradykinesia, dyskinesia, dystonia, dystonic tremor, essential tremor, extrapyramidal disorder, head titubation, hypertonia, intention tremor, joint stiffness, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, musculoskeletal stiffness, nuchal rigidity, oromandibular dystonia, parkinsonian gait, parkinsonian rest tremor, parkinsonism, rapid-onset dystonia-parkinsonism, resting tremor, salivary hypersecretion, torticollis, tremor, trismus

Somnolence: Sedation

Injection site reactions: Injection site nodule, injection site rash, injection site pruritus, injection site swelling, injection site pain, injection site mass, injection site bruising, injection site induration, injection site dermatitis, injection site oedema, injection site discoloration, injection

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site erythema, injection site irritation, injection site dryness, injection site inflammation, injection site injury, injection site paresthesia, injection site hematoma, injection site abscess, injection site warmth, injection site hypoesthesia

Depression: Depressed mood, depressed symptom, major depression, tearfulness

Routine Clinical Tests

The schedule for collection of routine clinical tests is presented in 8.1.1, Table 9 and Table 10.

Clinical Reviewer's Comment: The Applicant's scheduling of clinical tests was adequate to support the clinical safety review. Orthostatic blood pressure (BP) measurements were performed routinely with vital sign assessment and therefore risk of orthostatic hypotension could be assessed. The Investigator's Assessment of Most Recent Injection Site included pain, swelling, redness, and induration and was reported in 4-point categorical scale (absent, mild, moderate, and severe) at each injection for each participant. Local tolerability assessments also included administration of the VAS for evaluation of subjective pain perception at injection site.

Safety Results

Deaths

One death occurred in the development program, in Study 031-201-00181.

Subject _____ (b) (6), a 52-year-old Black female with schizophrenia and significant medical history of hypertension, diabetes mellitus, and tobacco consumption, experienced the fatal adverse event of cardiac arrest, 41 days after the fourth dose of the study drug.

Clinical Reviewer's Comment: The patient had several underlying risk factors for cardiac arrest, including diabetes, tobacco consumption, and hypertension. Although antipsychotics can increase cardiac risk factors (such as increasing the risk of diabetes and dyslipidemia), it is unlikely this death is immediately related to study drug.

Nonfatal Serious Adverse Events

Percentages of nonfatal SAEs were similar between the two arms in Study 031-201-00181 (6% in the Abilify Maintena group, 4% in the Aripiprazole 2M LAI 960 mg group, Table 20). Each SAE was reported in no more than one patient, except for auditory hallucinations, which were reported in two patients in the Aripiprazole 2M RTU LAI group.

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Table 20: Nonfatal Serious Adverse Events (Study 031-201-00181)

Preferred Term	Abilify Maintena N=134 n (%)	Aripiprazole 2M RTU LAI N=132 n (%)
Patients with any Serious Adverse Events[a]	8 (6)	5 (4)
Cholecystitis acute	1 (1)	0 (0)
Cellulitis	0 (0)	1 (1)
Septic shock	1 (1)	0 (0)
Adenocarcinoma of colon	1 (1)	0 (0)
Akathisia	1 (1)	1 (1)
Depression	1 (1)	0 (0)
Depressive symptom	1 (1)	0 (0)
Hallucination, auditory	0 (0)	2 (2)
Psychotic disorder	1 (1)	1 (1)
Schizophrenia	1 (1)	0 (0)
Suicide attempt	1 (1)	0 (0)

[a]Subjects with adverse events in multiple System Organ Classes (SOCs) were counted only once towards the total
Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (adsl.xpt) and Adverse-Event Analysis Dataset (adae.xpt) of Study 031-201-00181.

This table was generated excluding the single case of death, which is summarized separately.

In Study 031-201-00104, one subject experienced worsening of psychosis 143 days after receiving the study drug injection (780 mg) and one subject experienced two SAEs: a concussion with skull base fracture 118 days after receiving the study drug injection and paranoia 198 days after receiving the study drug injection (both at the dose of 780mg).

In Study 031-201-00279, two subjects experienced one SAE each, both in the single dose part of the study (Part A). One subject experienced infective arthritis 63 days after the study drug injection, and one subject experienced amphetamine acute intoxication 126 days after study drug injection.

Clinical Reviewer's Comment: Only auditory hallucinations were reported in more than one subject (two subjects in Study 031-201-00181). SAEs are mainly psychiatric in nature and likely related to the conditions (schizophrenia and bipolar disorder) rather than the study drug. SAEs that could be related to the aripiprazole 2M RTU LAI are those that could be sequelae of EPS (akathisia). The SAEs did not raise any new safety concerns. None of the SAEs reported in the supportive studies (Study 031-201-00104 and Study 031-201-00279) seem to be related to the

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study drug considering the long interval between the study drug administration and the onset of the SAE.

Dropouts or Discontinuations Due to Adverse Effects

In Study 031-201-00181, the percentage of patients with AEs leading to treatment discontinuation was lower in the Aripiprazole 2M RTU LAI group (3%) compared to the Ability Maintena group (8%; Table 21)

Table 21: Discontinuations due to adverse events (Study 031-201-00181)[a]

System Organ Class Preferred Term	Abilify Maintena N=134 n (%)	Aripiprazole 2M RTU LAI N=132 n (%)
Any TEAE with Discontinuation[a]	**10 (8)**	**4 (3)**
Infections and infestations	1 (1)	0
Septic shock	1 (1)	0
Nervous system disorders	5 (4)	2 (2)
Akathisia	2 (2)	2 (2)
Dyskinesia	1 (1)	0
Somnolence	1 (1)	0
Tremor	1 (1)	0
Psychiatric disorders	4 (3)	3 (2)
Anxiety	0	2 (2)
Depression	1 (1)	0
Depressive symptom	1 (1)	0
Psychotic disorder	1 (1)	1 (1)
Restlessness	0	1 (1)
Schizophrenia	1 (1)	0
Suicide attempt	1 (1)	0

[a]Patients who had multiple AEs in a system organ class leading to discontinuation were counted only once. This table was generated excluding the single case of death, which is summarized separately.
Source: Clinical Reviewer's Summary based on individual patient narratives of withdrawals due to adverse events (AEs), and Subject-Level Analysis Dataset (adsl.xpt) and Adverse-Event Analysis Dataset (adae.xpt) of Study 031-201-00181.

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In supportive Studies 031-201-00104 and 031-201-00279, no AEs lead to discontinuation of the IMP.

Clinical Reviewer's Comment: Overall, the safety findings from pivotal Study 031-201-00181, as well as from the supportive studies, are consistent with the known safety profile of Abilify Maintena (the LD). Discontinuation due to EPS (e.g., akathisia, tremor, and dyskinesia), as well as discontinuation due to exacerbation of underlying psychiatric disorders are expected.

Significant Adverse Events

In Study 031-201-00181, most AEs in the aripiprazole 2M RTU LAI group and Abilify Maintena group were reported as mild to moderate in severity. Five subjects in the aripiprazole 2M RTU LAI group had AEs assessed as severe (psychotic disorder, anxiety, cardiac arrest, and akathisia, each in one subject; and two events of akathisia in one subject) compared to four subjects in the LD group (septic shock, adenocarcinoma of colon, and akathisia, each in one subject; and encephalopathy, loss of consciousness, schizophrenia, and suicide attempt, all in one subject).

Treatment Emergent Adverse Events and Adverse Reactions

Table 22 reports TEAEs occurring in greater than 5% of patients by treatment group in Study 031-201-00181. Weight increase, akathisia, anxiety, and insomnia were the most frequently reported in both groups.

Of note, the frequency of injection site pain and headache in the aripiprazole 2M RTU LAI group was almost two-fold greater that in the aripiprazole 2M RTU LAI group (18% versus 9%, and 8% versus 4%, respectively).

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Table 22: Most Common TEAEs (≥ 5%) in Study 031-201-00181 by SOC and Preferred Term

System Organ Class Preferred Term	Abilify Maintena N=134 n (%)	Aripiprazole 2M RTU LAI N=132 n (%)
Gastrointestinal disorders		
Constipation	8 (6)	8 (6)
Toothache	10 (7)	2 (2)
General disorders and administration site conditions		
Injection site pain	12 (9)	24 (18)
Investigations		
Increased weight	28 (21)	30 (23)
Nervous system disorders		
Akathisia	12 (9)	13 (10)
Headache	5 (4)	10 (8)
Psychiatric disorders		
Anxiety	10 (7)	11 (8)
Insomnia	11 (8)	10 (8)

Source: Table 12.2.2.1-1, pg. 97 of Applicant's Clinical Study Report of Study 031-201-00181 and Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (adsl.xpt) and Adverse-Event Analysis Dataset (adae.xpt) of Study 031-201-00181 (the single case of deaths was excluded).

Clinical Reviewer's Comment: Events of injection site pain were more frequent in the aripiprazole 2M RTU LAI group compared to the LD. However, all events occurred within 2 days of the injection and lasted less than 5 days in all but four subjects (two subjects in each treatment group). In both treatment groups, the majority of injection site pain events occurred with the first injection, were mild and did not lead to drug discontinuation.

The study identified higher frequency of headache and toothache in the aripiprazole 2M RTU LAI group compared to the control group; however, this appears to be a random observation and is not expected to be clinically significant. Overall, the safety findings are consistent with the safety profile of the LD.

Laboratory Findings

The laboratory assessments were compared between treatment groups.

- Prolactin: Changes from baseline in prolactin levels were similar between aripiprazole 2M

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RTU LAI group and Abilify Maintena group (decreased of 6.1 ng/mL and 5.6 ng/mL respectively).

- Glucose: Glucose levels >200 mg were observed in seven subjects (7/128, 6%) in the aripiprazole 2M RTU LAI group compared to three subjects (3/126, 2%) in the Abilify Maintena group. Changes from baseline in glucose levels were higher in the aripiprazole 2M RTU LAI group (mean increase 5.3 mg/dL ± 59) compared to the Abilify Maintena group (mean decrease 0.9 mg/dL ± 37), but the difference was mainly driven by an outlier (one subject had a final glucose level >500 mg/dL).

- Hematology: Given that in clinical trials and post-marketing experience, events of leukopenia, neutropenia, and agranulocytosis have been reported temporally-related to antipsychotic agents, abnormal hematology values were evaluated and compared between treatment groups. One case of neutropenia was clinically meaningful in a subject in the Abilify Maintena group. In the laboratory dataset, shift in neutrophil values outside the normal range for at least one time point during the clinical trial occurred with comparable frequency in the aripiprazole 2M RTU LAI and Abilify Maintena groups, and none of these shifts were clinically meaningful, except for the case of neutropenia in the subject described in the Abilify Maintena group (neutrophils 0.65 10^9/L at Day 29, normalized at follow-up visits).

Clinical Reviewer's Comment: Overall, laboratory findings in all studies did not show any significant clinical difference with the safety profile of the LD.

Vital Signs

Vital sign measurements included systolic and diastolic BP, heart rate, and body temperature. Vital signs were obtained prior to PK blood draws and ECGs at the time points described in Table 9 and Table 10. At each time point, BP (systolic and diastolic) and heart rate were taken after subjects had been in the supine position for at least 5 minutes and again after subjects had been standing for 2 minutes, but not more than 3 minutes. Body temperature was taken with the subject in the supine position (only once).

Mean values and changes from baseline for vital signs were not notable for differences between the two treatment groups. Vital sign values were similar in the two groups, except for hypertension, more frequent in the Abilify Maintena group (Table 23).

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Table 23: Vital Signs – Changes from Baseline in Any Treatment Group, By Vital Sign Recording and MedDRA Preferred Term (Study 031-201-00181)

Vital signs changes from baseline (advs.xpt)	Abilify Maintena N=134 n (%)	Aripiprazole 2M RTU LAI N=132 n (%)
Hypertension	7 (5.2)	3 (2.3)
Orthostasis	2 (1.5)	2 (1.5)
Vital signs – Preferred Term (adae.xpt)		
BP increase	2 (1.5)	1 (0.8)
Body temperature increase	0	1 (0.8)
Heart rate increase	1 (0.7)	0
Hypertension	6 (4.5)	2 (1.5)
Weight decrease	3 (2.2)	2 (1.5)

Source: Clinical Reviewer's Summary based on Vital Signs Results Analysis Dataset (advs.xpt), and Subject-Level Analysis Dataset (adsl.xpt) and Adverse-Event Analysis Dataset (adae.xpt) of Study 031-201-00181.

Clinical Reviewer's Comment: The frequency of subjects with vital signs outside the normal range was similar in the two treatment groups, regardless as to whether values were analyzed through the vital sign database (advs.xpt) or through the AE database (adae.xpt). The aripiprazole 2M RTU LAI group had slightly lower cases of hypertension in both databases (adae.xpt and advs.xpt), which does not appear clinically significant in consideration of the small numbers. Overall, no pattern of vital sign changes that represented a new safety signal was found.

Electrocardiograms

Twelve-lead ECGs in triplicate (5 minutes apart) were recorded at Screening, Baseline, and at the time points indicated in Table 9 and Table 10.

There were no notable differences between the treatment groups in mean PR interval, QRS duration, QT interval, and respiratory rate at baseline and last visit. The incidence of ECG measurements of potential clinical relevance (not present at baseline but present post-baseline) was equally distributed between the two treatment groups:

- Bradycardia: n=2 (1.5%) in the Ability Maintena group

- Supraventricular premature beat: n=10 (7.6%) in the Abilify Maintena group versus n=13 (10%) in the aripiprazole 2M RTU LAI group

- Ventricular premature beat: n=12 (9.2%) in the Abilify Maintena group versus n=17 (13.1%) in the aripiprazole 2M RTU LAI group

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- Right bundle branch block: one case for each treatment group

- ST/T morphology indicative of cardiac ischemia: n=3 (2.3%) in the aripiprazole 2M RTU LAI group versus n=7 (5.3%) in the Abilify Maintena group

- ST/T morphology indicative of symmetrical T-wave inversion: n=8 (8.8%) in the aripiprazole 2M RTU LAI group versus n=10 (11.1%) in the Abilify Maintena group

There was one TEAE related to ECG (ECG T-wave inversion) in one subject (0.7%) in the Abilify Maintena group, compared to no subject in the 2M RTU LAI aripiprazole group.

Clinical Reviewer's Comment: Overall, ECG results do not show clinically significant trends consistent with a new safety signal for aripiprazole 2M RTU LAI.

QT

On average, both groups had decreased QTcF from baseline to last assessment (change mean ± SD = -2.6 ± 15 in the aripiprazole 2M RTU LAI group versus change mean ± SD = -1.7 ± 16 in the Abilify Maintena group). No patient had a QTc interval (QTcF) greater than 500 msec at the last assessment time point.

The incidence of QTc abnormalities of potential clinical relevance at any time was equally distributed between the two treatment groups:

- QTcB ≥ 450 msec and ≥10% increase: one case in the aripiprazole 2M RTU LAI group

- QTcF ≥ 450 msec and ≥10% increase: one case in the Abilify Maintena group

- QTcN ≥ 450 msec and ≥10% increase: one case in the Abilify Maintena group

- New onset QTcF >450 mg: one case (0.7%) in the aripiprazole 2M RTU LAI group versus n = 3 (2.2%) in the Abilify Maintena group

There were no TEAEs related to QT interval abnormalities.

Clinical Reviewer's Comment: In general, the effect of aripiprazole 2M RTU LAI on the QT was comparable to the effect of Abilify Maintena. Of note, during the screening, participants with QTcF ≥450 msec in males or ≥470 msec in females were excluded from the study. The safety of 2M RTU LAI aripiprazole on this subpopulation with QTc prolongation cannot be established with this study.

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Immunogenicity

N/A

Analysis of Submission-Specific Safety Issues

Injection Site Reactions

Local pain and other injection site reactions were identified as potential risks with the administration of aripiprazole long-acting injection.

Injection site AEs were reported in higher frequency in patients in the aripiprazole 2M RTU LAI group than in patients in the Abilify Maintena group. Table 24 summarizes all injection site AEs using a reviewer-generated customized grouping of preferred terms, as described in Section 8.2.3, Categorization of Adverse Events. None of the injection site AEs were serious, severe, or required treatment discontinuation.

Table 24: Injection Site Adverse Events (Study 031-201-00181)

Custom Query	Preferred Term	Abilify Maintena N=134 n (%)	Aripiprazole 2M RTU LAI N=132 n (%)
Injection Site Reactions	Total[a]	12 (9)	25 (19)
	Injection site pain	12 (9)	24 (18)
	Injection site mass	0	1 (<1)
	Injection site discomfort	0	1 (<1)

[a] Subjects with multiple adverse event terms within the same category were counted only once towards the category total
Source: Table CT-8.2.6, and Summary 12.5.5.3 of Applicant's Clinical Study Report of Study 031-201-00181 and Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (adsl.xpt) and Adverse-Event Analysis Dataset (adae.xpt) of Study 031-201-00181.

Investigator assessment
- Injection site redness: Investigator's assessment of the most recent injection site reported mild symptoms of redness in three subjects in the aripiprazole 2M RTU LAI group and one subject in the Abilify Maintena group in the first injection, one subject in the Abilify Maintena group at Day 29, one subject in the aripiprazole 2M RTU LAI group at Day 113, and in one subject in the aripiprazole 2M RTU LAI group in the last injection, as reported in the advas.xpt dataset.

- Injection site pain: Investigator's assessment of the most recent injection site reported moderate symptoms of pain in two subjects in the Abilify Maintena group, and in none in the aripiprazole 2M RTU LAI group. Mild symptoms of pain were reported in 11 subjects (8%, 11/130) in the aripiprazole 2M RTU LAI group and 7 subjects (5%, 7/133) in the Abilify

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Maintena group on Day 1, and in 5 subjects (4%, 5/132) in the aripiprazole 2M RTU LAI group and in 3 subjects (2%, 3/134) in the Abilify Maintena group on the last day.

- Injection site swelling/induration: There were no cases of swelling or induration, as assessed by the Investigator's assessment of the most recent injection site, in neither group.

Subject-reported assessment

The mean VAS scores for subject-reported rating of pain were similar in both treatment groups at the last injection: 0.8 pre-dose and 1.4 post-dose in the aripiprazole 2M RTU LAI group and 0.9 pre-dose and 1.3 post-dose in the Abilify Maintena group. At Day 1, four subjects, all in the aripiprazole 2M RTU LAI group had VAS scores > 30; at last visit, only one subject, in the aripiprazole 2M RTU LAI group, had score > 30. No subjects in the Abilify Maintena group had VAS scores > 30 during the study (source: Clinical Reviewer's Summary based on VAS Analysis Dataset [ADVAS.xpt] of Study 031-201-00181).

Clinical Reviewer's Comment: Despite getting half of the number of injections of the Abilify Maintena group, the aripiprazole 2M RTU LAI group had twice the frequency of TEAEs related to injection reactions. While these data could potentially represent a specific safety concern for this product, most injection reactions were mild, and none was serious or required discontinuation of treatment.

Extrapyramidal symptoms

Overall, the total number of EPS-related TEAEs EPS was higher in the aripiprazole 2M RTU LAI group compared to the Abilify Maintena group (27% versus 18%, respectively). The median time between last injection and onset of EPS was comparable between groups (Table 25).

Table 25: EPS-Related Treatment-Emergent Adverse Events (Study 031-201-00181)

Preferred term	Abilify Maintena N=134		Aripiprazole 2M RTU LAI N=132	
	n (%)	Days Since Last Dose Mean (SD) Median [Min, Max]	n (%)	Days Since Last Dose Mean (SD), Median [Min, Max]
Total[a]	18 (13.4)	11.6 (9.20), 8.0 [1, 29]	27 (20.5)	16.7 (15.7), 10 [0, 57]
Akathisia	12 (9.0)	10.6 (9.53), 8.0 [1, 29]	13 (9.8)	16.7 (15.9), 10 [1, 57]
Bradykinesia	0	-	1 (0.8)	0.2 (0), 0.2 [0, 0]
Dyskinesia	2 (1.5)	17.3 (11.1), 16.0 [7, 29]	4 (3.0)	10.8 (9.48), 10.2 [1, 22]
Extrapyramidal disorder	1 (0.7)	22.0 (0), 22. 0 [22, 22]	2 (1.5)	8.0 (9.90), 8.0 [1, 15]
Head titubation	1 (0.7)	8.0 (0), 8.0 [8, 8]	0	-

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Intention tremor	0	-	1 (0.8)	33.0 (0), 33.0 [33, 33]
Joint stiffness	0	-	2 (1.5)	44.5 (10.6), 44.5 [37, 52]
Muscle spasms	0	-	3 (2.3)	12.0 (13.1), 6.0 [3, 27]
Muscle twitching	0	-	2 (1.5)	24.1 (6.93), 24.1 [19, 29]
Musculoskeletal stiffness	0	-	2 (1.5)	28.7 (33.0), 28.7 [5, 52]
Oromandibular dystonia	0	-	2 (1.5)	14.8 (13.8), 14.8 [5, 25]
Parkinsonism	0	-	1 (0.8)	8.0 (0), 8.0 [8, 8]
Tremor	4 (3.0)	9.8 (7.58), 11.0 [1, 16]	1 (0.8)	4.0 (0), 4.0 [4, 4]
Trismus	0	-	1 (0.8)	5.3 (0), 5.3 [5, 5]

[a]Subjects with multiple EPS were counted only once towards the category total

EPS = extrapyramidal symptoms; SD = standard deviation

Source: Applicant's response to Division's Information request (NDA 217006, SDN 13, November 23, 2022).

EPS were also assessed using rating scales such as the SAS, the AIMS, and the BARS. The descriptive comparison between the two treatment groups did not show notable differences in the change from baseline in all EPS rating scales.

Clinical Reviewer's Comment: An information request was sent to the Applicant requesting the timing between last injection and onset of EPS adverse events in order to exclude a potential dose-dumping effect of aripiprazole 2M RTU LAI as cause of the higher incidence of EPS in the aripiprazole 2M RTU LAI group compared to the Abilify Maintena group. The timing between last injection and onset of EPS adverse events appeared similar in the two groups.

Other adverse events of special interest

- Weight increase: Weight increase is frequently observed with antipsychotics and occurred with similar frequency in the two treatment groups (Table 17, Table 20).

- Metabolic syndrome and glucose: Glucose levels were higher in the aripiprazole 2M RTU LAI (Table 22; Section 8, Safety Results – Laboratory Findings). There were two TEAEs related to increased glucose levels (PT: Diabetes mellitus; hyperglycemia) in two subjects (1.5 %) in the aripiprazole 2M RTU LAI group, and no subject in the Abilify Maintena group. No increased triglyceride or lipid levels were reported as TEAEs.

- Neutropenia: As described in Section 8, Safety Results – Laboratory Findings, neutropenia was observed in one case in the Abilify Maintena group only.

- Creatine phosphokinase (CPK): Twelve subjects in the aripiprazole 2M RTU LAI group had high CPK values, compared to one subject in the Abilify Maintena group, as observed in the

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adlb.xpt database. In 3 of these 12 subjects, the increased CPK level was clinically significant (although not serious) and was reported in the adae.xpt database. Of note, 11 of these 12 subjects had already elevated CPK levels at screening or baseline. CPK values reported in these subjects did not exceed 10 times the ULN for CPK.

Table 26: Other Adverse Events of Special Interest (Study 031-201-00181)

	Abilify Maintena N=134	Aripiprazole 2M RTU LAI N=132
Weight		
Gain ≥7% incr. from baseline n/total (%)	54/126 (43)	52/128 (41)
Change from baseline (kg) mean ± SD	3.0 ± 5.9	3.6 ± 5.9
Neutropenia n (%)	1 (1)	0
Prolactin ng/mL		
Change from baseline mean ± SD	-6.1 ± 12.9	-5.6 ± 11.8
Glucose mg/dL		
Change from baseline mean ± SD (%)	-0.9 ± 37 (3)	5.3 ± 59 (9)[a]
Glucose>200 mg/dL n/total (%)	3/126 (2)	7/128 (6)
CPK U/L		
CPK > 3 x ULN n/total (%)	1/126 (0.8)	12/128 (9.4)[b]
Suicide ideation/attempt	1/134 (0.8)	1/132 (0.7)

CPK = Creatine phosphokinase; SD = standard deviation; ULN = upper limit of the normal range
[a]One outlier with glucose level at end of study > 500 mg/dL
[b]Eleven subjects had increased CK levels at baseline or screening.
Source: Clinical Reviewer's Summary based on and Adverse-Event Analysis Dataset (adae.xpt) and Labs Analysis Dataset (adlb.xpt) of Study 031-201-00181.

Clinical Reviewer's Comment: In summary, the safety profile of aripiprazole 2M RTU LAI is consistent with the known safety profile of aripiprazole and submission-specific safety issues are similar to those reported in the label for Abilify Maintena. One notable exception is the higher frequency of injection site adverse reactions and EPS. Of note, the same number of subjects reported EPS (akathisia) as SAE in both treatment groups (Table 20), but more subjects discontinued treatment due to EPS in the Abilify Maintena group (Table 21). Injection site adverse reactions were not serious and did not require treatment discontinuation in either group. In addition, confounding factors can be responsible for differences observed in EPS between the two groups; for example, participants in the aripiprazole 2M RTU LAI group had a higher concomitant use of oral risperidone.

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Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

N/A

Safety Analyses by Demographic Subgroups

The limited number of exposures in this development program precludes meaningful subgroup analyses.

Specific Safety Studies/Clinical Trials

N/A

Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No new information about human carcinogenicity or tumor development was submitted with this application.

Human Reproduction and Pregnancy

No new information about human reproduction and pregnancy was submitted with this application. There were no pregnancies reported during the trial.

Pediatrics and Assessment of Effects on Growth

No pediatric data was submitted with this application.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No analyses or assessments regarding overdose, drug abuse potential, withdrawal, or rebound were conducted in these studies. Our understanding of these areas are mainly informed by Abilify Maintena, the LD, and trials with the oral formulation.

Safety in the Post market Setting

Safety Concerns Identified Through Postmarked Experience

Aripiprazole 2M RTU LAI is not currently marketed in any country. The following adverse reactions have been identified and added to product labeling since the initial approval of Abilify in 2002: occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm), pathological gambling, hiccups, blood glucose fluctuation, oculogyric crisis, and drug reaction with eosinophilia and systemic symptoms (DRESS).

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Expectations on Safety in the post market Setting

A PK bridge was established between aripiprazole 2M RTU LAI and the LD, Abilify Maintena. The post market safety profile is anticipated to be similar to that of the LD.

Integrated Assessment of Safety

The determination of safety for this product relies on investigations conducted with Abilify Maintena. Some comparative safety data was derived from bioequivalence/bioavailability studies for this product. These data were analyzed for potential safety issues specific to the 2M RTU formulation that might differ from the LD. There were no apparent issues with local tolerability. Overall, this safety review has not identified any unlabeled safety issues related to the aripiprazole 2M RTU LAI formulation that would preclude the approval of this NDA.

8.3. Statistical Issues

This development program did not include efficacy studies that would be subject to statistical review; see Section 6 for discussion of statistical issues related to PK comparison.

8.4. Conclusions and Recommendations

The safety profile of aripiprazole 2M RTU LAI is consistent with that of Abilify Maintena.

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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. The trial designs are similar to those for previously approved products for this indication. Evaluation of the data did not raise significant, unexpected safety or efficacy issues. Therefore, the Agency concluded that outside expertise was not necessary.

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10. Pediatrics

No new pediatric data was submitted with this application; this application relies on the Agency's findings of safety and effectiveness for the LD, Abilify Maintena. This product is a new dosage form of aripiprazole, therefore, in order to fulfill the Pediatric Research Equity Act (PREA) requirements, the Applicant submitted an initial Pediatric Study Plan (iPSP) with a justification for a full waiver for pediatric studies on the basis that studies would be unfeasible or highly impractical for both indications (schizophrenia and maintenance monotherapy treatment of bipolar I disorder). The Applicant's iPSP was reviewed by the Pediatric Review Committee in June 2019. An Agreed iPSP letter was issued on September 30, 2019. No additional pediatric trials will be required for this formulation. Pediatric labeling for the treatment of schizophrenia will be consistent with that of Abilify Maintena.

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11.   Labeling Recommendations

11.1. Prescription Drug Labeling

The prescribing information (PI) is generally consistent with that of Abilify Maintena. Below are changes introduced during the review cycle with respect to the PI submitted by the Applicant with this NDA.

(b) (4)

1 Page(s) of Draft labeling has been Withheld in Full as b4(CCI/TS) Immediately following this page

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12. Risk Evaluation and Mitigation Strategies (REMS)

There were no safety findings in the clinical review of this application that suggested the need for REMS.

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13.   Postmarketing Requirements and Commitment

Post marketing requirements or commitments were not deemed necessary.

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14. Deputy Division Director (Signatory) Comments

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

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15. Appendices

15.1. References

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15.2. Financial Disclosure

The submitted information including a list of clinical investigators are noted.

Covered Clinical Study (Name and/or Number): Study 031-201-00181

Was a list of clinical investigators provided:	Yes ☒ No ☐ (Request list from Applicant)
Total number of investigators identified: <u>21</u>	
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>	
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>	
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u>	

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Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>0</u>			
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐	(Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	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 ☐	No ☐	(Request explanation from Applicant)

15.3. Clinical Pharmacology

Individual Study Review (Pivotal BA Study: 031-201-00181)

Study # 031-201-00181   **Study Period**: 8/1/2019-7/8/2020
                                  Bioanalysis Period: 2/6/2020-11/23/2020
Title: A Phase 1b, Open-label, Multiple-dose, Randomized, Parallel-arm, Safety, Tolerability, and Pharmacokinetic Trial of Aripiprazole Intramuscular Depot Administered in the Gluteal Muscle in Adult Subjects with Schizophrenia or Bipolar I Disorder
EDR link: 031-201-00181

- **Primary objectives:**
  - To determine the safety and tolerability of multiple-dose administrations of aripiprazole in adult subjects with schizophrenia or bipolar I disorder.
  - To establish the similarity of aripiprazole concentrations on the last day of the dosing interval following the final administration of aripiprazole into the gluteal muscle site in adult subjects with schizophrenia or bipolar I disorder.
  - To establish the similarity of aripiprazole exposure over the dosing interval following the administration of aripiprazole into the gluteal muscle site in adult subjects with schizophrenia or bipolar I disorder.

- **Study Design:** This was a phase 1b, open-label, multiple-dose, randomized, parallel-arm, multicenter trial in adult subjects with schizophrenia or bipolar I disorder. After screening, eligible subjects were randomized (1:1) to receive multiple doses of either aripiprazole 2M LAI 960 mg (4 injections) or aripiprazole IM depot 400 mg (8 injections) over the course of 32 weeks. Randomization to the 2 trial treatments was stratified by the PK sampling schedule (robust or sparse) and disease type (schizophrenia or bipolar I disorder). Aripiprazole 2M LAI

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960 mg was administered at 56-day (± 2 days) intervals on Days 1, 57, 113, and 169 and aripiprazole IM depot 400 mg was administered at 28-day (± 2 days) intervals on Days 1, 29, 57, 85, 113, 141, 169, and 197. A final visit occurred 56 (± 2) days after the last dose of aripiprazole 2M LAI 960 mg or 28 (± 2) days after the last dose of aripiprazole IM depot 400 mg.

Subjects who did not have a history of tolerating aripiprazole received 3 single 10-mg doses of oral aripiprazole on 3 consecutive days (total of 30 mg) in addition to their current oral antipsychotic, mood stabilizer, and if applicable, antidepressant at least 14 days prior to the first administration of IMP to establish tolerability. At the time of administration of the first dose of IMP, subjects began a 7- to 14-day period (oral overlap) where they transitioned from their current oral antipsychotic to include injections of IMP, as outlined in Table 27 and dose adjustment for oral aripiprazole who were already on aripiprazole was listed in Table 28.

Table 27: Scenarios for Initiation of Oral Aripiprazole Overlap During the First 2 Weeks After the Initiation of IMP

Treatment	PK Sampling Schedule	Current Antipsychotic Medication[a]		
		Abilify Maintena[b] 300 or 400 mg	Oral Aripiprazole[c]	Non-aripiprazole Oral Antipyschotic
Aripiprazole 2M LAI 960 mg	Sparse	No oral overlap	7-day oral overlap with adjusted dose	Continue current antipsychotic for 7 days
	Robust[d]	Not applicable	Not applicable	(Switch to) Oral aripiprazole 10 to 20 mg: 7-day oral overlap
Aripiprazole IM depot 400 mg	Sparse	No oral overlap	14-day oral overlap with adjusted dose	Continue current antipsychotic for 14 days
	Robust[d]	Not applicable	Not applicable	(Switch to) Oral aripiprazole 10 to 20 mg: 14-day oral overlap

[a]Subjects with bipolar I disorder who are taking a mood stabilizer will be permitted to stay on their mood stabilizer over the course of the trial, and if taking an antidepressant, to continue treatment with their antidepressant unless it is unless the medication is prohibited during the trial (e.g., fluoxetine, fluoxetine/olanzapine).
[b] Subjects on an LAI other than Abilify Maintena are excluded from the trial. Subjects on Abilify Maintena as their current antipsychotic medication cannot enroll to the robust sampling schedule.
C For subjects who are taking oral aripiprazole 10 to 20 mg as their current antipsychotic, the dose will be reduced for the overlap period (Table 2).
[d] In order to be enrolled to the robust sampling schedule, subjects must have demonstrated prior tolerability to aripiprazole, must be stabilized on an existing non-aripiprazole antipsychotic, and must switch to oral aripiprazole on Day 1 for 7 or 14 days depending on the assigned IMP treatment.
-source: Tables 3.2.3-1 of CSR

Table 28: Dose Adjustment for Initiation of Oral Overlap for Subjects Currently Stabilized on Oral Aripiprazole

Current Dose of Oral Aripiprazole	Adjusted Dose of Oral Aripiprazole
10 - 20 mg	10 mg
> 20 - 30 mg	15 mg

-source: Tables 3.2.3-2 of CSR

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- **PK Sampling Scheme:**

Aripiprazole 2M LAI 960 mg:
  - *Sparse sampling schedule*: Days 1 (pre-dose and 4, 8, and 12 hours post-dose), 8, 15, 22, 29, 36, 43, 50, 57 (pre-dose), 85, 113 (pre-dose), 141, 169 (pre-dose and 4, 8, and 12 hours post-dose), 176, 183, 190, 197, 204, 211, 218, and 225/ET

  - *Robust sampling schedule*: Days 1 (pre-dose and 4, 8, and 12 hours post-dose), 2, 3, 5, 8, 10, 13, 15, 18, 22, 29, 36, 43, 50, 57 (pre-dose), 85, 113 (pre-dose), 141, 169 (pre-dose and 4, 8, and 12 hours post-dose), 170, 171, 173, 176, 178, 181, 183, 186, 190, 197, 204, 211, 218, and 225/ET

Aripiprazole IM depot 400 mg:
  - *Sparse sampling schedule*: Days 1 (pre-dose and 4, 8, and 12 hours post-dose), 8, 15, 22, 29 (pre-dose), 57 (pre-dose), 85 (pre-dose), 113 (pre-dose), 141 (pre-dose), 169 (pre-dose and 4, 8, and 12 hours post-dose), 197 (pre-dose and 4, 8, and 12 hours post-dose), 204, 211, 218, and 225/ET

  - *Robust sampling schedule*: Days 1 (pre-dose and 4, 8, and 12 hours post-dose), 2, 3, 5, 8, 10, 13, 15, 18, 22, 29 (pre-dose), 57 (pre-dose), 85 (pre-dose), 113 (pre-dose), 141 (pre-dose), 169 (pre-dose and 4, 8, and 12 hours post-dose), 170, 171, 173, 176, 178, 181, 183, 186, 190, and 197 (pre-dose and 4, 8, and 12 hours post-dose), 198, 199, 201, 204, 206, 209, 211, 214, 218, 225/ET.

- **Analytical Method:** LC/MS/MS (OP7HPP)

Table 29: Bioanalytical methods

Analyte		Aripiprazole (OPC-14597)	Dehydro-aripiprazole (OPC-14857)
Matrix		plasma	plasma
Standard Curve	Range (ng/mL)	0.500 to 500	0.500 to 500
	#Conc. points	9	9
	%CV	2.8-3.8	3.4-4.8
	%Bias	-2.6-2.0	-2.3-2.0
	R2	0.9942-0.9996	0.9902-0.9991
Quality Control	Range (ng/mL)	1.50-375	1.50-375
	#Conc. points	4	4
	%CV	3.0-7.3	3.7-5.2
	%Bias	-2.7-(-1.3)	-2.1-0.7
Long-term storage stability at -70°C (days)		1889	
Maximum storage duration at -70°C (days)		405	

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Performance	acceptable

-source: 14.5.1.1 of CSR

- **Results:**

Products used in the study is listed in Table 30.

Table 30: Products Used in the study

Aripiprazole IM depot
Abilify IM depot RTU 300 mg/mL: 18C95A300 in a vial
Abilify IM depot 400 mg/vial: 17G96A400
Commercial Abilify 10-mg and 15-mg tablets
Abilify 10 mg: ALS00918A and ALS00219A
Abilify 15 mg: AMS00319A

Study Population: Of the 266 enrolled subjects, 132 subjects (102 completed) in the aripiprazole 2M RTU 960 mg group and 134 subjects (92 completed) in the aripiprazole IM depot 400 mg group. Major demographic characteristics are summarized in Table 31. The completion rate at Week 32 was 77.3% in the aripiprazole 2M RTU 960 mg group and 68.7% in the aripiprazole IM depot 400 mg group.

Table 31: Demographic Summary (Randomized Sample)

Baseline Characteristics	Aripiprazole 2M LAI 960 mg	Aripiprazole IM Depot 400 mg
Males/Females	90/42	86/48
Schizophrenia/Bipolar	92/40	93/41
Age of 1st diagnosis Schizophrenia/Bipolar	27.5±10.4/ 31.3±13.6	25.8±9.7/ 32.3±13.3
Medication (oral aripiprazole/IM depot aripiprazole/others)	45/6/81	35/3/96
Race (Caucasian/Black/Asian/Other)	29/99/3/1	33/95/4/2
Age*	47.8±10.8	46.8±11.7
Weight (kg)*	84.7±14.7	85.8±16.4
PK sampling (robust/sparse)	42/90	42/92

*Data are presented as mean ± SD   -Source: Table 11.2-1/2 of CSR

CYP2D6 phenotype information in enrolled subjects in summarized in Table 32.

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Table 32: Summary of CYP2D6 Phenotypes

Predicted Phenotype	Aripiprazole 2M LAI 960 mg	Aripiprazole IM Depot 400 mg
Intermediate metabolizer	9	10
Normal metabolizer	71	72
Normal or intermediate metabolizer	36	27
Poor metabolizer	6	4
Unknown	5	14
No sample	5	7
Total	132	134

Source: Table 11.5.5-1 of CSR

Pharmacokinetics

Following first depot administration: aripiprazole plasma concentration versus time profiles following the first administration of aripiprazole 2M LAI 960 mg (+ 7-day overlap with 10 to 20 mg oral aripiprazole) or aripiprazole IM depot 400 mg (+ 14-day overlap with 10 to 20 mg oral aripiprazole) in the gluteal muscle of subjects enrolled to the robust sampling schedule are presented in Figure 13. A summary of aripiprazole PK parameters following the first administration of aripiprazole 2M LAI 960 mg or aripiprazole IM depot 400 mg is presented in Table 33.

Figure 13: Mean (SD) Aripiprazole Plasma Concentration versus Time Profiles following the First Administration of Aripiprazole 2M RTU 960 mg or Aripiprazole IM Depot 400 mg in Subjects Enrolled to the Robust Sampling Schedule

Aripiprazole 2M LAI 960 mg (Black; n = 42); Aripiprazole IM Depot 400 mg (Red; n = 42)
-Source: Figure 11.5.2.3.1.1.1-1 of CSR

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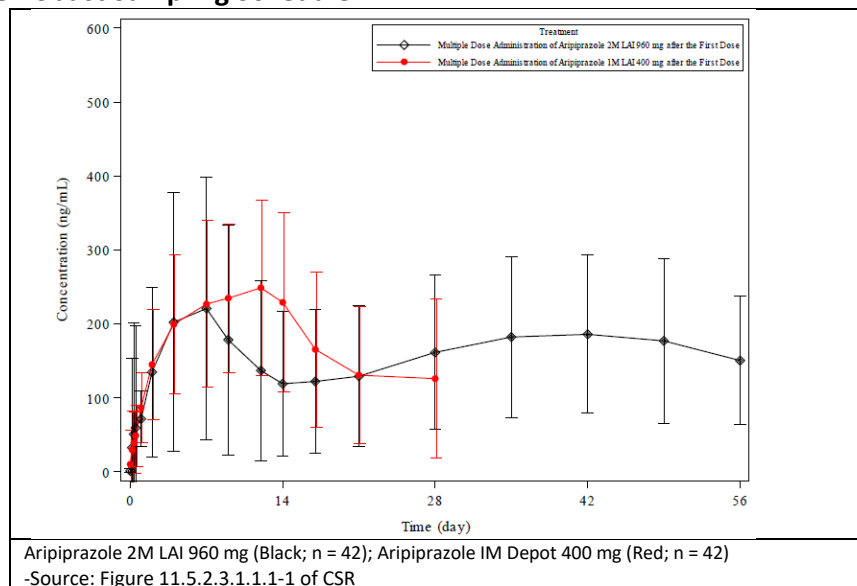
Table 33: Aripiprazole Pharmacokinetic Parameters Following the First Administration of Aripiprazole 2M RTU 960 mg or Aripiprazole IM Depot 400 mg

PK Parameter	Aripiprazole 2M LAI 960 mg		Aripiprazole IM Depot 400 mg	
	Mean (SD)	n	Mean (SD)	n
C_{max} (ng/mL)	286 (203)	37	280 (123)	35
C_7 (ng/mL)	221 (178)	41	227 (113)	42
C_{14} (ng/mL)	119 (98)	38	229 (121)	39
t_{max} (day)[a]	8.58 (3.92 - 55.9)	37	9.04 (3.83 - 27.9)	35
AUC_{0-56} (ng·day/mL)	9180 (4940)	37	ND	-
AUC_{0-28} (ng·day/mL)	4200 (3000)	38	5030 (2580)	35
C_{56} (ng/mL)	165 (91.7)	113[b]	ND	-
C_{28} (ng/mL)	ND	-	112 (82.9)	110[b]

ND = not determined. [a] Median (min - max). [b] Determined from subjects enrolled to the robust and sparse sampling schedules
-Source: Table 11.5.2.3.2.1-1 of CSR

Multiple Dose Administration: Aripiprazole plasma trough concentrations following each administration of aripiprazole 2M LAI 960 mg or aripiprazole IM depot 400 mg in the gluteal muscle are presented in Figure 14. Aripiprazole plasma concentration versus time profiles following the fourth administration of aripiprazole 2M LAI 960 mg or the seventh and eighth administration of aripiprazole IM depot 400 mg are presented in Figure 15. A summary of aripiprazole PK parameters following the fourth administration of aripiprazole 2M LAI 960 mg or the seventh and eighth administration of aripiprazole IM depot 400 mg is presented in Table 34. The GMR and 90% CI for PK parameters of aripiprazole following the fourth administration of aripiprazole 2M LAI 960 mg or the seventh and eighth administration of aripiprazole IM depot 400 mg are presented in Table 35.

Figure 14: **Mean (SD) Aripiprazole Trough Plasma Concentration Versus Time Profiles Following Multiple Dose Administration of Aripiprazole 2M RTU 960 mg (Black)
    or Aripiprazole IM Depot 400 mg (Red)**

Source: Figure 11.5.2.3.1.2.1-1of CSR

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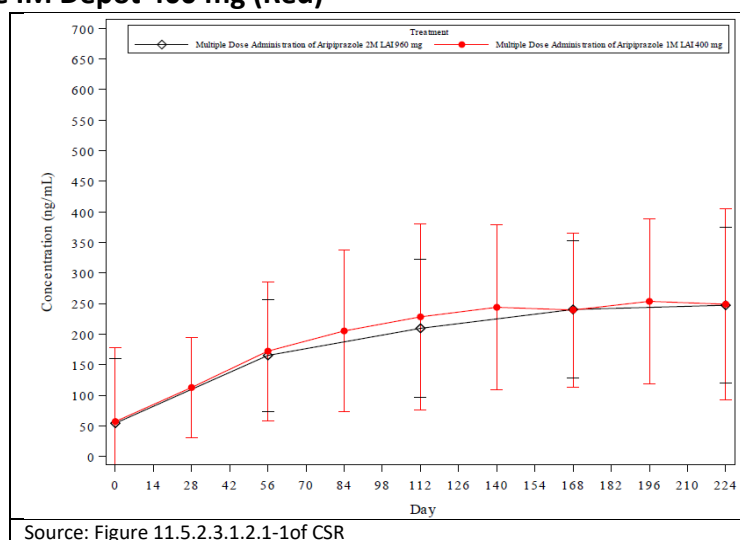
Figure 15: Mean (SD) Aripiprazole Plasma Concentration Versus Time Profiles Following the Fourth Administration of Aripiprazole 2M RTU 960 mg or the Seventh and Eighth Administration of Aripiprazole IM Depot 400 mg

Aripiprazole 2M LAI 960 mg (Black; n = 102);
Aripiprazole IM Depot 400 mg (Red; n = 93)
- Source: Figure 11.5.2.3.1.2.1-2of CSR
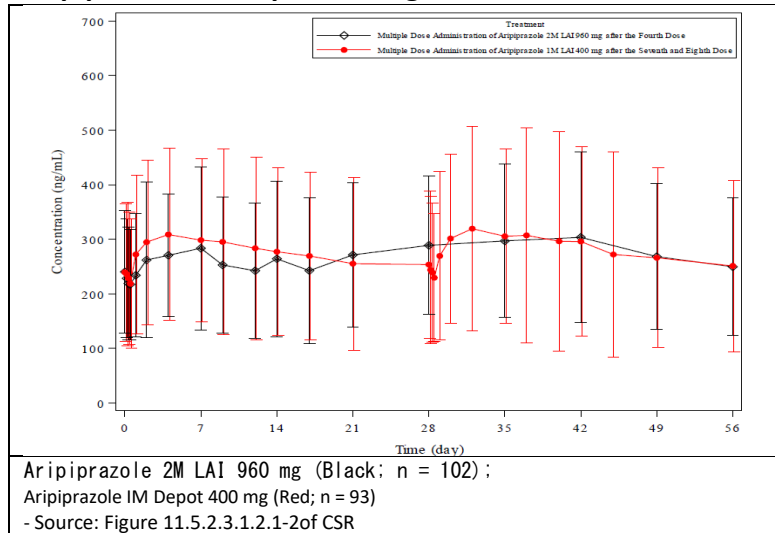
Table 34: Mean (SD) Aripiprazole Pharmacokinetic Parameters Following the Fourth Administration of Aripiprazole 2M RTU 960 mg or the Seventh and Eighth Administration of Aripiprazole IM Depot 400 mg

PK Parameter	Aripiprazole 2M LAI 960 mg Fourth Dose	Aripiprazole IM Depot 400 mg Seventh Dose	Aripiprazole IM Depot 400 mg Eighth Dose
C_{max} (ng/mL)	342 (157)[b]	339 (168)[d]	344 (212)[f]
t_{max} (day)[a]	28.0 (0.930 - 49.0)[b]	6.97 (1.05 - 28.0)[d]	4.07 (0.00 - 28.0)[f]
AUC_{0-56} (ng·day/mL)	14700 (7460)[b]	ND	ND
AUC_{0-28} (ng·day/mL)	7190 (3470)[b]	7760 (4300)[d]	7840 (5170)[f]
AUC_{29-56} (ng·day/mL)	7500 (4200)[b]	ND	ND
PTF%	63.4 (25.1)[b]	ND	48.3 (19.0)[f]
C_{28} (ng/mL)	ND	255 (137)[e]	257 (162)[g]
C_{56} (ng/mL)	250 (128)[c]	ND	ND

[a]Median (min - max). [b]n = 34. [c]n = 96. [d]n = 33. [e]n = 88. [f]n = 32. [g]n = 82.
Source: Table 11.5.2.3.2.2-1 of CSR

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Table 35: Geometric Mean Ratios and 90% Confidence Intervals for Aripiprazole Pharmacokinetic Parameters Following the Fourth Administration of Aripiprazole 2M RTU 960 mg or the Seventh and Eighth Administration of Aripiprazole IM Depot 400 mg

	PK Parameter	GMR	90% CI	P-value
Aripiprazole 2M LAI 960 mg (T) versus Aripiprazole IM Depot 400 mg (R)	AUC^a	1.006^c	0.851 - 1.190	0.0129
	$C_{56}/C_{28}{}^b$	1.011^d	0.893 - 1.145	0.0011
	$C_{max}{}^b$	1.071^c	0.903 - 1.270	0.0029

[a] AUC_{0-56} following the fourth administration of aripiprazole 2M LAI 960 mg or the sum of AUC_{0-28} following the seventh and eighth administration of aripiprazole IM depot 400 mg.
[b] Following the fourth administration of aripiprazole 2M LAI 960 mg or the eighth administration of aripiprazole IM depot 400 mg.
[c] n = 34 aripiprazole 2M LAI 960 mg, 32 aripiprazole IM depot 400 mg.
[d] n = 96 aripiprazole 2M LAI 960 mg, 82 aripiprazole IM depot 400 mg.

Source: Tables 11.5.2.4-1 of CSR

Table 36: Dehydro-Aripiprazole Exposure (Mean) Following the Fourth Dose Administration of Aripiprazole 2M RTU 960 mg or the Eighth Administration of Aripiprazole IM Depot 400 mg

	PK Parameter	Aripiprazole 2M RTU 960 mg	Aripiprazole IM Depot 400 mg
Aripiprazole	C_{max} (ng/mL)	342	344
	AUC_{tau} (day*ng/mL)	14700	7840
Dehydro-aripiprazole	C_{max} (ng/mL)	105	105
	AUC_{tau} (day*ng/mL)	4590	2440
Ratio (Dehydro-aripiprazole /aripiprazole)	Cmax	0.307	0.305
	AUCtau	0.312	0.311

- **Applicant's Summary & Conclusions:**
  - Aripiprazole 2M LAI 960 mg had a similar aripiprazole AUC_{0-56} following the fourth dose compared to the sum of AUC_{0-28} following the seventh and eighth dose of aripiprazole IM depot 400 mg (GMR [90% CI]: 1.006 [0.851, 1.190]).

  - Aripiprazole 2M LAI 960 mg had a similar aripiprazole C_{56} following the fourth dose compared to C28 following the eighth dose of aripiprazole IM depot 400 mg (GMR [90% CI]: 1.011 [0.893, 1.145]).

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- o Multiple-dose administrations of aripiprazole 2M LAI 960 mg into the gluteal muscle site were generally safe and well tolerated in subjects with schizophrenia or bipolar I disorder and did not show any new safety concerns.

- **Reviewers' Comments and Conclusions**
  - o We agree with the study design, dosage, subject numbers, type, PK sampling and analysis strategy.

  - o <u>Formulation</u>: the product used in this study was presented in a vial, not the commercial presentation of prefilled syringe (PFS). The potential implication of not using the final to-be-marketed presentation is discussed in the CMC section.

  - o <u>Potential dose dumping:</u> efforts were made to identify any potential dose dumping cases in subjects who received aripiprazole 2M RTU LAI. The maximal $C_{max,ss}$ of aripiprazole was 1090 ng/mL and 1150 ng/mL, respectively, following Aripiprazole 2M RTU 960 mg 4th dose administration and Aripiprazole IM depot 400 mg 8th dose administration. Concentration time profiles were also evaluated, and no evidence of dose-dumping was observed.

  - o We agree with the Applicant's conclusions.

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Pharmacometrics

Population Pharmacokinetic Analyses:

The Applicant submitted pharmacokinetic (PK) analysis reports 31-18-205-report-body.pdf, 31-21-201-report-body.pdf, and 31-21-202-report-body.pdf to module 5335 of sequence 0001. Report 31-18-205-report-body.pdf describes early population PK (PPK) modeling efforts and development of an older version of the PPK model. Report 31-21-201-report-body.pdf describes the development of the final PPK model. Report 31-21-202-report-body.pdf describes simulations conducted using the final PPK model. For this reason, reports 31-21-201-report-body.pdf, and 31-21-202-report-body.pdf will be assessed below and report 31-18-205-report-body.pdf will not be further discussed.

Population Pharmacokinetic Modeling:

The Applicant submitted report 31-21-201-report-body.pdf, titled "Population Pharmacokinetic Analysis of Aripiprazole Administered as a Novel Long-Acting Injectable Formulation in Adult Subjects" to module 5335 of sequence 0001. The objectives of the analyses in this report are to characterize aripiprazole pharmacokinetics of the RTU LAI and IM formulations as well as to assess the impact of potential intrinsic and extrinsic factors on aripiprazole PK.

PK data for the RTU LAI formulation were available from three studies. PK data for oral and IM data were available from seven studies. There were 17113 PK observations from n=1191 subjects in the dataset. Details regarding the studies from which the PK data for these analyses originated from are found in the table below.

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Table 37: Summary Studies Involved in PPK Analyses

Table 3.1.1-1		Summary of Trial Designs for RTU LAI Formulation Trials				
Trial Number	Phase	Trial Design	Population	Formulation	Number of Subjects/ Samples	Dosing Regimen
031-201-00104	1	Open-label, Single Ascending Dose, Parallel Arm Trial to Determine the Pharmacokinetics, Safety, and Tolerability of Aripiprazole 2 Month Intramuscular Depot Administered Gluteally in Adult Subjects with Schizophrenia	Subjects with Schizophrenia	RTU LAI	36/932	Single gluteal injection of RTU LAI formulation 780 mg (Cohort 1) and 1200 mg (Cohort 2)
031-201-00181	1b	Open-label, Multiple-dose, Randomized, Parallel-arm, Safety, Tolerability, and Pharmacokinetic Trial of Aripiprazole Intramuscular Depot Administered in the Gluteal Muscle in Adult Subjects With Schizophrenia or Bipolar I Disorder	Subjects With Schizophrenia or Bipolar I Disorder	RTU LAI/IM depot	266/6282	Group 1: Multiple doses of RTU LAI 960 mg (Days 1, 57, 113, 169) Group 2: Multiple doses of IM depot 400 mg (Days 1, 29, 57, 85, 113, 141, 169, 197)
031-201-00279	1	Open-label, Single- and Multiple-dose, Pharmacokinetic, Safety, and Tolerability Trial of Aripiprazole Long-acting Injectable Administered in the Deltoid or Gluteal Muscle in Adult Subjects with Schizophrenia or Bipolar I Disorder	Subjects with Schizophrenia or Bipolar I Disorder	RTU LAI	72/1685	Part A Group 1: Single dose RTU LAI 420 mg either gluteal or deltoid injection Group 2: Multiple doses RTU LAI 420 mg (Days 1, 29, 57, 85, 113) either gluteal or deltoid injection Part B Group 1: Single dose RTU LAI 420 mg in gluteal site with fast or slow injection Group 2: Single dose RTU LAI 420 mg

Source: Sequence 0001, module 5335, 31-21-205-report-body.pdf, page 20.

Table 38: Summary Studies Involved in PPK Analyses (Continued)

Table 8.1-1		Summary of Trial Designs for Oral and IM Depot Formulation Trials				
Trial Number	Phase	Trial Design	Population	Formulation	Number of Subjects/ Samples	Dosing Regimen
31-98-206	1	Double-blind, placebo-controlled trial of the effect of orally administered ketoconazole on aripiprazole PK	Healthy Subjects	Oral	23/758	Oral aripiprazole 15 mg on Days 1 and 16 (oral ketoconazole 200mg once daily on Days 15-28)
31-98-207	1	Open-label trial of orally administered aripiprazole PK in subjects who are poor or extensive CYP-2D6 metabolizers and the effect of oral quinidine on aripiprazole PK in EM	Healthy Subjects	Oral	29/555	Group 1 (CYP2D6 EM) and 3 (CYP2D6 PM): One dose oral aripiprazole 10 mg Group 2 (CYP2D6 EM): One dose oral aripiprazole 10 mg on Day 1 and oral quinidine 166 mg once daily on Days 1-13
CN138020	1	Open-label, 2-phase, non-randomized ascending dose, sequential panel trial	Subjects with Schizophrenia or Schizoaffective Disorder	Oral/IM depot	13/254	Treatment Phase 1: One 5-mg dose IM standard formulation Treatment Phase 2: One 15-, 50-, 100-, 200-, 300- or 400-mg dose IM Depot formulation
31-05-244	1b	Open-label, parallel arm, multiple dose tolerability, pharmacokinetics and safety study in adult patients with schizophrenia following administration of aripiprazole intramuscular (IM) depot formulation once every four weeks	Subjects with Schizophrenia	IM depot	37/799	Group 1: 400 mg Group 2: 300 mg Group 3: 200 mg IM depot injection every 4 weeks for 5 months

Source: Sequence 0001, module 5335, 31-21-205-report-body.pdf, page 51.

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Table 39: Summary Studies Involved in PPK Analyses (Continued)

Table 8.1-1		Summary of Trial Designs for Oral and IM Depot Formulation Trials				
Trial Number	**Phase**	**Trial Design**	**Population**	**Formulation**	**Number of Subjects/ Samples**	**Dosing Regimen**
31-07-246	3	Randomized, double-blind, placebo-controlled trial to evaluate the efficacy, safety, and tolerability of an IM Depot formulation of aripiprazole as maintenance treatment	Subjects with Schizophrenia	Oral/IM depot	561/3787	Treatment phase 1: oral conversion of antipsychotic(s) to 10 or 15 mg aripiprazole Treatment phase 2: stablize on oral aripiprazole 10-30 mg (daily) **Treatment Phase 3 (single-blind):** stablize on IM depot 400 or 300 mg every 4 weeks for 12-36 weeks (continued oral aripiprazole 10 or 15 mg during first 2 weeks) **Treatment Phase 4 (double-blind):** 400 mg or 300 mg aripiprazole IM depot every 4 weeks for 52 weeks
31-11-290	1	Open-label, randomized, parallel-arm, bioavailability trial of Aripiprazole IM Depot administered in the deltoid or gluteal muscle in adult subjects with schizophrenia.	Subjects with Schizophrenia	IM depot	35/905	Single dose of IM Depot 400 mg (injected to either gluteal or deltoid muscle)
31-12-298	1b	Open-label, multiple-dose, safety and tolerability study of aripiprazole IM Depot administered in the deltoid muscle in adult subjects with Schizophrenia	Subjects with Schizophrenia	IM depot	119/1156	Group 1: 400 mg gluteal injection (Day 1) followed by multiple dose 400 or 300 mg deltoid Injections (Days 29, 57, 85, 113) **Group 2:** 400 or 300 mg deltoid injections (Days 1, 29, 57, 85, 113) (Subjects allowed to take current antipsychotic, including oral aripiprazole, for 14 days after the first M depot injection)

Source: Sequence 0001, module 5335, 31-21-205-report-body.pdf, page 52.

The schedule of PK sampling times for these studies is found in the table below.

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Table 40: PK Sampling Schedule

Table 3.1.2-1	Pharmacokinetic Sampling Plan for RTU LAI Formulation Trials
Trial Number	**Time After First Dose**
031-201-00104	Day 1 (predose [within 2 hours prior to dosing] and 4, 8, and 12 hours postdose) and on Days 2, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 25, 28, 35, 42, 49, 56, 63, 70, 77, 84, 98, 112, 126, 154, and 182
031-201-00181	**Sparse sampling (2M RTU LAI):** Day 1 (predose, 4, 8, 12 hours postdose), Days 8, 15, 22, 29, 36, 43, 50, 57 (predose), 85, 113 (predose), 141, 169 (predose, 4, 8, 12 hours postdose), 176, 183, 190, 197, 204, 211, 218, 225 **Sparse sampling (IM depot):** Days 1 (predose, 4, 8, 12 hours postdose), Days 8, 15, 22, 29 (predose), 57 (predose), 85 (predose), 113 (predose), 141 (predose), 169 (predose, 4, 8, 12 hours postdose), 197 (predose, 4, 8, 12 hours postdose), 204, 211, 218, 225 **Robust Sampling (2M RTU LAI):** Days 1 (predose, 4, 8, 12 hours postdose), Days 2, 3, 5, 8, 10, 13, 15, 18, 22, 29, 36, 43, 50, 57 (predose), 113 (predose), 169 (predose, 4, 8, 12 hours postdose), 170, 171, 173, 176, 178, 181, 183, 186, 190, 197, 204, 211, 218, 225 **Robust Sampling (IM depot):** Days 1 (predose, 4, 8, 12 hours postdose), Days 2, 3, 5, 8, 10, 13, 15, 18, 22, 29 (predose), 57 (predose), 85 (predose), 113 (predose), 141 (predose), 169 (predose, 4, 8, 12 hours postdose), 170, 171, 173, 176, 178, 181, 183, 186, 190, 197 (predose, 4, 8, 12 hours postdose), 198, 199, 201, 204, 206, 209, 211, 214, 218, 225
031-201-00279	**Part A – Single dose:** Day 1 (predose, 4, 8, 12 hours postdose), 2, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 25, 29, 36, 43, 50, 57, 64, 71, 78, 85, 99, and 113 **Part A – Multiple dose:** Day 1 (predose, 4, 8, 12 hours postdose), 8, 15, 22, 29 (predose), 57 (predose), 85 (predose), 113 (predose, 4, 8, 12 hours postdose), 114, 115, 117, 119, 120, 121, 123, 125, 127, 129, 131, 133, 134, 137, 141, 148, 155, 162, 169 **Part B –** Day 1 (predose, 4, 8, 12 hours postdose), Days 2, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 25, 29, 36, 43, and 50

Source: Sequence 0001, module 5335, 31-21-205-report-body.pdf, page 21.

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Table 41: PK Sampling Schedule (Continued)

Table 8.2-1	Pharmacokinetic Sampling Plan for Oral and IM Depot Formulation Trials
Trial Number	**Time After First Dose**
31-98-206	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 168, 216, and 312 hours post dose on Days 1 and 16
31-98-207	Pre-dose, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, and 312 hours post dose
CN138020	Pre-dose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 3648, 72, 96, 120, 168, 264, 360, 456, and 528 hours post dose for Treatment Phase 1 and 2; + Day 28, 35, 42, 56, 70, 84, 112, 140, 168 or until 2 consecutive LLOQ for Treatment Phase 2
31-05-244	Pre-dose, Day 7, Day 14, and Day 21 for each injection; Pre-dose, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 168, 264, 336, 504, 672, 1008, and 1344 hours after the fifth injection
31-07-246	Treatment Phase 3: Weeks 1, 2, 4, 8, 12, and 36/End of Phase Treatment Phase 4: Weeks 2, 4, 6, and 8
31-11-290	Pre-dose on Day 1 and at 4, 8, and 12 hours post-dose, and on Days 2, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 25, 28, 35, 42, 49, 56, 63, 70, 77, 84, 98, 112, and 126.
31-12-298	2 Sampling schemes (site dependent): Sparse sampling: Days 1 (pre-dose), 8 (±2 days), 15 (±2 days), 22 (±2 days), 29 (pre-dose), 57 (pre-dose), 85 (pre-dose), 113 (pre-dose), 120 (±2 days), 127 (±2 days), 134 (±2 days), and 141 Robust Sampling: Days 1 (pre-dose), 3, 5, 8, 10, 13, 15, 18, 22, 29 (pre-dose), 57 (pre-dose), 85 (pre-dose), 113 (pre-dose), 115, 117, 120, 122, 125, 127, 130, 134, and 141.

Source: Sequence 0001, module 5335, 31-21-205-report-body.pdf, page 53.

Previous PPK Model: The Applicant used a population PK model as a starting model to build on with new PK data. The starting model, found in report 31-11-287, was previously reviewed by OCP[1] and found to adequately describe the aripiprazole PK observations for both the oral and IM formulations. The previous PPK model utilizes three compartments, linear elimination, and absorption process that varies by formulation. The oral formulation utilizes a sequential zero-order first order elimination process. The gluteal IM formulation involves a depot compartment with a first order absorption rate constant for the drug existing the depot into the central compartment. All routes of administration share common values of apparent clearance (CL/F) and apparent volume of distribution of the central compartment (Vc/F).

Between subject variability was estimated for CL/F, Vc, oral absorption, and gluteal absorption. There were no off-diagonal elements in the variance-covariance matrix. Separate CL/F values were estimated for poor CYP2D6 metabolizers and non-poor-CYP2D6 metabolizers. Covariates on CL/F include a proportional change in the presence of concomitant strong CYP2D6 inhibitors a proportional change in the presence of concomitant strong CYP3A4 inhibitors. Covariates on gluteal IM absorption rate constant include sex and body mass index (BMI). IM gluteal bioavailability is expressed relative to oral bioavailability.

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[1] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8027edbf

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Current PPK Model: The PPK model in the current submission retained all estimates of fixed effects and between subject variability from the IM PK model in report 31-11-287. In the current PPK model, Sponsor estimated fixed effects for the absorption of the new IM route (i.e. IM Maintena administered into the deltoid), estimated fixed effect of the absorption of the new RTU LAI formulation, estimated between subject variability terms for the new fixed effect terms, and estimated residual variability.

Similar to the gluteal IM route, the deltoid IM route each utilize a separate depot compartment with a separate first order absorption rate constant. For the RTU LAI formulation, the dose is split between two depots in parallel, one which uses zero-order absorption and one which uses time-lagged first order absorption. A separate Vc/F value is included for the RTU LAI formulation (VcRTU) in order to describe the longer apparent terminal half-life compared to other formulations.

Between subject variability was estimated for VcRTU, deltoid absorption, duration of zero-order absorption for RTU LAI, fraction of first order absorption for RTU LAI, and RTU LAI first order absorption with no off-diagonal elements in the variance-covariance matrix. Sex is a covariate on the RTU LAI absorption rate constant and fraction of RTU LAI that undergoes first order absorption.

Three proportional residual error model terms were used: a) for oral and IM depot formulations, b) for oral and IM depot formulations in phase 3 study 31-07-246, and c) for the RTU LAI formulation. An additive residual error model term was also used for the RTU LAI formulation. The estimates for the final PPK model (100-s2-01.ctl) are presented in the table below.

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Table 42: Parameter Estimates for final PPK Model (100-s2-01)

Parameter	Unit	Definition	Estimate	RSE%	Bootstrap Median [95% CI]	Shrinkage (%)
CL_EM	L/h	Apparent clearance for subjects who are not poor CYP2D6 metabolizers	3.71	-	-	-
CL_PM	L/h	Apparent clearance for subjects who are poor CYP2D6 metabolizers	1.88	-	-	-
2D6_CL	-	Proportional change in apparent clearance in presence of a strong CYP2D6 inhibitor	-0.511	-	-	-
3A4_CL	-	Proportional change in apparent clearance in presence of a strong CYP3A4 inhibitor	-0.237	-	-	-
VC	L	Apparent central volume of distribution for Oral and IM Depot	93.4	-	-	-
VCRTU	L	Apparent central volume of distribution for RTU LAI	2035	0.02	2154 [1822-2542]	-
Q1	L/h	Apparent inter-compartmental clearance 1	0.591	-	-	-
VP1	L	Apparent volume of distribution in Peripheral compartment 1	118	-	-	-
Q2	L/h	Apparent inter-compartmental clearance 2	28.8	-	-	-
VP2	L	Apparent volume of distribution in Peripheral compartment 2	134	-	-	-
R1	mg/h	Rate of dose into oral absorption compartment	9.33	-	-	-
KAPO	1/h	First-order absorption rate constant for Oral	0.54	-	-	-
KAGLU	1/h	First-order absorption rate constant for IM Depot in gluteal site	0.000904	-	-	-
KADEL	1/h	First-order absorption rate constant for IM Depot in deltoid site	0.000776	-	-	-
BMI_KAGLU	-	Effect of BMI on KAGLU and KADEL: power for (BMI/28)	-0.975	-	-	-
SEX_KAGLU	-	Proportional shift of KAGLU and KADEL for males	0.346	-	-	-
DUR0	h	Duration of zero-order absorption for RTU LAI	162	6.5	164 [150-194]	-

CV = coefficient of variation; SD = standard deviation.

Source: Sequence 0001, module 5335, 31-21-205-report-body.pdf, page 41.

**Table 43: Parameter Estimates for final PPK Model (100-s2-01; Continued)**

Parameter	Unit	Definition	Estimate	RSE%	Bootstrap Median [95% CI]	Shrinkage (%)
FRAC1	-	Fraction of first-order absorption for RTU LAI on transformed scale	3.82 (79.3%)	6.3	4.07 [2.86-5.33] (80.3% [74.1% - 84.2%])	-
SEX_FRAC1	-	Proportional shift of FRAC1 for males	-0.556	7.8	-0.56 [-0.71- -0.39]	-
SEX_KARTU	-	Proportional shift of KARTU for males	0.907	0.1	0.815 [0.435-1.233]	-
ALAG1	h	Lag-time of first-order absorption for RTU LAI	419	0.7	419 [416-457]	-
KARTU	1/h	First-order absorption rate constant for RTU LAI	0.00127	0.03	0.00130 [0.00109- 0.00162]	-
FREL_MAINTENA	-	Relative bioavailability of IM Depot compared to Oral	1.48	-	-	-
FREL_RTU	-	Relative bioavailability of RTU LAI compared to Oral	1.58	1.9	1.594 [1.500 − 1.645]	-
Inter-individual variability: variance (CV%)						
CL	-	IIV on CL_EM and CL_PM	0.155 (39.3)	4.7	0.150 [0.136-0.161]	8.4
VC	-	IIV on VC and VCRTU	1.87 (136.7)	6.2	1.83 [1.63-2.31]	33.3
KAPO	-	IIV on KAPO	0.434 (65.9)	-	-	62.4
KAGLU	-	IIV on KAGLU	0.359 (59.9)	-	-	19.3
KADEL	-	IIV on KADEL	0.237 (48.7)	-	-	17.7
DUR0	-	IIV on DUR0	1.01 (100.7)	8.8	0.958 [0.523-1.29]	10.0
FRAC1	-	IIV on FRAC1	0.634 (79.6)	13.2	0.654 [0.410-0.776]	19.2
KARTU	-	IIV on KARTU	0.307 (55.4)	13.4	0.331 [0.168-0.438]	32.0
Residual variability: variance (CV% or SD)						
PRO	-	Proportional error for Oral and IM Depot	0.0660 (25.7)	0.8	0.0660 [0.0611-0.0727]	3.8
PRO_PH3	-	Proportional error for Oral and IM Depot in Phase 3 study (Study 31-07-246)	0.0772 (27.8)	1.8	0.0782 [0.0722-0.0852]	12.2
PRO_RTU	-	Proportional error for RTU LAI	0.0650 (25.5)	0.9	0.0664 [0.0567-0.0757]	7.1
ADD_RTU	-	Additive error for RTU LAI	1.81 (1.35)	9.6	1.44 [0.737-3.59]	7.1

CV = coefficient of variation; SD = standard deviation.

Source: Sequence 0001, module 5335, 31-21-205-report-body.pdf, page 42.

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The diagnostic plots are presented in the figures below.

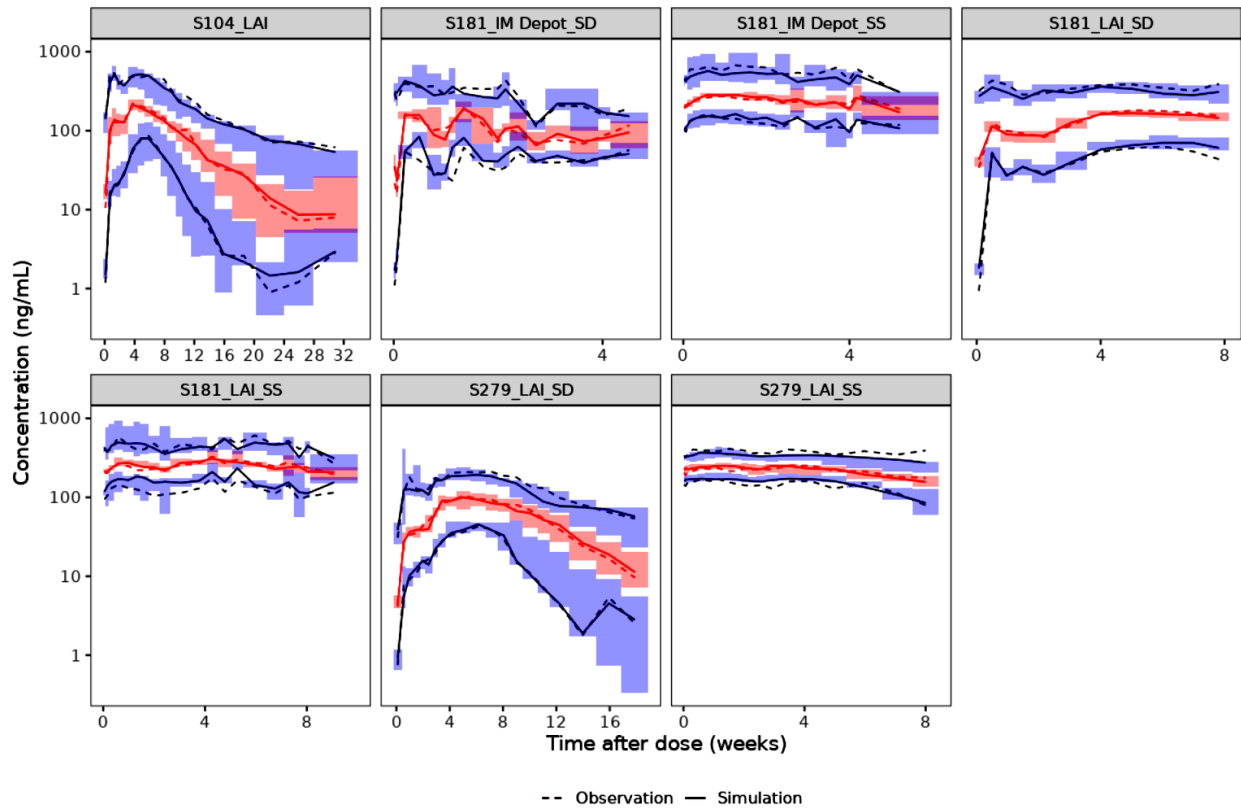**Figure 16: Diagnostic Plots for Final PPK Model**
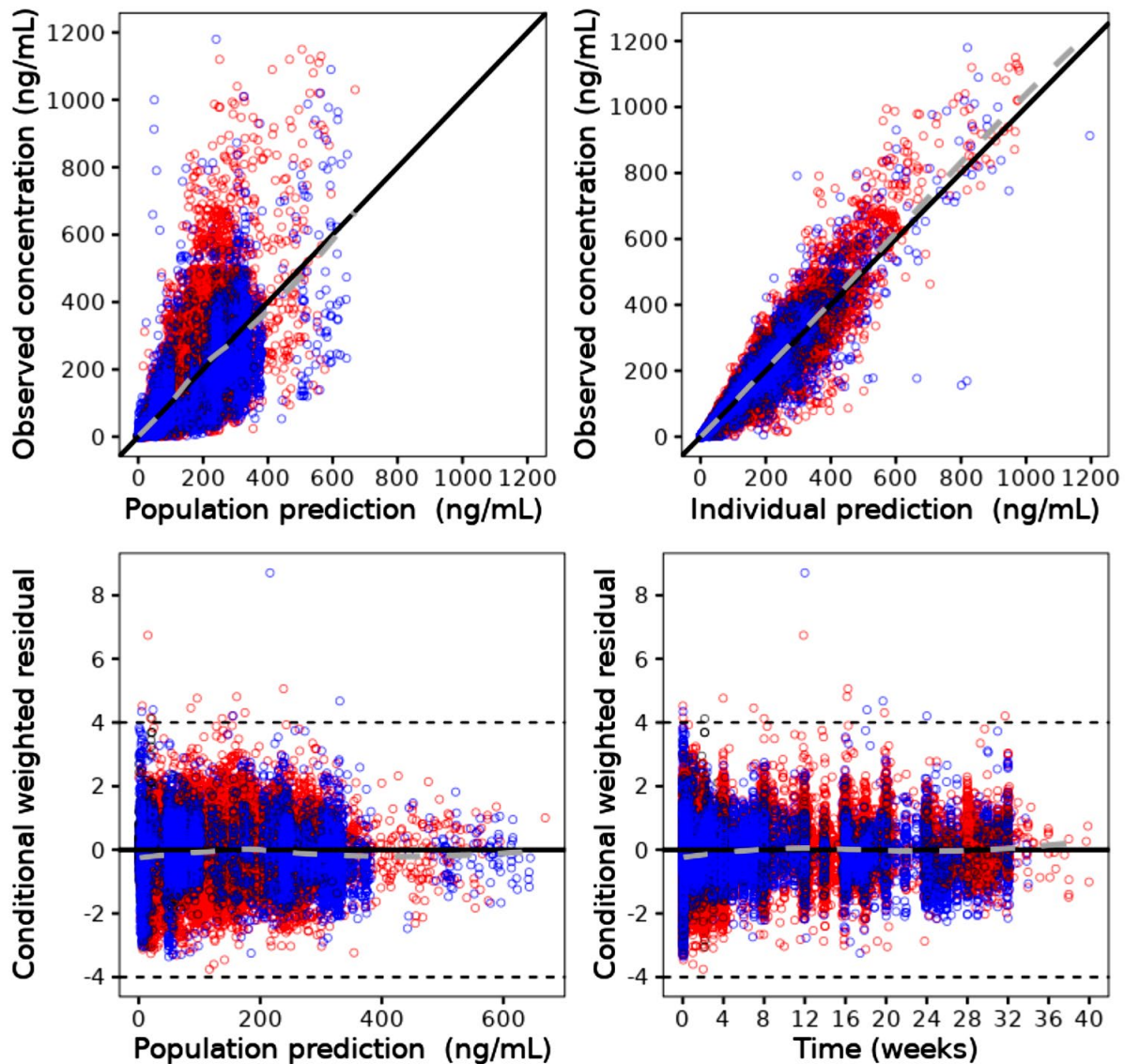
Circles represent observed data (black: oral, red: IM Depot, blue: RTU LAI); the black line is the line of unity (upper panels) and a horizontal line with intercept zero (lower panels); the grey dotted line represents a locally estimated scatterplot (LOESS) smoother.
Source: Sequence 0001, module 5335, 31-21-205-report-body.pdf, page 45.

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Figure 17: Nonparametric VPC for final PPK Model

S104 = Trial 031-201-00104; S181 = Trial 031-201-00181; S279 = Trial 031-201-00279; SD = single dose; SS = steady-state following multiple doses. Note: The dotted lines represent the median (red) with 5th and 95th percentile (black) of the observed aripiprazole concentrations time course. The solid lines represent the median (red) with 5th and 95th percentile (black) of the simulated aripiprazole concentrations time course. The shaded regions represent the 95% confidence interval of the simulated median (red), the 5th, and the 95th percentile (blue).
Source: Sequence 0001, module 5335, 31-21-205-report-body.pdf, page 47.

OCP Reviewer Comment: The Applicant started their analyses using a PPK model (from report 31-11-287) that was previously reviewed by OCP as a foundation for modeling the RTU LAI PK. In the clinical pharmacology general review of NDA 202971 for Abilify Maintena archived on 06/04/2012[2], on page 46, the OCP DPM reviewer concluded "The sponsor's population PK model adequately describes the aripiprazole PK observations for both the oral and IM formulations." The Applicant kept the majority of the PPK parameters estimates from the model described in report 31-11-287 (fixed effect estimates and between subject variability estimates). The Applicant estimated the fixed effect absorption parameters for the new route (IM Abilify Maintena administered into the deltoid) and the new formulation (the RTU LAI formulation). The Applicant also assessed between subject variability terms for the new fixed effect parameters such as IM deltoid Maintena absorption, between subject variability for RTU LAI,

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[2] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8027edbf

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and residual variability. The Applicant's approach of leveraging the existing Abilify Maintena IM PPK model as a starting point is acceptable.

Eta shrinkage is low for the terms that were estimated in the current PPK model (i.e., KaDEL, DUR0, FRAC1, KaRTU). Eta shrinkage is 62.4% for oral formulation absorption rate constant KAPO. This is likely due to the relatively fast absorption for the oral route compared to other routes and thus fewer PK samples acquired during oral absorption phase compared to the absorption phase for other routes.

The diagnostic plots in Figure 16 do not suggest the presence of bias with respect to concentration or time after administration. The VPC (Figure 17) does not suggest any concerns about model performance across studies. The Sponsor's retention of covariates from the IM Ability Maintena PPK model (report 31-11-287) is reasonable. The correlation matrix indicates low correlation among parameters in the final model. The RSEs are acceptable for fixed effects and random effects. Overall, the PPK model is acceptable.]

Population Pharmacokinetic Simulation:

The Applicant submitted report 31-21-202-report-body.pdf, titled "Model-based Simulation to Inform Dosing Strategies for a Novel Long-Acting Injectable Formulation of Aripiprazole in Adult Subjects" to module 5335 of sequence 0001. The objectives these analyses are to utilize the population PK model to simulate PK profiles in various scenarios in order to optimize the dosing regimen of aripiprazole RTU LAI.

The scenarios assessed consist of: 1) treatment initiation, 2) pharmacogenomics (CYP2D6 poor metabolizers [PM] versus extensive metabolizers [EM]), 3) drug interactions (concomitant strong 2D6 inhibitors or strong 3A4 inhibitors), 4) steady-state, 5) dosing flexibility (early administration), 6) missed/delayed dose (late administration), and 7) dose dumping. Each simulation scenario is discussed in more detail below.

1. **Treatment initiation**: Simulation of patients initiating a 960 mg Q8W RTU LAI regimen without prior oral aripiprazole stabilization, with overlapping 10 mg or 20 mg QD oral aripiprazole for the first 14 days. The results of these simulations are presented in section 6 of this review (Figure 5, Figure 6).

2. **Pharmacogenomics**: Simulation of the steady-state PK following 300 mg q4w IM depot (the approved dose regimen for 2D6 poor metabolizers in the Abilify Maintena label) versus the 720 mg q8w RTU LAI dose regimen proposed for 2D6 poor metabolizers. The results are found in section 6 (Figure 2).

3. **Drug Interactions**: Simulation of the impact of concomitant long-term administration of either a CYP2D6 inhibitor or a CYP3A4 inhibitor at treatment initiation or at steady-state. Results are found in section 6 (Figure 3, Figure 4).

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4. **Steady-State**: Simulation of steady-state PK following administration of the proposed RTU LAI. The results are found in section 6 (Figure 10, Figure 11). These results are used for assessment of other scenarios (i.e., dosing flexibility and missed/delayed dosing).

5. **Dosing Flexibility**: Simulation of administering the RTU LAI up to 2 weeks early at steady-state. Results are presented in section 6 (Figure 10).

6. **Missed/Delayed Dose**: Simulation of administering the RTU LAI late (up to 14 weeks late) at steady-state. Results are presented in section 6 (Figure 11).

7. **Dose Dumping**: The dose dumping simulations do not provide any additional information beyond the assessment performed by the reviewer using the observed PK data. As such, the dose dumping simulations will not be further discussed. Please refer to section 6 for additional discussion regarding dose dumping.

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