EMA/CHMP/231170/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Asimtufii

International non-proprietary name: aripiprazole

Procedure No. EMEA/H/C/005929/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

Administrative information

Invented name of the generic/hybrid medicinal product:	Asimtufii
INN (or common name) of the active substance(s):	*aripiprazole*
Active substance(s):	aripiprazole
Applicant:	Otsuka Pharmaceutical Netherlands B.V.
Applied Indication(s):	Asimtufii is indicated for the maintenance treatment of schizophrenia in adult patients stabilised with aripiprazole.
Pharmaco-therapeutic group (ATC Code):	Psycholeptics, other antipsychotics, ATC code: N05AX12
Pharmaceutical form(s) and strength(s):	960 mg and 720 mg prolonged-release suspension for injection in pre-filled syringe

List of abbreviations

Quality

AAS	Atomic Absorption Spectrometry
AP	Applicant's Part (or Open Part) of a ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CMS	Concerned Member State
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
DP	Decentralised (Application) Procedure
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EP	European Pharmacopoeia
FT-IR	Fourier Transform infrared spectroscopy
GC	Gas chromatography
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICP-OES	Inductively coupled plasma – optical emission spectroscopy
IPC	In-process control
IR	Infrared
IU	International Units
LDPE	Low Density Polyethylene
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MEB	Medicines Evaluation Board
MEK	Methyl ethyl ketone
MO	Major objection
MS	Mass Spectrometry
MTBE	Methyl *tert*-Butyl Ether
ND	Not detected
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OC	Other concern
OOS	Out of Specifications
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet

PP	Polypropylene
PVC	Poly vinyl chloride
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of a ASMF
RPM	Reference Medicinal Product
RRT	Relative retention time
RSD	Relative standard deviation
SmPC	Summary of Product Characteristics
TEA	Triethylamine
TTC	Threshold of Toxicological Concern
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRD	X-Ray Diffraction

Non-clinical

Term	**Definition**
2M RTU LAI	2-month ready-to-use long-acting injectable
5-HT	Serotonin
AUC	Area under the concentration-time curve
AUC_{∞}	Area under the concentration-time curve from time 0 to infinity
AUC_t	Area under the concentration-time curve calculated to the last observable concentration at time, t
CNS	Central nervous system
C_{max}	Maximum (peak) plasma drug concentration
CYP	Cytochrome P450
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DNA	Deoxyribonucleic acid
hERG/IKr	Human ether-a-go-go-related gene/rectifier potassium current
IC_{50}	Half maximal inhibitory concentration
IM	Intramuscular
MAA	Marketing authorization application
MTD	Maximum tolerated dose
PK	Pharmacokinetics
t_{max}	Time to maximum (peak) plasma concentration

Clinical	Once monthly
1M	
2M	2-month
5-HT	5-hydroxytryptamine
AE	Adverse event
AESI	Adverse events of special interest
AIMS	Abnormal Involuntary Movement Scale
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
AUC_{0-28}	Area under the concentration-time curve of aripiprazole from time zero to 28 days postdose
AUC_{0-56}	Area under the concentration-time curve of aripiprazole from time zero to 56 days postdose

AUC_{29-56}	Area under the concentration-time curve of aripiprazole from 29 to 56 days postdose
BARS	Barnes Akathisia Rating Scale
BfArM	Federal Institute for Drugs and Medical Devices
BMS	Bristol-Myers Squibb Company
C_{max}	Maximum (peak) plasma concentration of the drug
C_{min}	Minimum (trough) plasma concentration of the drug
C_{28}	Plasma concentration of aripiprazole 28 days postdose
C_{56}	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
CI	Confidence interval
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CYP2D6	Cytochrome P450 2D6
D	Dopamine
ECG	Electrocardiogram
EM	Extensive metabolizer
EMA	European Medicines Agency
EPS	Extrapyramidal symptoms
E-R	Exposure-response (model)
EU	European Union
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
GMR	Geometric means ratio
IM	Intramuscular
IMP	Investigational medicinal product
LAI	Long-acting injectable
MADRS	Montgomery-Asberg Depression Rating Scale
MD	Multiple dose
ND	Not determined
OPC	Otsuka Pharmaceuticals Company, Ltd
PANSS	Positive and Negative Syndrome Scale
PFS	Prefilled syringe
PK	Pharmacokinetics
PM	Poor metabolizer
popPK	Population pharmacokinetics
PT	Preferred term
PTF%	Peak-to-trough percent fluctuation
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QTc	QT interval corrected for heart rate
R	Reference
RTU	Ready-to-use
SAP	Statistical analysis plan
SAS	Simpson-Angus Neurologic Rating Scale
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	Standard deviation
SWN-S	Subjective Well-being under Neuroleptic Treatment-Short Form
T	Test
t_{max}	Time to maximum (peak) plasma concentration
TEAE	Treatment-emergent adverse event

US	United States
WBC	White blood cell
YMRS	Young Mania Rating Scale

1. Rapporteur Recommendation

Based on the review of the data on quality, BE, safety and efficacy, the hybrid application for Asimtufii in the maintenance treatment of schizophrenia in adult patients stabilised with aripiprazole

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (see section 5.).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Quality:

1. Nitrosamines Risk Assessment

Deficiencies arising from concerns over the restricted part of the ASMF are mentioned in the appendix (this appendix is not supplied to the applicant). These concerns will be conveyed in confidence to the holder of the ASMF **(MO).**

Clinical

2. In line with the requirements following from the selected legal basis (Article 10(3) of Directive 2001/83/EC), the pivotal study submitted to establish a bridge to the EU/EEA reference medicinal product should be conducted against the EU/EEA reference medicinal product. Therefore, the applicant is invited to provide results of a clinical study conducted against the EU/EEA reference medicinal product as part of the hybrid application pursuant to Article 10(3) of Directive 2001/83/EC **(MO)**.

1.1. Questions to be posed to additional experts

N/A

1.2. Proposal for inspection

1.2.1. GMP inspection(s)

N/A

1.2.2. GCP inspection(s)

N/A

1.3. Similarity with authorised orphan medicinal products

N/A

1.4. Derogation(s) from market exclusivity

N/A

2. Executive summary

2.1. Problem statement

Schizophrenia is a severely debilitating mental illness characterized by delusions, hallucinations, and disordered cognition. Based on a systematic review of global data, the age-standardized point prevalence of schizophrenia in 2016 was estimated to be approximately 0.3% and did not vary widely across countries or regions.1 The worldwide lifetime prevalence of the disease has been estimated to be approximately 0.9% across diverse geographic, cultural, and socioeconomic categories.2 The course of schizophrenia is typically characterized by acute episodes of psychotic behaviors occurring at varying intervals between periods of relative symptomatic stability. Medication adherence in patients with schizophrenia is generally poor and several studies have demonstrated that the strongest predictor of further relapse is nonadherence with antipsychotic medications.3,4 Long-acting injectable formulations are designed to mitigate many of the challenges of poor treatment adherence through a simplified treatment regimen that ensures continuous longer-term exposure to medication; this, in turn, has been associated with improved patient outcomes.5,6,7

Aripiprazole (OPC-14597, Lu AF41155) is a dopamine serotonin system stabilizer, for which efficacy is thought to be mediated through a combination of partial agonism at dopamine D2 and serotonin 5-HT1A receptors and antagonism at serotonin 5-HT2A receptors. Aripiprazole was approved in oral tablet form as Abilify® by the United States (US) Food and Drug Administration (FDA) for the treatment of schizophrenia on 15 Nov 2002 and subsequently approved in the European Union (EU), Canada, and other global regions for different indications in several formulations (oral disintegrating tablets, oral solution, IM injectable).

Abilify Maintena® (aripiprazole), a prolonged-release suspension for once monthly intramuscular (IM) injection (hereafter referred to as aripiprazole IM depot), is indicated for the maintenance treatment of schizophrenia at a dose of 400 mg and 300 mg once monthly (deltoid or gluteal IM administration) in adult patients. Aripiprazole IM depot was approved by the FDA in 2013 for the treatment of schizophrenia and has since been approved globally for the treatment of schizophrenia/bipolar I disorder in the US, EU, Canada, and other countries.

2.2. About the product

Aripiprazole 2M RTU LAI is a new formulation provided in a single chamber type prefilled syringe (PFS) that does not require reconstitution. The new formulation is intended for dosing every 2 months via IM injection in the gluteal muscle in the same patient population as indicated for the aripiprazole IM depot formulation. The aripiprazole RTU LAI formulation is engineered with a higher aripiprazole concentration compared to the aripiprazole IM depot formulation. The extension of the dosing interval for aripiprazole 2M RTU LAI is primarily achieved via an increase in the dose, while maintaining exposure and minimum aripiprazole plasma concentrations similar to that of aripiprazole IM depot after multiple doses. The new formulation provides a stable aripiprazole suspension of 300 mg/mL (960 mg/syringe and 720 mg/syringe).

2.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical development programme is based on the published studies available for the reference product and relevant guidelines particularly Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms EMA/CHMP/EWP/280/96 Rev1. The following guidelines are applicable:

- Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**).

- Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009)

The applicant has received scientific advice given by BfArM concerning non-clinical and clinical aspects.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

The applicant has provided EudraGMP Certificates of GMP Compliance of a Manufacturer, for all declared manufacturers of the drug product. According to the certificates, sterile manufacturing and / or batch control is allowed for respective sites.

Valid QP declaration for each API manufacturing site has been provided. However clarification is needed if QP declaration is based on on-site audit – Parc C of this declaration has not been clearly filled. (OC)

GLP

The applicant included a statement confirming that:
The Single Intramuscular Dose Irritation Study of OPC-14597 Suspension for Depot Injection (New Component) in Beagle Dogs (Study No. 035591) and the 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 (Study No. 035592) were performed in compliance with:
- The Guidelines for Safety Studies of Pharmaceutical Drugs (Notification No. 88) issued by the Ministry of Health and Welfare, Japan, on 10 Aug 1993.
- Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies (Notification No. 443), issued by the Ministry of Health and Welfare, Japan, on 2 Jul 1996.
- The Good Laboratory Practice (GLP) Standards for Safety Studies on Drugs (Ordinance No. 21 issued by the Ministry of Health and Welfare, Japan, on 26 Mar 1997; partially revised by Ordinance No. 114 issued by the Ministry of Health, Labour and Welfare, on 13 Jun 2008).
The non-GLP PK Study 031R33 was carried out in compliance with "Guidelines for animal care and use in Otsuka Pharmaceutical Co., Ltd. and in-house regulations for animal experiments in Otsuka Pharmaceutical Co., Ltd.
The non-GLP PK Studies P210290 and P210291 fulfil the Criteria for Reliability of Application Data Article 43, Enforcement Regulations, Law Ensuring Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices, etc.

GCP
The applicant submitted statement that the clinical trials conducted to support this submission were performed in accordance with the principles of GCP, as defined by the ICH. Clinical trials carried out outside the EU were conducted in accordance with the principles of GCP and the ethical requirements equivalent to the provisions of Directive 2001/20/EC.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

- Article 10(3) of Directive 2001/83/EC, as amended– relating to applications for hybrid medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Abilify Maintena, 300mg, 400mg, powder and solvent for prolonged-release suspension for injection, powder and solvent for prolonged-release suspension for injection in pre-filled syringe
- Marketing authorisation holder: Otsuka Pharmaceuticals Netherlands
- Date of authorisation: 15-11-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: 300 mg - EU/1/13/882/001, 003, 005, 007

  400 mg - EU/1/13/882/002, 004, 006, 008

Medicinal product authorised in the Union /Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Abilify Maintena, 300mg, 400mg, powder and solvent for prolonged-release suspension for injection, powder and solvent for prolonged-release suspension for injection in pre-filled syringe
- Marketing authorisation holder: Otsuka Pharmaceuticals Netherlands
- Date of authorisation: 15-11-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: 300 mg - EU/1/13/882/001, 003, 005, 007

  400 mg - EU/1/13/882/002, 004, 006, 008

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Abilify Maintena, 300mg, 400mg, powder and solvent for prolonged-release suspension for injection, powder and solvent for prolonged-release suspension for injection in pre-filled syringe
- Marketing authorisation holder: Otsuka Pharmaceuticals Netherlands
- Date of authorisation: 15-11-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: 300 mg - EU/1/13/882/001, 003, 005, 007

  400 mg - EU/1/13/882/002, 004, 006, 008

2.5.2. Orphan designation

Not applicable.

2.5.3. Similarity with orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products.

2.5.4. Derogation(s) from orphan market exclusivity

N/A

2.5.5. Information on paediatric requirements

Not applicable

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as prolonged-release suspension for injection containing 960 mg and 720 mg of aripiprazole (as monohydrate) as active substance.

Other ingredients are: Carmellose sodium, Macrogol 400, Povidone K17, Sodium chloride, Sodium dihydrogen phosphate monohydrate, Sodium hydroxide, Water for injection

The product is available in pre-filled syringe with plunger stopper and tip-cap and plunger rod and finger grip. Each pack containing one pre-filled syringe, and two sterile safety needles: one 38 mm (1.5 inch) 22 gauge and one 51 mm (2 inch) 21 gauge.

3.1.2. Active Substance

No information concerning the drug substance from the drug product manufacturer is provided. Due to relationship between API manufacturers and DP manufacturer this is acceptable.

3.1.2.1. General Information

The chemical name of aripipazole monohydrate sterile is 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril, as monohydrate (1:1) corresponding to the molecular formula $C_{23}H_{27}Cl_2N_3O_2 \bullet H_2O$. It has a relative molecular mass of 466.40 g/mol and the following structure:

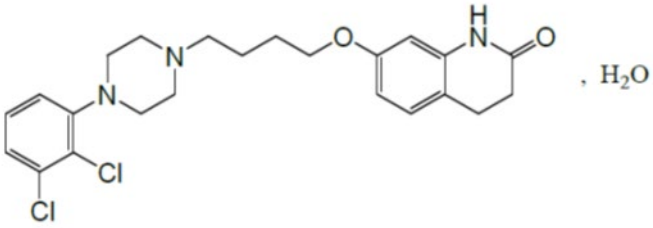


Figure 1: Active substance structure

The structure of aripiprazole monohydrate is elucidated from the route of synthesis and elemental and

spectral analyses (UV, IR, NMR and mass spectra).

Potential isomerism of the active substance has been discussed.

Polymorphism has been observed for Aripiprazole monohydrate / Aripiprazole monohydrate sterile.

There is no monograph of Aripiprazole monohydrate in the European Pharmacopoeia.

3.1.2.2. Manufacture, process controls and characterisation

Quality of the active substance is documented by full Module 3.2.S and by ASMF. Sterilisation of the active substance is considered as drug product manufacturing – MO identified in relation to ASMF RP procedure connected with limited information on manufacturing available for drug product manufacturer has not been solved.

Detailed information on the manufacturing of the active substance has been provided in the full Module 3.2.S and the restricted part of the ASMF – questions have been raised in relation to manufacturing process (no responses to ASMF RP have been presented).

Sterile aripiprazole monohydrate is manufactured by an aseptic process from anhydrous aripiprazole oral grade (intermediate). The commercial process for the preparation of anhydrous aripiprazole consists of four steps.

Presented information on starting materials is now acceptable.

The characterisation of the active substance and its impurities are generally in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. However, nitrosamines risk assessment is still not fully acceptable and requires further clarification from the ASMF holder

Primary packaging of sterile Aripiprazole complies with EC 10/2011 as amended.

3.1.2.3. Specification (s)

Manufacturer 1

The active substance specification includes tests for appearance, identity (IR, XRPD), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), residue on ignition (USP), bacterial endotoxins (USP), sterility (USP).

The specification for sterile Aripiprazole monohydrate has been established taking into account the physicochemical properties for Aripiprazole monohydrate, its use in a sterile injection and the specification of anhydrous Aripiprazole (intermediate).

As the applied drug substance is intended for EU market the references of pharmacopoeial methods in the specification and relevant sections of the dossier are changed from USP to equivalent Ph. Eur. methods.

Generally the analytical methods used have been adequately described except for method for testing sterility. Missing description of this method is provided. The test methods of drug-related impurities (HPLC, Conditions-1 and-2) and assay (HPLC) for sterile Aripiprazole monohydrate are established based on those for anhydrous Aripiprazole.

Validation data are presented for GC method for testing residual solvents, HPLC method for content of Aripiprazole, HPLC methods (Conditions-1 and-2) for testing related substances of Aripiprazole, sterility method and bacterial endotoxins method. Completed validation of GC and HPLC methods are presented. However one question concerning validation of HPLC Conditions 2 method should be resolved.

Satisfactory information regarding the reference standards used for assay testing has been presented. Information for impurity reference standards are still requested.

Batch analysis data for the following batches of the active substance are provided:

- 21 representative batches used for pre-clinical, clinical and stability studies. The batches were tested according to the specifications which have been valid at the time of batch release.
- 6 typical batches and used for commercial production. The batches were tested according to the proposed specification. Batch size of these batches is stated as requested.

The results are within the specifications and consistent from batch to batch.

Container closure systems: Compliance with Ph. Eur. 3.1.4 and 3.2.2 and Commission Regulation (EU) No 10/2011 is confirmed. However, some issues should be resolved

3.1.2.4. Stability

Stability data according to the ICH guidelines were provided.

All tested parameters were within the specifications.

The stability results indicate that the active substance manufactured by the proposed supplier is stable.

Manufacturer 2:

The active substance specification includes tests for appearance, identity (IR, XRPD), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), residue on ignition (USP), bacterial endotoxins (Ph. Eur./USP), sterility (Ph. Eur./USP).

The specification for sterile Aripiprazole monohydrate has been established taking into account the physicochemical properties for Aripiprazole monohydrate, its use in a sterile injection and the specification of anhydrous Aripiprazole.

As the applied drug substance is intended for EU market the references of pharmacopoeial methods in the specification and relevant sections of the dossier are changed from EP/USP or USP to equivalent Ph. Eur. methods.

The analytical methods used have been adequately described. The analytical procedures used for the control of Aripiprazole oral grade and sterile Aripiprazole monohydrate have been transferred. However the corrected section 3.2.S.4.2 is missing and should be presented.

Validation data are presented only for methods used for testing bacterial endotoxins, sterility and bioburden. The updated section 3.2.S.4.3 is completed by the validation data for the following analytical methods: GC method for determination of residual solvent, HPLC method for determination of Aripiprazole content, HPLC method for determination of related impurities, Condition 1 and HPLC method for determination of related impurities, Condition 2.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for the following batches of the active substance are provided:

- 11 sterile Aripiprazole monohydrate batches
- 6 batches

The batches were tested according to the specifications which have been valid at the time of batch release. The results are within the specifications and consistent from batch to batch.

Primary packaging of sterile Aripiprazole monohydrate: Specifications and certificate of analysis, drawing and technical data are in compliance with EU law relating to materials and articles intended to come into contact with foodstuffs.

3.1.2.1. Stability

Stability data for 13 batches of active substance from the proposed manufacturer stored in the intended commercial package are presented according to the ICH guideline.

All tested parameters were within the specifications.

The stability results indicate that the active substance manufactured by the proposed supplier is stable.

3.1.3. Finished Medicinal Product

3 . 1 . 3 . 1 . Description of the product and Pharmaceutical Development

Aripiprazole 2M RTU LAI was developed for patient treatment, while allowing for increased time between dosing and maintenance of long-term effect. The finished product has been developed to be a hybrid equivalent to the reference medicinal product. Consequently, the objective was to prepare a product essentially similar to the reference medicinal product.

Almost all excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. Sodium Dihydrogen Phosphate Monohydrate has in-house specification, mostly based on Sodium Dihydrogen Phosphate Dihydrate Ph. Eur. monograph. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The discriminatory power of the dissolution method has been demonstrated.

The selected syringe material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

3.1.3.2. Pharmaceutical Development

Drug Product has been developed with regards to previous formulation, already approved Abilify Maintena. The applicant has described differences between both products, including slightly different pharmaceutical form. This product is an aqueous injectable suspension which is formulated by dispersing aripiprazole monohydrate into aqueous vehicle solution with the aid of excipients. Abilify Maintena is a lyophilized cake of aripiprazole monohydrate crystals which is reconstituted to an aqueous suspension prior to administration.

Major Objection regarding "low" strength has been resolved by comparison and development data,

3.1.3.3. Manufacture of the product and process controls

The manufacturing process consists of 5 main steps, as declared by the applicant. The process is considered to be a standard manufacturing process by the Manufacturer, however as in line with ANNEX II TO NOTE FOR GUIDANCE ON PROCESS VALIDATION CHMP/QWP/848/99 AND EMEA/CVMP/598/99NON STANDARD PROCESSES, proposed Drug Product is classified as Specialised Pharmaceutical Dose – as suspension, and prolonged release preparation, and with regards to non-standard methods of sterilisation (aseptic processing). Validation of the manufacturing process has been provided to resolve Major Objection.

3.1.3.4. Product specification (s)

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with ICH Q3D. No further control in the finished product specification is deemed necessary. The information on the control of elemental impurities is satisfactory. A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed, however as it has been presented only in form of simple description, further data, along with proper declaration of risk / no risk identified has been requested. in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). As currently nitrosamine data is not considered adequate, Major Objection has been raised. While the applicant has provided response to MO, it is not considered sufficient and further data is expected – according to the conclusion presented by the applicant a risk of presence of nitrosamines is very low, what is not equal to "no risk". Therefore it should be either declared as "no risk has been identified" or that the risk has been identified and proceed with step 2 confirmatory testing of the drug product.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis results are provided for 3 batches of 600 mg/syringe and 960 mg/syringe batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. 600 mg/syringe is considered purely informative, and batch analysis for 720 mg/syringe is expected to be delivered.

3.1.3.5. Stability of the product

Stability data from 3 batches of 600 mg/syringe and 3 batches of 960 mg/syringe batches of finished product stored for up to 12 months under long term conditions (25°C/40%) and for up to 6 months under accelerated conditions (40°C/75%RH) according to the ICH guidelines were provided. The batches of Asimtufii are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The analytical procedures used are stability indicating. The analytical methods used were the same as for release and were stability indicating.

Observed physical and chemical changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC (section 6.3) are acceptable for 960 mg/syringe. Stability results are awaited for 720 mg/syringe, however since MO regarding "low" dose is considered resolved and bracketing procedure based on 600 mg/syringe is considered acceptable.

3.1.3.6. Post approval change management protocol(s)

Not applicable.

3.1.3.7. Adventitious agents

No excipients derived from animal or human origin have been used.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Two major objections have been raised in relation to drug substance and drug product.

The level of other information provided to support the application at this stage cannot be considered as satisfactory. A number of other concerns are raised in relation to general properties and control of the active substance as well as the drug product manufacturing, control of the drug product and stability.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The presented dossier is considered not acceptable at this stage, as the CHMP has identified two Major Objections related to drug substance and drug product which may have a potential impact on the safe and effective use of the medicinal product.

3.1.6. Recommendation(s) for future quality development

Not applicable.

3.2. Non clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data.

Pharmacodynamic, pharmacokinetic and toxicological properties of aripiprazole are well known.

However, to address possible differences in pharmacokinetics and toxicology of aripiprazole in the proposed 2M RTU LAI formulation, the applicant performed a limited pharmacokinetics and toxicology non-clinical development program consisting of single- and repeat-dose local irritation studies in the dog and a single-dose PK study in the rat. Moreover, effect of heat, pressure, exercise and anti-inflammatory agent (diclofenac) on the PK profile of aripiprazole when administered to rats using the aripiprazole 2M RTU LAI formulation was studied by the applicant.

3.2.1. Pharmacology

No new pharmacodynamics and safety pharmacology studies have been performed by the applicant. This is acceptable given that oral aripiprazole was approved in the EU in 2004 and the IM depot formulation was approved in the EU in 2013. Therefore, it is agreed that a pharmacodynamic characteristics of aripiprazole has been extensively described and supported by the clinical evidence. In conclusion no further pharmacodynamic and safety pharmacology studies are considered necessary to support the current MAA.

3.2.2. Pharmacokinetics

The PK of aripiprazole was adequately characterized in vivo studies in mice, rats, dogs, and monkeys, and in model test systems in vitro in the previously approved MAA (EMEA/H/C/000471) for the oral tablet. In addition, several additional PK studies were conducted in rats (including the single-dose PK study RN014075) and minipigs for the aripiprazole IM depot formulation. The results of these studies are described in MAA (EMEA/H/C/0002755).

A single-dose study RN014075 aimed to study a PK of a 50 mg/kg aripiprazole of either the IM depot or 2M RTU LAI formulation in male Sprague Dawley rats was performed by the applicant.

Serum aripiprazole concentrations were similar between the 2 formulations (Figure 2) and there were no meaningful difference in the PK parameters between the 2 injectable formulations (Table 5).

Table 1

Table 2.6.6.2-1 Mean PK Parameters in Male Rats Treated Intramuscularly with Aripiprazole IM Deport or RTU Formulation (50 mg/kg) (Mean ± S.D.)			
Formulation	**AUC_{84d} (ng d/mL)**	**C_{max} (ng/mL)**	**T_{max} (day)**
Aripiprazole IM Depot	433.38 ± 62.85	30.00 ± 2.73	6.0 ± 0.0
RTU Formulation	431.10 ± 62.15	25.38 ± 4.54	6.5 ± 1.2

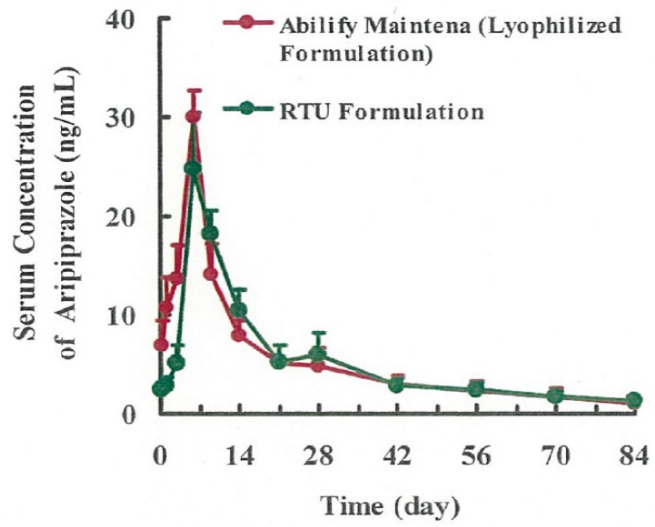


Figure 2 Serum Concentrations of Aripiprazole Following an Intramuscular Injection at a Dose of 50 mg/kg in Male Rats (n=6, Mean ± S.D.)

Studies to assess the influence of stress factors (RN036018) and immune/inflammatory response modulators (RN036019) on the drug release profiles of aripiprazole from the aripiprazole 2M RTU LAI formulation were conducted by the applicant in rats to support the current MAA.

Study RN036018

Study title: Effect of the Applied Stress on the Plasma Concentration-time Profile of OPC-31 After Intramuscular Injection of OPC-31 RTU Formulation to Rats
Study objective: To evaluate the effect on plasma OPC-31 concentration of various stress stimuli applied for 21 days in rats to which OPC-31 RTU formulation was administered once intramuscularly.
Study design:
A total of 6 test groups consisted of control, anesthesia control, physical stimulation, exercise stimulation, whole body heat stimulation, and local heat stimulation groups were established. These stresses were applied for 21 consecutive days from the day of test article administration. OPC-31 RTU formulation was administered once intramuscularly to rats at a dose of 50 mg/kg with blood collection performed before administration and 6 hours after administration, and on days 1, 2, 4, 6, 8, 10, 12, 15, 18, and 21 after administration to determine OPC-31 in plasma.

To evaluate the effect of these stimulations on the systemic exposure and pharmacokinetics of OPC-31, the maximum plasma concentration (Cmax), the time to reach Cmax (tmax), the area under the concentration-time curve calculated to the last observable concentration at time t (AUCt) and from time zero to infinity (AUC∞), and the mean residence time from time zero to infinity (MRT∞) were determined.

Results

Results showed that exercise and the application of physical pressure and heat (whole body or near administration site) had minimal effect on the exposure of aripiprazole as changes in C_{max} or area under the concentration-time curve (AUC) were < 2 fold after the application of stress. Specifically, changes in area under the concentration-time curve calculated to the last observable concentration at time, t (AUC_t), ie, 0 to 21 days, and area under the concentration-time curve from time 0 to infinity (AUC_∞) were ≤ 1.4-fold and changes in C_{max} were ≤ 1.5-fold. The application of direct pressure caused the greatest change in C_{max} (1.5-fold) and AUC_t (1.4-fold), although there was no change in AUC_∞. Mean residence time and time to maximum (peak) plasma concentration (t_{max}) were similar across all groups.

Table 2: Pharmacokinetic parameters for OPC-31 after a single intramuscular administration to rats with various stress stimulations

Dose (mg/kg)		C_{max} (ng/mL)	t_{max} (day)	AUC_t (ng·day/mL)	AUC_∞ (ng·day/mL)	MRT_∞ (day)
50 Control	Mean	26.22	7.2	267.7	349.3	16.62
	SD	5.12	1.8	54.3	70.7	5.99
	Ratio[1)]	1.0	1.0	1.0	1.0	1.0
50 Exercise stimulation	Mean	25.36	6.8	273.3	325.8	13.32
	SD	2.20	1.1	37.6	42.1	1.04
	Ratio[1)]	1.0	0.9	1.0	0.9	0.8
50 Anesthesia control	Mean	19.26	7.2	203.0	309.2	19.29
	SD	3.80	1.8	18.0	116.5	9.75
	Ratio[2)]	1.0	1.0	1.0	1.0	1.0
50 Physical stimulation	Mean	28.00	6.0	274.9	328.1	13.16
	SD	4.41	0.0	30.3	35.1	2.25
	Ratio[2)]	1.5	0.8	1.4	1.1	0.7
50 Whole body heat stimulation	Mean	23.66	6.8	235.1	300.0	15.18
	SD	2.46	1.8	20.8	83.8	6.44
	Ratio[2)]	1.2	0.9	1.2	1.0	0.8
50 Local heat stimulation	Mean	25.42	6.8	230.2	302.3	18.36
	SD	8.26	1.1	68.0	67.3	13.52
	Ratio[2)]	1.3	0.9	1.1	1.0	1.0

Study RN036019

Study title: Effect of an Anti-inflammatory Agent on the Plasma Concentration-time Profile of OPC-31 After Intramuscular Injection of OPC-31 RTU Formulation to Rats.

Study objective: To evaluate the effect on plasma OPC-31 concentration after a single intramuscular administration of OPC-31 RTU formulation of repeated oral administration of diclofenac sodium for 7 days in rats.

Study design:

The effect on plasma OPC-31 concentration was evaluated after a single intramuscular administration of OPC-31 RTU formulation conducted in parallel with repeated oral administration of diclofenac sodium for 7 days in rats.

OPC-31 RTU formulation was administered once intramuscularly to rats at a dose of 50 mg/kg. Diclofenac sodium was orally administered at doses of 2 and 5 mg/kg once daily for 7 days from the day of OPC-31 RTU formulation administration. PK blood collection was performed before administration, 6 hours after administration, and on days 1, 2, 4, 6, 8, 10, 12, 15, 18, and 21 after administration to determine OPC-31 in plasma.
To evaluate the diclofenac sodium-treatment on the systemic exposure and pharmacokinetics of OPC-31, the maximum plasma concentration (Cmax), the time to reach Cmax (tmax), the area under the concentration-time curve calculated to the last observable concentration at time t (AUCt) and from time zero to infinity (AUC∞), and the mean residence time from time zero to infinity (MRT∞) were determined.
When rats were treated with diclofenac sodium at 2 mg/kg for 7 days, no obvious change was observed in the systemic exposure to OPC-31. The ratios of Cmax, AUCt and AUC∞ values from treated rats to those from the control were 1.0. The tmax and MRT∞ were almost the same as the control.
By the diclofenac sodium-treatment at 5 mg/kg for 7 days, the systemic exposure to OPC- 31 was slightly decreased. The ratios of Cmax, AUCt and AUC∞ values from treated rats to those from the control were 0.7 to 0.9. The tmax and MRT∞ tended to extend.

Results
Results from **RN036019** showed that diclofenac low dose (2 mg/kg) had no effect on exposure (C_{max} and AUC) or t_{max} of aripiprazole. At the diclofenac high dose of 5 mg/kg, exposure to aripiprazole (C_{max} only) was minimally decreased and t_{max} was prolonged by 2.8 days.

Table 3: Pharmacokinetic parameters for OPC-31 after a single intramuscular administration to rats with diclofenac sodium-treatment for 7 days.

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

3.2.3. Toxicology

3.2.3.1. Local tolerance

Study 035591

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

Study objective: To determine the irritation potential of the new component of OPC-14597 suspension for depot injection when given intramuscularly as a single dose to beagle dogs, and to determine the reversibility of injection site changes.

Study design: Three groups of 9 beagle dogs each were given a single intramuscular (IM) 1.4 mL dose of 0 (saline control), 0 (vehicle control), or 300 mg/mL of OPC-14597 suspension in the right hindlimb (thigh). The possible maximal clinical dose is expected to be 400 mg/body, and thus the

corresponding dose volume of 1.4 mL was selected in the present study. Parameters for evaluation included daily general condition, injection site observation, and periodic hematology and quantification of aspartate aminotransferase (AST) and creatine kinase (CK). Periodic body weights and daily food consumption were also evaluated. At scheduled necropsies on Days 8, 29 and 57, the injection sites of 3 dogs/group were examined. The injection sites of all animals were collected for histopathological examination. Plasma samples for evaluation of systemic exposure to OPC-14597 were collected periodically during the study.

Results:
No animals died or were sacrificed in the moribund state during this study. There were also no clinical signs that were associated with pain due to the IM injection of OPC- 14597, and no significant injection site changes in any treated animals.
Hematological tests showed increased white blood cells (neutrophils and monocytes) in the treated animals on Day 2, as a result of acute inflammation at the injection site, and these changes disappeared on Day 8.
At necropsy, white focus was evident in the injection site muscles for all treated animals sacrificed on Days 8, 29 and 57, and the size gradually decreased over time.
The white focus was characterized microscopically by granulomatous inflammation. The localized inflammatory responses principally consisted of accumulation of macrophages with vacuoles or foamy cytoplasm around weakly eosinophilic deposits (interpreted as drug). The severity of the inflammation was comparable through Day 29 but decreased on Day 57. There was no evidence of any muscle necrosis at the injection sites of any treated animals.
None of the data of the body weight, food consumption and blood biochemistry (AST and CK) showed any changes, which were considered to be drug-related.
The plasma concentrations of OPC-14597 in the treated animals gradually increased, and the mean Tmax was 16 days, and the mean Cmax was 28.99 ng/mL. The mean AUC28d and AUC56d were respectively 515.4 ng·d/mL and 898.9 ng·d/mL, and the mean plasma concentration of OPC-14597 at 56 days after administration (7.470 ng/mL) was half of that at 28 days after administration.

Table 4: 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

Table 5 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

Study 035592

Study title: 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

Study objective: To determine the irritation potential of the new component of OPC-14597 suspension for depot injection when intramuscularly given to beagle dogs for 52 weeks, and to determine the reversibility of injection site changes after the following 26-week withdrawal period.

Study design:
Groups of 9 male beagle dogs received 1.4 mL intramuscular injection of physiological saline (negative control), 0 mg/mL OPC-14597 solution (vehicle control) or 300 mg/mL of OPC-14597 suspension alternately into the right and left biceps femoris muscle once every 4 weeks. The possible maximal clinical dose is expected to be 400 mg/body, and thus the corresponding dose volume of 1.4 mL was selected. Parameters for evaluation included daily general conditions, injection site observation, and periodic hematology and quantification of plasma aspartate aminotransferase (AST) and creatine

kinase (CK). Periodic body weights and daily food consumption were also evaluated. The first, second and last 3 dogs of each group were allocated to necropsy and examine the injection sites at the end of the 24- and 52-week dosing periods and 26-week withdrawal period, respectively. The injection sites of all animals were collected for histopathological examination.

Results:
No drug-related deaths occurred although 1 animal died due to spontaneous acute heart failure at Week 20 of the recovery period.
During the course of the study, there were no clinical signs that were associated with pain due to the intramuscular injection of OPC-14597, and no significant injection site changes in any treated animals. Hematological tests also showed no drug-related abnormalities and there were no increase in AST or CK suggesting muscular damages.
None of the data of the body weight and food consumption showed any abnormalities, which were considered to be drug-related.
At the end of the 24- and 52-week dosing periods, white foci were evident in the injection site muscles of all treated animals. The white focus was characterized microscopically by granulomatous inflammation. The localized inflammatory responses consisted of accumulation of macrophages with vacuoles or foamy cytoplasm around weakly eosinophilic deposits (interpreted as drug). Foreign body giant cells, lymphocytes, neutrophils, capillary proliferation and fibroblast proliferation with a small amount of collagen fiber were occasionally present within the areas of granulomatous inflammation. The examination with polarized light of selected unstained frozen sections, which were obtained from the treated animals, revealed the presence of birefringent crystal-like material (deposited drug) within the focus of granulomatous inflammation at the injection sites. The severity of granulomatous inflammation at Week 52 was comparable to that observed at Week 24.
At the end of the 26-week recovery period, the white foci still existed in the injection site muscles of the treated animals, and granulomatous inflammation was observed microscopically as well as the presence of birefringent crystal-like material. However, the size of the white foci obviously became smaller, and the severity of granulomatous inflammation was alleviated when compared to that observed at the end of the dosing period.

3.2.4. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of ASIMTUFII manufactured by Otsuka Pharmaceutical Netherlands B.V. is considered unlikely to result in any significant increase in the combined sales volumes for all aripiprazole containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

ASIMTUFII is not prescribed for any new indication and will only replace existing products already on the EU market. Thus, marketing authorisation of ASIMTUFII will only lead to redistribution of the market share in the EU and will not result in an increase of the total exposure of aripiprazole to the environment from the prescribed use of the product.

The applicant substantiated that no "significant increase of environmental exposure to the drug substance" is to be expected from the intended Marketing Authorisation due to the following reasons:

• Aripiprazole containing medicinal products are authorised and marketed worldwide and in the European Community since 2004.
• The patent for Abilify expired 2014. Generic drug products with aripiprazole as active substance in different (oral) formulation entered the market.
• Thus, the marketing authorisation of ASIMTUFII and generic drug products will only lead to redistribution of market shares in Europe but not to an increase of the total amount of aripiprazole used and as a consequence, both facts will not result in an increase of the total exposure of aripiprazole to the environment during storage, distribution, use and disposal.
• In clinical practice the successful treatment of schizophrenia may require switching between antipsychotics. The reasons for changing treatments include inadequate or complete lack of efficacy,

partial compliance or noncompliance with medication, and the presence of adverse events such as movement disorders, weight gain, somnolence, endocrine side effects, and metabolic dysfunction.
• The possibility of exacerbation of psychotic symptoms due to withdrawal of the original antipsychotic before the new antipsychotic has become effective is a major consideration. Conversely, when drugs with long half-lives are quickly replaced with new treatments, consideration must be given to possible excessive drug effects. From applicant's point of view the numbers of patients, which will be switching from oral aripiprazole (10 mg to 30 mg tablets) and other oral or injectable antipsychotics to ASIMTUFII will not result in an increase of the total exposure of aripiprazole to the environmental during use of aripiprazole.

The applicant acknowledged that the study on transformation in water/sediment systems (OECD 308) showed that the active substance aripiprazole has to be considered as very persistent (vP) according to the DT50 value of 379 d at 12°C (177 d at 20°C) in water/sediment (total system).

Table 6

Substance (INN/Invented Name): Aripiprazole monohydrate			
CAS-number (if available): 129722-12-9 (monohydrate: 851220-85-4)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	FDA 3.02	log Dow (pH 5): 2.7 log Dow (pH 7): 2.95 log Dow (pH 9): 2.89	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	≤ 4.5 (2.95 at pH 7)	not B
Persistence	DT50	379 d (12 °C)	vP
Toxicity	NOEC	2.61 µg/L	T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (prevalence)	0.032	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	-	-	(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 0.43 d, 6.47 d $DT_{50, sediment}$ = n.c. $DT_{50, whole\ system}$ = 379 d, 85 d at 12 °C % shifting to sediment > 10	vP

Aripiprazole is an ionisable compound and shows a pH dependent Kow. The measured Kow values of the provided FDA 3.02 study shows mean Kows up to 897 at the screening points pH 7 and 9. Additionally in the Dossier „2.3.S.1 General information" the applicant documented Kow data >1000 up from pH 6. The results are very close to the bioaccumulation trigger of 1000 (log Kow: 3.0). Due to such special cases the Q+A document clearly supports further investigations to exclude the existing uncertainties of the possible bioaccumulation behavior.
The applicant declared that study (OECD 123) on the octanol water partition coefficient will be provided in August 2023.
Depending on the result a bioaccumulation study may be required.

The total forecasted use of aripiprazole for the year 2026 in the EC27 based on sales figures for aripiprazole all dosage form in 2020:

4,561.83 kg aripiprazole (sales data 2020)

Estimation of Predicted Environmental Concentration (PEC) regarding a conservative growth rate of 15 % - Forecast data Aripiprazole 2026

Period	2020	2022	2023	2024	2025	2026
kg	4,561.83	6,033.02	6,937.97	7,978.66	9,175.46	**10,551.78**

Estimation of Predicted Environmental Concentration (PEC) aripiprazole (all dosage forms) in 2027

$$\mathbf{F_{pen\text{-}mod}}\ [\%] = \frac{\text{consumption [mg*year}^{-1}\text{]} * 100}{\text{DDD [mg*d}^{-1}\text{*inhab]} * \text{inhabitants [inhab]} * 365\ \text{d*year}^{-1}}$$

$$\mathbf{F_{pen\text{-}mod}}\ [\%] = \frac{10551780000 * 100}{20 * 447010000 * 365} = \mathbf{0.32}$$

Fpen-mod	Market penetration modified by Midas data	
Consumption	Amount of drug sold in 2027	10551780000 mg
DDD	Defined Daily Dose (Maximum Daily Dose)	20 mg/(inh·d)
Inhabitants	Population European Countries EC 2027	447,01 Mio (https://de.statista.com)

$$\mathbf{PEC_{SW\text{-}mod}} = \frac{\text{DOSEai x } F_{pen\text{-}mod} \text{ x (1-METAB)}}{\text{WASTEWinhab x DILUTION}}$$

$$\mathbf{PEC_{SW\text{-}mod}} = \frac{20 \text{ x } 0.0032 \text{ x } (1\text{-}0.24)}{200 \text{ x } 10} = 0.000024 \text{ mg/L} = \mathbf{0.024\ \mu g/L}$$

$PEC_{SW\text{-}mod}$	Predicted environmental concentration in surface water	
DOSEai	maximum daily dose per inhabitant	20 mg / (inh · d)
$F_{pen\text{-}mod}$	market penetration modified	0.24 % = 0.0024
METAB	Metabolism removal	0.24
WASTEWinhab	amount of wastewater per inhabitant per day	200 (L / (inh · d)
DILUTION	dilution factor	10 [Default]

The $PEC_{SW\text{-}refined}$ estimated above is used directly for the assessment of impact to surface water species and micro-organisms. The EMA CHMP Guidance indicates that the groundwater concentration, PEC_{GW} can be estimated from $PEC_{SW\text{-}refined}$.

$\mathbf{PEC_{GW}} = PEC_{SW\text{-}mod}$ x 0.25

$\mathbf{PEC_{GW}} = 0.024\ \mu g/L$ x 0.25 = **0.006 µg/L**

PEC/PNEC assessments

The PECs in relevant environmental compartments are compared to the PNECs for these compartments in accordance with the EMA CHMP guidance by calculation of PEC/PNEC ratios. This information are summarised below:

Compartment	PEC	PNEC	PEC/PNEC
PEC_{SW-mod}	0.024	0.261	0.092
PEC_{GW}	0.006	0.261	0.023
PEC_{micro}	0.024	10000	0.0000024

If the ratio PECSurfaceWater: PNECWater for the drug substance aripiprazole is below 1, then further testing in the aquatic compartment will not be necessary and it can be concluded that the drug substance aripiprazole and/or its metabolites are unlikely to represent a risk to the aquatic environment.

PEC/PNEC ratios in Tier A for aripiprazole are below 1 concluding that aripiprazole and/or its metabolites are unlikely to represent a risk to the aquatic environment. Since both sediment and terrestrial studies are triggered, an updated risk assessment must be provided for these compartments as well.

The applicant presented the result from the study in units of µg/g diet and justified why it was not possible to convert this result to mg/kg soil. The calculation of the PECsoil was provided by the applicant.

logKow: The required study according to OECD 123 on the octanol-water partition coefficient of aripiprazole can be submitted as post-authorisation measure by Q3 2023 as already suggested by the applicant. A respective letter of agreement should be provided, including the anticipated time schedule. Depending on the result a bioaccumulation study may be required **(OC).**

3.2.5. Discussion on non-clinical aspects

No new pharmacodynamics and safety pharmacology studies have been performed by the applicant. This is acceptable given that oral aripiprazole was approved in the EU in 2004 and the IM depot formulation was approved in the EU in 2013. Therefore, it is agreed that a pharmacodynamic characteristics of aripiprazole has been extensively described and supported by the clinical evidence. In conclusion no further pharmacodynamic and safety pharmacology studies are considered necessary to support the current MAA.

However, to address possible differences in pharmacokinetics and toxicology of aripiprazole in the proposed 2M RTU LAI formulation, the applicant performed a limited pharmacokinetics and toxicology non-clinical development program consisting of single- and repeat-dose local irritation studies in the dog and a single-dose PK study in the rat. Moreover, effect of heat, pressure, exercise and anti-inflammatory agent (diclofenac) on the PK profile of aripiprazole when administered to rats using the aripiprazole 2M RTU LAI formulation was studied by the applicant.

Studies to assess the influence of stress factors (RN036018) and immune/inflammatory response modulators (RN036019) on the drug release profiles of aripiprazole from the aripiprazole 2M RTU LAI formulation were conducted by the applicant in rats to address possible changes in aripiprazole PK.

Results of the Study RN036018 did not indicate that exercise and the application of physical pressure and heat (whole body or near administration site) should be expected to result in a clinically relevant changes in the exposure of aripiprazole.

However, results of the Study RN036019 showed that concomitant administration of aripiprazole RTU formulation and a high dose of diclofenac resulted in decreased Cmax (31.53 ng/ml vs 21.79ng/ml) and prolonged tmax (6.8 days vs 9.6 days). Moreover, AUCt and AUCinf were decreased in following exposure to diclofenac high dose. Nevertheless, these data were not considered adequate for inclusion at the SPC.

No repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity studies have not been performed with the RTU formulation. This is acceptable taking into account that repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity studies of aripiprazole by oral and IM administration have been accepted during EMEA/H/C/000471 and EMEA/H/C/0002755 procedures.

Two local tolerance studies have been performed by the applicant.

In a single intramuscular dose irritation study 035591 in Beagle Dogs, no concerning safety findings were identified. No animals died during the 8-week observation period. Small and transient erythema was observed in one treated animal between Days 3 and 7. Transient increase in white blood cells caused most probably by acute inflammation at the injection sites is not of concern. No increase in AST or CK suggesting muscular damages was reported in any treated animals. White focus in the injection site muscles observed at necropsy for all treated animals gradually decreased in size over time but did not completely resolve after 8 weeks. No drug-related changes in body weight and food consumption were observed.

In a fifty-two-week intermittent with 26-week Recovery Test intramuscular dose irritation study 035592 in Beagle Dogs one death at Recovery Week 20 was reported. Pathological examinations revealed that the cause of death was an acute heart failure due to extended myocardial necrosis predominantly in the left ventricular papillary muscle with contraction band necrosis. Based on the previous studies, the death was incidental, and was not considered related to the administration of the test article.

Although at the end of the 24- and 52-week dosing periods, white foci characterized microscopically by granulomatous inflammation were observed in the injection site muscles of all treated animals, there were no clinical signs that were associated with pain due to the intramuscular injection of OPC-14597. Nevertheless, it can be concluded, that no concerning safety finding were identified in the study.

logKow: The required study according to OECD 123 on the octanol-water partition coefficient of aripiprazole can be submitted as post-authorisation measure by Q3 2023 as already suggested by the applicant. A respective letter of agreement should be provided, including the anticipated time schedule.

Depending on the result a bioaccumulation study may be required (OC).

3.2.6. Conclusion on non-clinical aspects

There is one remaining OC to be addressed by the applicant. Asimtufii could be approvable from a non-clinical perspective.

3.3. Clinical aspects

3.3.1. Exemption

No information regarding evaluation of the lower dose of 720 mg RM RTU LAI was provided.
It is agreed that section 5.1.3 of the Guideline on the Pharmacokinetic and Clinical Evaluation of Modified Release Dosage Forms it is stated that "Whenever there are several strengths or when several single units can be taken simultaneously to achieve the desired dose, dose proportionality for different strengths / doses of the modified release formulations should be adequately addressed. Dose proportionality should be evaluated by means of a single dose and, in case of drug accumulation, a multiple dose study, where the PK parameters of interest of all the strengths/doses are compared after dose adjustment." However, it is also stated for generics in section 6.4.2 that "If the originator product is marketed in only one concentration and the different doses are achieved by choosing the total

volume to be injected any dose should be acceptable for a bioequivalence trial in case dose proportionality has been shown for the reference" and "In situations where it is not possible to perform single dose studies with an intramuscular/subcutaneous depot formulation in healthy volunteers for safety or ethical reasons, multiple dose studies in patients are acceptable to show bioequivalence". Less than dose-proportional increases in aripiprazole and dehydro-aripiprazole concentrations and AUC parameters are observed after monthly Abilify Maintena injections of 300 mg to 400 mg. However, in study 031-201-00104 less than proportional increase in aripiprazole Cmax and more than dose proportional increase in AUCt and AUCinf were reported based on mean values corrected for dose.

Therefore, the applied product should be compared also at the 720 mg strength versus 300 mg of Abilify Maintena to confirm the same degree of non-linearity as observed in Abilify Maintena the intended use is to switch from the one monthly injection or it is claimed to be equivalent to it. If the applied product exhibited a different non-linearity or dose-proportionality, the evidence of efficacy and safety of the one-monthly 300 mg strength to the bimonthly 720 mg strength would not be possible.

Based on the results presented by the applicant it can be considered that aripiprazole 2M RTU LAI PK is linear from a dose range of 420 mg to 1200 mg. The final popPK model support predicted aripiprazole concentrations following a 720 mg dose of aripiprazole 2M RTU LAI.

Tabular overview of clinical studies

To support the application, the applicant has submitted three pharmacokinetics studies.

Table 7: Tabular overview of clinical studies

Type of Trial (Trial Phase)	Protocol Number Location of Trial	Trial Objective(s)	Trial Design and Type of Control	Investigational Medicinal Product; Dosage Regimen; Route of Administration	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Subjects	Treatment Duration
PK, Safety (Phase 1b) (pivotal study)	031-201-00181 United State	**Primary:** Safety and tolerability of multiple-dose administrations of aripiprazole in adults 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 adults with schizophrenia or bipolar I disorder	Open-label, multipledose, randomized, parallel-arm, multicenter trial	Aripiprazole 2M LAI 960 mg (test) Aripiprazole IM depot 400 mg (reference)	132 134	Adults with schizophrenia or bipolar disorder	2-month injection (total of 4 injections) administered every 56 days (± 2 days) over the course of 32 weeks 1-month injection (total of 8 injections) administered every 28 days (± 2 days) over the course of 32 weeks

		To establish the similarity of aripiprazole exposure over the dosing interval following the administration of aripiprazole into the gluteal muscle site in adults with schizophrenia or bipolar I disorder **Secondary:** 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					
PK, Safety (Phase 1)	031-201-00104 United States	**Primary:** Safety and tolerability of single ascending dose administrations of the aripiprazole LAI in adult subjects with schizophrenia **Secondary:** PK of aripiprazole and its metabolite(s), including the major metabolite dehydroaripiprazole, following single ascending dose administrations of the aripiprazole LAI in adult	Open-label, single ascending dose, parallelarm, multicenter trial	**Cohort 1:** 780 mg aripiprazole IM (gluteal) **Cohort 2:** 1200 mg aripiprazole IM (gluteal)	18 18	Adults with schizophrenia	Single dose on Day 1

		subjects with schizophrenia					
PK, Safety (Phase 1)	031-201-00279 United States	**Primary:** PK of 420 mg aripiprazole 1M LAI RTU following deltoid or gluteal muscle administration in adult subjects with schizophrenia or bipolar I disorder **Secondary:** Safety and tolerability of single- and multiple-dose administrations of 420 mg aripiprazole 1M LAI RTU in adult subjects with schizophrenia or bipolar I disorder	Two-part, open-label, single- and multipledose, multicenter trial	420 mg aripiprazole 1M LAI RTU as: **Part A:** Single dose IM (deltoid) Single dose IM (gluteal) Multiple doses IM (deltoid) Multiple doses IM (gluteal) **Part B:** Single dose IM (gluteal) within 3 seconds Single dose IM (gluteal) within 7 to 8 seconds	12 12 14 14 10 10	Adults with schizophrenia or bipolar I disorder	**Part A:** Single dose on Day 1 for subjects in the singledose group and as multiple doses (a total of 5 administrations [Days 1, 29, 57, 85, and 113]) for subjects in the multipledose group **Part B:** Single dose, injection (within 3 seconds), on Day 1 Single dose, injection (within 7 to 8 seconds), on Day 1

3.3.2. Clinical pharmacology

3.3.2.1. Pharmacokinetics

Study 031-201-00181: 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

Methods

- **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 a screening period of up to 30 days (which included a washout of previous medications), 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 960 mg was administered at 56-day (± 2 days) intervals and aripiprazole IM depot 400 mg was administered at 28-day (± 2 days) intervals. 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.

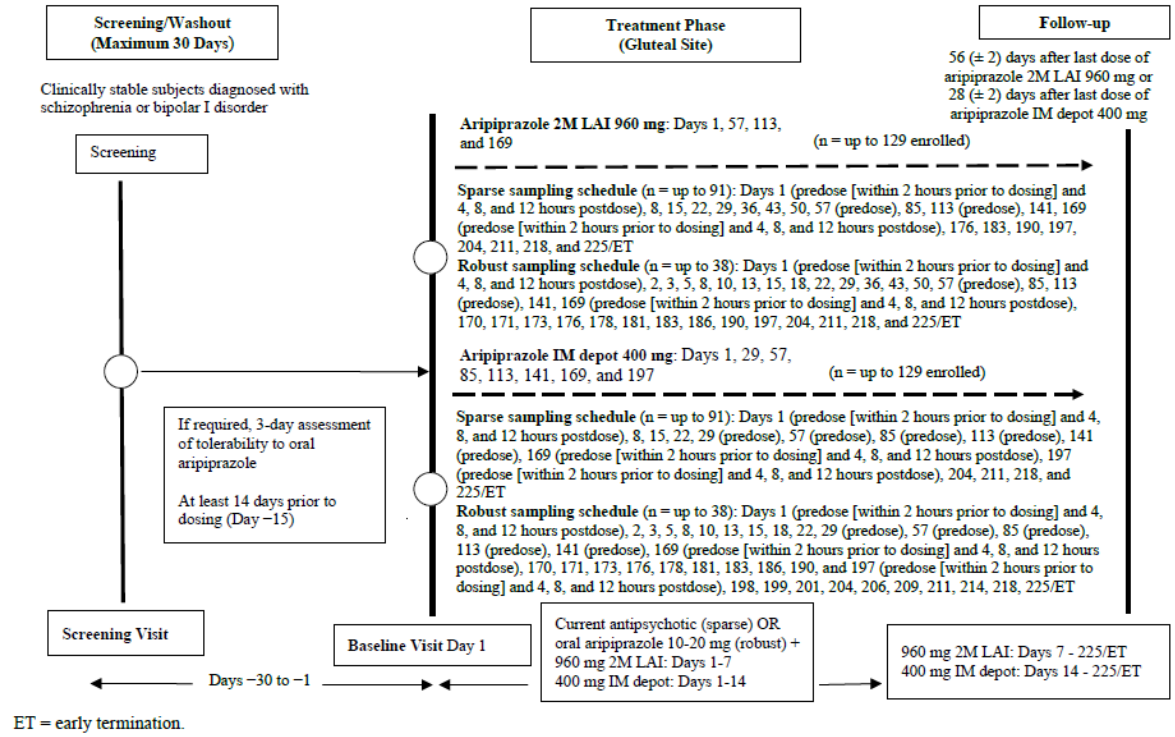


Figure 3 Trial Design Schematic

Primary Endpoints

Safety

Safety and tolerability were based on reported adverse events (AEs), vital signs, electrocardiograms (ECGs), clinical laboratory monitoring (serum chemistry, hematology, and urinalysis), physical examinations, extrapyramidal symptoms (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, the Investigator's Assessment of Most Recent Injection Site, and suicidality via the Columbia-Suicide Severity Rating Scale (C-SSRS).

Pharmacokinetic

The following primary PK parameters were estimated for aripiprazole:

☐ Plasma concentration of aripiprazole 56 days postdose (C56) of aripiprazole 2M LAI 960 mg after the fourth dose and plasma concentration of aripiprazole 28 days postdose (C28) of aripiprazole IM depot 400 mg after the eighth dose over the course of 32 weeks.

☐ Area under the concentration-time curve of aripiprazole from time zero to 56 days postdose (AUC0-56) for aripiprazole 2M LAI 960 mg after the fourth dose or area under the concentration-time curve of aripiprazole from time zero to 28 days postdose (AUC0-28) for aripiprazole IM depot 400 mg 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

Pharmacokinetic

The following PK parameters were estimated for aripiprazole after the administration of aripiprazole 2M LAI 960 mg and aripiprazole IM depot 400 mg:

☐ Maximum (peak) plasma concentration of the drug (Cmax) and time to maximum (peak) plasma concentration (tmax) after the first and fourth doses of aripiprazole 2M LAI 960 mg.
☐ AUC0-56 and C56 after the first dose of aripiprazole 2M LAI 960 mg.
☐ AUC0-28 and area under the concentration-time curve of aripiprazole from 29 to 56 days postdose (AUC29-56) after the fourth dose of aripiprazole 2M LAI 960 mg.
☐ Peak-to-trough percent fluctuation (PTF%) after the fourth dose of aripiprazole 2M LAI 960 mg.
☐ Cmax and tmax after the first, seventh, and eighth doses of aripiprazole IM depot 400 mg.
☐ AUC0-28 and C28 after the first dose of aripiprazole IM depot 400 mg.
☐ PTF% after the eighth dose of aripiprazole IM depot 400 mg.

After the first dose of investigational medicinal product (IMP), the following PK parameters were estimated for aripiprazole after administration of aripiprazole 2M LAI 960 mg + oral aripiprazole 10 to 20 mg for 7 days and aripiprazole IM depot 400 mg + oral aripiprazole 10 to 20 mg for 14 days (this endpoint was only for subjects enrolled to the robust sampling schedule):
☐ Plasma concentration of aripiprazole 7 days postdose (C7)
☐ Plasma concentration of aripiprazole 14 days postdose (C14).

Efficacy
The efficacy of aripiprazole IM depot administration in the gluteal muscle 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 Neuroleptic Treatment-Short Form (SWN-S), Montgomery-Asberg 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).

Number of Subjects: A total of 266 subjects were enrolled, randomized, and treated (received at least 1 dose of investigational medicinal product [IMP]): 132 subjects in the aripiprazole 2M LAI 960 mg group and 134 subjects in the aripiprazole IM depot 400 mg group. Of the 266 enrolled subjects, 185 had schizophrenia and 81 had bipolar I disorder, and 84 were in the robust PK sampling group and 182 were in the sparse PK sampling group.

Duration of Treatment: The trial consisted of a screening period of up to 30 days and a treatment period of 169 (± 2) days with a follow-up period of 56 (± 2) days after administration of the final dose for the aripiprazole 2M LAI 960 mg treatment group, or a treatment period of 197 days with a follow-up period of 28 (± 2) days after administration of the final dose for the aripiprazole IM depot 400 mg treatment group. Individual participation for both treatment groups was approximately 255 (± 2) days.

Trial Assessments:
Safety: Standard safety variables examined included adverse events (AEs), vital signs, electrocardiograms (ECGs), clinical laboratory tests (serum chemistry, hematology, and urinalysis), physical examinations, extrapyramidal symptoms (EPS) (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, the Investigator's Assessment of Most Recent Injection Site, and the Columbia-Suicide Severity Rating Scale (C-SSRS).
Pharmacokinetics: Blood samples were collected to determine plasma concentrations of aripiprazole and its major metabolite, dehydro-aripiprazole, after administration of aripiprazole 2M LAI 960 mg or aripiprazole IM depot 400 mg over the course of 32 weeks, to include 7 or 14 days of oral overlap of 10 to 20 mg aripiprazole administered with aripiprazole 2M LAI 960 mg or aripiprazole IM depot 400 mg, respectively, starting on Day 1 (first day of dosing). To obtain a good distribution of PK sampling times, the trial sites were divided into either sparse (majority of the sites) or robust (extensive) PK sampling trial sites.
Pharmacogenomics: A pharmacogenomic sample was collected on Day 1 prior to dosing in order to extract deoxyribonucleic acid (DNA) for the determination of genotypes related to cytochrome P450 (CYP) 2D6 drug metabolizing enzymes.

Efficacy: The efficacy assessments included 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 Neuroleptic Treatment-Short Form (SWN-S), Montgomery-Asberg Depression Rating Scale (MADRS; bipolar subjects only), YoungMania Rating Scale (YMRS; bipolar subjects only), and Clinical Global Impression - Bipolar Version (CGI-BP; bipolar subjects only).

- **Criteria for Evaluation (including Pharmacokinetic variables)**

The primary endpoints were as follows:

Safety: Safety and tolerability were based on reported AEs, vital signs, ECGs, clinical laboratory monitoring (serum chemistry, hematology, and urinalysis), physical examinations, EPS (the SAS, AIMS, and BARS), VAS scores for pain perception, the Investigator's Assessment of Most Recent Injection Site, and suicidality via the C-SSRS.

Pharmacokinetics: The following primary PK parameters were estimated for aripiprazole:

- Plasma concentration of aripiprazole 56 days postdose (C56) of aripiprazole 2M LAI 960 mg after the fourth dose and plasma concentration of aripiprazole 28 days postdose (C28) of aripiprazole IM depot 400 mg after the eighth dose over the course of 32 weeks.

- Area under the concentration-time curve of aripiprazole from time zero to 56 days postdose (AUC0-56) for aripiprazole 2M LAI 960 mg after the fourth dose or area under the concentration-time curve of aripiprazole from time zero to 28 days postdose (AUC0-28) for aripiprazole IM depot 400 mg 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.

The secondary endpoints were as follows:

Pharmacokinetics: The following PK parameters were estimated for aripiprazole after the administration of aripiprazole 2M LAI 960 mg and aripiprazole IM depot 400 mg:
☐ Maximum (peak) plasma concentration of the drug (Cmax) and time to maximum (peak) plasma concentration (tmax) after the first and fourth doses of aripiprazole 2M LAI 960 mg.
☐ AUC0-56 and C56 after the first dose of aripiprazole 2M LAI 960 mg.
☐ AUC0-28 and area under the concentration-time curve of aripiprazole from 29 to 56 days postdose (AUC29-56) after the fourth dose of aripiprazole 2M LAI 960 mg.
☐ Peak-to-trough percent fluctuation (PTF%) after the fourth dose of aripiprazole 2M LAI 960 mg.
☐ Cmax and tmax after the first, seventh, and eighth doses of aripiprazole IM depot 400 mg.
☐ AUC0-28 and C28 after the first dose of aripiprazole IM depot 400 mg.
☐ PTF% after the eighth dose of aripiprazole IM depot 400 mg.

After the first dose of IMP, the following PK parameters were estimated for aripiprazole after administration of aripiprazole 2M LAI 960 mg + oral aripiprazole 10 to 20 mg for 7 days and aripiprazole IM depot 400 mg + oral aripiprazole 10 to 20 mg for 14 days (this endpoint was only for subjects enrolled to the robust sampling schedule):
☐ Plasma concentration of aripiprazole 7 days postdose (C7)
☐ Plasma concentration of aripiprazole 14 days postdose (C14)
Efficacy: The efficacy of aripiprazole IM depot administration in the gluteal muscle was assessed by the PANSS (schizophrenia subjects only), CGI-S (schizophrenia subjects only), CGI-I, SWN-S, MADRS (bipolar subjects only), YMRS (bipolar subjects only), and CGI-BP (bipolar subjects only).

- **Population(s) studied**

Trial Population

The trial population included male and female subjects between 18 to 64 years of age, inclusive, with a current diagnosis of schizophrenia or bipolar I disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria. Subjects entering the trial must have demonstrated prior tolerability to aripiprazole. In addition, subjects must have been clinically stable (based on investigator judgment, subject/caregiver report, and/or documentation) for at least 2 months prior to screening AND must have been on a stable dose of 1 of the following oral atypical antipsychotic medications for at least 2 months prior to screening: aripiprazole, brexpiprazole, risperidone, olanzapine, quetiapine, paliperidone, cariprazine, lurasidone, ziprasidone, or asenapine. Other oral non-aripiprazole, antipsychotic medications may have been allowed if approved by the medical monitor and sponsor; however, clozapine was not allowed.
Additionally, subjects with bipolar I disorder who were stabilized on their current medications for at least 2 months prior to screening may have continued their mood stabilizer (eg, lithium, valproic acid, lamotrigine) and antidepressant (eg, citalopram, escitalopram, sertraline).Test and reference products
All IMP was manufactured by Otsuka Pharmaceutical Co, Ltd (Tokushima, Japan).

Test product:

Aripiprazole 2M LAI 960 mg was supplied as aripiprazole IM depot 300 mg/mL ready-to-use (RTU) single-dose vials.

Lot number: 18C95A300

Reference product:

Aripiprazole IM depot 400 mg was supplied as single-dose lyophilized vials.
Lot number: 17G96A400

Aripiprazole tablets for oral overlap were provided from a commercial supply.

Commercial Abilify 10-mg and 15-mg tablets

- Abilify 10 mg: ALS00918A and ALS00219A
- Abilify 15 mg: AMS00319A

According to the information provided by the applicant, the Reference Medicinal Product (RMP) used in the study was not identical to the commercial Abilify Maintena approved in the EU, but was produced as a specific clinical batch from the same manufacturing facility and production line that manufactures the EU commercial batch. The applicant conducted testing of the RMP lot used in the pivotal clinical trial, which showed that the RMP lot was within approved EU specifications and highly similar to 3 other EU released commercial batches.

However, as set out in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**),for Article 10(3) marketing authorisation applications reference must be made to the dossier of a reference medicinal product for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Articles 8(3), 10a, 10b or 10c of Directive 2001/83/EC, as amended. The product used as reference product in the bioequivalence study should be part of the global marketing authorisation of the reference medicinal product (as defined in Article 6(1) second subparagraph of Directive 2001/83/EC).

The applicant’s choice for a non-EU/EEA reference medicinal product is therefore not acceptable.

In line with the requirements following from the selected legal basis (Article 10(3) of Directive 2001/83/EC), the pivotal study submitted to establish a bridge to the EU/EEA reference medicinal product should be conducted against the EU/EEA reference medicinal product. Therefore, the applicant

is invited to provide results of a clinical study conducted against the EU/EEA reference medicinal product as part of the hybrid application pursuant to Article 10(3) of Directive 2001/83/EC **(MO)**.

- **Analytical methods**

A validation procedure was performed to analyze OPC-14597 (aripiprazole) and OPC- 14857 (dehydro-aripiprazole major metabolite of aripiprazole) in human plasma with sodium heparin as an anticoagulant by HPLC with MS/MS detection (6825-275).

Calibration curves for both analytes ranged from 0.500 to 500 ng/mL. The following parameters were addressed during the study and were acceptable: selectivity, precision, accuracy, sensitivity (0.500 ng/mL), dilution integrity (10x), recovery, and reinjection reproducibility. Stability analyses have been approved for OPC-14597 and OPC-14857 at room temperature for 6 hours, in injector at 5°C for 92 hours, in whole-blood at room temperature for 2 hours; in whole-blood under wet ice conditions for 2 hours; in whole blood at 2 to 8°C for 101 hours; in the extracts at 2 to 8°C for 101 hours; at room temperature for 98 hours, at -10 to -30°C for 845 days, at -60 to -80°C for 768 days and at -60 to -80°C for 1889 days. Hemolysis and lipemic plasma did not affect OPC-14597 or OPC-14597 determination in human plasma. Citalopram, risperidone, olanzapine, quetiapine,ziprasidone, or palipridone did not change the quantification of OPC-14597 or OPC-14597 in human plasma. Freeze-thaw stability was approved for 5 cycles in temperature ranges from -10 to -30°C and from -60 to -80°C. No matrix and carryover effects were observed.
All parameters recommended for analytical method validation were addressed (EMEA/CHMP/EWP/192217/2009) and met the acceptance criteria. Validation is acceptable.

According to the above validation procedure, a bioanalytical assessment was performed - Determination of OPC-14597 and OPC-14857 in human plasma by HPLC with MS/MS detection (031-201-00181) supporting pivotal studies.

Human plasma samples with heparin anticoagulant (a total of 6626 samples) were analyzed for OPC-14597 and OPC-14597 by the HPLC with MS/MS detection. Samples were stored for a maximum time of 405 days. That storage conditions cover validated conditions (maximum validated -60 to -80°C for 1889 days). High analytical results, especially nearly Cmax, were within the range of the calibration curve.
Incurred sample reproducibility was performed for nearly 5% of samples, and for OPC-14597, 99.8% of results were acceptable as repeated samples had relative differences not exceeding 20% compared to the first evaluation. For OPC-14857, 99.5% of the results were consistent with the original measurements. ISR was acceptable. Bioanalysis is acceptable.

- **Statistical methods**

Determination of Sample Size: To establish the similarity in primary PK variables, the lower bound of the 90% confidence interval (CI) of the geometric means ratio (GMR) of C56 and AUC0-56 after the fourth dose of aripiprazole 2M LAI 960 mg to C28 after the eighth dose and the sum of AUC0-28 values after the seventh and eighth doses of aripiprazole IM depot 400 mg should have been greater than 80%, respectively. It was estimated that a total of at least 100 subjects (ie, 50 per group) completing the trial would have at least 80% power to ensure that the lower limit of the 90% CI of the GMR of C56 after the fourth dose of aripiprazole 2M LAI 960 mg (test) to C28 after the eighth dose of aripiprazole IM depot 400 mg (reference) was greater than 0.80, assuming that the actual GMR of concentrations was 1.0 and the coefficient of variation (CV) was 46%. Among these 100 subjects, at least 30 completers enrolled to the robust PK sampling schedule would provide at least 80% power to ensure that the lower limit of the 90% CI of the GMR of AUC0-56 of aripiprazole 2M LAI 960 mg (test) to the sum of AUC0-28 values of aripiprazole IM depot 400 mg (reference) after the seventh and eighth doses was greater than 0.80, assuming the actual GMR of concentrations was 1.15 and the CV was 40%.
The assumption of CV used in the sample calculation was based on the PK data in the previous multiple-dose aripiprazole IM depot PK Trial 31-12-298. Assuming a dropout rate of 34%,

approximately 152 to 258 subjects were estimated to be enrolled to have 100 to 170 completers based on the proposed interim analysis.

Subject Samples: The datasets for analyses were defined as the following:
☐ Randomized sample consists of all subjects who were randomized.
☐ Safety sample includes all randomized subjects who received at least 1 dose of aripiprazole injection, regardless of any protocol violation.
☐ Pharmacokinetics sample consists of all dosed subjects who had 1 or more evaluable aripiprazole PK parameters. For analysis of the primary PK endpoint, only the completers with available values of the primary endpoints after the last scheduled injection were included.
☐ Efficacy sample includes all randomized subjects who received at least 1 dose of aripiprazole injection and had at least 1 efficacy assessment.

Safety: All safety analyses were summarized as descriptive statistics for the safety sample by treatment formulation and disease type, in addition to all treated subjects.

Pharmacokinetics: The 90% CIs of the GMR of C56 of aripiprazole after the fourth injection of aripiprazole 2M LAI 960 mg (test) to C28 after the eighth injection of aripiprazole IM depot 400 mg (reference) were provided. Similarly, the 90% CIs of the GMR of AUC0-56 of aripiprazole after the fourth injection of aripiprazole 2M LAI 960 mg (test) to the sum of AUC0-28 after the seventh and eighth injections of aripiprazole IM depot 400 mg (reference) were provided for subjects with robust PK sampling schedules. The GMRs and corresponding 90% CIs were derived from the analysis of variance including treatment formulation, PK sampling schedule (if applicable), and disease population as fixed effects. Only subjects who received the fourth dose of aripiprazole 2M LAI 960 mg or the seventh and eighth dose of aripiprazole IM depot 400 mg and had C56, C28, AUC0-28, and AUC0-56 values determined for the respective treatments were included in the analysis.
The 90% CIs of the GMR of Cmax of aripiprazole after the fourth injection of aripiprazole 2M LAI 960 mg (test) to Cmax after the eighth injection of aripiprazole IM depot 400 mg (reference) were provided using the same statistical method for the primary PK endpoint.
Efficacy: All efficacy assessments were summarized for the efficacy sample at each mapped trial week by treatment formulation and disease type (if applicable).

- ***Results***

Disposition, Demographics, and Baseline Characteristics:

A total of 394 subjects were screened and 266 subjects were enrolled, randomized, and treated (received at least 1 dose of IMP): 132 subjects in the aripiprazole 2M LAI 960 mg group and 134 subjects in the aripiprazole IM depot 400 mg group. Of the 266 enrolled subjects, 185 had schizophrenia and 81 had bipolar I disorder, and 84 were in the robust PK sampling group and 182 were in the sparse PK sampling group.
All 266 randomized subjects took at least one dose of IMP and were included in the safety and efficacy analyses. Of the 132 subjects in the aripiprazole 2M LAI 960 mg group, 102 subjects (77.3%) completed the trial and 30 subjects (22.7%) discontinued from the trial. Of the 134 subjects in the aripiprazole IM depot 400 mg group, 92 subjects (68.7%) completed the trial and 42 subjects (31.3%) discontinued from the trial. The most frequently reported reason for discontinuation from the trial in both treatment groups was withdrawal by subject: 16 of 132 subjects (12.1%) in the aripiprazole 2M LAI 960 mg group and 18 of 134 subjects (13.4%) in the aripiprazole IM depot 400 mg group.

Of the 266 randomized subjects, 176 (66.2%) were male and 90 (33.8%) were female.
Over two-thirds of the subjects (194 of 266 subjects [72.9%]) were black or African American. The overall mean age was 47.3 years (range: 18 - 64 years) and the mean body mass index was 28.4 kg/m2 (range: 17.0 - 36.1 kg/m2).
Demographic characteristics were generally well balanced between the treatment groups. The mean PANSS, CGI-S, CGI-BP, MADRS, YMRS, and SWN-S scores at baseline were similar between the

2 treatment groups.

Psycholeptics were the most frequently reported medications being taken prior to the start of IMP and were taken by all subjects. The use of oral antipsychotics taken prior to the start of IMP was generally well balanced between the 2 treatment groups.

Pharmacokinetic Profile

Pharmacokinetic data were available from a total of 266 subjects; 113 and 96 subjects were included in the PK analysis following the first and fourth dose of aripiprazole 2M LAI 960 mg, respectively, and 110, 88, and 82 subjects were included in the PK analysis following the first, seventh, and eighth dose of aripiprazole IM depot 400 mg, respectively.

First Dose Administration Aripiprazole Concentrations Following the First Administration of Aripiprazole 2M LAI 960 mg or Aripiprazole IM Depot 400 mg in the Gluteal Muscle

Mean (SD) 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 4.

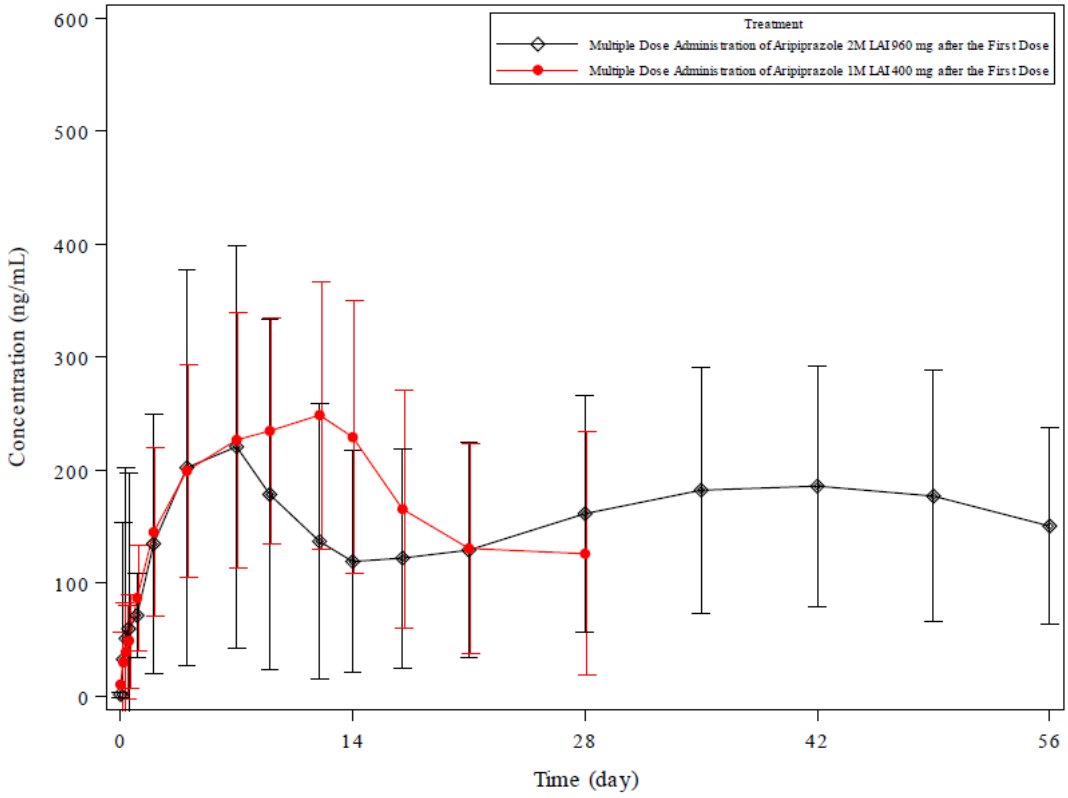


Figure 4 Mean (SD) Aripiprazole Plasma Concentration Versus Time Profiles Following the First Administration of Aripiprazole 2M LAI 960 mg (Black; n = 42) or Aripiprazole IM Depot 400 mg (Red; n = 42) in the Gluteal Muscle of Subjects With Schizophrenia or Bipolar Disorder Enrolled to the Robust Sampling Schedule.

Dehydro-aripiprazole Concentrations Following the First Administration of Aripiprazole 2M LAI 960 mg or Aripiprazole IM Depot 400 mg in the Gluteal Muscle

Mean (SD) dehydro-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 5.

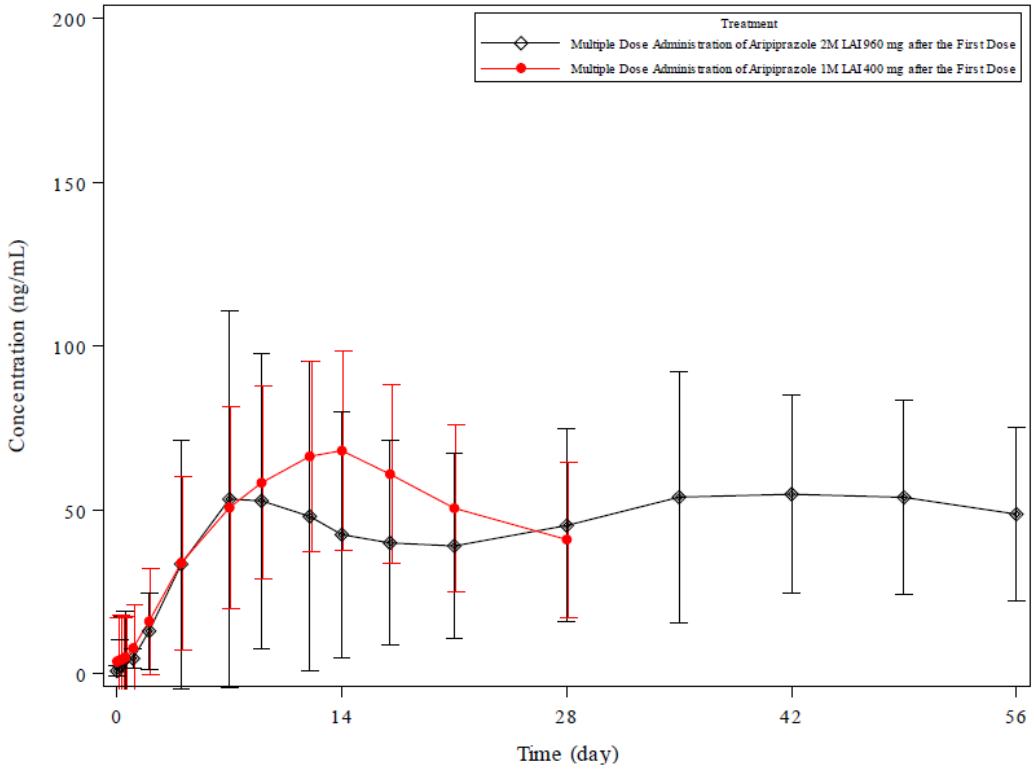


Figure 5 Mean (SD) Dehydro-aripiprazole Plasma versus Time Profiles Following the First Administration of Aripiprazole 2M LAI 960 mg (Black; n = 42) or Aripiprazole IM Depot 400 mg (Red; n = 42) in the Gluteal Muscle of Subjects With Schizophrenia or Bipolar Disorder Enrolled to the Robust Sampling Schedule.

Multiple Dose Administration

Aripiprazole Concentrations Following Multiple Administrations of Aripiprazole 2M LAI 960 mg or Aripiprazole IM Depot 400 mg in the Gluteal Muscle.

Mean (SD) 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 6. Mean (SD) 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 in the gluteal muscle are presented in Figure 7.

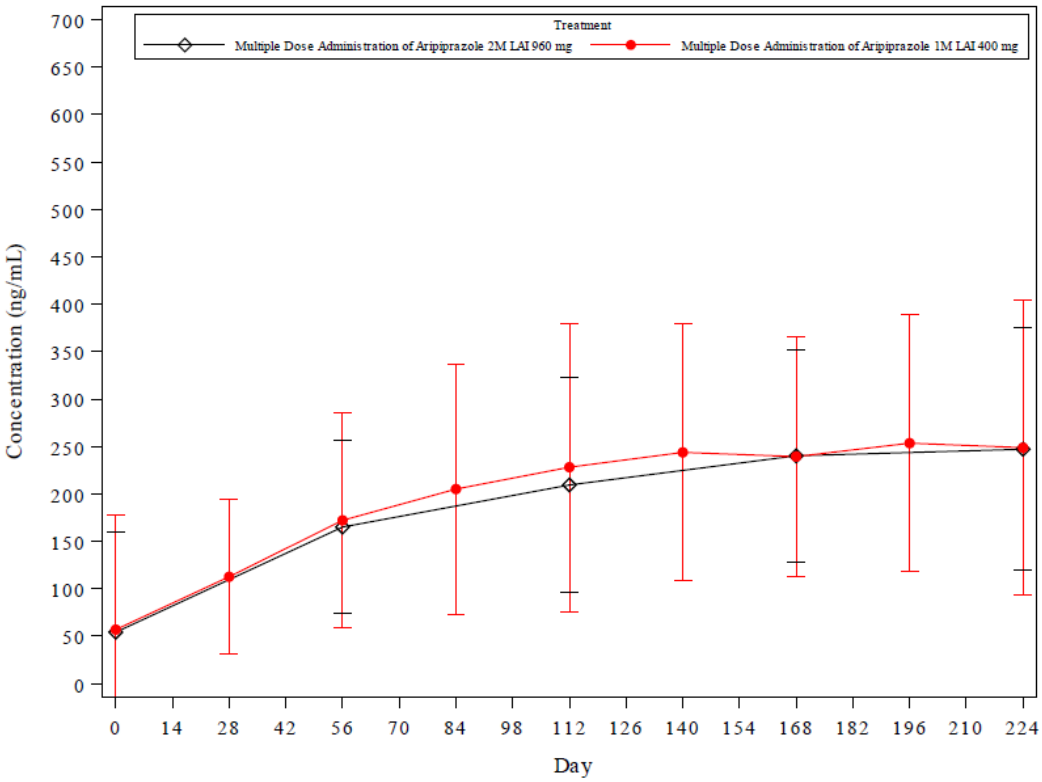


Figure 6 Mean (SD) Aripiprazole Trough Plasma Concentration Versus Time Profiles Following Multiple Dose Administration of Aripiprazole 2M LAI 960 mg (Black) or Aripiprazole IM Depot 400 mg (Red) in the Gluteal Muscle of Subjects With Schizophrenia or Bipolar Disorder.

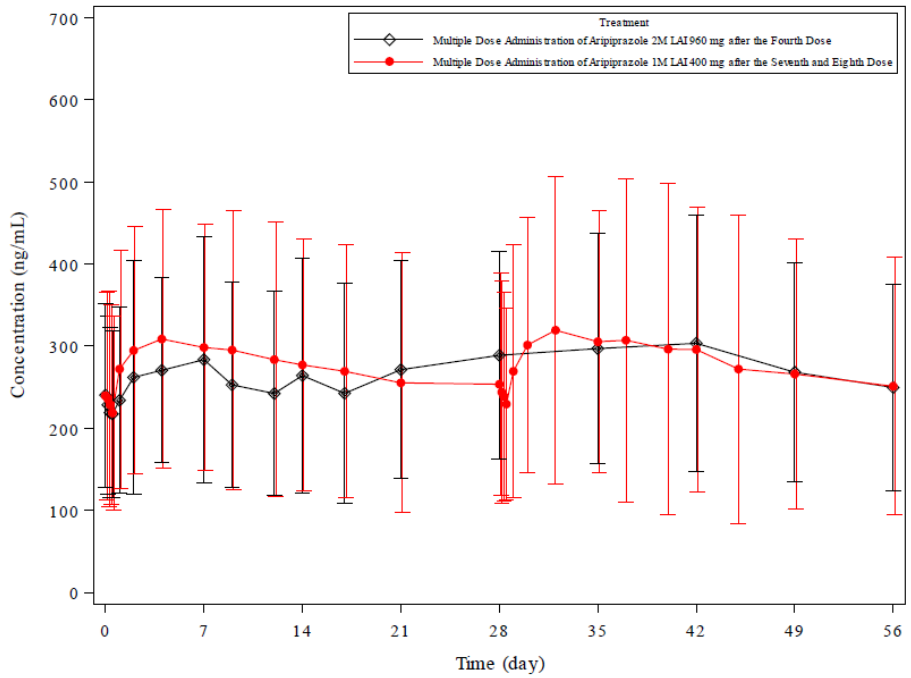


Figure 7 Mean (SD) Aripiprazole Plasma Concentration Versus Time Profiles Following the Fourth Administration of Aripiprazole 2M LAI 960 mg (Black; n = 102) or the Seventh and Eighth Administration of Aripiprazole IM Depot 400 mg (Red; n = 93) in the Gluteal Muscle of Subjects With Schizophrenia or Bipolar Disorder.

Dehydro-aripiprazole Concentrations Following Multiple Administrations of Aripiprazole 2M LAI 960 mg or Aripiprazole IM Depot 400 mg in the Gluteal Muscle.

Mean (SD) dehydro-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 8.

Mean (SD) dehydro-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 in the gluteal muscle are presented in Figure 9.

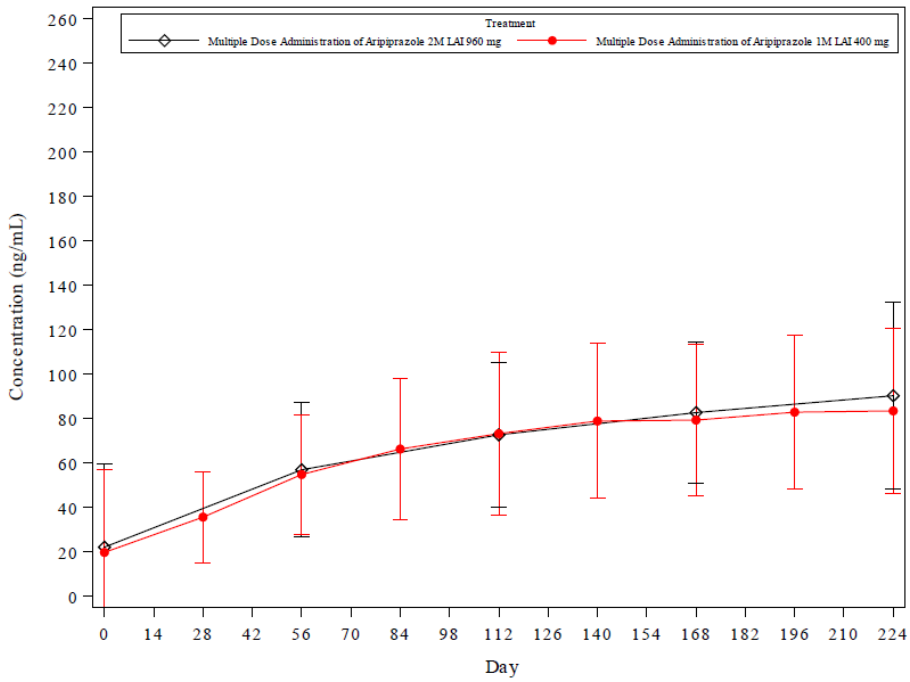


Figure 8 Mean (SD) Dehydro-aripiprazole Trough Plasma Concentration Versus Time Profiles Following Multiple Dose Administration of Aripiprazole 2M LAI 960 mg (Black) or Aripiprazole IM Depot 400 mg (Red) in the Gluteal Muscle of Subjects With Schizophrenia or Bipolar Disorder.

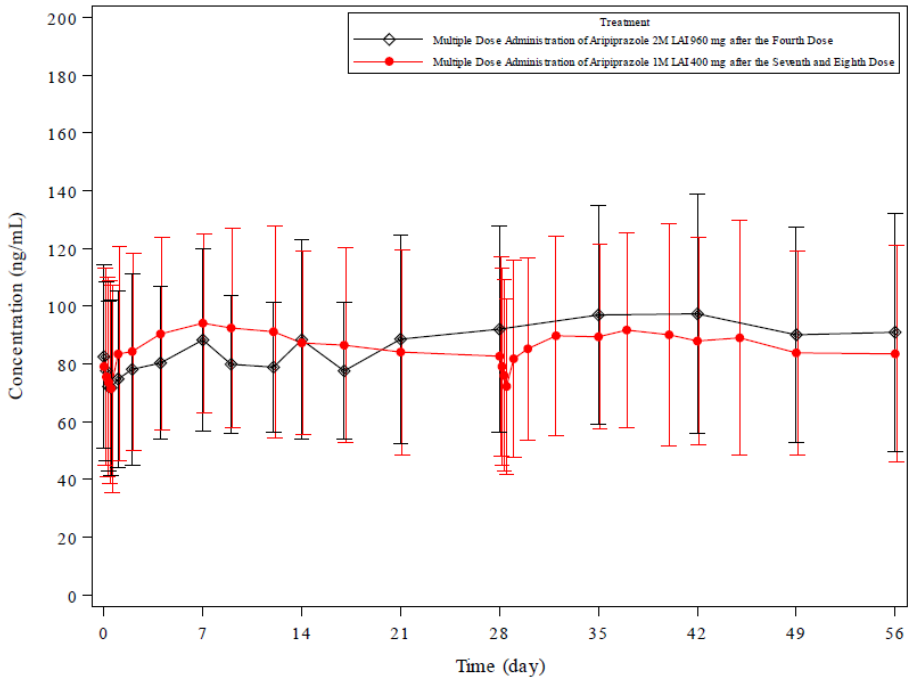


Figure 9 Mean (SD) Dehydro-aripiprazole Plasma Concentration Versus Time Profiles Following the Fourth Administration of Aripiprazole 2M LAI 960 mg (Black; n = 102) or the Seventh and Eighth Administration of Aripiprazole IM Depot 400 mg (Red; n = 93) in the Gluteal Muscle of Subjects With Schizophrenia or Bipolar Disorder

Pharmacokinetic Parameters

A summary of aripiprazole PK parameters following the first administration of aripiprazole 2M LAI 960 mg or aripiprazole IM depot 400 mg in the gluteal muscle of subjects enrolled to the robust sampling schedule is presented in Table 11.

Table 8: Aripiprazole Pharmacokinetic Parameters Following the First Administration of Aripiprazole 2M LAI 960 mg or Aripiprazole IM Depot 400 mg in the Gluteal Muscle of Subjects With Schizophrenia or Bipolar Disorder.

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.
aMedian (min - max).
bDetermined from subjects enrolled to the robust and sparse sampling schedules.

A summary of dehydro-aripiprazole PK parameters following the first administration of aripiprazole 2M LAI 960 mg or aripiprazole IM depot 400 mg in the gluteal muscle of subjects enrolled to the robust sampling schedule is presented in **Error! Reference source not found.**.

Table 9: Dehydro-aripiprazole Pharmacokinetic Parameters Following the First Administration of Aripiprazole 2M LAI 960 mg or Aripiprazole IM Depot 400 mg in the Gluteal Muscle of Subjects With Schizophrenia or Bipolar Disorder

PK Parameter	Aripiprazole 2M LAI 960 mg		Aripiprazole IM Depot 400 mg	
	Mean (SD)	n	Mean (SD)	n
C_{max} (ng/mL)	78.7 (64.6)	37	73.3 (31.7)	35
C_7 (ng/mL)	53.3 (57.6)	41	50.7 (30.7)	42
C_{14} (ng/mL)	42.4 (37.5)	38	68.1 (30.5)	39
t_{max} (day)[a]	35.9 (6.76 - 56.0)	37	13.9 (6.93 - 28.0)	35
AUC_{0-56} (ng·day/mL)	2590 (1500)	37	ND	-
AUC_{0-28} (ng·day/mL)	1120 (897)	38	1390 (629)	35
C_{56} (ng/mL)	56.6 (30.4)	113[b]	ND	-
C_{28} (ng/mL)	ND	-	35.3 (20.7)	110[b]

aMedian (min - max).
bDetermined from subjects enrolled to the robust and sparse sampling schedules.

Multiple Dose Administration

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 in the gluteal muscle is presented in **Error! Reference source not found.**.

Table 10: Mean (SD) Aripiprazole Pharmacokinetic Parameters Following the Fourth Administration of Aripiprazole 2M LAI 960 mg or the Seventh and Eighth Administration of Aripiprazole IM Depot 400 mg in the Gluteal Muscle of Subjects With Schizophrenia or Bipolar Disorder.

PK Parameter	Aripiprazole 2M LAI 960 mg	Aripiprazole IM Depot 400 mg	Aripiprazole IM Depot 400 mg
	Fourth Dose	Seventh Dose	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.

A summary of dehydro-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 in the gluteal muscle is presented in Table 14.

Table 11: Mean (SD) Dehydro-aripiprazole Pharmacokinetic Parameters Following the Fourth Administration of Aripiprazole 2M LAI 960 mg or the Seventh and Eighth Administration of Aripiprazole IM Depot 400 mg in the Gluteal Muscle of Subjects With Schizophrenia or Bipolar Disorder

PK Parameter	Aripiprazole 2M LAI 960 mg	Aripiprazole IM Depot 400 mg	Aripiprazole IM Depot 400 mg
	Fourth Dose	Seventh Dose	Eighth Dose
C_{max} (ng/mL)	105 (27.3)[b]	107 (35.7)[d]	105 (40.2)[f]
t_{max} (day)[a]	28.0 (0.170 - 56.0)[b]	7.10 (0.500 - 28.0)[d]	8.03 (0.00 - 28.1)[f]
AUC_{0-56} (ng·day/mL)	4590 (1280)[b]	ND	ND
AUC_{0-28} (ng·day/mL)	2220 (629)[b]	2450 (921)[d]	2440 (1020)[f]
AUC_{29-56} (ng·day/mL)	2350 (714)[b]	ND	ND
PTF%	58.9 (19.9)[b]	ND	46.0 (16.2)[f]
C_{28} (ng/mL)	ND	82.9 (35.1)[e]	84.9 (38.6)[g]
C_{56} (ng/mL)	91.3 (41.1)[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.

Statistical Analysis of Pharmacokinetic Parameters

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 below.

Geometric Mean Ratios and 90% Confidence Intervals for Aripiprazole Pharmacokinetic Parameters Following the Fourth Administration of Aripiprazole 2M LAI 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.

The GMR and 90% CI for PK parameters of dehydro-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 below.

Geometric Mean Ratios and 90% Confidence Intervals for Dehydro-Aripiprazole Pharmacokinetic Parameters Following the Fourth Administration of Aripiprazole 2M LAI 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]	0.963[c]	0.847 - 1.095	0.0092
	C_{56}/C_{28}[b]	1.066[d]	0.954 - 1.191	< 0.0001
	C_{max}[b]	1.017[c]	0.896 - 1.155	0.0012

[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.

Since the 90% CIs of the primary PK parameters (plasma concentration of aripiprazole 56 days postdose (C56) of aripiprazole 2M LAI 960mg after the fourth dose and plasma concentration 28 days postdose C28 of aripiprazole IM depot 400 mg after the eighth dose over the course of 32 weeks and AUC of aripiprazole from time zero to 56 days postdose (AUC0-56) for aripiprazole 2M LAI 960 mg after the fourth dose or area under the concentration-time curve of aripiprazole from time zero to 28 days postdose (AUC0-28) for aripiprazole IM depot 400 mg after the seventh and eighth doses) were within the predefined limits of 80%-125% it can be agreed that PK similarity of the test product and the reference product has been demonstrated (plasma concentration - GMR [90% CI]: 1.011 [0.893, 1.145], AUC - GMR [90% CI]: 1.006 [0.851, 1.190]).
However, 90% CI of the test product Cmax following the fourth dose and Cmax following the eighth dose of the reference product aripiprazole IM depot 400 mg was not withing the predefined (GMR [90% CI]: 1.071 [0.903, 1.270]). The applicant is invited to discuss the clinical relevance of differences in the shape of the plasma-concentration profiles **(OC).**

Single dose administration of aripiprazole 2M LAI 960 mg or aripiprazole IM depot 400 mg resulted in similar mean Cmax (286 ng/ml vs 280 ng/ml) and median tmax (8.58 day vs 9.04 day).
However, it is noted that administration of aripiprazole 2M LAI 960 mg + oral aripiprazole 10 to 20 mg for 7 days resulted in similar mean concentrations 7 days postdose but approximately 50% lower concentrations 14 days postdose compared to administration of aripiprazole IM depot 400 mg + oral aripiprazole 10 to 20 mg for 14 days; mean aripiprazole concentrations were higher 28 days postdose in the aripiprazole 2M LAI 960 mg group compared to the aripiprazole IM depot 400 mg group (175 ng/mL versus 112 ng/mL). Moreover, mean peak-to-trough percent fluctuation following multiple administrations of aripiprazole 2M LAI 960 mg was larger (63%) compared to aripiprazole IM depot 400 mg (48%).

Mean aripiprazole exposure following multiple administrations of aripiprazole 2M LAI 960 mg from 0 to 28 days postdose and 29 to 56 days postdose was comparable (7190 ng·day/mL vs 7500 ng·day/mL), which indicates that aripiprazole exposure remains consistent during the entire dosing interval.

Efficacy Results:

Efficacy was assessed as exploratory endpoints. No clinically relevant differences were reported between both treated groups of patients with schizophrenia in PANSS, CGI-S, CGI-I and SWN-S. Moreover, no clinically meaningful difference was demonstrated between the 2 treatment groups for the MADRS total score or YMRS total score for subjects with bipolar I disorder.
However, as the study was open-label and the patients were concomitantly treated with other antipsychotics, the results are very difficult to interpret and should be treated with caution.

Table 12: Mean Change From Baseline in PANSS Total Score – LOCF (Efficacy Sample - Schizophrenia Subjects)

Trial Week[a]	Statistic	Aripiprazole 2M LAI 960 mg	Aripiprazole IM Depot 400 mg
Baseline	n	92	93
	Mean (SD)	62.0 (13.5)	61.8 (13.5)
Week 4	n	88	85
	Mean (SD)	-0.8 (10.3)	-0.6 (6.7)
Week 8	n	89	85
	Mean (SD)	-1.1 (12.5)	-0.7 (6.6)
Week 16	n	89	85
	Mean (SD)	-0.7 (10.7)	-0.6 (7.4)
Week 24	n	89	85
	Mean (SD)	-1.5 (12.0)	-0.9 (8.4)
Week 28	n	89	85
	Mean (SD)	-1.6 (12.0)	0.2 (9.7)
Week 32	n	89	85
	Mean (SD)	-2.6 (11.7)	-1.7 (8.5)

Table 13: Mean Change From Baseline in CGI-S Score – LOCF (Efficacy Sample - Schizophrenia Subjects)

Trial Week[a]	Statistic	Aripiprazole 2M LAI 960 mg	Aripiprazole IM Depot 400 mg
Baseline	n	92	93
	Mean (SD)	3.3 (0.9)	3.1 (0.9)
Week 4	n	88	85
	Mean (SD)	-0.1 (0.6)	0.0 (0.6)
Week 8	n	89	85
	Mean (SD)	-0.1 (0.7)	0.1 (0.7)
Week 16	n	89	85
	Mean (SD)	-0.1 (0.7)	-0.0 (0.6)
Week 24	n	89	85
	Mean (SD)	-0.2 (0.7)	-0.1 (0.6)
Week 28	n	89	85
	Mean (SD)	-0.2 (0.7)	0.0 (0.7)
Week 32	n	89	85
	Mean (SD)	-0.3 (0.6)	-0.1 (0.7)

Table 14: Mean Change From Baseline in MADRS Total Score - LOCF (Efficacy Sample - Bipolar I Disorder Subjects)

Trial Week[a]	Statistic	Aripiprazole 2M LAI 960 mg	Aripiprazole IM Depot 400 mg
Baseline	n	40	41
	Mean (SD)	10.9 (9.4)	13.5 (9.7)
Week 4	n	37	40
	Mean (SD)	-2.8 (8.1)	-3.9 (8.5)
Week 8	n	39	40
	Mean (SD)	-2.7 (10.5)	-2.0 (9.3)
Week 16	n	39	40
	Mean (SD)	-1.8 (9.8)	-1.3 (8.4)
Week 24	n	39	40
	Mean (SD)	-1.7 (10.0)	-2.8 (11.3)
Week 28	n	39	40
	Mean (SD)	-3.7 (9.8)	-3.6 (11.0)
Week 32	n	39	40
	Mean (SD)	-3.5 (9.1)	-3.3 (12.5)

- ***Safety data***

Extent of Exposure

All 266 randomized subjects received at least 1 dose of IMP and were included in the safety analyses. For the first injection, all subjects received their assigned dose of aripiprazole 2M LAI 960 mg or aripiprazole IM depot 400 mg.

A one-time dose reduction was permitted due to possible safety and tolerability issues.

Most subjects (131 of 132 subjects [99.2%] in the aripiprazole 2M LAI 960 mg group and 132 of 134 subjects [98.5%] in the aripiprazole IM depot 400 mg group) had no dose adjustment during the trial (ie, they remained on their assigned dose). In the aripiprazole 2M LAI 960 mg group, 1 subject had their dose decreased to 660 mg (per protocol) at the second injection. In the aripiprazole IM depot 400 mg group, 1 subject had their dose decreased to 300 mg (per protocol) at the second injection, and 1 subject had their dose decreased to 300 mg (per protocol) at the fourth and fifth injections and then increased back to 400 mg at the sixth injection.

Adverse Events

Brief Summary of Adverse Events

Overall, a total of 497 TEAEs were reported for 189 of 266 subjects (71.1%). The overall incidence of TEAEs was similar between the 2 treatment groups: 94 of 132 subjects (71.2%) in the aripiprazole 2M LAI 960 mg group and 95 of 134 subjects (70.9%) in the aripiprazole IM depot 400 mg group (Table 3.3.2.1.9.). Serious TEAEs were reported in 6 subjects (4.5%) in the aripiprazole 2M LAI 960 mg group and 8 subjects (6.0%) in the aripiprazole IM depot 400 mg group. Treatment-emergent AEs resulting in the discontinuation of IMP occurred in 4 subjects (3.0%) in the aripiprazole 2M LAI 960 mg group and 10 subjects (7.5%) in the aripiprazole IM depot 400 mg group. There was 1 death in this trial, in the aripiprazole 2M LAI 960 mg group.

Table 15: Summary of Adverse Events, All Causalities (Safety Sample)

	Aripiprazole 2M LAI 960 mg						Aripiprazole IM Depot 400 mg					
	Schizophrenia		Bipolar I Disorder		Total		Schizophrenia		Bipolar I Disorder		Total	
Number of:	**n**	**(%)[a]**	**n**	**(%)[a]**	**n**	**(%)[a]**	**n**	**(%)[a]**	**n**	**(%)[a]**	**n**	**(%)[a]**
Subjects treated	92	(100.0)	40	(100.0)	132	(100.0)	93	(100.0)	41	(100.0)	134	(100.0)
Total number of injections	322	(0.0)	136	(0.0)	458	(0.0)	581	(0.0)	271	(0.0)	852	(0.0)
Subjects with adverse events	62	(67.4)	33	(82.5)	95	(72.0)	60	(64.5)	38	(92.7)	98	(73.1)
Adverse events	199	(0.0)	120	(0.0)	319	(0.0)	155	(0.0)	101	(0.0)	256	(0.0)
Subjects with treatment-emergent adverse events	61	(66.3)	33	(82.5)	94	(71.2)	59	(63.4)	36	(87.8)	95	(70.9)
Treatment-emergent adverse events[b]	168	(0.0)	109	(0.0)	277	(0.0)	138	(0.0)	82	(0.0)	220	(0.0)
Subjects with serious treatment-emergent adverse events	5	(5.4)	1	(2.5)	6	(4.5)	5	(5.4)	3	(7.3)	8	(6.0)
Subjects with non-serious treatment-emergent adverse events	59	(64.1)	33	(82.5)	92	(69.7)	57	(61.3)	35	(85.4)	92	(68.7)
Subjects with severe treatment-emergent adverse events	5	(5.4)	0	(0.0)	5	(3.8)	3	(3.2)	1	(2.4)	4	(3.0)
Subjects discontinued investigational medicinal product due to adverse events	3	(3.3)	1	(2.5)	4	(3.0)	7	(7.5)	3	(7.3)	10	(7.5)
Deaths	1	(1.1)	0	(0.0)	1	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)

Display of Adverse Events

Treatment-emergent Adverse Events

The overall incidence of TEAEs was similar between the 2 treatment groups: 94 of 132 subjects (71.2%) in the aripiprazole 2M LAI 960 mg group and 95 of 134 subjects (70.9%) in the aripiprazole IM depot 400 mg group.

Table 3.3.2.1.10. shows the incidence of TEAEs occurring in ≥ 5% of subjects in any treatment group. The most frequently reported TEAEs (occurring in ≥ 10% of subjects in any treatment group) were as follows:

- Injection site pain: 24 of 132 subjects (18.2%) in the aripiprazole 2M LAI 960 mg group and 12 of 134 subjects (9.0%) in the aripiprazole IM depot 400 mg group.
- Weight increased: 30 of 132 subjects (22.7%) in the aripiprazole 2M LAI 960 mg group and 28 of 134 subjects (20.9%) in the aripiprazole IM depot 400 mg group.

Table 16: Incidence of Treatment-emergent Adverse Events Occurring in Greater Than or Equal to 5% of Subjects in Any Treatment Group, by SOC and MedDRA Preferred Term (Safety Sample)

	Aripiprazole 2M LAI 960 mg			Aripiprazole IM Depot 400 mg		
	Schizophrenia (N=92)	Bipolar I Disorder (N=40)	Total (N=132)	Schizophrenia (N=93)	Bipolar I Disorder (N=41)	Total (N=134)
System Organ Class MedDRA Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Gastrointestinal disorders						
Constipation	4 (4.3)	4 (10.0)	8 (6.1)	5 (5.4)	3 (7.3)	8 (6.0)
Toothache	0 (0.0)	2 (5.0)	2 (1.5)	4 (4.3)	6 (14.6)	10 (7.5)
General disorders and administration site conditions						
Injection site pain	14 (15.2)	10 (25.0)	24 (18.2)	9 (9.7)	3 (7.3)	12 (9.0)
Investigations						
Weight increased	20 (21.7)	10 (25.0)	30 (22.7)	17 (18.3)	11 (26.8)	28 (20.9)
Nervous system disorders						
Akathisia	8 (8.7)	5 (12.5)	13 (9.8)	7 (7.5)	5 (12.2)	12 (9.0)
Headache	6 (6.5)	4 (10.0)	10 (7.6)	2 (2.2)	3 (7.3)	5 (3.7)
Psychiatric disorders						
Anxiety	6 (6.5)	5 (12.5)	11 (8.3)	5 (5.4)	5 (12.2)	10 (7.5)
Insomnia	8 (8.7)	2 (5.0)	10 (7.6)	8 (8.6)	3 (7.3)	11 (8.2)

Treatment-emergent Adverse Events Related to the Investigational Medicinal Product

The overall incidence of TEAEs considered by the investigator as potentially related to the IMP was slightly higher in the aripiprazole 2M LAI 960 mg group (73 of 132 subjects [55.3%]) compared to the aripiprazole IM depot 400 mg group (61 of 134 subjects [45.5%]).

Table 20 shows the incidence of TEAEs considered by the investigator as potentially related to the IMP and occurring in ≥ 5% of subjects in any treatment group. All injection site pain events and all but 1 event of increased weight in each treatment group were considered by the investigator to be related to the IMP.
Another frequently reported TEAE (occurring in at least 5% of subjects in any treatment group) that was considered by the investigator to be related to the IMP was akathisia, occurring in 12 subjects in each treatment group.

Table 17: Incidence of Treatment-emergent Adverse Events Considered by the Investigator as Potentially Related to the IMP and Occurring in Greater Than or Equal to 5% of Subjects in Any Treatment Group, by SOC and MedDRA Preferred Term (Safety Sample)

	Aripiprazole 2M LAI 960 mg			Aripiprazole IM Depot 400 mg		
	Schizophrenia (N=92)	Bipolar I Disorder (N=40)	Total (N=132)	Schizophrenia (N=93)	Bipolar I Disorder (N=41)	Total (N=134)
System Organ Class MedDRA Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
General disorders and administration site conditions						
Injection site pain	14 (15.2)	10 (25.0)	24 (18.2)	9 (9.7)	3 (7.3)	12 (9.0)
Investigations						
Weight increased	20 (21.7)	9 (22.5)	29 (22.0)	16 (17.2)	11 (26.8)	27 (20.1)
Nervous system disorders						
Akathisia	8 (8.7)	4 (10.0)	12 (9.1)	7 (7.5)	5 (12.2)	12 (9.0)

Analysis of Adverse Events

The most frequently reported TEAEs (occurring in ≥ 10% of subjects in any treatment group) were injection site pain and increased weight. Both of these TEAEs are consistent with the known safety profile of aripiprazole. Increased weight occurred at a similar incidence in both treatment groups (22.7% in the aripiprazole 2M LAI 960 mg group and 20.9% in the aripiprazole IM depot 400 mg group), whereas the incidence of injection site pain in the aripiprazole 2M LAI 960 mg group (18.2%) was approximately twice the incidence in the aripiprazole IM depot 400 mg group (9.0%). None of the events of increased weight or injection site pain were assessed by the investigator as severe or serious.

Although 24 of 132 subjects (18.2%) in the aripiprazole 2M LAI 960 mg group and 12 of 134 subjects (9.0%) in the aripiprazole IM depot 400 mg group experienced TEAEs of injection site pain, all events of injection site pain occurred within 2 days of the injections. The majority resolved within 5 days (22 subjects in the aripiprazole 2M LAI 960 mg group and 11 subjects in the aripiprazole IM depot 400 mg group); 2 subjects in each treatment group had injection site pain lasting longer than 5 days. In both treatment groups, the majority of injection site pain events coincided with the first injection (15.9% in the aripiprazole 2M LAI 960 mg group and 5.2% in the aripiprazole IM depot 400 mg group); fewer events of injection site pain were attributable to subsequent injections of IMP in both treatment groups.

The majority of TEAEs were mild or moderate in severity. There were 5 subjects in the aripiprazole 2M LAI 960 mg group who had TEAEs that were assessed as severe: psychotic disorder, anxiety, cardiac arrest, and akathisia (each in 1 subject), and 2 events of akathisia in 1 subject. There were 4 subjects in the aripiprazole IM depot 400 mg group who had TEAEs that were assessed as severe: septic shock, adenocarcinoma of colon, and akathisia (each in 1 subject); and encephalopathy, loss of consciousness, schizophrenia, and suicide attempt (all in 1 subject). With the exception of akathisia in both treatment groups, none of the other severe TEAEs were assessed by the investigator as related to the IMP

Deaths

There was 1 death (cardiac arrest) in the aripiprazole 2M LAI 960 mg group in a participant between the ages of 50 and 55 with schizophrenia and physical comorbidities. The subject was noted to have abnormal ECG findings during screening that were considered as not significant or exclusionary for the subject's participation in the trial by the investigator. There were no significant changes to the ECG findings during subsequent visits when compared to the ECG findings during the screening period. The subject's last dose of IMP was administered on Day 170. The death occurred on Day 211. The event of

cardiac arrest with a fatal outcome was assessed as unrelated to the IMP by both the investigator and the sponsor. The subject's significant medical history was considered as potential risk factors for the reported fatal event.

Other Serious Adverse Events

Serious TEAEs occurred in 6 of 132 subjects (4.5%) in the aripiprazole 2M LAI 960 mg group and 8 of 134 subjects (6.0%) in the aripiprazole IM depot 400 mg group (Table 21). The events that occurred in more than 1 subject were auditory hallucination (2 subjects in the aripiprazole 2M LAI 960 mg group) and psychotic disorder (1 subject in each treatment group). The serious TEAEs that were assessed by the investigator as related to the IMP included auditory hallucination (1 subject in the aripiprazole 2M LAI 960 mg group) and akathisia (1 subject in each treatment group).

Table 18: Incidence of Serious Treatment-emergent Adverse Events by SOC and MedDRA Preferred Term (Safety Sample)

	Aripiprazole 2M LAI 960 mg			Aripiprazole IM Depot 400 mg		
	Schizophrenia (N=92)	Bipolar I Disorder (N=40)	Total (N=132)	Schizophrenia (N=93)	Bipolar I Disorder (N=41)	Total (N=134)
System Organ Class MedDRA Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subject With Any Treatment Emergent Adverse Events[a]	5 (5.4)	1 (2.5)	6 (4.5)	5 (5.4)	3 (7.3)	8 (6.0)
Cardiac disorders	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac arrest	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)
Cholecystitis acute	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)
Infections and infestations	1 (1.1)	0 (0.0)	1 (0.8)	1 (1.1)	0 (0.0)	1 (0.7)
Cellulitis	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)
Adenocarcinoma of colon	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)
Nervous system disorders	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	1 (2.4)	1 (0.7)
Akathisia	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	1 (2.4)	1 (0.7)
Psychiatric disorders	2 (2.2)	1 (2.5)	3 (2.3)	2 (2.2)	2 (4.9)	4 (3.0)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.7)
Depressive symptom	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.7)
Hallucination, auditory	1 (1.1)	1 (2.5)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Psychotic disorder	1 (1.1)	0 (0.0)	1 (0.8)	1 (1.1)	0 (0.0)	1 (0.7)
Schizophrenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)
Suicide attempt	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)

Adverse Events Leading to Discontinuation of Investigational Medicinal Product

Treatment-emergent AEs resulting in the discontinuation of IMP occurred in 4 subjects (3.0%) in the aripiprazole 2M LAI 960 mg group and 10 subjects (7.5%) in the aripiprazole IM depot 400 mg group (Table 22). The events that occurred in more than 1 subject were akathisia (2 subjects in each treatment group), anxiety (2 subjects in the aripiprazole 2M LAI 960 mg group), and psychotic disorder (1 subject in each treatment group). All events of akathisia and 1 event of anxiety, as well as the events of somnolence, restlessness, dyskinesia, and tremor, were assessed by the investigator as related to the IMP.

Table 19: Incidence of Treatment-emergent Adverse Events Resulting in the Discontinuation of IMP by SOC and MedDRA Preferred Term (Safety Sample).

	Aripiprazole 2M LAI 960 mg			Aripiprazole IM Depot 400 mg		
	Schizophrenia (N=92)	Bipolar I Disorder (N=40)	Total (N=132)	Schizophrenia (N=93)	Bipolar I Disorder (N=41)	Total (N=134)
System Organ Class MedDRA Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subject With Any Treatment Emergent Adverse Events[a]	3 (3.3)	1 (2.5)	4 (3.0)	7 (7.5)	3 (7.3)	10 (7.5)
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)
Nervous system disorders	1 (1.1)	1 (2.5)	2 (1.5)	4 (4.3)	1 (2.4)	5 (3.7)
Akathisia	1 (1.1)	1 (2.5)	2 (1.5)	1 (1.1)	1 (2.4)	2 (1.5)
Dyskinesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)
Tremor	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)
Psychiatric disorders	3 (3.3)	0 (0.0)	3 (2.3)	2 (2.2)	2 (4.9)	4 (3.0)
Anxiety	2 (2.2)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.7)
Depressive symptom	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.7)
Psychotic disorder	1 (1.1)	0 (0.0)	1 (0.8)	1 (1.1)	0 (0.0)	1 (0.7)
Restlessness	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Schizophrenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)
Suicide attempt	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)

Injection Site Assessments

For the majority of subjects (> 95%), the investigator's assessment of the most recent injection site was rated as "absent" for symptoms of pain, swelling, redness, and induration after the first and last injections. There were no reported symptoms of swelling or induration. Mild symptoms of redness were observed in 3 subjects in the aripiprazole 2M LAI 960 mg group and 1 subject in the aripiprazole IM depot 400 mg group after the first injection, and in 1 subject in the aripiprazole 2M LAI 960 mg group after the last injection.
The overall mean VAS scores for subject-reported rating of pain were similar in both treatment groups at the last injection: 0.8 predose and 1.4 postdose in the aripiprazole 2M LAI 960 mg group and 0.9 predose and 1.3 postdose in the aripiprazole IM depot 400 mg group.
Both assessments reflected injections with minimal reactions following administration for all subjects.
Injection site-related TEAEs were reported in 25 of 132 subjects (18.9%) in the aripiprazole 2M LAI 960 mg group and in 12 of 134 subjects (9.0%) in the aripiprazole IM depot 400 mg group, with the most frequently reported event being injection site pain.

Supportive PK 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 trial was designed to determine the safety, pharmacokinetics (PK), and tolerability of single-dose administrations of 780 mg (Cohort 1) and 1200 mg (Cohort 2) of Aripiprazole Long Acting Injectable (Ari LAI) formulation in the gluteal muscles of adult subjects with schizophrenia. The Ari LAI is an extended release presentation intended for dosing every 2 months.

Objectives:
The primary objective of this trial was to determine the safety and tolerability of single ascending dose administrations of the Ari LAI in adult subjects with schizophrenia.
The secondary objective of this trial was to determine the PK of aripiprazole and its metabolite(s), including the major metabolite dehydro-aripiprazole, following single ascending dose administrations of the Ari LAI in adult subjects with schizophrenia.

Methodology:
This was an open-label, single ascending dose, parallel-arm, multiple-center trial.
The trial was conducted at 3 trial sites and was comprised of 2 cohorts (18 subjects per cohort; to ensure at least 12 completers per cohort). The trial population included males and females between 18 and 64 years, inclusive, at the time of the screening visit with a current diagnosis of schizophrenia as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.
Subjects provided signed informed consent and were screened between Days −30 and −1 prior to administration of the investigational medicinal product (IMP). Those who met the inclusion criteria and did not fulfil any of the exclusion criteria returned to the trial site on Day −1 or Day 1 and were assigned to the cohort enrolling at the time of check-in.
Predose assessments and administration of the IMP were completed on Day 1.
Subjects were housed at the respective trial site clinic for 21 days after administration of the IMP and continued to participate as outpatients during the remaining trial period.
Following discharge from the trial site, the subjects were required to remain at the site for all scheduled assessments and PK sample collections. After administration of the IMP, subjects were followed for 26 weeks (182 days) or until plasma concentrations of aripiprazole were below the limit of quantification (BLQ) based on monthly PK sampling. At the sponsor's discretion, subjects could be discontinued from the study after Day 182 and before the aripiprazole concentration was BLQ. Subjects were informed prior to or on Day 182 if they needed to return to the trial site for unscheduled visits for monthly PK sampling. For the duration of the trial, subjects continued to receive their current oral antipsychotic medication concomitant with the IMP.

To be eligible for this trial, all subjects were required to have an individually documented history of previously tolerating aripiprazole according to the investigator's judgment. Subjects who did not have a history of tolerating aripiprazole were administered 10 mg doses of oral aripiprazole 3 times (total of 30 mg) daily, in addition to their current oral antipsychotic medication, not less than 14 days prior to administration of the IMP to establish their tolerability, per the investigator's judgment, to aripiprazole. If deemed necessary by the investigator, the subject was housed in the trial site clinic during these 3 days.
A single dose of IMP was administered to subjects. Concomitant with the IMP and for the duration of the trial, subjects continued to receive their current oral antipsychotic medication. As the administration of the IMP constituted an additional antipsychotic medication to the subject's treatment regimen, investigators were to consider a reduction of the dose of the oral antipsychotic medication to the mid to lower range of the recommended dose range described in the Prescribing Information during the first 1 to 5 weeks after administration of the IMP.
During the trial, aripiprazole concentrations were expected to peak during the 1- to 2-week period after administration of the IMP. Accordingly, the dose of oral antipsychotic medication was to be further adjusted at the discretion of the investigator and in consultation with the sponsor and/or medical monitor based on the subject's symptoms as well as the observed safety and tolerability profile for the subject. After the fifth week of administration of IMP, investigators determined whether there should be an increase in the dose of the oral antipsychotic medication to the original pretrial dose. If the investigator determined that a switch in oral antipsychotics was clinically indicated, either due to lack of efficacy or emergence of treatment-limiting adverse events (AEs), the switch could be made after discussion with the medical monitor and sponsor.
Investigators were required to ensure that subjects were on adequate dose of oral antipsychotic medication upon discontinuation from the trial.
Within each cohort, 2 subjects were dosed initially and observed for at least 14 days, after which the remaining subjects in the cohort were dosed. Dosing in Cohort 2 did not begin until the safety and

tolerability data from at least 12 of 18 subjects who had completed Day 14 in Cohort 1 had been reviewed by the principal investigator and Otsuka Pharmaceutical Development & Commercialization, Inc. staff, including the project leader, Clinical Safety & Pharmacovigilance representative, medical monitor/designee, and clinical pharmacology representative. The sponsor or investigator had the authority to modify or stop escalation to the higher dose cohort upon their clinical judgment.
An optional blood sample was taken from consenting subjects for future biospecimen research.

Number of Subjects:
Overall, 56 subjects were screened. Thirty-six of these subjects were enrolled and 20 were screen failures. Twenty-nine (80.6%) of enrolled subjects completed the study and 7 (19.4%) discontinued. Of the 7 subjects who discontinued the study, 4 withdrew consent and 3 were lost to follow-up.

Diagnosis and Main Criteria for Inclusion:
Healthy male and female individuals between 18 and 64 years, inclusive, at the screening visit with a current diagnosis of schizophrenia as defined by DSM-5 criteria.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration, and Lot No.(s.):
A single dose of 780 mg or 1200 mg of IMP (Ari LAI, 300 mg/mL) was injected intramuscularly (IM) as a single injection in the gluteal muscle. The injection volume for the 780 mg dose was 2.6 mL and the injection volume for the 1200 mg dose was 4 mL.

Duration of Treatment:
The duration of treatment for each individual subject, including screening, in clinic period(s), a single dose of IMP, and outpatient visits, was approximately 8 months.

Analytical methods
According to the validation procedure (6825-275), a bioanalytical assessment was performed – Determination of OPC-14597 and OPC-14857 in human plasma by HPLC with MS/MS detection (031-201-00104) supporting clinical study 031-201-00104.
Human plasma samples with heparin as an anticoagulant (a total of 999 samples) were analyzed for OPC-14597 and OPC-14597 by the HPLC with MS/MS detection.
Samples were stored for a maximum time of 430 days. That storage conditions cover validated conditions (maximum validated -60 to -80°C for 1889 days). High analytical results, especially nearly Cmax, were within the range of the calibration curve.
Incurred sample reproducibility was performed for nearly 10% (103 for both analytes), and for OPC-14597, 95% of the results were acceptable as repeated samples had relative differences not exceeding 20% compared to the first evaluation. For OPC-14857, 94% of the results were consistent with the original measurements. ISR was acceptable. Bioanalysis is acceptable.

Statistical Methods:
Determination of Sample Size:
Sample size was determined from practical consideration and is not based on a formal computation. At least 18 subjects per cohort (with 12 completers) was considered sufficient to assess the PK, safety, and tolerability of single ascending dose administrations of the IMP in adult subjects with schizophrenia.

Subject Samples:

Pharmacokinetics/pharmacodynamics:
The PK analysis dataset included all subjects that were administered a dose of IMP and had at least 1 postdose evaluable plasma concentration.

Safety:
The safety analysis dataset included all subjects that were administered a dose of IMP.

Results

Pharmacokinetic Profile

Aripiprazole Concentrations Following a Single Dose of 780 mg or 1200 mg Ari LAI to the Gluteal Muscle

Mean (SD) aripiprazole plasma concentration versus time profiles following administration of a single dose of 780-mg or 1200-mg aripiprazole to the gluteal muscle are presented in Figure 10.

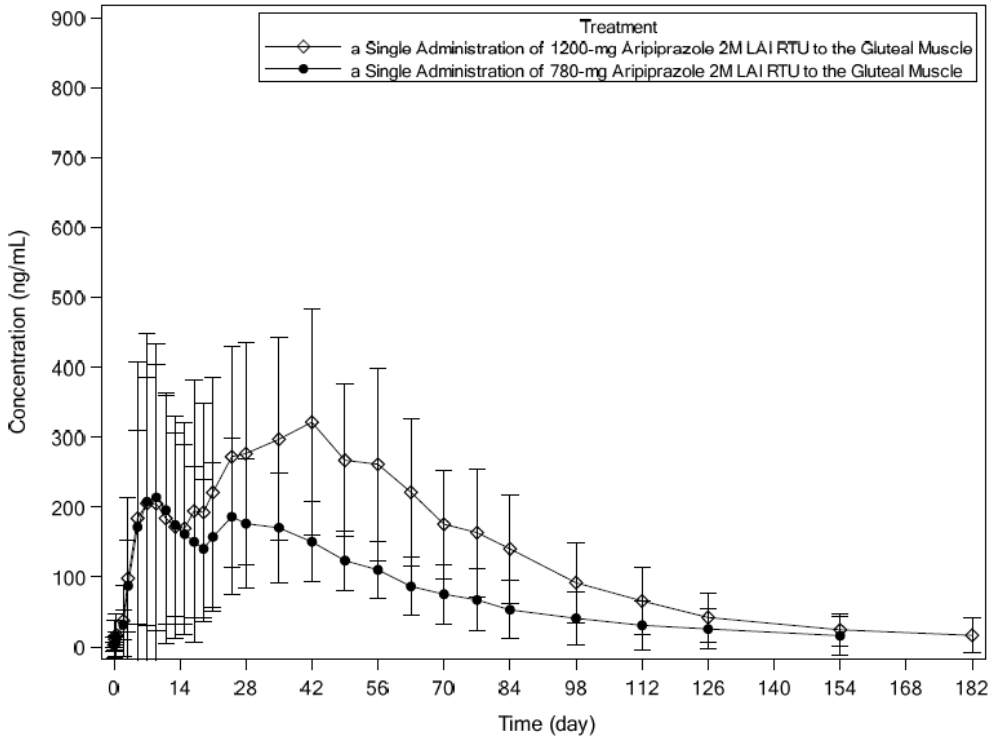


Figure 10 Mean (SD) Aripiprazole Plasma Concentration versus Time Profiles Following Administration of a Single Dose of 780-mg (N = 18) or 1200 mg (N = 13) Ari LAI to the Gluteal Muscle of Subjects with Schizophrenia

Dehydro-aripiprazole Concentrations Following a Single Dose of 780 mg or 1200 mg Ari LAI to the Gluteal Muscle

Mean (SD) dehydro-aripiprazole plasma concentration versus time profiles following administration of a single dose of 780 mg or 1200 mg Ari LAI to the gluteal muscle are presented in Figure 11.

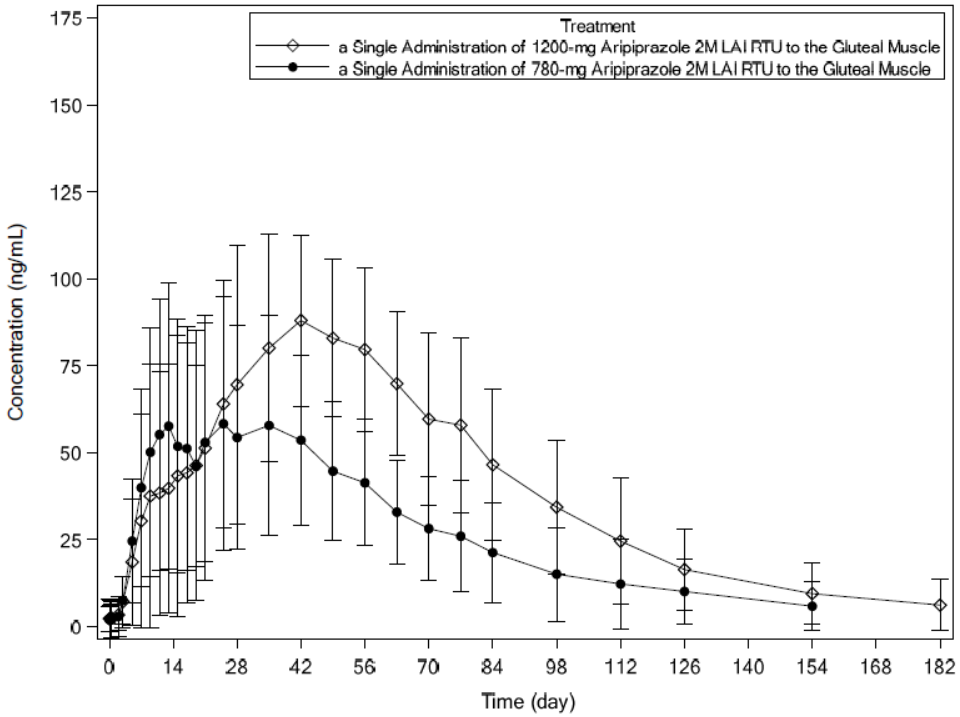


Figure 11 Mean (SD) Dehydro-Aripiprazole Plasma Concentration versus Time Profiles Following Administration of a Single Dose of 780-mg (N = 18) or 1200 mg (N = 13) Ari LAI to the Gluteal Muscle of Subjects with Schizophrenia

Pharmacokinetic Parameters

A summary of aripiprazole PK parameters following administration of a single dose of 780 mg or 1200 mg aripiprazole to the gluteal muscle in subjects with schizophrenia is presented in Table 23.

Table 20: Mean (SD) Aripiprazole Pharmacokinetic Parameters Following Administration of a Single Dose of 780-mg or 1200-mg Ari LAI to the Gluteal Muscle of Subjects with Schizophrenia

PK Parameter	Aripiprazole 2M RTU LAI 780 mg (N = 18)	Aripiprazole 2M RTU LAI 1200 mg (N = 13)
C_{max} (ng/mL)	271 (157)	391 (200)
t_{max} (day)[a]	25.1 (4.07-76.0)	41.0 (6.09-61.9)
AUC_t (ng·day/mL)	12600 (3710)	23800 (7620)
AUC_∞ (ng·day/mL)	13400 (4600)[b]	24700 (8080)[c]
$t_{1/2}$ (day)	22.1 (16.5)[b]	20.0 (9.2)[c]
CL/F (mL/day/kg)	763 (299)[b]	596 (207)[c]
C_{max}/Dose(ng/mL/mg)	0.347 (0.201)	0.326 (0.167)
AUC_t/Dose([ng·day/mL]/mg)	16.1 (4.75)	19.8 (6.35)
AUC_∞/Dose([ng·day/mL]/mg)	17.2 (5.90)[b]	20.6 (6.73)[c]

A summary of dehydro-aripiprazole PK parameters following administration of a single dose of 780-mg or 1200-mg Ari LAI to the gluteal muscle in subjects with schizophrenia is presented in Table 24.

Table 21: Mean (SD) Dehydro-Aripiprazole Pharmacokinetic Parameters Following Administration of a Single Dose of 780-mg or 1200-mg Ari LAI to the Gluteal Muscle of Subjects with Schizophrenia

PK Parameter	Aripiprazole 2M RTU LAI 780 mg (N = 18)	Aripiprazole 2M RTU LAI 1200 mg (N = 13)
C_{max} (ng/mL)	79.4 (35.6)	105 (29.1)
t_{max} (day)[a]	29.6 (7.88-111.0)	55.0 (14.2-78.0)
AUC_t (ng·day/mL)	4250 (1310)	7230 (1310)
AUC_∞ (ng·day/mL)	4490 (1440)[b]	7630 (1470)[c]
$t_{1/2}$ (day)	25.5 (13.3)[b]	22.9 (9.6)[c]
C_{max}/Dose(ng/mL/mg)	0.102 (0.0457)	0.0872 (0.0243)
AUC_t/Dose([ng·day/mL]/mg)	5.45 (1.68)	6.02 (1.09)
AUC_∞/Dose([ng·day/mL]/mg)	5.76 (1.84)[b]	6.36 (1.22)[c]

Safety Evaluation

Extent of Exposure
During the study, 18 subjects received one 780 mg dose and 18 subjects received one 1200 mg dose of Ari LAI.

Adverse Events

Brief Summary of Adverse Events
Overall, 23 of 36 (63.9%) of subjects experienced at total of 83 AEs during the study. Two subjects in the 780 mg Ari LAI group experienced at least 1 SAE. One subject in the 1200 mg Ari LAI group experienced a severe AE.

Display of Adverse Events

Treatment-emergent Adverse Events
23 of 36 (63.9%) of subjects experienced at least 1 TEAE during the study. The most common TEAEs reported by subjects were injection site pain (30.6%), insomnia (22.2%), and headache (11.1%). No withdrawals were due to TEAEs.

Treatment-emergent Adverse Events Related to the Investigational Medicinal Product
Sixteen of 36 subjects (44.4%) experienced at least 1 potentially related TEAE. The most common potentially related AEs, regardless of group, were injection site pain (11 subjects, 30.6%), insomnia (8 subjects, 22.2%), and headache (4 subjects, 11.1%).
Rates of potentially related AEs were similar between groups with the exception of injection site pain, which was reported in 8 subjects (44.4%) in the 1200 mg Ari LAI group and 3 subjects (16.7%) in the 780 mg Ari LAI group.

Deaths
There were no deaths in this trial.

Other Serious Adverse Events
Two subjects experienced 4 not related SAEs. One subject experienced a psychotic disorder and 1 subject experienced a concussion, skull fractured base, and paranoia.

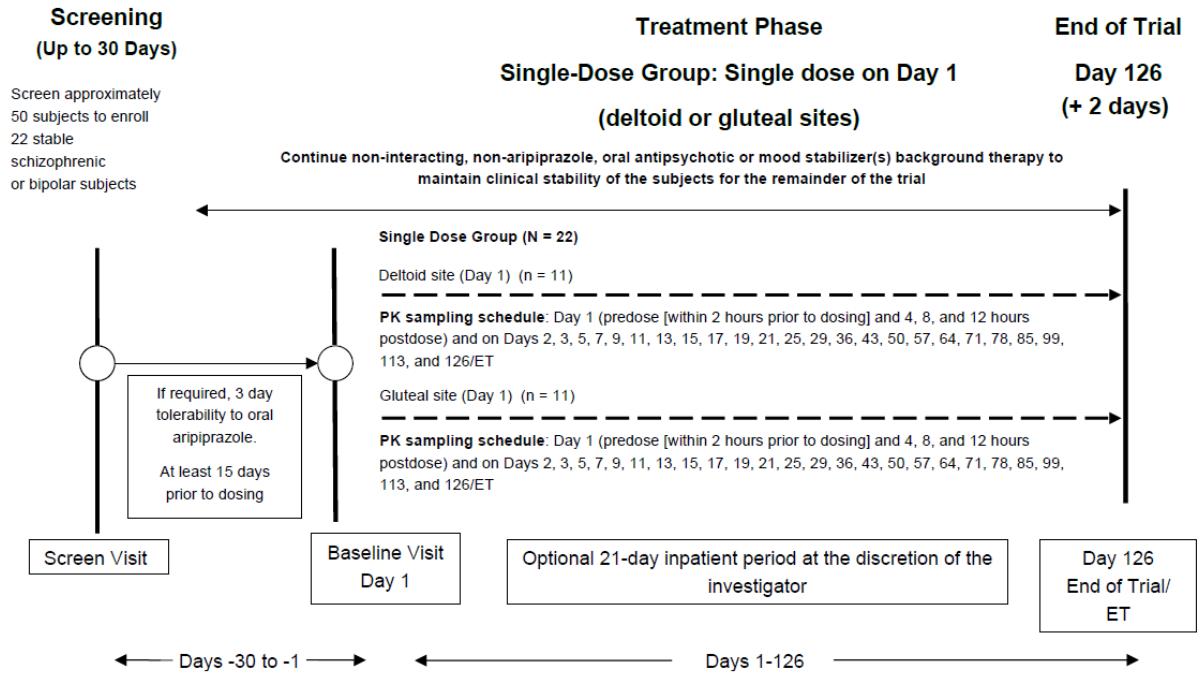
Study 031-201-00279

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 trial was designed to assess the pharmacokinetics (PK), safety, and tolerability of single- and multiple-dose administrations of 420 mg aripiprazole 1M LAI RTU formulation in the deltoid and gluteal muscles of adult subjects with schizophrenia or bipolar I disorder. The 420 mg aripiprazole 1M LAI formulation is an extended-release, RTU presentation that is different from Abilify Maintena and is intended for 1M dosing. The RTU formulation is also being studied as a twice monthly duration at higher doses. The aripiprazole LAI formulation has been assessed previously at higher single dose levels of 780 and 1200 mg (Trial 031-201-00104) to evaluate the feasibility of extension of the dosing interval. This trial is intended to evaluate the new aripiprazole 1M LAI RTU formulation at a lower dose of 420 mg administered 1M.

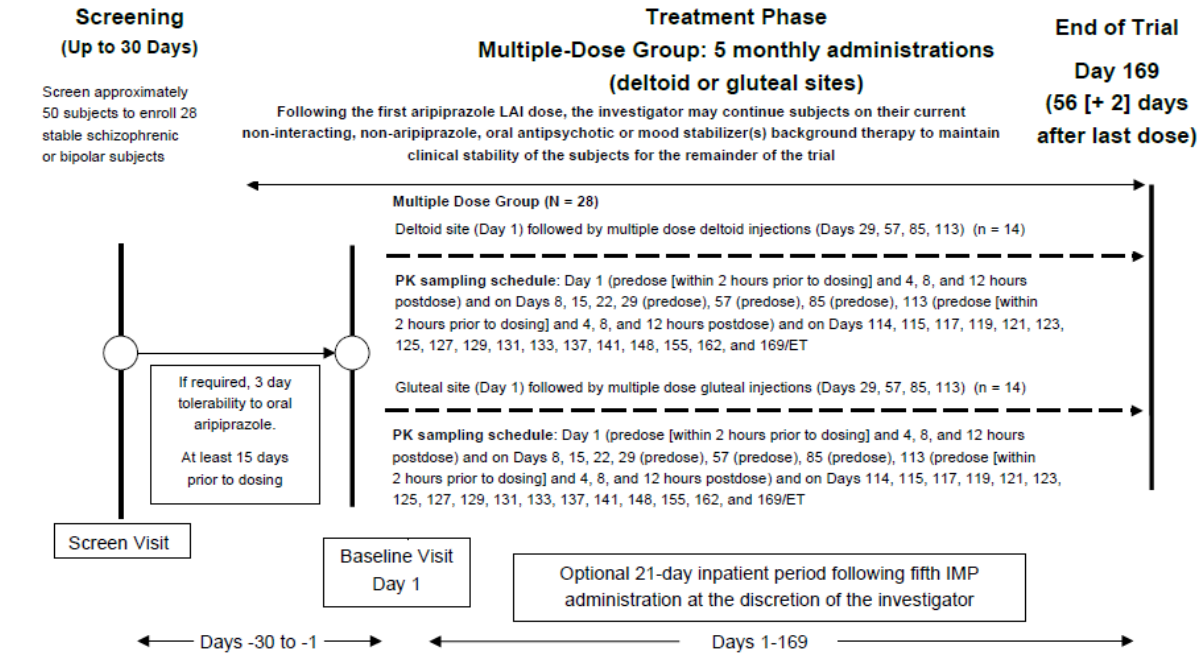
Objectives: The primary objective of the trial was to evaluate the PK of 420 mg aripiprazole 1M LAI RTU following deltoid or gluteal muscle administration in adult subjects with schizophrenia or bipolar I disorder.
The secondary objective of the trial was to determine the safety and tolerability of single and multiple-dose administrations of 420 mg aripiprazole 1M LAI RTU in adult subjects with schizophrenia or bipolar I disorder.

Methodology: This was 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 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. Part A evaluated single and multiple doses of the Investigational medicinal product (IMP) administered either in the deltoid or gluteal muscle sites. Part B evaluated a single dose of the IMP administered in the gluteal muscle site at 2 injection durations in a single group of subjects. A second group for Part B was originally planned but a decision was made by the sponsor to complete the trial without enrolling Group 2.



ET = early termination; N, n = number of subjects.

Figure 12 Trial Design Schematic (Part A - Single-Dose Group)



IMP = investigational medicinal product; LAI = long-acting injectable.

Figure 13 Trial Design Schematic (Part A - Multiple-Dose Group)

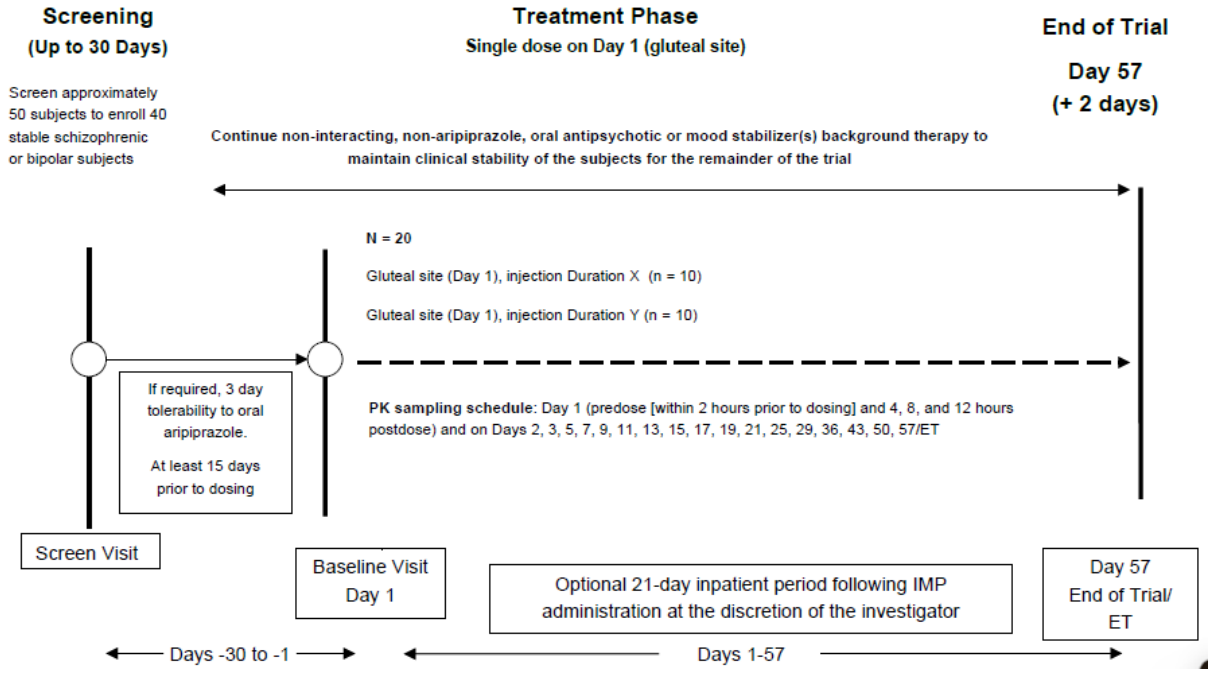


Figure 14 Trial Design Schematic (Part B)

To be eligible for this trial, subjects had prior demonstration of tolerability to aripiprazole according to the investigator's judgment, which was documented for each subject.
In Part A, for subjects in the single-dose group, 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. Subjects who were stable could have been discharged after the 12-hour procedures on Day 1. All subjects remained in the trial site clinic at the discretion of the investigator for a maximum of 21 days, after which they were discharged. Following discharge from the trial site, the subjects returned to the trial site for all scheduled assessments and PK sample collections. A final trial visit occurred on Day 126 (+ 2 days).
In Part A, for subjects in the multiple-dose group, 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 4 additional monthly administrations in the same injection site as the first dose (for a total of 5 monthly administrations for each subject [Days 1, 29, 57, 85, and 113]). Following the first aripiprazole 1M LAI RTU dose, the subjects were allowed to continue on their current non-aripiprazole oral antipsychotic therapy or mood stabilizer(s) medication to maintain clinical stability of the subjects for the remainder of the trial. Subjects who were stable could have been discharged after the 12-hour procedures on Day 1. After the fifth administration of the IMP, all subjects remained in the trial site clinic at the discretion of the investigator for a maximum of 21 days, after which they were discharged (on Day 134). Following discharge from the trial site, the subjects returned to the trial site for all scheduled assessments and PK sample collections. A final trial visit occurred on Day 169 (56 [+ 2] days after the last aripiprazole 1M LAI RTU administration).

Given the addition of a second antipsychotic (IMP) to subjects in the single dose group, investigators considered enrollment of clinically stable subjects for which the current oral non-aripiprazole antipsychotic or mood stabilizer(s) medication was in the mid to lower range of the recommended dose range, as defined by the product label. Subjects entering this trial were on a stable dose of one of the following atypical oral non aripiprazole antipsychotic medications at an adequate dose (eg, low to mid-range of the recommended dose range for the treatment of schizophrenia or bipolar I disorder, according to the manufacturer labeling) for at least 14 days prior to the administration of aripiprazole LAI: brexpiprazole, risperidone, olanzapine, quetiapine, ziprasidone, paliperidone, cariprazine, lurasidone, and asenapine; or, for subjects with bipolar I disorder, stabilized on their current regimen of non-aripiprazole mood stabilizer(s) (lithium, valproic acid, lamotrigine), antidepressants (citalopram, escitalopram, sertraline), or antipsychotic medications (quetiapine, lurasidone). Other oral non-aripiprazole antipsychotic medications were allowed if approved by the medical monitor and sponsor; however, clozapine was not allowed. Nonoral formulations of these antipsychotic medications were also not allowed. The use of any inhibitors and inducers of cytochrome P450 (CYP)3A4 and inhibitors of CYP2D6 isozymes were not allowed.

Part B was comprised of a single group of 20 subjects who were randomized to an injection duration (Duration X [within 3 seconds] or Duration Y [within 7 to 8 seconds]) according to a 1:1 randomization schedule prior to dosing on Day 1. A second group of subjects was originally planned but were not enrolled at the discretion of the sponsor.
Subjects received a single dose of 420 mg aripiprazole 1M LAI RTU in the gluteal muscle site. Eligible subjects in Part B 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.
Given the addition of a second antipsychotic (IMP) to subjects in Part B, investigators considered enrollment of clinically stable subjects for which the current oral non-aripiprazole antipsychotic or mood stabilizer(s) medication was in the mid to lower range of the recommended dose range, as defined by the product label. Subjects entering this trial were on a stable dose of atypical oral non-aripiprazole antipsychotic medications at an adequate dose as described above for the single dose group.
After the administration of aripiprazole 1M LAI RTU, subjects in Part B were followed for 57 days for PK and safety assessments. Subjects who were stable were discharged after the 12-hour procedures on Day 1. All subjects remained in the trial site clinic at the discretion of the investigator for a maximum of 21 days, after which they were discharged. Following discharge from the trial site, the subjects

returned to the trial site for all scheduled assessments and PK sample collections. A final trial visit was to have occurred on Day 57 (+ 2 days).

Number of Subjects: Seventy-two subjects were enrolled, including 24 subjects in Part A (Single Dose), 28 subjects in Part A (Multiple Dose), and 20 subjects in Part B. Forty-eight subjects were screen failures.
Of the 24 subjects in Part A (Single Dose), 20 subjects (83.3%) completed and 4 subjects (16.7%) discontinued the trial. The reasons for discontinuation were withdrawal by subject (3/24 subjects [12.5%]) and lost to follow-up (1/24 subjects [4.2%]).
Of the 28 subjects in Part A (Multiple Dose), 21 subjects (75.0%) completed and 7 subjects (25.0%) discontinued the trial. The reasons for discontinuation were withdrawal by subject (5/28 subjects [17.9%]) and lost to follow-up (2/28 subjects [7.1%]).
Of the 20 subjects in Part B, 19 subjects (95.0%) completed and 1 subject (5.0%) discontinued the trial. The reason for discontinuation was withdrawal by subject (1/20 subjects [5.0%]).

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration, and Lot No.(s.):

The IMP was supplied as OPC-14597 Aripiprazole IM Depot RTU, 300 mg/mL (Lot No. 18C95A300), 4 mL vials to the investigator(s) and the persons designated by the investigator(s) or institutions(s) by the sponsor or designated agent. The volume of IMP dose was 1.4 mL for a total dose of 420 mg.

In Part A, aripiprazole 1M LAI RTU was injected in the deltoid or gluteal muscle sites (1:1 randomization) as a single dose on Day 1 for subjects in the single-dose group and as multiple doses (a total of 5 administrations [Days 1, 29, 57, 85, and 113]) for subjects in the multiple-dose group. The injection site remained the same throughout the duration of the trial. Subjects in the multiple-dose group were allowed a one-time IMP dose reduction to 300 mg due to safety and tolerability reasons.
In Part B, aripiprazole 1M LAI RTU was injected as 1 of 2 injection durations (1:1 randomization) in the gluteal muscle site as a single dose on Day 1. The injection site remained the same throughout the duration of the trial.

Duration of Treatment: The planned duration of this trial was as follows:

Part A
The total duration of the trial for subjects in the single and multiple dose groups was up to approximately 156 and 199 days, respectively, including the following trial periods:
☐ Screening: Days −30 to −1 (30 days)
☐ Check in: Day −1
☐ Single Dose Group Treatment Phase: Days 1 to 126/early termination (ET)
☐ Multiple Dose Group Treatment Phase: Days 1 to 169/ET

Part B
The total duration of the trial for subjects in Part B was up to approximately 87 days, including the following trial periods:
☐ Screening: Days −30 to −1 (30 days)
☐ Check in: Day −1
☐ Treatment Phase: Days 1 to 57/ET

Trial Assessments: Trial assessments included the following:
☐ *Pharmacokinetic*: *Part A*: Plasma concentrations of aripiprazole and its major metabolite, dehydro-aripiprazole, after administration of a single dose of 420 mg aripiprazole 1M LAI RTU over the course of 126 days (single dose group) and after the first and fifth doses of 420 mg aripiprazole 1M LAI RTU (Days 1 and 113) over the course of 169 days (multiple dose group). *Part B*: Plasma concentrations of aripiprazole and its major metabolite, dehydro-aripiprazole, after administration of a single dose of 420 mg aripiprazole 1M LAI RTU over the course of 57 days.

☐ *Efficacy*: Positive and Negative Syndrome Scale (PANSS; subjects with schizophrenia only), Clinical Global Impression - Severity (CGI-S), Subjective Well-being under Neuroleptic Treatment-Short Form (SWN-S), Young Mania Rating Scale (YMRS; bipolar subjects only), Montgomery-Asberg Depression Rating Scale (MADRS; bipolar subjects only), and Clinical Global Impression – Bipolar Version (CGI-BP; bipolar subjects only).
☐ *Safety*: adverse events (AEs), clinical laboratory monitoring (serum chemistry, hematology, urinalysis), serum prolactin, physical examinations, vital signs, ECGs, suicidality via the Columbia Suicide Severity Rating Scale (C-SSRS), extrapyramidal symptoms (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, and Investigator's Assessment of Most Recent Injection Site.
☐ *Screening/Other*: Documentation of medical history, psychiatric history, and prior/concomitant medications; measurements of height and weight and calculation of BMI; confirmation of schizophrenia or bipolar disorder diagnosis using the DSM-5; serum hepatitis and human immunodeficiency virus screen; urine drug and alcohol test (via breathalyzer or urine test); serum or urine pregnancy test; pharmacogenomics blood sample; and future biospecimen research blood sample (optional).

Criteria for Evaluation:

Primary Endpoints: For subjects in Part A (Single Dose) and Part B, the following PK parameters were assessed for plasma aripiprazole and its major metabolite, dehydroaripiprazole: maximum (peak) plasma concentration of the drug (Cmax), plasma concentration of the drug at 28 days postdose (C28), time to maximum (peak) plasma concentration (tmax), area under the concentration-time curve from time zero to time t (the last observable concentration; AUCt), area under the concentration-time curve from time zero to 28 days postdose (AUC0-28), area under the concentration-time curve from time zero to infinity (AUC∞), terminal phase elimination half-life (t1/2), apparent clearance of the drug from plasma after extravascular administration (CL/F) (for aripiprazole only).
For subjects in Part A (Multiple Dose), the following PK parameters were assessed for plasma aripiprazole and its major metabolite, dehydro-aripiprazole, following the fifth dose of 420 mg aripiprazole 1M LAI RTU: Cmax, C28 (following the first dose and fifth dose), tmax, AUC0-28, t1/2, CL/F (for aripiprazole only), and ratio of dehydro-aripiprazole to aripiprazole C28 and AUC0-28.

Secondary Endpoints: Efficacy measures were used to confirm clinical stability of subjects over the course of this trial using the PANSS (subjects with schizophrenia only), CGI-S, SWN-S, MADRS (bipolar subjects only), YMRS (bipolar subjects only), and CGI-BP (bipolar subjects only).
Safety and tolerability were based on reported AEs, vital signs, ECGs, clinical laboratory monitoring (serum chemistry, hematology, and urinalysis), serum prolactin, physical examinations, VAS scores for injection site pain perception, investigator's assessment of most recent injection site, suicidality via the C-SSRS, and assessment of EPS via the SAS, AIMS, and BARS.

Analytical methods
According to the validation procedure (6825-275), a bioanalytical assessment was performed – Determination of OPC-14597 and OPC-14857 in human plasma by HPLC with MS/MS detection (031-201-00279) supporting clinical study 031-201-00279.
Human plasma samples with heparin as an anticoagulant (a total of 1803 samples) were analyzed for OPC-14597 and OPC-14597 by the HPLC with MS/MS detection. Samples were stored for a maximum of 454 days (within validated conditions). High analytical results, especially nearly Cmax, were in the range of the calibration curve.
Incurred sample reproducibility was performed for nearly 10% (185 for both analytes) of samples. For OPC-14597, 100% of the results were acceptable as repeated samples had relative differences not exceeding 20% compared to the first evaluation. For OPC-14857, 99.5% of the results were consistent with the original measurements. ISR was acceptable.
Bioanalysis is acceptable.

Statistical Methods:
Determination of Sample Size: Twenty-two subjects were included in Part A (Single Dose) and 28 subjects were included in Part A (Multiple Dose), and were randomized (1:1 ratio) to gluteal or deltoid injection sites. Based on the assumption of 30% discontinuation rate, approximately 16 subjects in the single dose group and 20 subjects in the multiple dose group were anticipated to complete Part A. An equal number of subjects received aripiprazole 1M LAI RTU in the deltoid and gluteal injection sites. If there was evidence that the number of completers dropped below 36, the sponsor could have enrolled more subjects into the trial. In Part B, 20 subjects were randomized to injection Duration X and Y in a 1:1 ratio.

Subject Samples:
☐ Randomized Analysis Set: The Randomized Analysis Set included all subjects who were randomized into the trial.
☐ PK Analysis Set: The PK Analysis Set included all subjects that were administered a dose of IMP and had at least 1 postdose evaluable plasma concentration.

Efficacy Analysis Set: The Efficacy Analysis Set included all randomized subjects who received at least one dose of aripiprazole injection and had at least one evaluable efficacy assessment.

☐ Safety Analysis Set: The Safety Analysis Set included all subjects that were administered any dose of IMP.

Primary Pharmacokinetic Endpoints: Aripiprazole and dehydro-aripiprazole concentrations and PK parameters were summarized descriptively by injection site in Part A and by injection duration in Part B.
As an exploratory analysis, the point estimate and 90% confidence interval (CI) of the geometric mean ratio (GMR; deltoid versus gluteal administration in Part A and fast vs slow injection duration in Part B) for the following PK concentration/parameters of aripiprazole were calculated:

☐ Cmax, C28, AUC0-28, and AUC∞ for the single dose group in Part A and in Part B.
☐ C28 following the first injection and Cmax, C28, and AUC0-28 following the fifth dose of IMP for the multiple dose group in Part A.

The natural log transformation of the PK parameters was performed first. And a mixed effect model with injection site (Part A) or injection duration (Part B) as factors, subject as a random effect was fit. The anti-log for the estimated difference between deltoid and gluteal injection site (Part A) or slow and fast injection (Part B) was the estimate of GMR. And the antilog for the 90% CI for the difference was the 90% CI for the GMR.
The analysis was performed using the MIXED procedure in SAS.

Efficacy Endpoints: Summary statistics and changes from baseline for efficacy measures including PANSS total score (schizophrenia subjects), PANSS positive and negative subscale scores (schizophrenia subjects), CGI-S score (schizophrenia subjects) SWN-S total score, MADRS score (bipolar subjects), YMRS score (bipolar subjects), and CGI-BP severity of illness score (bipolar subjects) were provided by visit and subject group.

Safety Endpoints: Summary statistics were provided by visit and subject group for safety variables based upon all available data.

Summary of Results:
Disposition, Demographics, and Baseline Characteristics:
Subject Disposition: A total of 120 subjects were screened and 72 subjects were enrolled in the trial. Of those subjects, 52 were randomized to Part A and 20 were randomized to Part B. In Part A (Single Dose), 24 subjects were randomized and treated with IMP. Of the 24 subjects, 20 subjects (83.3%)

completed and 4 subjects (16.7%) discontinued the trial. The reasons for discontinuation were withdrawal by subject (3/24 subjects [12.5%]) and lost to follow-up (1/24 subjects [4.2%]).

In Part A (Multiple Dose), 28 subjects were randomized and treated with IMP. Of the 28 subjects, 21 subjects (75.0%) completed and 7 subjects (25.0%) discontinued the trial. The reasons for discontinuation were withdrawal by subject (5/28 subjects [17.9%]) and lost to follow-up (2/28 subjects [7.1%]).

In Part B, 20 subjects were randomized to and treated with IMP. Of the 20 subjects, 19 subjects (95.0%) completed and 1 subject (5.0%) discontinued the trial. The reason for discontinuation was withdrawal by subject (1/20 subjects [5.0%]).

Subject Demographics and Baseline Characteristics: In Part A (Single Dose), the overall mean age was 44.3 years and was similar across the administration site groups (46.9 and 41.6 years for the deltoid and gluteal groups, respectively). The number of male (14/24 subjects [58.3%]) and female (10/24 subjects [41.7%]) subjects were generally similar across the administration site groups (7/12 males [58.3%] and 5/12 females [41.7%] for the deltoid and gluteal groups, respectively). The majority of subjects were Black or African American (15/24 subjects [62.5%]), White (8/24 subjects [33.3%]), and not Hispanic or Latino (21/24 subjects [87.5%]).

In Part A (Multiple Dose), the overall mean age was 48.8 years and was similar across the administration site groups (49.4 and 48.2 years for the deltoid and gluteal groups, respectively). The number of male (15/28 subjects [53.6%]) and female (13/28 subjects [46.4%]) subjects were generally similar across the administration site groups (7/14 males [50.0%] and 7/14 females [50.0%] for the deltoid and gluteal groups, respectively). The majority of subjects were Black or African American (22/28 subjects [78.6%]), White (5/28 subjects [17.9%]), and not Hispanic or Latino (28/28 subjects [100%]).

In Part B, the overall mean age was 49.5 years and was similar across the administration site groups (48.4 and 50.5 years for the Duration X and Duration Y groups, respectively).

The number of male subjects (13/20 subjects [65.0%]) was generally greater than female subjects (7/20 subjects [35.0%]) across the administration site groups (7/10 males [70.0%] and 3/10 females [30.0%] for the Duration X group and 6/10 males [60.0%] and 4/10 females [40.0%] for the Duration Y group). The majority of subjects were Black or African American (16/20 subjects [80.0%]), White (3/20 subjects [15.0%]), and not Hispanic or Latino (20/20 subjects [100%]).

Pharmacokinetic Profile

Part A

Single Dose Administration

Aripiprazole Concentrations Following Single-Dose Administration of 420 mg Aripiprazole 1M LAI RTU in the Deltoid or Gluteal Muscle

Mean (SD) aripiprazole plasma concentration versus time profiles following a single dose administration of 420 mg aripiprazole 1M LAI RTU in the deltoid or gluteal muscle are presented in Figure 15

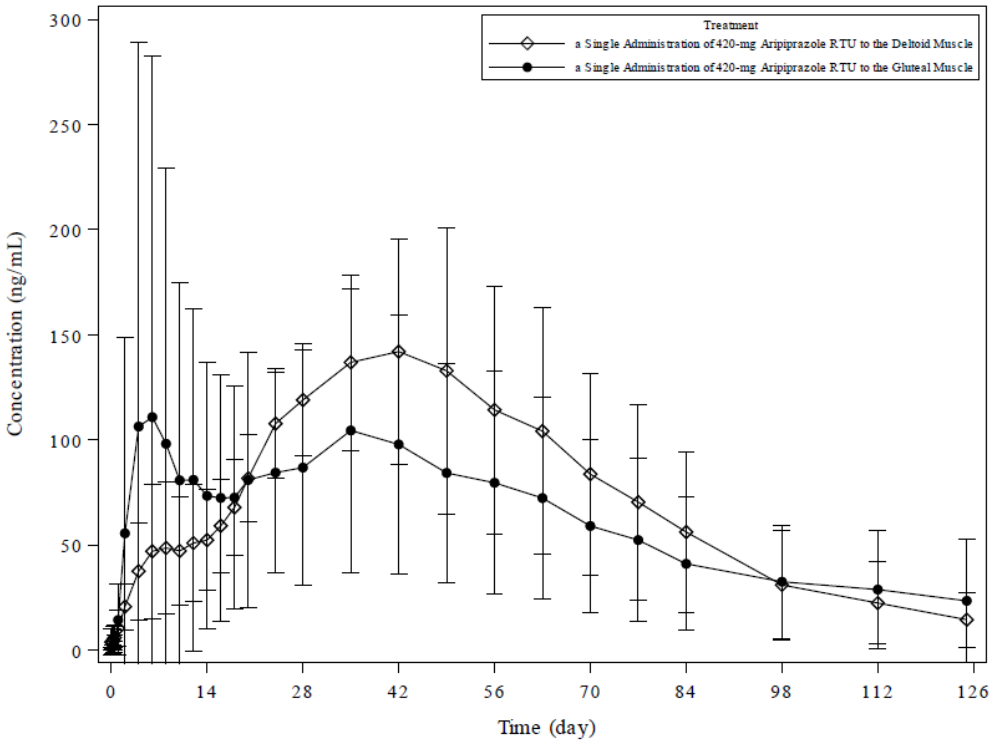


Figure 15 Mean (SD) Aripiprazole Plasma Concentration versus Time Profiles Following Single-Dose Administration of 420 mg Aripiprazole 1M LAI RTU in the Deltoid Muscle (n = 12) or Gluteal Muscle (n = 12) of Subjects with Schizophrenia or Bipolar Disorder.

Dehydro-aripiprazole Concentrations Following Single-Dose Administrations of 420 mg Aripiprazole 1M LAI RTU in the Deltoid or Gluteal Muscle

Mean (SD) dehydro-aripiprazole plasma concentration versus time profiles following a single-dose administration of 420 mg aripiprazole 1M LAI RTU in the deltoid or gluteal muscle are presented in Figure 16.

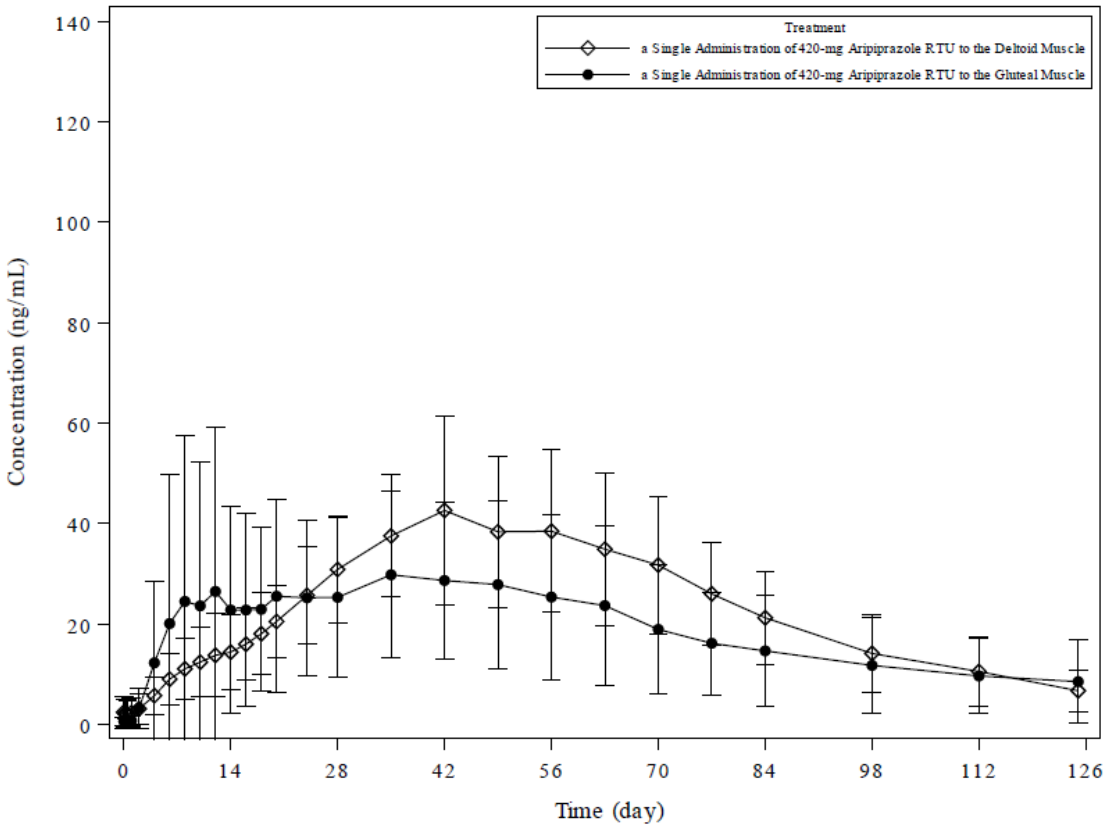


Figure 16 Mean (SD) Dehydro-aripiprazole Plasma Concentration versus Time Profiles Following Single-Dose Administration of 420 mg Aripiprazole 1M LAI RTU in the Deltoid Muscle (n = 12) or Gluteal Muscle (n = 12) of Subjects with Schizophrenia or Bipolar Disorder

Multiple Dose Administration

Aripiprazole Concentrations Following Monthly Administrations of 420 mg Aripiprazole 1M LAI RTU in the Deltoid or Gluteal Muscle

Mean (SD) aripiprazole plasma trough concentrations following each monthly administration of 420 mg aripiprazole 1M LAI RTU in the deltoid or gluteal muscle are presented in Figure 17. Mean (SD) aripiprazole plasma concentration versus time profiles following the fifth monthly administration of 420 mg aripiprazole 1M LAI RTU in the deltoid or gluteal muscle are presented in Figure 18.

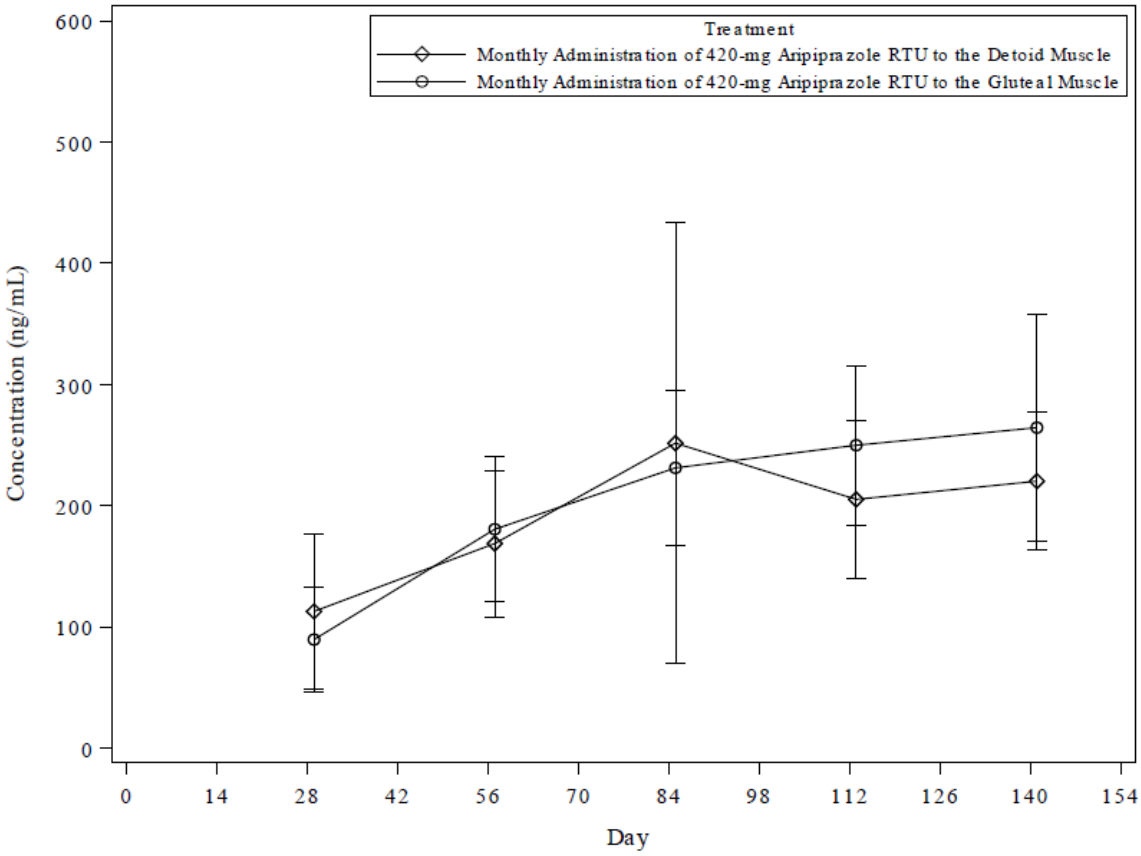


Figure 17 Mean (SD) Aripiprazole Trough Plasma Concentration versus Time Profiles Following Monthly Administration of 420-mg Aripiprazole 1M LAI RTU LAI RTU to the Deltoid Muscle (N = 14) or Gluteal Muscle (N = 14) of Subjects with Schizophrenia or Bipolar Disorder

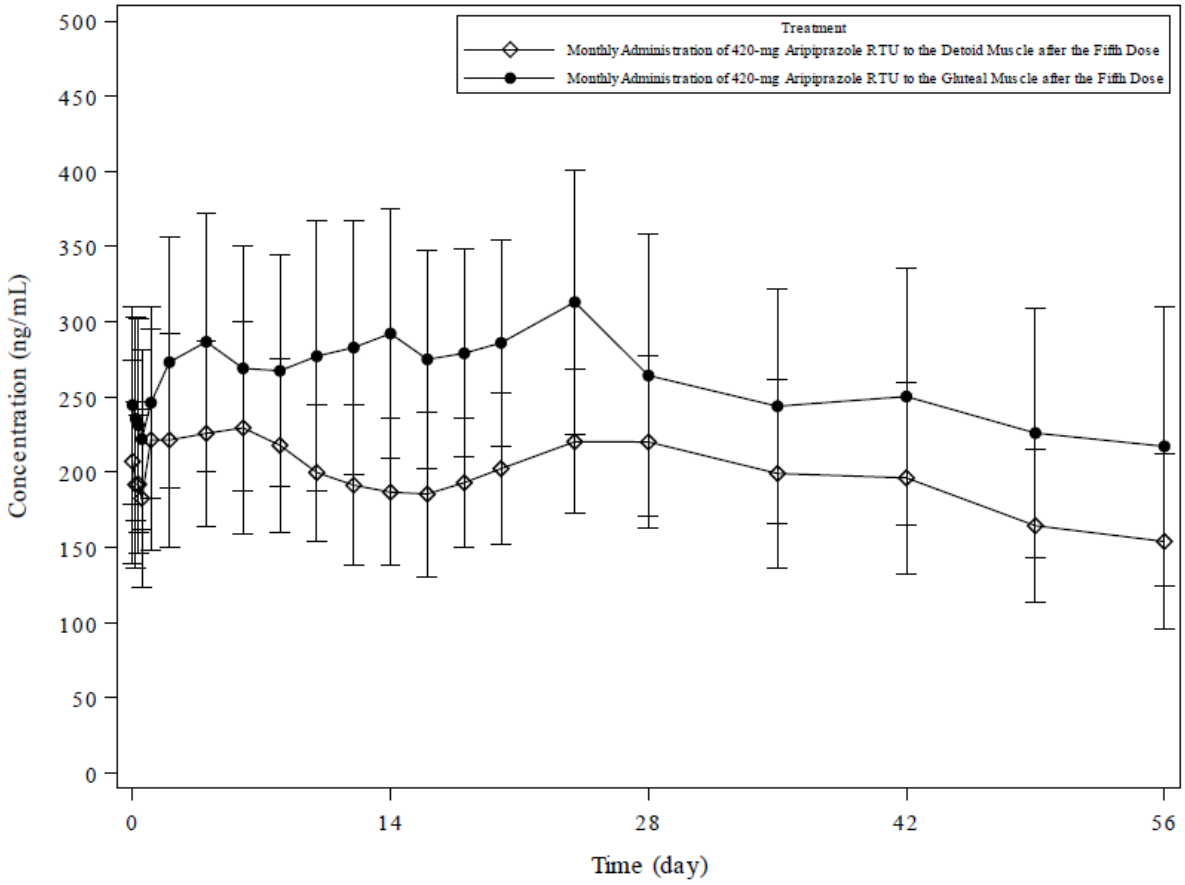


Figure 18 Mean (SD) Aripiprazole Plasma Concentration versus Time Profiles after the Fifth Dose Following Monthly Administration of 420 mg Aripiprazole 1M LAI RTU in the Deltoid Muscle (n = 12) or Gluteal Muscle (n = 14) of Subjects with Schizophrenia or Bipolar Disorder

Dehydro-aripiprazole Concentrations Following Monthly Administrations of 420 mg Aripiprazole 1M LAI RTU in the Deltoid or Gluteal Muscle

Mean (SD) dehydro-aripiprazole plasma trough concentrations following each monthly administration of 420 mg aripiprazole 1M LAI RTU in the deltoid or gluteal muscle are presented in Figure 19. Mean (SD) dehydro-aripiprazole plasma concentration versus time profiles following the fifth monthly administration of 420 mg aripiprazole 1M LAI RTU in the deltoid or gluteal muscle are presented in Figure 20.

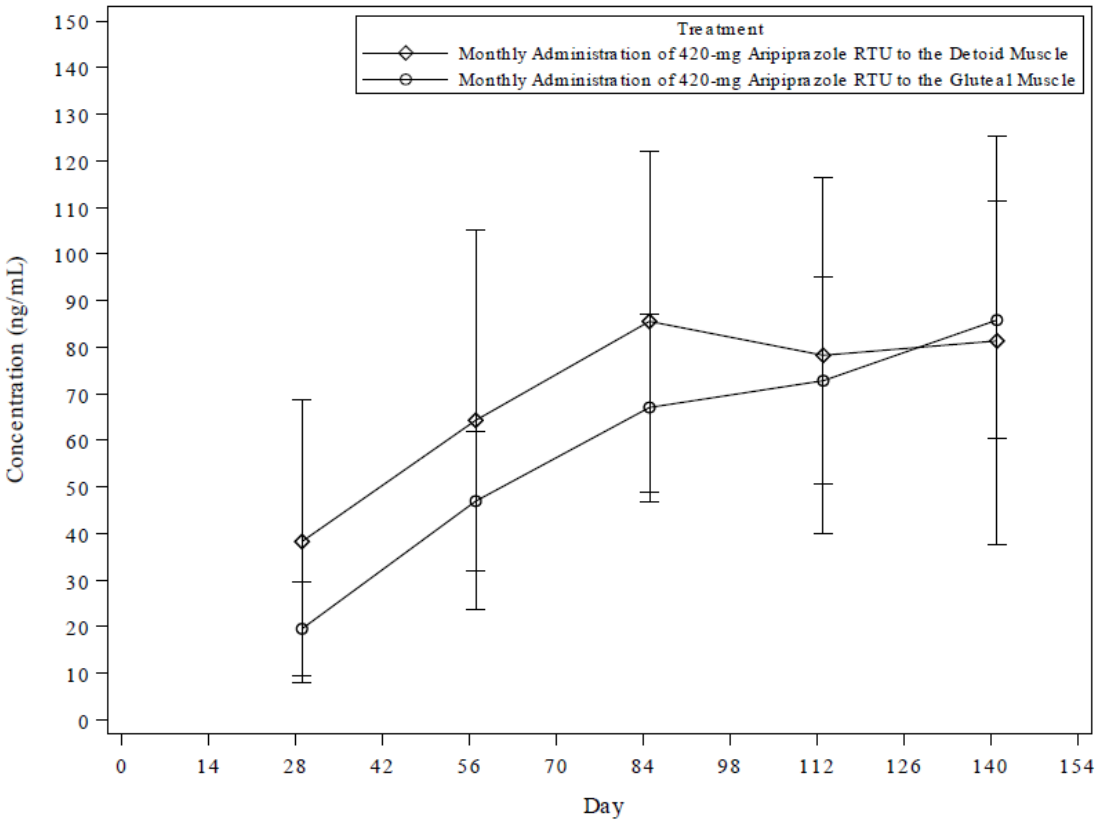


Figure 19 Mean (SD) Dehydro-aripiprazole Trough Plasma Concentration versus Time Profiles Following Monthly Administration of 420-mg Aripiprazole 1M LAI RTU to the Deltoid Muscle (N = 14) or Gluteal Muscle (N = 14) of Subjects with Schizophrenia or Bipolar Disorder

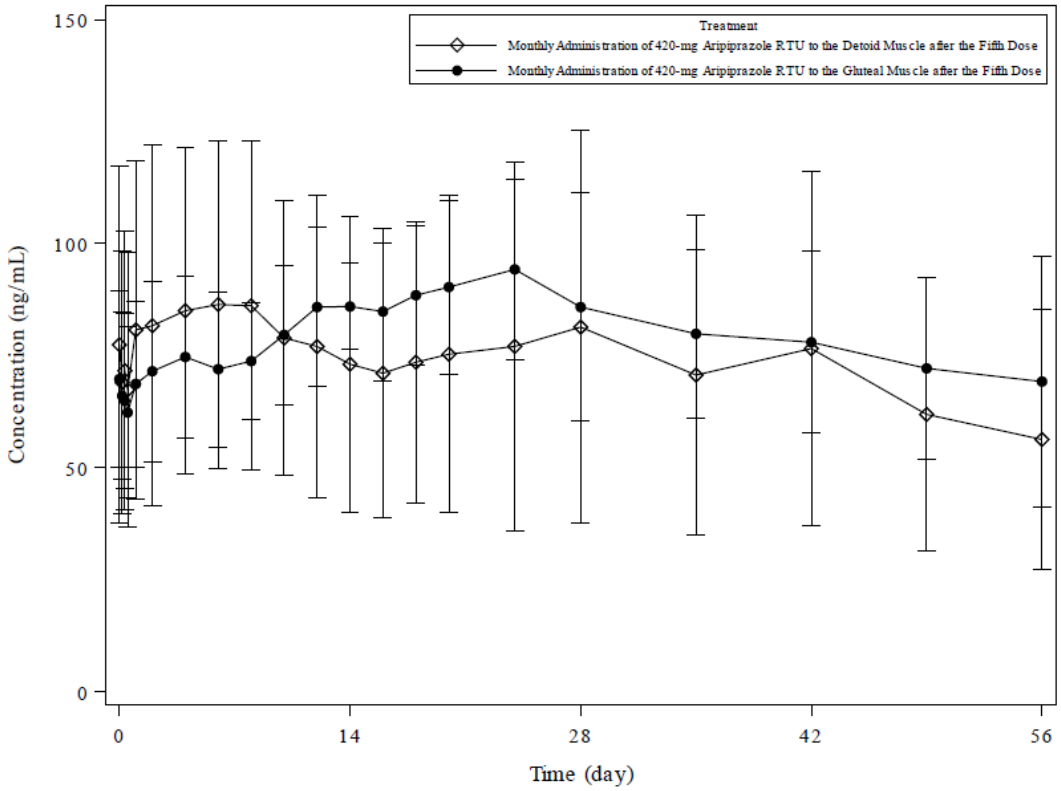


Figure 20 Mean (SD) Dehydro-aripiprazole Plasma Concentration versus Time Profiles After the Fifth Dose Following Monthly Administration of 420 mg Aripiprazole 1M LAI RTU in the Deltoid Muscle (n = 12) or Gluteal Muscle (n = 14) of Subjects with Schizophrenia or Bipolar Disorder.

Part B

Aripiprazole Concentrations Following Single-Dose Administration of 420 mg Aripiprazole 1M LAI RTU in the Gluteal Muscle at a Fast Injection Duration (Within 3 Seconds) or at a Slow Injection Duration (7 to 8 Seconds)

Mean (SD) aripiprazole plasma concentration versus time profiles following a single dose administration of 420 mg aripiprazole 1M LAI RTU in the gluteal muscle at a fast injection duration (within 3 seconds) or at a slow injection duration (7 to 8 seconds) are presented in Figure 21.

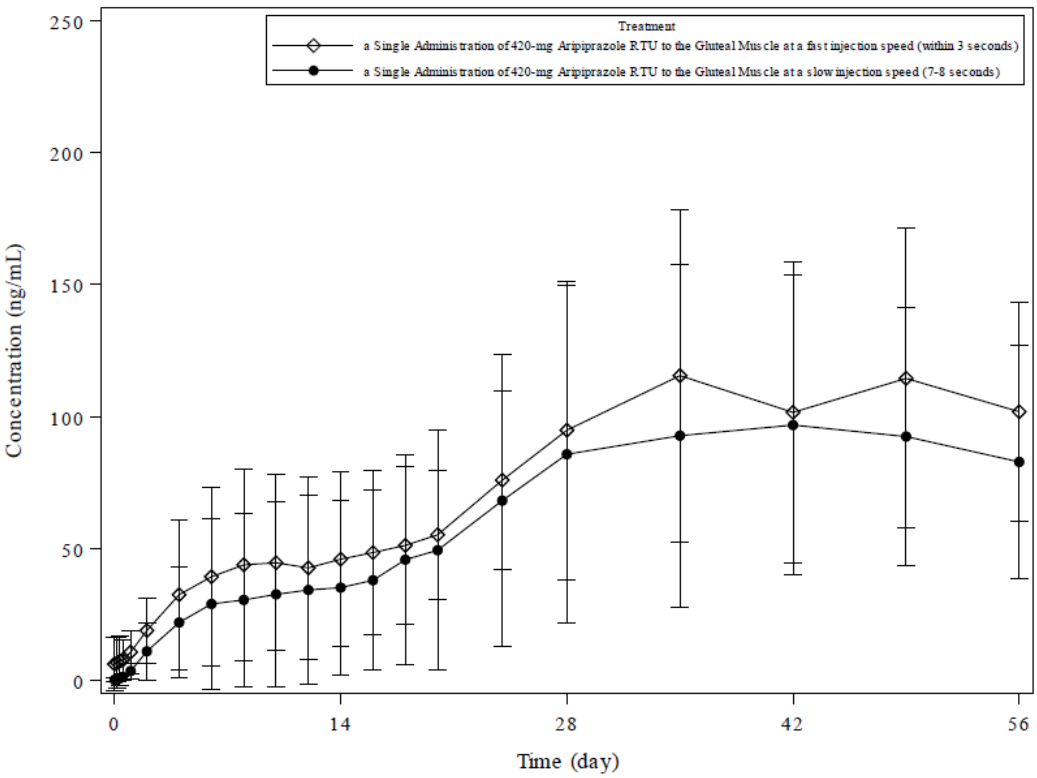


Figure 21 Mean (SD) Aripiprazole Plasma Concentration versus Time Profiles Following Single-Dose Administration of 420 mg Aripiprazole 1M LAI RTU in the Gluteal Muscle of Subjects with Schizophrenia or Bipolar Disorder at a Fast Injection Duration (Within 3 Seconds; n = 10) or at a Slow Injection Duration (7 to 8 Seconds; n = 10)

Dehydro-aripiprazole Concentrations Following Single-Dose Administration of 420 mg Aripiprazole 1M LAI RTU in the Gluteal Muscle at a Fast Injection Duration (Within 3 Seconds) or at a Slow Injection Duration (7 to 8 Seconds)

Mean (SD) dehydro-aripiprazole plasma concentration versus time profiles following a single-dose administration of 420 mg aripiprazole 1M LAI RTU in the gluteal muscle at a fast injection duration (within 3 seconds) or at a slow injection duration (7 to 8 seconds) are presented in Figure 22.

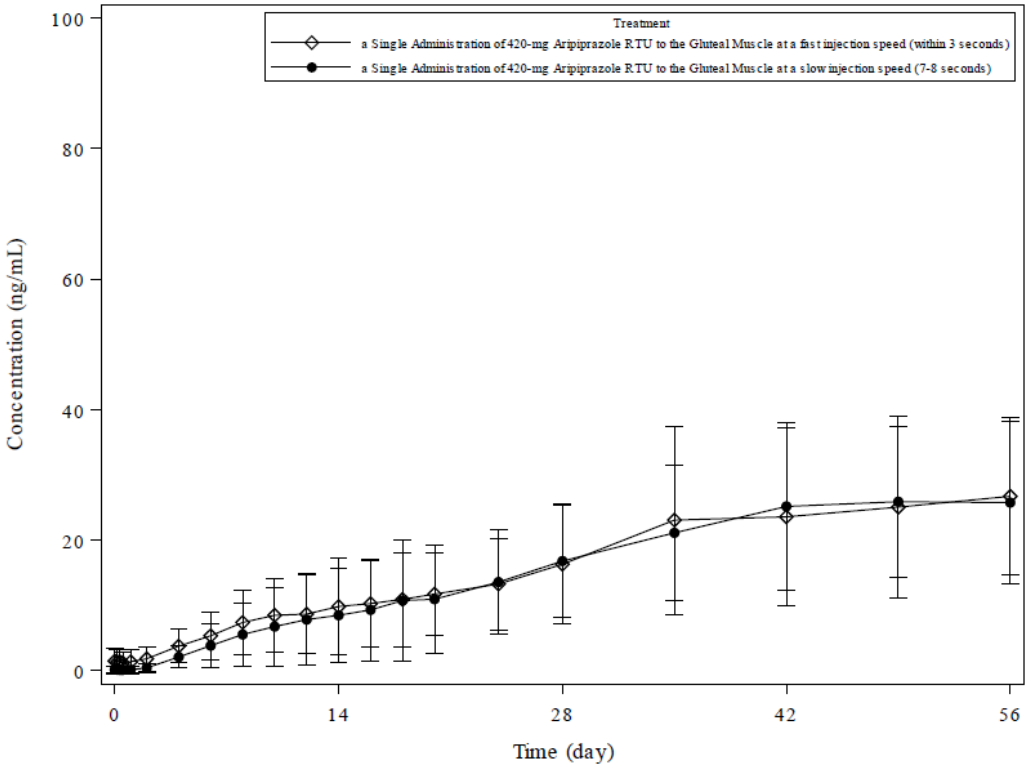


Figure 22 Mean (SD) Dehydro-aripiprazole Plasma Concentration versus Time Profiles Following Single-Dose Administration of 420 mg Aripiprazole 1M LAI RTU in the Gluteal Muscle of Subjects with Schizophrenia or Bipolar Disorder at a Fast Injection Duration (Within 3 Seconds; n = 10) or at a Slow Injection Duration (7 to 8 Seconds; n = 10)

Pharmacokinetic Parameter Analysis

Part A

Single Dose Administration

A summary of aripiprazole PK parameters following single-dose administration of 420 mg aripiprazole 1M LAI RTU in the deltoid muscle or gluteal muscle of subjects with schizophrenia or bipolar disorder is presented in Table 25.

Table 22: Mean (SD) Aripiprazole Pharmacokinetic Parameters Following Single-Dose Administration of 420 mg Aripiprazole 1M LAI RTU in the Deltoid Muscle (n = 12) or Gluteal Muscle (n = 12) of Subjects with Schizophrenia or Bipolar Disorder

PK Parameters	Deltoid Administration	Gluteal Administration
C_{max} (ng/mL)	158 (53.6)[a]	196 (159)[d]
C_{28} (ng/mL)	119 (26.6)[a]	86.8 (56.2)[e]
t_{max} (day)[b]	41.97 (19.80 - 49.08)[a]	39.05 (3.79 - 83.95)[d]
AUC_{0-28} (ng·day/mL)	1790 (483)[a]	2150 (2070)[e]
AUC_t (ng·day/mL)	9610 (3470)[c]	7820 (2600)[d]
AUC_∞ (ng·day/mL)	9800 (4500)[f]	8400 (3070)[a]
$t_{1/2}$ (day)	21.4 (6.40)[f]	21.4 (14.3)[a]
CL/F (mL/day)	0.585 (0.240)[f]	0.644 (0.216)[a]

A summary of dehydro-aripiprazole PK parameters following single-dose administration of 420 mg aripiprazole 1M LAI RTU in the deltoid muscle or gluteal muscle of subjects with schizophrenia or bipolar disorder is presented in Table 26.

Table 23: Mean (SD) Dehydro-aripiprazole Pharmacokinetic Parameters Following Single-Dose Administration of 420 mg Aripiprazole 1M LAI RTU in the Deltoid Muscle (n = 12) or Gluteal Muscle (n = 12) of Subjects with Schizophrenia or Bipolar Disorder

Table 11.4.2.4.1.1-2 Mean (SD) Dehydro-aripiprazole Pharmacokinetic Parameters Following Single-Dose Administration of 420 mg Aripiprazole 1M LAI RTU in the Deltoid Muscle (n = 12) or Gluteal Muscle (n = 12) of Subjects with Schizophrenia or Bipolar Disorder		
PK Parameters	**Deltoid Administration**	**Gluteal Administration**
C_{max} (ng/mL)	47.4 (17.8)[a]	46.8 (27.4)
C_{28} (ng/mL)	30.9 (10.7)[a]	25.3 (16.0)[e]
t_{max} (day)[b]	42.02 (34.86 - 69.91)[a]	38.51 (7.79 - 124.93)
AUC_{0-28} (ng·day/mL)	440 (170)[a]	566 (520)[e]
AUC_t (ng·day/mL)	3070 (827)[c]	2380 (903)
AUC_∞ (ng·day/mL)	3230 (930)[d]	2580 (812)[a]
$t_{1/2}$ (day)	22.5 (5.5)[d]	25.3 (18.7)[a]

A summary of the exploratory analysis of the geometric mean ratio (deltoid versus gluteal administration) and 90% confidence interval (CI) of the PK parameters of aripiprazole and dehydro-aripiprazole following single-dose administration of 420 mg aripiprazole 1M LAI RTU is presented in Table 27.

Table 24: Geometric Mean Ratios (Deltoid/Gluteal) and 90% Confidence Intervals for Aripiprazole and Dehydroaripiprazole Pharmacokinetic Parameters Following Single-Dose Administration of 420 mg Aripiprazole 1M LAI RTU in the Deltoid Muscle (n = 12) or Gluteal Muscle (n = 12) of Subjects with Schizophrenia or Bipolar Disorder

Analyte	PK Parameter	GMR (Deltoid/Gluteal)	90% CI	Within Subject CV%	P-value
Aripiprazole	C_{max}[a]	0.925	0.648 - 1.321	51.21	0.6454
	C_{28}[b]	1.579	1.110 - 2.245	49.24	0.0185
	AUC_{0-28}[b]	1.143	0.700 - 1.867	72.35	0.3210
	AUC_∞[c]	1.133	0.780 - 1.647	41.73	0.2818
Dehydro-aripiprazole	C_{max}[a]	1.080	0.765 - 1.526	49.40	0.3516
	C_{28}[b]	1.480	0.909 - 2.410	71.88	0.0903
	AUC_{0-28}[b]	1.063	0.599 - 1.887	88.41	0.4280
	AUC_∞[d]	1.278	0.925 - 1.764	37.57	0.1011

Multiple Dose Administration

A summary of aripiprazole PK parameters following monthly administration of 420 mg aripiprazole 1M LAI RTU in the deltoid muscle or gluteal muscle of subjects with schizophrenia or bipolar disorder is presented in **Error! Reference source not found.**.

Table 25: Mean (SD) Aripiprazole Pharmacokinetic Parameters Following Monthly Administration of 420 mg Aripiprazole 1M LAI RTU in the Deltoid Muscle (n = 14) or Gluteal Muscle (n = 14) of Subjects with Schizophrenia or Bipolar Disorder

First Dose PK Parameters	Deltoid Administration	Gluteal Administration
C_{28} (ng/mL)	113 (64.2)	89.5 (43.6)
Fifth Dose PK Parameters	**Deltoid Administration**	**Gluteal Administration**
C_{max} (ng/mL)	261 (55.5)[a]	338 (90.0)[d]
C_{28} (ng/mL)	220 (56.9)[a]	264 (93.7)[d]
t_{max} (day)[b]	26.61 (0.00 - 41.85)[a]	13.07 (3.87 - 41.92)[d]
AUC_{0-28} (ng·day/mL)	5630 (812)[a]	7790 (2210)[e]
AUC_t (ng·day/mL)	10700 (2350)[c]	14900 (3680)[e]
AUC_∞ (ng·day/mL)	22040 (11400)[f]	24800 (7300)[f]
$t_{1/2}$ (day)	ND[f]	ND[f]
CL/F (mL/day)	ND[f]	ND[f]

A summary of dehydro-aripiprazole PK parameters following monthly administration of 420 mg aripiprazole 1M LAI RTU in the deltoid muscle or gluteal muscle of subjects with schizophrenia or bipolar disorder is presented in Table 29.

Table 26: Mean (SD) Dehydro-aripiprazole Pharmacokinetic Parameters Following Monthly Administration of 420 mg Aripiprazole 1M LAI RTU in the Deltoid Muscle (n = 14) or Gluteal Muscle (n = 14) of Subjects with Schizophrenia or Bipolar Disorder

First Dose PK Parameters	Deltoid Administration	Gluteal Administration
C_{28} (ng/mL)	38.3 (30.4)	19.6 (10.2)
Fifth Dose PK Parameters	**Deltoid Administration**	**Gluteal Administration**
C_{max} (ng/mL)	109 (35.7)[a]	104 (19.5)[d]
C_{28} (ng/mL)	81.3 (43.8)[a]	85.8 (25.5)[d]
t_{max} (day)[b]	27.96 (0.00 - 41.93)[a]	19.87 (0.00 - 56.01)[d]
AUC_{0-28} (ng·day/mL)	2070 (800)[a]	2260 (397)[e]
AUC_t (ng·day/mL)	3720 (1260)[c]	4460 (789)[e]
AUC_∞ (ng·day/mL)	ND[f]	ND[f]
$t_{1/2}$ (day)	ND[f]	ND[f]

A summary of the ratio of dehydro-aripiprazole to aripiprazole C28 (following the first dose and the fifth dose) and AUC0-28 (following the fifth dose only) of 420 mg aripiprazole 1M LAI RTU in the deltoid and gluteal muscle sites are presented in **Error! Reference source not found.**.

Table 27: Mean (SD) Ratio of Dehydro-aripiprazole to Aripiprazole Pharmacokinetic Parameters Following Monthly Administration of 420 mg Aripiprazole 1M LAI RTU in the Deltoid Muscle (n = 14) or Gluteal Muscle (n = 14) of Subjects with Schizophrenia or Bipolar Disorder

First Dose PK Parameters	Deltoid Administration	Gluteal Administration
C_{28} Ratio	0.329 (0.132)	0.227 (0.083)
Fifth Dose PK Parameters	**Deltoid Administration**	**Gluteal Administration**
C_{28} Ratio	0.359 (0.134)[a]	0.337 (0.078)[b]
AUC_{0-28} Ratio	0.361 (0.113)[a]	0.304 (0.077)[c]

A summary of the exploratory analysis of the geometric mean ratio (deltoid versus gluteal administration) and 90% CI of the PK parameters of aripiprazole and dehydroaripiprazole following monthly administration of 420 mg aripiprazole 1M LAI RTU is presented in **Error! Reference source not found.**.

Table 28: Geometric Mean Ratios (Deltoid/Gluteal) and 90% Confidence Intervals for Aripiprazole and Dehydroaripiprazole Pharmacokinetic Parameters Following Monthly Administration of 420 mg Aripiprazole 1M LAI RTU in the Deltoid Muscle (n = 14) or Gluteal Muscle (n = 14) of Subjects with Schizophrenia or Bipolar Disorder

Analyte	PK Parameter	GMR (Deltoid/Gluteal)	90% CI	Within Subject CV%	P-value
Aripiprazole	C_{28} - First Dose	1.204	0.852 - 1.703	57.82	0.1839
	C_{max} - Fifth Dose[a]	0.786	0.648 - 0.954	26.63	0.9778
	C_{28} - Fifth Dose[a]	0.850	0.665 - 1.087	34.15	0.8663
	AUC_{0-28} - Fifth Dose[b]	0.744	0.621 - 0.891	24.23	0.9947
Dehydro-Aripiprazole	C_{28} - First Dose	1.716	1.128 - 2.612	72.66	0.0186
	C_{max} - Fifth Dose[a]	1.016	0.824 - 1.252	28.84	0.4494
	C_{28} - Fifth Dose[a]	0.870	0.632 - 1.198	45.42	0.7695
	AUC_{0-28} - Fifth Dose[b]	0.874	0.699 - 1.092	30.19	0.8457

Part B

A summary of aripiprazole PK parameters following single-dose administration of 420 mg aripiprazole 1M LAI RTU in the gluteal muscle of subjects with schizophrenia or bipolar disorder at a fast injection duration (within 3 seconds) or at a slow injection duration (7 to 8 seconds) is Table 29.

Table 29: Mean (SD) Aripiprazole Pharmacokinetic Parameters Following Single-Dose Administration of 420 mg Aripiprazole 1M LAI RTU in the Gluteal Muscle of Subjects with Schizophrenia or Bipolar Disorder at a Fast Injection Duration (within 3 Seconds; n = 10) or at a Slow Injection Duration (7 to 8 Seconds; n = 10)

PK Parameters	Fast Injection (within 3 Seconds)	Slow Injection (7 to 8 Seconds)
C_{max} (ng/mL)	131 (61.0)[a]	106 (62.1)[a]
C_{28} (ng/mL)	94.8 (56.6)[b]	85.7 (63.9)[b]
t_{max} (day)[c]	48.75 (7.76 - 56.05)[a]	48.91 (28.85 - 55.99)[a]
AUC_{0-28} (ng·day/mL)	1400 (788)[b]	1240 (1090)[b]
AUC_t (ng·day/mL)	4400 (1880)[a]	3690 (2400)[a]
AUC_∞ (ng·day/mL)	ND[d]	ND[d]
$t_{1/2}$ (day)	ND[d]	ND[d]
CL/F (mL/day)	ND[d]	ND[d]

A summary of dehydro-aripiprazole PK parameters following single-dose administration of 420 mg aripiprazole 1M LAI RTU in the gluteal muscle of subjects with schizophrenia or bipolar disorder at a fast injection duration (within 3 seconds) or at a slow injection duration (7 to 8 seconds) is presented in Table 33.

Table 30: Mean (SD) Dehydro-aripiprazole Pharmacokinetic Parameters Following Single-Dose Administration of 420 mg Aripiprazole 1M LAI RTU in the Gluteal Muscle of Subjects with Schizophrenia or Bipolar Disorder a Fast Injection Duration (within 3 Seconds; n = 10) or at a Slow Injection Duration (7 to 8 Seconds; n = 10)

PK Parameters	Fast Injection (within 3 Seconds)	Slow Injection (7 to 8 Seconds)
C_{max} (ng/mL)	29 (13.8)[a]	29.6 (13.7)[a]
C_{28} (ng/mL)	16.3 (9.17)[b]	16.8 (8.65)[b]
t_{max} (day)[c]	55.78 (35.00 - 56.05)[a]	55.89 (41.82 - 56.04)[a]
AUC_{0-28} (ng·day/mL)	246 (145)[b]	249 (173)[b]
AUC_t (ng·day/mL)	924 (446)[a]	881 (414)[a]
AUC_∞ (ng·day/mL)	ND[d]	ND[d]
$t_{1/2}$ (day)	ND[d]	ND[d]

A summary of the exploratory analysis of the geometric mean ratio (deltoid versus gluteal administration) and 90% CI of the PK parameters of aripiprazole and dehydroaripiprazole following single-dose administration of 420 mg aripiprazole 1M LAI RTU is presented in Table 31.

Table 31: Geometric Mean Ratios (Fast Injection/Slow Injection) and 90% Confidence Intervals for Aripiprazole and Dehydroaripiprazole Pharmacokinetic Parameters Following Single-Dose Administration of 420 mg Aripiprazole 1M LAI RTU in the Gluteal Muscle of Subjects with Schizophrenia or Bipolar Disorder a Fast Injection Duration (within 3 Seconds; n = 10) or at a Slow Injection Duration (7 to 8 Seconds; n = 10)

Analyte	PK Parameter	GMR (Fast Injection/ Slow Injection)	90% CI	Within Subject CV%	P-value
Aripiprazole	C_{max}[a]	1.259	0.794 - 1.997	60.69	0.1976
	C_{28}[b]	1.190	0.670 - 2.114	72.78	0.3007
	AUC_{0-28}[b]	1.343	0.729 - 2.474	78.59	0.2046
	AUC_∞[c]	1.218	0.181 - 8.184	25.01	0.3155
Dehydro-Aripiprazole	C_{max}[a]	0.961	0.627 - 1.473	55.63	0.5637
	C_{28}[b]	0.934	0.582 - 1.500	57.94	0.5982
	AUC_{0-28}[b]	1.041	0.592 - 1.830	71.26	0.4510
	AUC_∞	ND	ND	ND	ND

Safety

Brief Summary of Adverse Events

Overall, 12 of 24 (50.0%) subjects experienced a total of 22 AEs during Part A (Single Dose), 15 of 28 (53.6%) subjects experienced a total of 30 AEs during Part A (Multiple Dose), and 10 of 20 (50.0%) subjects experienced a total of 12 AEs during Part B of the trial.

In Part A (Single Dose), of the 24 subjects who received a single dose of IMP, 11 subjects (45.8%) experienced TEAEs. The incidences of TEAEs were 5/12 (41.7%) subjects in the deltoid group and 6/12 (50.0%) subjects in the gluteal group. The TEAEs were mild or moderate in severity and there were no severe TEAEs. One serious adverse event (SAE) of arthritis infective occurred in 1/12 subjects (8.3%) in the deltoid group and 1 SAE of toxicity to various agents occurred in 1/12 subjects (8.3%) in the gluteal group. Other SAEs occurred during the screening phase and were not considered TEAEs.

In Part A (Multiple Dose), of the 28 subjects who received at least 1 dose of IMP, 15 subjects (53.6%) experienced TEAEs. The incidences of TEAEs were 8/14 (57.1%) subjects in the deltoid group and 7/14

(50.0%) subjects in the gluteal group. The TEAEs were mild or moderate in severity and there were no severe TEAEs or SAEs.

In Part B, of the 20 subjects who received a single dose of IMP, 10 subjects (50.0%) experienced TEAEs. The incidences of TEAEs were 5/10 (50.0%) subjects in both the deltoid and gluteal groups. The TEAEs were mild or moderate in severity and there were no severe TEAEs or SAEs.
No deaths occurred during this trial and no subjects were discontinued from IMP due to AEs. There were no notable differences for the incidence of TEAEs between the deltoid and gluteal sites or between injection durations.

Display of Adverse Events

Treatment-emergent Adverse Events
In Part A (Single Dose), the incidence of TEAEs was 45.8% (11/24 subjects), including 41.7% (5/12 subjects) in the deltoid group and 50.0% (6/12 subjects) in the gluteal group. Treatment-emergent AEs that occurred at an incidence of ≥ 2 subjects were akathisia (2/24 subjects [8.3%]) including 1/12 subjects (8.3%) in both the deltoid and gluteal groups. The incidences of mild TEAEs were 37.5% (9/24 subjects), including 25.0% (3/12 subjects) in the deltoid group and 50.0% (6/12 subjects) in the gluteal group. The incidences of moderate TEAEs were 12.5% (3/24 subjects), including 16.7% (2/12 subjects) in the deltoid group and 8.3% (1/12 subjects) in the gluteal group.
No severe TEAEs were reported.
In Part A (Multiple Dose), the incidence of TEAEs was 53.6% (15/28 subjects), including 57.1% (8/14 subjects) in the deltoid group and 50.0% (7/14 subjects) in the gluteal group.
Treatment-emergent AEs that occurred at an incidence of ≥ 2 subjects were arthralgia (2/28 subjects [7.1%], including 2/14 subjects [14.3%] in the deltoid group and 0/14 subjects [0.0%] in the gluteal group), pain in extremity (2/28 subjects [7.1%], including 2/14 subjects [14.3%] in the deltoid group and 0/14 subjects [0.0%] in the gluteal group), akathisia (3/28 subjects [10.7%], including 2/14 subjects [14.3%] in the deltoid group and 1/14 subjects [7.1%] in the gluteal group), and headache (2/28 subjects [7.1%], including 0/14 subjects [0.0%] in the deltoid group and 2/14 subjects [14.3%] in the gluteal group). The incidences of mild TEAEs were 50.0% (14/28 subjects), including 57.1% (8/14 subjects) in the deltoid group and 42.9% (6/14 subjects) in the gluteal group. The incidences of moderate TEAEs were 14.3% (4/28 subjects [2/14 subjects in each group, deltoid and gluteal]). No severe TEAEs were reported.
In Part B, the incidence of TEAEs was 50.0% (10/20 subjects), including 50.0% (5/10 subjects) in the deltoid group and 50.0% (5/10 subjects) in the gluteal group. Treatment emergent AEs that occurred at an incidence of ≥ 2 subjects were upper respiratory tract infection (2/20 subjects [10.0%]) including 1/10 subjects (10.0%) in both the deltoid and gluteal groups. The incidences of mild TEAEs were 40.0% (8/20 subjects [4/10 subjects in each group, deltoid and gluteal]). The incidences of moderate TEAEs were 10.0% (2/20 subjects [1/10 subjects in each group, deltoid and gluteal]). No severe TEAEs were reported.

Treatment-emergent Adverse Events Related to the Investigational Medicinal Product

In Part A (Single Dose), potentially IMP-related TEAEs were reported in 5/24 subjects (20.8%), including 3/12 subjects (25.0%) in the deltoid group and 2/12 subjects (16.7%) in the gluteal group. Treatment-emergent AEs that occurred at an incidence of ≥ 2 subjects were akathisia (2/24 subjects [8.3%]) including 1/12 subjects (8.3%) in both the deltoid and gluteal groups.
In Part A (Multiple Dose), potentially IMP-related TEAEs were reported in 6/28 subjects (21.4%), including 3/14 subjects (21.4%) in both the deltoid and gluteal groups.
Treatment-emergent AEs that occurred at an incidence of ≥ 2 subjects were akathisia (3/28 subjects [10.7%]), including 2/14 subjects (14.3%) in the deltoid group and 1/14 subjects (7.1%) in the gluteal group.
In Part B, potentially IMP-related TEAEs were reported in 5/20 subjects (25.0%), including 2/10 subjects (20.0%) in the deltoid group and 3/10 subjects (30.0%) in the gluteal group. There were no potentially IMP related TEAEs that occurred at an incidence of ≥ 2 subjects.

3.3.2.2. Clinical studies in special populations

N/A

3.3.2.3. In vitro biomarker test for patient selection for efficacy

N/A

4.1.1.1. Analysis performed across trials (pooled analyses and meta-analysis)

Population Pharmacokinetic Analysis of Aripiprazole Following Oral Administration and Intra-Muscular Injection in the Gluteal or Deltoid Muscle in Adult Subjects

Protocol No. 31-18-205

Objectives:

The overall objective of this analysis was to include the deltoid site of injection by expanding an existing population Pharmacokinetic (PK) model that was previously used to describe aripiprazole PK following oral administration and intra-muscular (IM) depot injection (mostly in the gluteus maximus). This model, later referred to as the combined model, was then used for PK simulations to examine several initiation regimens of the aripiprazole IM depot formulation.

Population PK modeling:
☐ Expand the existing model to develop a combined model that includes the deltoid IM injection
☐ Evaluate the adequacy of the combined model with diagnostic plots and visual predictive checks (VPCs)

Model Simulation:
☐ Apply the model to simulate PK profiles of aripiprazole following several initiation regimens of oral and IM depot formulations of aripiprazole

Data/Number of Subjects:

PK data included in this analysis consists of the analysis data from a previously submitted population PK analysis report for gluteal and oral administration (Report 31-11-287) and aripiprazole concentrations following deltoid or gluteal injections from two additional trials (Trials 31-11-290 and 31-12-298). PK data from Report 31-11-287 contained 6,153 aripiprazole concentrations from 663 subjects who received aripiprazole oral administration and/ or IM injection in gluteus maximus (95% of IM data), triceps (2% of IM data), and thigh (4% of IM data); PK data from Trials 31-11-290 and 31-12-298 contained 2,061 aripiprazole concentrations from 154 subjects who received either gluteal or deltoid IM injection of aripiprazole. The final combined analysis data included a total of 8,214 aripiprazole concentrations (16% oral, 65% gluteal, 16% deltoid, and 3% triceps or thigh administration) from 817 subjects.
Below is a brief description of the data sources:
Report 31-11-287: Population PK analysis to describe aripiprazole PK following oral and IM administration (not including deltoid injection) to healthy adult subjects or adults with schizophrenia and simulate aripiprazole exposure following various dosing regimens to inform dosing recommendation. PK data for this analysis were collected from 5 trials (Trials 31-98-206, 31-98-207, CN138020, 31-05-244, and 31-07-246).
Trial 31-11-290: Phase 1, open-label, randomized, parallel-arm, bioavailability trial of aripiprazole IM Depot administered in the deltoid or gluteal muscle in adult subjects with schizophrenia.
Trial 31-12-298: Phase 1b, open-label, multiple-dose, safety and tolerability study of aripiprazole IM Depot administered in the deltoid muscle in adult subjects with schizophrenia.

The population consisted of 65% males, the age ranged from 18 to 62 years with a median at 41 years, while the body weight ranged from 40.8 to 175 kg with a median at 79.3 kg. Based on the standard weight categories associated with the body mass index (BMI), approximately 2%, 35%, 32%, and 31% of the population were of underweight, normal, overweight and obese, respectively. There were 5 (<1%) and 46 (6%) subjects classified as ultra-rapid and poor Cytochrome P450 2D6 (CYP2D6) metabolizers respectively; 10 (1%) subjects did not have information on metabolizing status; the remaining 756 (92%) subjects were either extensive or intermediate metabolizers. Of the 8,214 aripiprazole concentrations, 627 (7.5%) were collected in presence of strong inhibitors of CYP2D6 or CYP3A4.

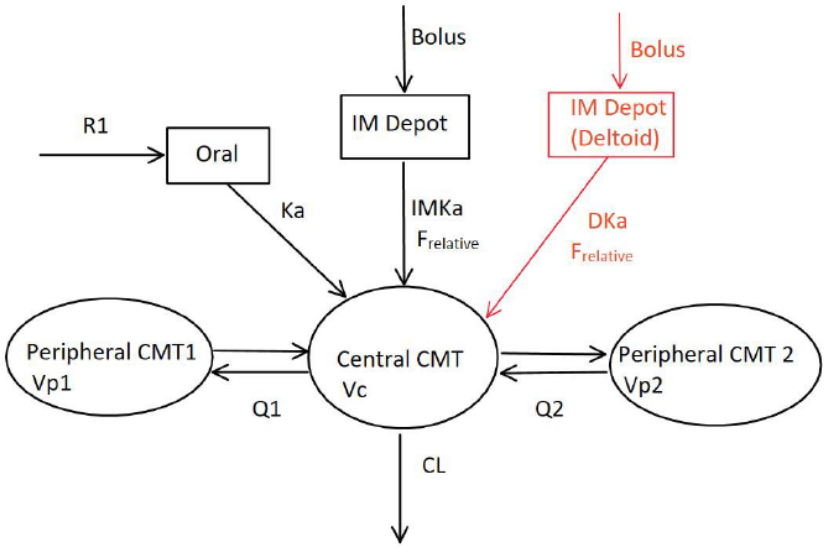
Methods of Analysis:

Pharmacokinetic Modeling: The general procedure for the expansion of the population PK model of aripiprazole following oral and IM administration is outlined below:
☐ Start with the population PK model described in Report 31-11-287; which is a linear 3-compartment model with sigmoid (sequential zero and first order) absorption for oral administration and first-order absorption for IM injection of aripiprazole
☐ Add a deltoid depot compartment to the original model and determine absorption parameters for deltoid IM injection with the additional data from Trials 31-11-290, and 31-12-298; population means of the other PK parameters of this combined model were fixed to the final estimates in the original model
☐ Evaluate the final combined oral and IM model which best
described all PK data
☐ Perform VPCs on the final combined model
Model Simulation: The general procedure for the simulation using the final combined population PK model is outlined below:
☐ Define dosing scenarios for simulations by considering different starting doses as well as reduced number of days for oral administration after initial IM dose
☐ For simulations, randomly generate individual PK parameters for each subject in the analysis dataset from the final combined population PK model
☐ Perform simulations with the subjects in the analysis dataset with model generated individual PK parameters; compute summary statistics for the PK profiles simulated and present graphically
Population PK modeling and simulation was performed using the nonlinear mixed effects modeling program NONMEM (version 7.4.3) in RStudio (version 1.0.153) through the R package *metrumrg*. The firstorder conditional estimation method with interaction was used for all stages of the model development process. Post-modeling analysis was conducted using R Version 3.3.3 or above.

Results

Population Pharmacokinetics Modeling:

A linear 3-compartment model with sigmoid absorption for oral administration and first-order absorption for IM injection, with separate absorption rate constants (DKa and IMKa) for deltoid and other IM injections (mainly gluteal) could adequately describe aripiprazole PK following oral, gluteal IM, and deltoid IM administrations. A schematic drawing of the model structure is shown below:



Note: Update of the original model from Report 31-11-287, which represents the deltoid IM injection, is shown in orange color.

Model parameters were estimated as described below:

☐ Population PK parameters: Deltoid IM first-order absorption rate constant (DKa) was estimated, all other population PK parameters were fixed to the value estimated in the original model

☐ Inter-individual variability (IIV): IIV for the oral first-order absorption rate constant (Ka) was fixed to the value estimated in the original model, IIV for the apparent clearance (CL), apparent central volume of distribution (Vc), and the gluteal and deltoid IM first-order absorption rate constants (IMKa and DKa) were estimated. It was assumed that covariate effect remains the same as the original model in Report 31-11-287, and that the gender and BMI effect on IMKa, estimated from data following IM injection in gluteus maximus mainly, is also present for the deltoid injection. No additional covariate analysis was performed.

Parameter definition and values are shown in the table below.

Table 32

Parameter Values of the Combined Model for Aripiprazole Following Oral Administration and IM Injection			
Parameter	**Unit**	**Definition**	**Estimate [RSE%]**
Fixed Effects			
R1	mg/hr	Rate of dose into oral absorption compartment	9.33 Fixed
Ka	1/hr	Oral first-order absorption rate constant	0.540 Fixed
CL	L/hr	Apparent clearance for subjects who are not poor CYP2D6 metabolizers	3.71 Fixed
CLpm	L/hr	Apparent clearance for subjects who are poor CYP2D6 metabolizers	1.88 Fixed
CL_INH2D6	-	Proportional change in CL in presence of a strong CYP2D6 inhibitor	-0.511 Fixed
CL_INH3A4	-	Proportional change in CL in presence of a strong CYP3A4 inhibitor	-0.237 Fixed
Vc	L	Apparent central volume of distribution	93.4 Fixed
Q1	L/hr	Inter-compartmental clearance 1	0.591 Fixed
Vp1	L	Volume of distribution in Peripheral compartment 1	118 Fixed
Q2	L/hr	Inter-compartmental clearance 2	28.8 Fixed
Vp2	L	Volume of distribution in Peripheral compartment 2	134 Fixed
IMKa	1/hr	Gluteal IM first-order absorption rate constant	0.000904 Fixed
DKa	1/hr	Deltoid IM first-order absorption rate constant	0.000776 [6.2%]
IM Ka_BMI	-	Effect of BMI on IMKa and DKa: power for (BMI/28)	-0.975 Fixed
IM Ka_male	-	Proportional shift of IM Ka for males	0.346 Fixed
$F_{relative}$	-	Relative bioavailability for IM Depot	1.48 Fixed
Random Effect: Inter-Individual Variability (CV %)			
Ka	-	IIV on oral Ka	65.9 % Fixed
CL or CLpm	-	IIV on Apparent clearance for all subjects	39.1% [6.1%]
Vc	-	IIV on Vc	148% [2.5%]
IMKa	-	IIV on gluteal IM Ka	60.0% [7.7%]
DKa		IIV on deltoid IM Ka	48.9% [24.4%]
Residual Variability (CV%)			
Phase 1	-	Proportional residual error for Phase 1 data	0.0693 (26.3%)
Phase 3	-	Proportional residual error for Phase 3 data	0.0600 (24.5%)

Model Simulations:
For all simulation scenarios, 3 aripiprazole concentration levels were included as target exposure references:
1) the median of the simulated steady-state minimum concentration (Cmin,ss) values following once daily oral administration of 10 mg aripiprazole (94.0 ng/mL),
2) the 75th percentile of the simulated steady-state maximum concentration values (Cmax,ss) following once daily oral administration of 30 mg aripiprazole (534 ng/mL),
3) the 95th percentile of the simulated Cmax,ss following once daily oral administration of 30 mg aripiprazole (741 ng/mL).
In addition, the median PK profile of aripiprazole following the existing IM Depot initiation regimen (14 days of oral aripiprazole 10 to 20 mg along with 1 injection of IM Depot 400 mg on Day 1) was also used as reference for the simulations of other initiation and dosing regimens.

The model was applied to simulate following scenarios:

☐ alternative initiation regimens at different dose levels
☐ Contribution from Oral and IM Administration
☐ subjects categorized as poor or extensive CYP2D6 metabolizers
☐ subjects with prior oral aripiprazole stabilization
☐ re-initiation if a maintenance IM depot dose is missed

Simulation Results
Alternative Initiation Regimens at Different Dose Strength

Alternative initiation regimens with a single oral dose and two IM Depot dose administered on Day 1 at different dose strength were simulated. Simulated PK profile following an initiation regimen with a single dose of 20 mg aripiprazole oral tablet + 2x400 mg IM Depot formulation and simulated PK profiles following the existing initiation regimen (10-20 mg oral tablet x 14 Days + 400 mg IM Depot formulation) are compared and presented in Figure 23 when both of the 2x400 mg dose were administered to the same muscle (gluteal or deltoid) and Figure 24 when each of the two 400 mg dose was administered to gluteal (400 mg) and deltoid muscle (400 mg).

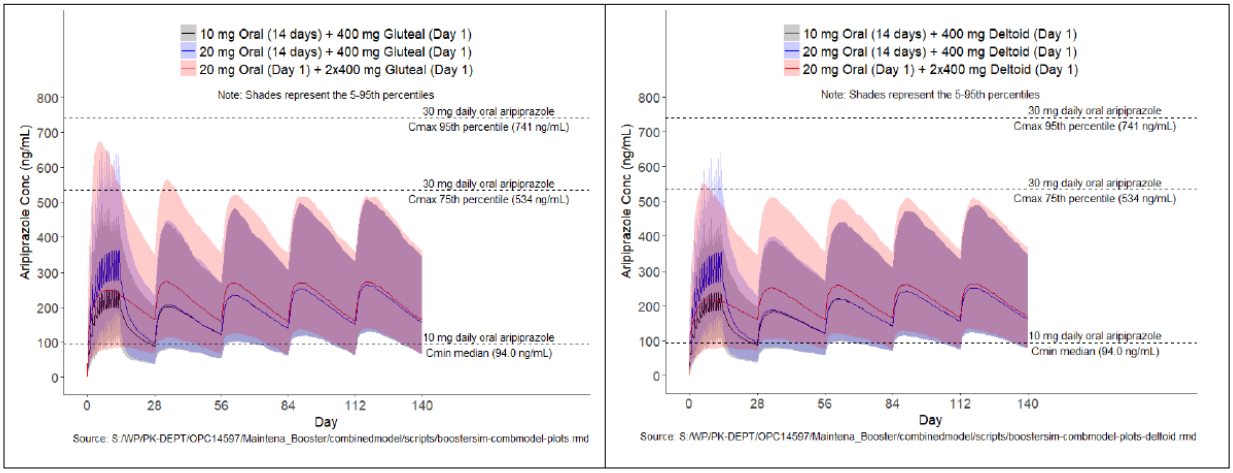


Figure 23 Simulated Median (5-95th Percentile) Aripiprazole PK Following 20 mg Oral (Day 1) + 2x400 mg IM Depot (Day 1) Compared to Simulated Median (5-95th Percentile) Aripiprazole PK Following the Existing Initiation Regimen with the IM Depot Dose Injected to Gluteal (Left) or Deltoid (Right) Muscles, Followed by 400 mg IM Depot Dose Every 28 Days

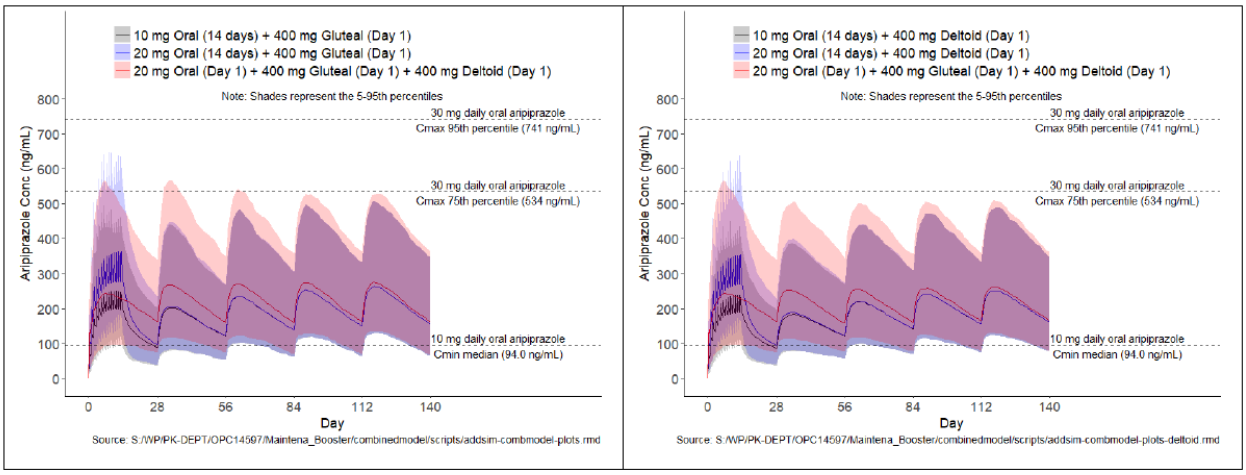


Figure 24 Simulated Median (5-95th Percentile) Aripiprazole PK Following 20 mg Oral (Day 1) + 400 mg IM Depot Gluteal (Day 1) + 400 mg IM Depot Deltoid (Day 1) Compared to Simulated Median (5-95th Percentile) Aripiprazole PK Following the Existing Initiation

Regimen with the IM Depot Dose Injected to Gluteal (Left) or Deltoid (Right) Muscles, Followed by 400 mg IM Depot Dose Every 28 Days.

Conclusions

- A linear 3-compartment model with sigmoid absorption for oral administration and first-order absorption for IM injection, with separate absorption rate constants for deltoid and gluteal can adequately describe and predict aripiprazole PK following oral administration and IM injection in deltoid and gluteal muscles.
- Application of the model provided simulations for alternative dosing scenarios in comparison with the current treatment initiation of the aripiprazole IM depot formulation.

Population Pharmacokinetic Analysis of Aripiprazole Administered as a Novel Long-Acting Injectable Formulation in Adult Subjects

Protocol No. 31-21-201

Objectives:
The objectives of this analysis were to:
☐ Develop a population PK model to characterize the pharmacokinetics of aripiprazole when administered as a novel ready-to-use (RTU) long-acting injectable (LAI) formulation (referred to as RTU LAI throughout).
☐ Extend a prior population PK model, described in Report 31-18-205 (itself an extension of the model from Report 31-11-287), so as to obtain a combined model for the RTU LAI formulation in addition to the previously studied intramuscular (IM) depot and oral formulations of aripiprazole.
☐ Explore the effects of potential extrinsic and intrinsic covariates on the absorption characteristics of aripiprazole following RTU LAI administration.

Design:
The final population PK analysis included a total of 1,191 subjects from 10 trials, of which 240 (20.2%) received the novel RTU LAI formulation. There were 8,899 aripiprazole concentrations included in the analysis. A brief description of the data sources follows:
Trial 031-201-00104: Phase 1, open-label, single ascending dose, parallel arm trial to determine the PK, safety, and tolerability of aripiprazole RTU LAI 780 mg and 1200 mg administered in the gluteal muscle in adult subjects with schizophrenia.
Trial 031-201-00181: Phase 1b, open-label, multiple-dose, randomized, parallel arm, safety, tolerability, and PK pivotal trial of aripiprazole 2M RTU LAI 960 mg and IM depot 400 mg administered in the gluteal muscle in adult subjects with schizophrenia or bipolar I disorder.
Trial 031-201-00279: Phase 1, open-label, single- and multiple-dose, PK, safety, and tolerability trial of aripiprazole RTU LAI 420 mg administered in the deltoid or gluteal muscle in adult subjects with schizophrenia or bipolar I disorder (note that the deltoid injection site was studied in Trial 031-201-00279, but only the gluteal injection site is intended to be used for RTU LAI).
Report 31-18-205: Population PK analysis of aripiprazole following oral administration and IM depot injection in the gluteal or deltoid muscle in adult subjects. PK data for this analysis were collected from 7 trials: Trials 31-98-206, 31-98-207, CN138020, 31-05-244, 31-07-246, 31-11-290 and 31-12-298. (Note that the analysis in Report 31-18-205 was itself an extension of the model from Report 31-11-287, which was the original population PK modeling work for the IM depot formulation of aripiprazole, but which did not include the deltoid injection site.)
The 817 subjects included in Report 31-18-205 consisted of 65% males, ranging in age from 18 to 62 years (median 41 years), and body weight from 40.8 to 175 kg (median 79.3 kg). There were 5 (< 1%) and 46 (6%) subjects classified as ultrarapid and poor Cytochrome P450 2D6 (CYP2D6) metabolizers respectively; 10 (1%) subjects did not have information on metabolizing status; the remaining 756 (92%) subjects were either extensive or intermediate metabolizers The 374 subjects from the additional 3 trials consisted of 65.5% males, ranging in age from 18 to 64 years (median 50 years). There were 15 (4%) classified as poor metabolizers (PM) of CYP2D6. The gluteal injection site was used exclusively in Trials 031-201-00104 and 031-201-00181, and predominantly (63.9% of subjects) in Trial 031-201-00279.

Only subjects who received at least one dose of aripiprazole in oral tablet, IM depot or RTU LAI formulation and had at least 1 evaluable aripiprazole concentration were included in the analysis.

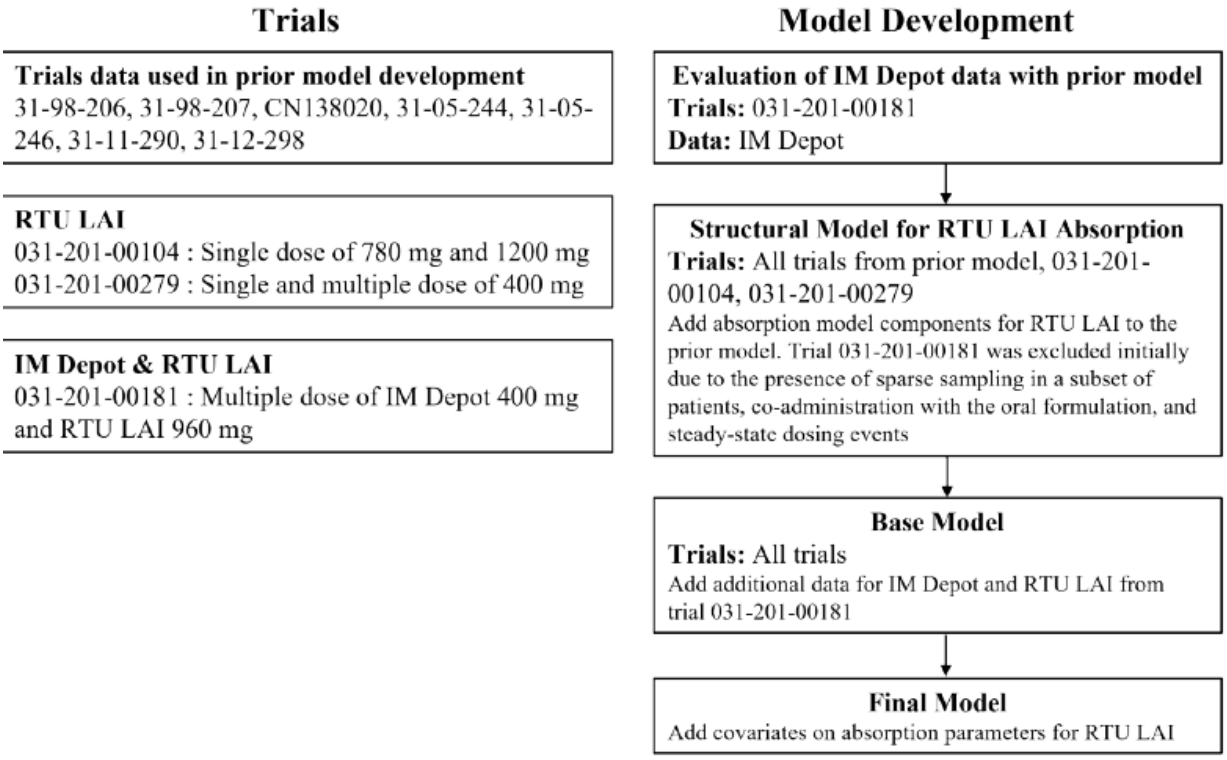


Figure 25 Flow Chart of Major Model Development Steps

Methods of analysis

The *prior model* used as a starting point for this analysis was described in Report 31-18-205 (itself an extension of the model from Report 31-11-287). It consisted of a 3-compartment model with linear elimination, sigmoid (sequential zero-order followed by first-order) absorption for oral administration, and first order absorption for the IM depot formulation. Data for the RTU LAI formulation was added and the structural model was adapted to account for this new formulation, specifically its absorption. In the *prior model*, the terminal phase was elimination driven for the oral route and absorption-driven for the IM depot formulation (flipflop kinetics). Covariate effects included CYP2D6 metabolizer status on apparent clearance (CL/F), concomitant CYP2D6 and CYP3A4 strong inhibitors on CL/F, as well as injection site, sex and body mass index (BMI) on the first-order absorption rate constant (Ka) for the IM depot formulation. All fixed-effects parameters from the *prior model* were kept fixed throughout the model development. The random effects parameters for Ka of the oral and IM depot routes (both gluteal and deltoid injection sites) were also kept fixed, but those for apparent clearance and central volume of distribution were re-estimated, as were the parameters describing residual variability.
A suitable structural model for describing the RTU LAI formulation's absorption was determined using standard approaches (minimizing objective function value, goodness-of-fit and convergence diagnostics). Potential covariate effects on the absorption parameters of the RTU LAI formulation were assessed graphically and formally tested using a modified stepwise approach. Covariates evaluated included standard demographic variables (age, sex, BMI) and factors known to potentially affect absorption (injection site, injection volume). The final model's predictive performance was assessed by traditional prediction-corrected visual predictive checks (pcVPC) and by nonparametric visual predictive checks (npVPC).
Simulations of typical profiles were performed to visualize the impact of covariate effects on the concentration-time profile and steady-state exposure metrics of aripiprazole following multiple administrations of 2M RTU LAI 960 mg.

The population PK model was developed using non-linear mixed effects modelling software (NONMEM) (version 7.4.2; Icon Development Solutions, Ellicott City, MD, USA). Estimation was performed by first order conditional estimation with interaction (FOCEI) or, if convergence could not be achieved satisfactorily, by stochastic approximation expectation-maximization (SAEM) followed by importance sampling (IMP) for evaluating the minimum value of the objective function (MVOF). Nonparametric bootstrap was used to quantify parameter uncertainty. R (version 4.0.5; R Foundation for Statistical Computing, Vienna Austria) and RStudio (version 1.2.5042; RStudio, Inc.), were used for data preparation, graphical analysis, model diagnostics, and statistical summaries. Perlspeaks- NONMEM (version 4.9.3) was used for running models and model evaluation.

Results

Exploratory data analysis showed that the PK of aripiprazole administered by RTU LAI formulation exhibits a characteristic profile with 2 distinct peaks. After repeated dosing (ie, starting at the Day 169 visit in Trial 031-201-00181), the first peak occurs approximately 5 days post dose and the second peak occurs approximately 28 days post dose. The double peak was modeled by parallel zero order and first-order absorption processes, with a time lag on the first order process.

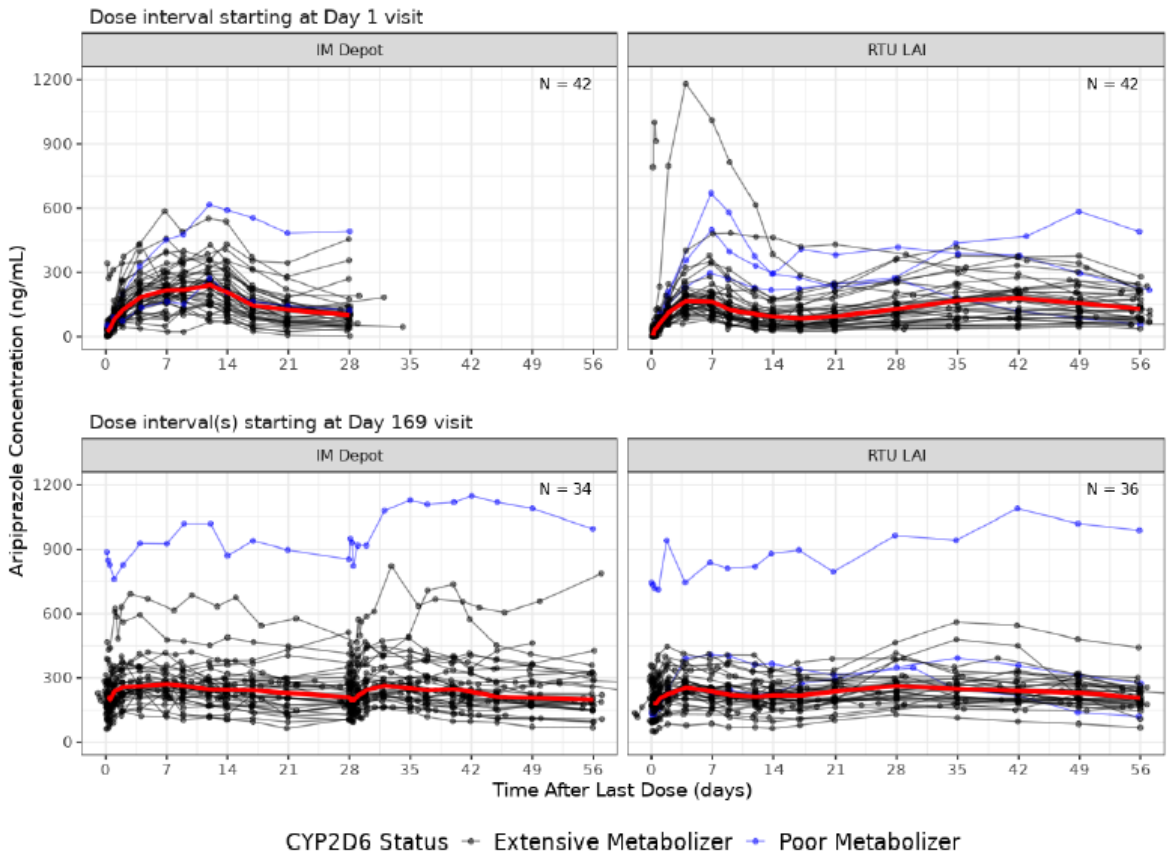
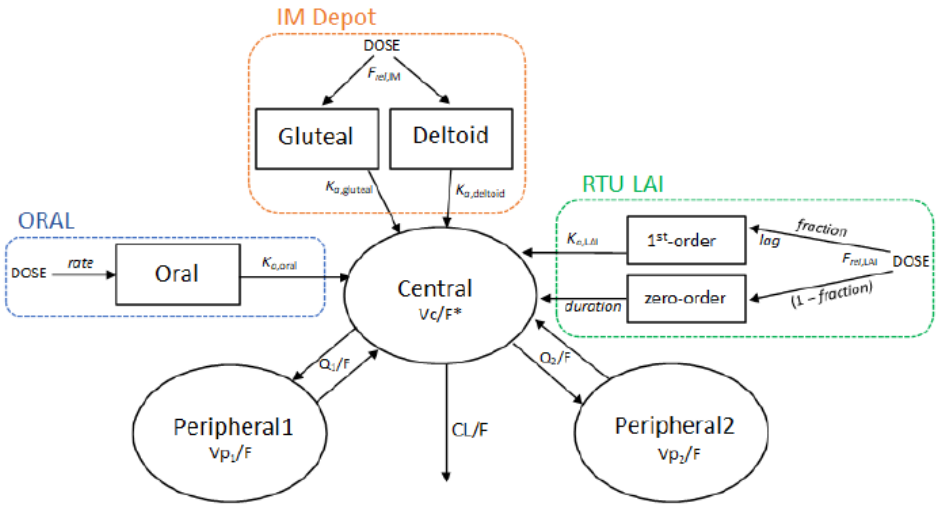


Figure 26 Spaghetti Plots of Aripiprazole Concentration Versus Time After Last Dose Following 2M RTU LAI 960 mg or Monthly IM Depot 400 mg for Robust Sampling Group in Trial 031 201 00181 by CYP2D6 Status (Blue and Black) Overlaid with Median (Red)

The final population PK model is a 3-compartment model with linear elimination and different absorption models for each of the three formulations. A schematic drawing of the model structure is shown below:



All disposition parameters (apparent clearances and volumes) are shared between formulations and were fixed as in the *prior model* of Report 31-18-205 with the exception of apparent central volume (VC) of distribution. The VC of distribution had a different numerical value for the RTU LAI formulation, which can be attributed to the fact that the terminal half-life is absorption driven. Consistent with the IM depot formulation, sex was identified as a significant covariate on the absorption of the RTU LAI formulation. A diagonal matrix was used for interindividual variability. Estimation was performed with the SAEM+IMP method. Predictive performance of the model based on pcVPC and npVPC was adequate.
Parameter definitions and estimates are shown in the table below.

Table 33

PK Parameters for the Final Model				
Parameter	**Unit**	**Definition**	**Estimate**	**RSE%**
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
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
FRAC1	-	Fraction of first-order absorption for RTU LAI on transformed scale	3.82 (79.3%)	6.3
SEX_FRAC1	-	Proportional shift of FRAC1 for males	-0.556	7.8
SEX_KARTU	-	Proportional shift of KARTU for males	0.907	0.1
ALAG1	h	Lag-time of first-order absorption for RTU LAI	419	0.7
KARTU	1/h	First-order absorption rate constant for RTU LAI	0.00127	0.03

PK Parameters for the Final Model				
Parameter	**Unit**	**Definition**	**Estimate**	**RSE%**
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
Inter-individual variability: variance (CV%)				
CL	-	IIV on CL_EM and CL_PM	0.155 (39.3)	4.7
VC	-	IIV on VC and VCRTU	1.869 (136.7)	6.2
KAPO	-	IIV on KAPO	0.434 (65.9)	-
KAGLU	-	IIV on KAGLU	0.359 (59.9)	-
KADEL	-	IIV on KADEL	0.237 (48.7)	-
DUR0	-	IIV on DUR0	1.014 (100.7)	8.8
FRAC1	-	IIV on FRAC1	0.634 (79.7)	13.2
KARTU	-	IIV on KARTU	0.307 (55.4)	13.4
Residual variability: variance (CV% or SD)				
PRO	-	Proportional error for Oral and IM Depot	0.0660 (25.7)	0.8
PRO_PH3	-	Proportional error for Oral and IM Depot in Phase 3 study (Study 31-07-246)	0.0772 (27.8)	1.8
PRO_RTU	-	Proportional error for RTU LAI	0.0650 (25.5)	0.8
ADD_RTU	-	Additive error for RTU LAI	1.81 (1.35)	9.6

CI = confidence interval; EM = Extensive metabolizers; IIV = inter-individual variability; SD = standard deviation.
Note: '-' indicates not applicable. Parameters with no RSE% are those that were held fixed during estimation.

According to the final population PK model, for typical subjects (ie, at the typical values of the parameters), the first peak in concentration occurs at 6.75 day (162.1 hours) postdose for the RTU LAI formulation. The fractions absorbed by the first-order and zero order processes are 79.3% (= 100% × 3.824 × (1 + 3.824)—1) and 20.7% respectively in females; these fractions change to 62.7% and 37.3% respectively in males. The first order absorption starts after a lag of 17.5 days (419 hours). In females, the absorption rate constant for the first-order process is 0.00127 per hour, corresponding to an absorption half-life of 22.7 days (545 hours); the absorption rate constant and absorption half-life in males are 0.00242 per hour and 11.9 days respectively. Thus, following the first dose the second peak occurs at 41- and 32-days post dose for typical female and male subjects respectively, and at steady state the second peak occurs at 33- and 28-days post dose for typical female and male subjects respectively (note: these times were derived by simulation of the typical profiles). The relative bioavailability of the RTU LAI formulation is 1.58 compared to the oral formulation, and 1.06 compared to the IM depot formulation.

Model-based Simulation to Inform Dosing Strategies for a Novel Long-Acting Injectable Formulation of Aripiprazole in Adult Subjects

Protocol No. 31-21-202

Objectives

The objectives of this analysis were to utilize a previously developed population pharmacokinetic (PK) model for aripiprazole to perform model-based simulations to explore various aspects of aripiprazole ready-to-use (RTU) long-acting injectable (LAI) dosing such as: (1) treatment initiation, (2) genetic

factors (cytochrome P450 [CYP] 2D6 poor metabolizers [PMs] vs extensive metabolizers [EMs]), (3) drug-drug interactions (concomitant use with CYP2D6 or CYP3A4 strong inhibitors), (4) steady-state, (5) dosing flexibility (early or late administration), and (6) missed/delayed dose.

Method of analysis

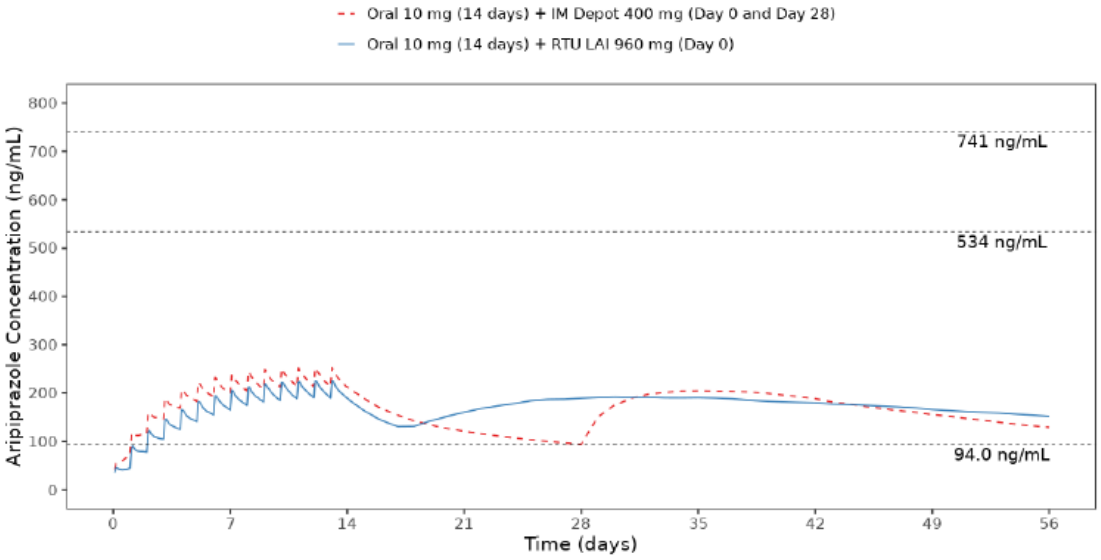
The reference regimen for aripiprazole RTU LAI is 960 mg every 8 weeks (Q8W), the regimen used in pivotal Trial 031-201-00181. Simulation scenarios were designed to study various aspects of aripiprazole RTU LAI dosing:

Treatment initiation: To evaluate the initiation of treatment with aripiprazole RTU LAI, various prior treatment scenarios were considered:
• With prior oral aripiprazole stabilization (10 mg, 20 mg, or 30 mg)
• Without prior oral aripiprazole stabilization
• Switching from aripiprazole IM depot
To reach therapeutic concentrations more rapidly (given the very slow absorption of aripiprazole RTU LAI), two treatment initiations strategies were considered:
• Fourteen (14) days of oral overlap (10 mg or 20 mg)
• Two injection start, consisting of one 960 mg dose of aripiprazole RTU LAI and one 400 mg dose of aripiprazole IM depot at separate injection sites together with a single 20 mg dose of oral aripiprazole on the first day of treatment.
Genetic factors. Evaluate lower dose for CYP2D6 PMs.
Drug-drug interactions: Evaluate lower dose with concomitant use of CYP2D6 or CYP3A4 strong inhibitors.
Steady-state: Compare the steady-state exposure levels of aripiprazole RTU LAI 960 mg Q8W and 720 mg Q8W to aripiprazole IM depot 400 mg Q4W.
Dosing flexibility: Early and late administration of Q8W dosing by 14 days.
Missed/delayed doses: Impact of imperfect adherence with the Q8W dosing interval, with doses delayed by 2, 4, 6, and 8 weeks.

Dose dumping: Administration of 960 mg aripiprazole RTU LAI as an intravenous bolus dose, which represents the most severe form of dose dumping (ie, rapid absorption of an entire aripiprazole RTU LAI dose immediately after its administration).
A simulation population of N = 1000 virtual patients was constructed.
Individual PK parameters for the virtual patients were derived from patients' covariates and random effects according to the population PK model and used to simulate individual PK profiles according to each dosing scenario. Random effects and covariates were resampled from the subjects that had the most relevant and robust information with respect to each parameter to best reflect the target patient population.
Rich PK profiles were simulated by sampling concentrations every 2 hours post dose for 24 hours following oral dosing, and every 24 hours post dose following IM Depot or RTU LAI dosing.
Simulation results were presented graphically by plotting the median over time.
The following exposure metrics were derived from the individual rich PK profiles:
Maximum concentration (Cmax).
Concentration at the end of the dosing interval (eg, C56 if the dosing interval is 56 days).
Average concentration over the dosing interval (Cavg).
Area under the concentration-time curve from time 0 to the end of the dosing interval (eg, AUC0-56 if the dosing interval is 56 days).
Summary statistics (eg, mean, standard deviation [SD], median, and key percentiles) of the exposure metrics were presented in tabular format.

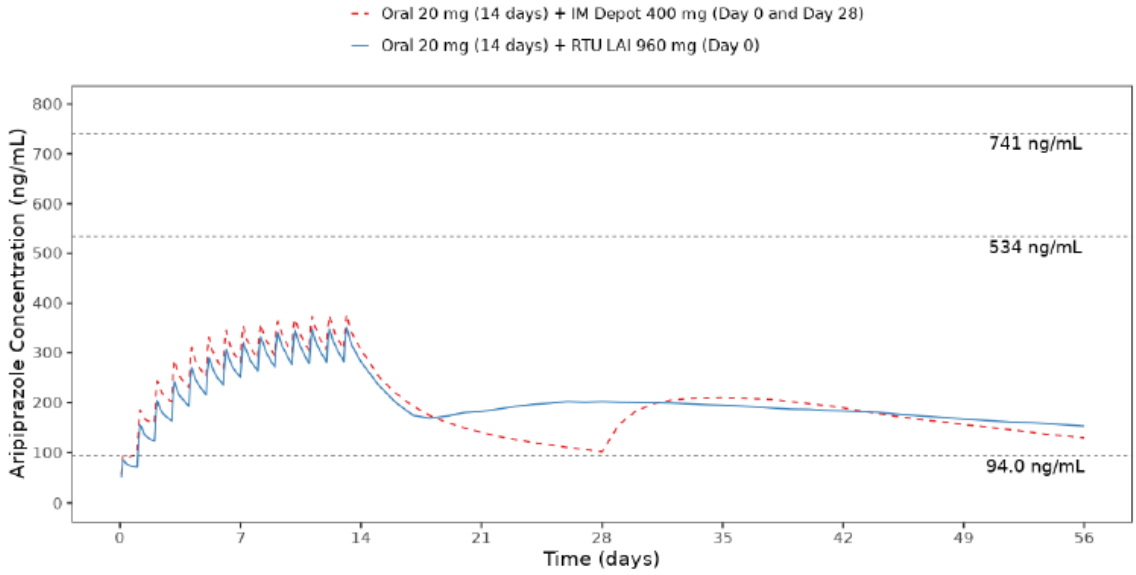
Results

Treatment initiation:
Compared to 400 mg every 4 weeks (Q4W) IM depot, a regimen of 960 mg Q8W RTU LAI resulted in comparable median plasma concentrations, with less overall variability, in all simulations scenarios, including:
In patients with or without prior oral aripiprazole stabilization (10 mg, 20 mg, or 30 mg), with overlapping 10 mg or 20 mg once daily (QD) oral aripiprazole for the first 14 days.
In patients already stabilized on 400 mg Q4W IM depot.
The two injection start resulted in a more rapid and stable treatment initiation.



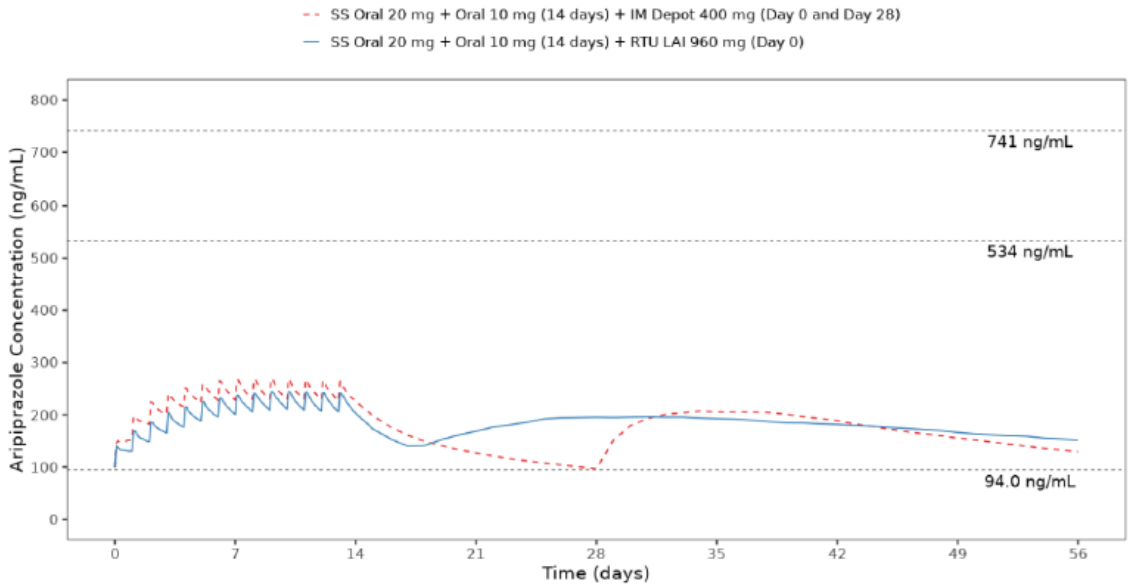
Group	Parameter	Mean	SD	5th	25th	Median	75th	95th
Oral 10 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	C56 (ng/mL)	147	80.1	62.0	90.0	129	182	283
Oral 10 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	Cmax (ng/mL)	283	123	133	198	261	343	493
Oral 10 mg (14 days) + IM Depot 400 mg (Day 0 and Day 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

Figure 27 Simulated Median Aripiprazole Concentration Time Profile Following Administration of 400 mg Aripiprazole IM Depot (Day 0 and Day 28) or 960 mg Aripiprazole RTU LAI (Day 0) with 14 Days of 10 mg Oral Aripiprazole (Day 0 to Day 13) in Subjects Without Prior Oral Aripiprazole Stabilization



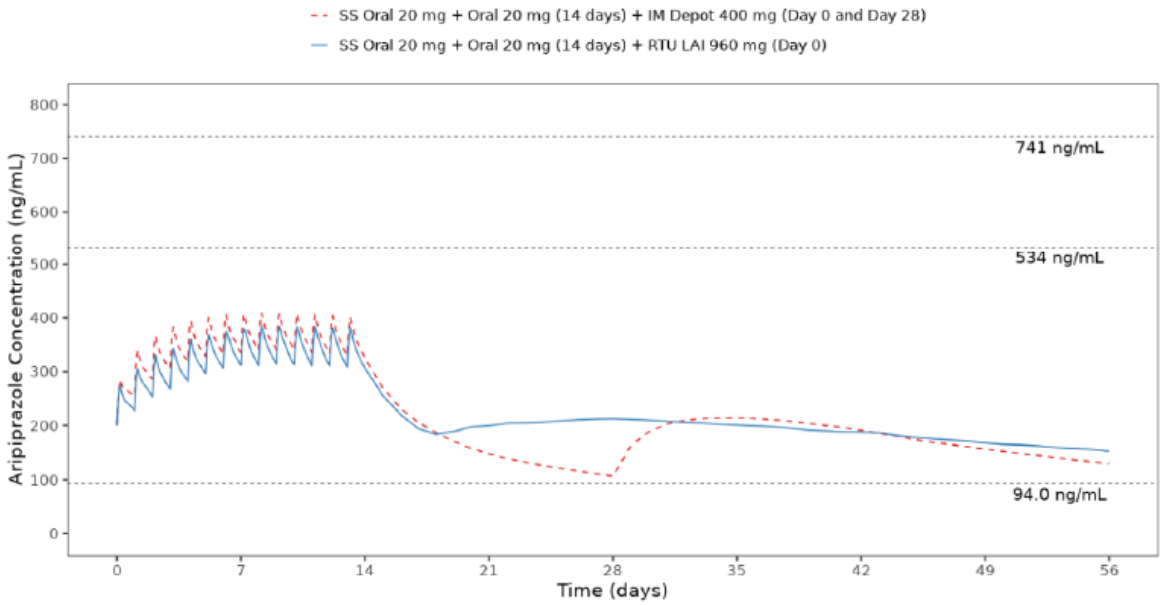
Group	Parameter	Mean	SD	5th	25th	Median	75th	95th
Oral 20 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	C56 (ng/mL)	148	82.1	62.1	90.2	129	183	285
Oral 20 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	Cmax (ng/mL)	412	157	208	301	386	501	673
Oral 20 mg (14 days) + IM Depot 400 mg (Day 0 and Day 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

Figure 28 Simulated Median Aripiprazole Concentration Time Profile Following Administration of 400 mg Aripiprazole IM Depot (Day 0 and Day 28) or 960 mg Aripiprazole RTU LAI (Day 0) with 14 Days of 20 mg Oral Aripiprazole (Day 0 to Day 13) in Subjects Without Prior Oral Aripiprazole Stabilization



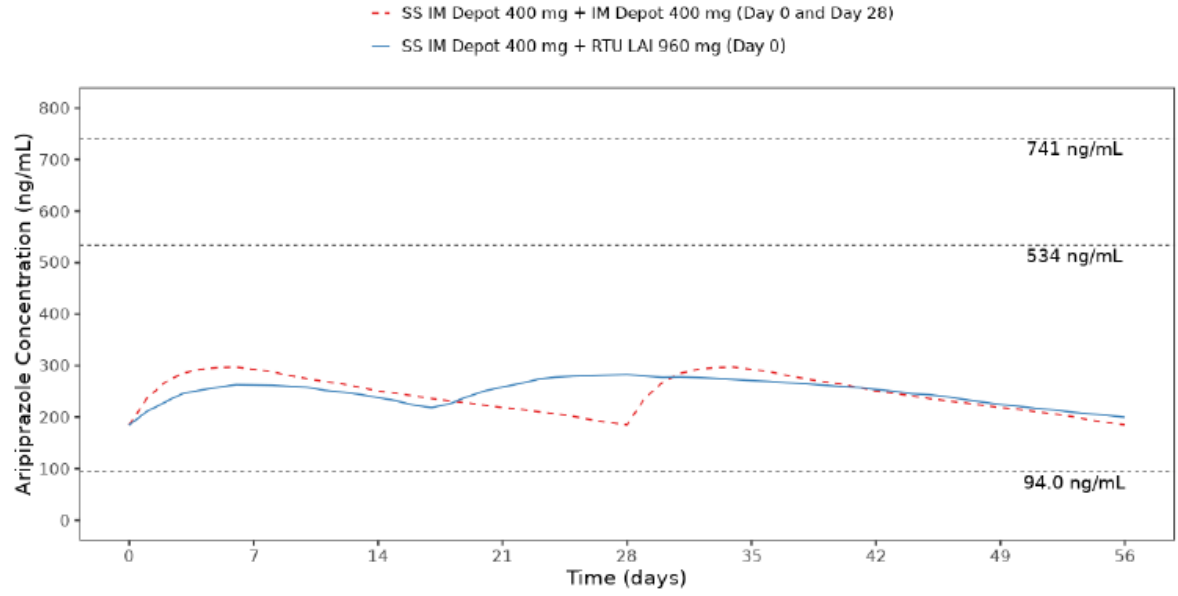
Group	Parameter	Mean	SD	5th	25th	Median	75th	95th
SS Oral 20 mg + Oral 10 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	C56 (ng/mL)	148	82.0	62.1	90.1	129	182	284
SS Oral 20 mg + Oral 10 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	Cmax (ng/mL)	304	138	141	208	277	375	532
SS Oral 20 mg + Oral 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

Figure 29 Simulated Median Aripiprazole Concentration Time Profile Following Administration of 400 mg Aripiprazole IM Depot (Day 0 and Day 28) or 960 mg Aripiprazole RTU LAI (Day 0) 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 20 mg + Oral 20 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	C56 (ng/mL)	150	86.1	62.1	90.3	130	183	289
SS Oral 20 mg + Oral 20 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	Cmax (ng/mL)	453	189	220	323	418	554	760
SS Oral 20 mg + Oral 20 mg (14 days) + IM Depot 400 mg (Day 0 and Day 28)	AUC0-56 (ng·day/mL)	13807	7106	5686	9064	12408	16831	26374
SS Oral 20 mg + Oral 20 mg (14 days) + RTU LAI 960 mg (Day 0)	C56 (ng/mL)	163	79.2	62.7	111	153	202	302
SS Oral 20 mg + Oral 20 mg (14 days) + RTU LAI 960 mg (Day 0)	Cmax (ng/mL)	459	250	213	311	408	533	824
SS Oral 20 mg + Oral 20 mg (14 days) + RTU LAI 960 mg (Day 0)	AUC0-56 (ng·day/mL)	13957	6076	6278	9797	12965	16879	24068

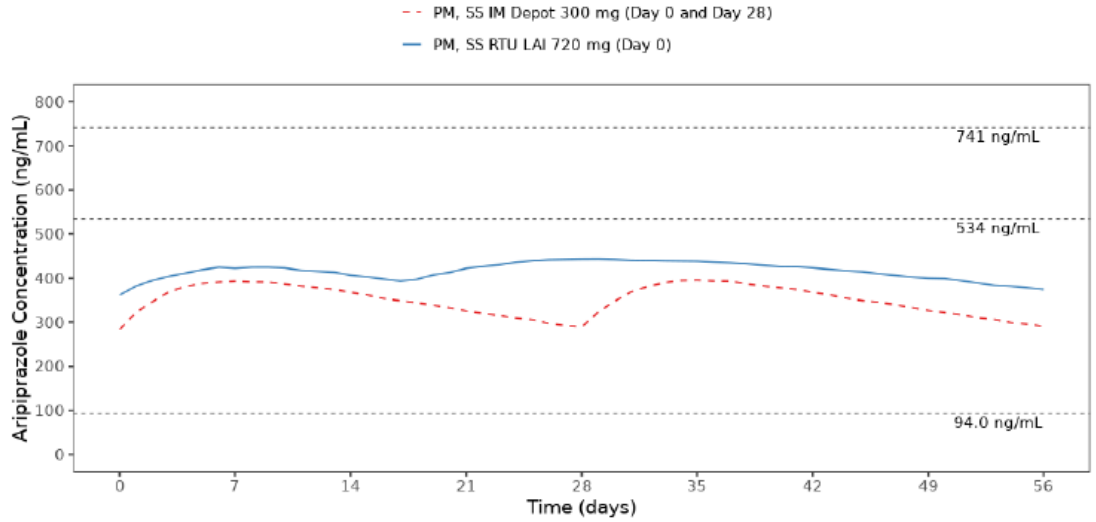
Figure 30 Simulated Median Aripiprazole Concentration Time Profile Following Administration of 400 mg Aripiprazole IM Depot (Day 0 and Day 28) or 960 mg Aripiprazole RTU LAI (Day 0) with 14 Days of 20 mg Oral Aripiprazole (Day 0 to Day 13) in Subjects Already Stabilized on 20 mg Oral Aripiprazole



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

Figure 31 Simulated Median Aripiprazole Concentration Time Profile Following Administration of 400 mg Aripiprazole IM Depot (Day 0 and Day 28) or 960 mg Aripiprazole RTU LAI (Day 0) in Subjects Already Stabilized on 400 mg Aripiprazole IM Depot

Genetic factors:
In CYP2D6 PMs, compared to 300 mg Q4W IM depot, a regimen of 720 mg
Q8W RTU LAI resulted in non-inferior median steady-state plasma concentrations, with less overall variability.



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

Figure 32 Simulated Median Steady-State Aripiprazole Concentration Time Profile Following Administration of 300 mg Q4W Aripiprazole IM Depot or 720 mg Q8W Aripiprazole RTU LAI in CYP2D6 Poor Metabolizers

Drug-drug interactions:
For treatment initiation with 14 days or 10 mg oral overlap, and similarly at steady-state, a 720 mg Q8W RTU LAI regimen with a concomitant CYP3A4 strong inhibitor resulted in comparable median plasma concentrations to 960 mg Q8W RTU LAI without concomitant CYP3A4 or CYP2D6 strong inhibitors, while 720 mg Q8W RTU LAI regimen with a concomitant CYP2D6 strong inhibitor resulted in higher median plasma concentrations.

Steady-state:
At steady-state, compared to 400 mg Q4W IM depot, a regimen of 960 mg Q8W RTU LAI resulted in non-inferior median plasma concentrations, with less overall variability. A regimen of 720 mg Q8W RTU LAI resulted in comparable trough median plasma concentrations.

Dosing flexibility:
With a 960 mg Q8W RTU LAI regimen, at steady-state, 14 days early or late dose administration did not pose a significant concern in terms of either trough or maximum median plasma concentrations.

Missed/delayed doses:
With a 960 mg Q8W RTU LAI regimen, at steady-state, delaying dose administration by 2, 4, 6, and 8 weeks was evaluated. The trough median plasma concentrations at the time the dose was administered were 191 ng/mL, 144 ng/mL, 110 ng/mL, and 80.1 ng/mL, respectively. Fifty-six (56) days following administration of the subsequent dose, the trough median plasma concentrations were 231 ng/mL, 217 ng/mL, 205 ng/mL, and 196 ng/mL, respectively, where in the last case the dose was given with 14 days of 10 mg oral overlap.

Dose dumping:
Administration of 960 mg aripiprazole RTU LAI as an intravenous bolus dose resulted in a very high maximum median plasma concentration of 7,350 ng/mL, which descended to reach a level similar to the normal 960 mg aripiprazole RTU LAI administration after approximately 7 days.

Conclusions

The simulations showed a favorable PK exposure profile for aripiprazole RTU LAI compared to aripiprazole IM depot and oral aripiprazole, with a longer dosing interval and comparable or non-inferior and generally less variable plasma concentrations at steady-state. These results will serve to inform and optimize the dosing regimen for aripiprazole RTU LAI treatment initiation and maintenance under different patient scenarios.

4.1.2. Discussion on clinical efficacy

No dedicated efficacy studies were conducted.

For a detailed description of efficacy data obtained in PK studies please see Pharmacokinetics section.

4.1.3. Clinical safety

No dedicated safety studies were conducted.

For a detailed description of safety data obtained in PK studies please see Pharmacokinetics section.

4.1.3.1. Safety in special populations

N/A

4.1.3.2. Immunological events

N/A

4.1.3.3. Safety related to drug-drug interactions and other interactions

N/A

4.1.3.4. Discontinuation due to adverse events

Please see description of safety data obtained from the PK studies in the relevant section of the AR.

4.1.4. Post marketing experience

Since initial marketing approval in 2002, aripiprazole oral formulations have continually demonstrated favorable risk-benefit profiles for the approved indications. Similarly, aripiprazole IM depot (initially approved in 2013 with subsequent approvals in other regions) has continually demonstrated a favorable risk-benefit profile for the treatment of patients with schizophrenia, as documented through regular safety reports. The safety profile of aripiprazole IM depot has been monitored and assured throughout subsequent submissions that leveraged PK modeling data to add additional injection

locations (deltoid administration, first approved in 2015 with subsequent approvals in other regions) and new initiation regimens (two-injection start, first approved in 2020 with subsequent approvals in other regions). Of particular note, analysis of AE reporting following approval of the two-injection start regimen (ie, two injections of 400 mg aripiprazole IM depot and one dose of 20 mg oral aripiprazole) shows no increases in AE reporting rates compared to AE reporting rates prior to approval of the alternative initiation regimen. This further supports the sponsor's conclusion from the conducted trials that administration of a higher dose of aripiprazole (2 × 400 mg of aripiprazole IM depot for the two-injection start and as proposed for 960 mg aripiprazole 2M RTU LAI) is safe for patients.
The sponsor will continue to monitor suspect adverse reactions in association with the use of aripiprazole IM depot as part of routine safety surveillance. Continuous safety monitoring will ensure that updated safety information is available.

4.1.5. Discussion on clinical safety

A total of 240 subjects were enrolled and received at least one dose of aripiprazole RTU LAI in the combined trials (Trial 031-201-00181 [N = 132]; Trial 031-201-00104 [N = 36], and Trial 031-201-00279 [N = 72]).
In Study 031-201-00181 the overall incidence of TEAEs was comparable between the 2 study groups: 71.2% vs 70.9% in the aripiprazole 2M LAI 960 mg group and in the aripiprazole IM depot 400 mg group, respectively. Serious TEAEs were reported in 6 subjects (4.5%) in the aripiprazole 2M LAI 960 mg group and 8 subjects (6.0%) in the aripiprazole IM depot 400 mg group. There was 1 death (cardiac arrest) in the aripiprazole 2M LAI 960 mg group in a participant between the ages of 50 and 55 with schizophrenia and physical comorbidities .

The most frequently reported TEAE with relevant difference in the incidence between both study groups was injection site pain, which was reported in 18.2%of subjects in the aripiprazole 2M LAI 960 mg group and 9.0%of subjects in the aripiprazole IM depot 400 mg group.

The overall incidence of TEAEs considered by the investigator as potentially related to the IMP was higher in the aripiprazole 2M LAI 960 mg group (73 of 132 subjects [55.3%]) compared to the aripiprazole IM depot 400 mg group (61 of 134 subjects [45.5%]). None of the events of increased weight or injection site pain were considered by the investigator as severe or serious.

There were 5 subjects in the aripiprazole 2M LAI 960 mg group who had severe TEAEs: psychotic disorder, anxiety, cardiac arrest, and akathisia (each in 1 subject), and 2 events of akathisia in 1 subject. There were 4 subjects in the aripiprazole IM depot 400 mg group who had severe TEAEs: septic shock, adenocarcinoma of colon, and akathisia (each in 1 subject); and encephalopathy, loss of consciousness, schizophrenia, and suicide attempt (all in 1 subject).

Treatment-emergent AEs resulting in the discontinuation of IMP occurred in 4 subjects in the aripiprazole 2M LAI 960 mg group and 10 subjects in the aripiprazole IM depot 400 mg group. The events that occurred in more than 1 subject were akathisia, anxiety, and psychotic disorder. All events of akathisia and 1 event of anxiety, as well as the events of somnolence, restlessness, dyskinesia, and tremor, were assessed by the investigator as related to the IMP.
No clinically concerning laboratory abnormalities were reported during the study.
Treatment-emergent EPS-related AEs were reported in 18.2% of subjects in the aripiprazole 2M LAI 960 mg group and in 13.4% of subjects in the aripiprazole IM depot 400 mg group.
There were 2 TEAEs related to suicidal ideation/suicide, both in subjects with schizophrenia: 1 TEAE of suicidal ideation in the aripiprazole 2M LAI 960 mg group and 1 TEAE of suicide attempt in the aripiprazole IM depot 400 mg group.

In study 031-201-00104 63.9% of subjects experienced at least 1 TEAE, with a comparable prevalence between both groups (66.7% vs 61.1%). The most commonly reported were injection site pain (30.6%), insomnia (22.2%) and headache (11.1%).

In study 031-201-00279 the most frequently reported TEAEs were akathisia (8.3%), arthralgia (7.1%), pain in extremity (7.1%), akathisia (10.7%) and headache (7.1%). In total 4 serious adverse events were observed (single SAEs of arthritis infective, toxicity to various agents, pyelonephritis, and psychotic agitation). None of the serious TEAEs were considered to be related to IMP. No deaths occurred during the study and no subjects were discontinued from IMP due to AEs. There were no clinically relevant findings with regard to mean changes in vital signs, ECG, weight, EPS (SAS, AIMS, and BARS), suicidality, injection site, or laboratory values.

Overall, no new emerging safety issues were reported in the conducted studies.

4.1.6. Conclusions on clinical aspects

In view of the requirements for an application under the selected legal basis (hybrid application pursuant to Article 10(3) of Directive 2001/83/EC), a bridge needs to be established between the test medicinal product (Asimtufii) and the EU/EEA reference medicinal product (Abilify Maintena) in order to allow reference to be made to the EU/EEA reference medicinal product's pre-clinical and clinical data.

In line with the requirements following from the selected legal basis (Article 10(3) of Directive 2001/83/EC), the pivotal study submitted to establish a bridge to the EU/EEA reference medicinal product should be conducted against the EU/EEA reference medicinal product. Therefore, the applicant is invited to provide results of a clinical study conducted against the EU/EEA reference medicinal product as part of the hybrid application pursuant to Article 10(3) of Directive 2001/83/EC **(MO)**.

The applicant is invited to discuss the clinical relevance of differences in the shape of the plasma-concentration profiles **(OC)**.

4.2. Risk management plan

4.2.1. Safety Specification

4.2.1.1. Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	EPS, including tardive dyskinesia
Important potential risks	Orthostatic hypotension
Missing information	Use in pregnancy and lactation Use in elderly patients above 65 years of age

4.2.2. Discussion on safety specification

4.2.3. Conclusions on the safety specification

Having considered the data in the safety specification, it is agreed that the safety concerns listed by the applicant are appropriate.

4.2.4. Pharmacovigilance plan

No additional pharmacovigilance activities are planned. Reference is made to studies previously finalised for aripiprazole. This is acceptable. Thus, routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

4.2.5. Risk minimisation measures

The proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

4.2.6. Conclusion on the RMP

The RMP is acceptable. No new risks have been identified for the generic product that are not recognised for the reference product and there are no outstanding issues.

4.3. Pharmacovigilance

4.3.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

4.3.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

5. Benefit/risk assessment

This application concerns a hybrid version of aripiprazole, prolonged-release suspension for injection in pre-filled syringe. The EU/EEA reference medicinal product Abilify Maintena is indicated for the maintenance treatment of schizophrenia in adult patients stabilised with aripiprazole.

Nonclinical studies have been provided for this application and considered sufficient. From a clinical perspective, this application does not contain new data on pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from the reference product and published literature was considered sufficient.

The comparative bioavailability study 031-201-00181 forms the pivotal study with an open-label, multiple-dose (MD), randomised, parallel-arm design. The study design is considered adequate in terms ofchoice of dose, sampling points, overall sampling time as well as wash-out period. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate. However, in line with the requirements following from the selected legal basis (Article 10(3) of Directive 2001/83/EC), the pivotal study submitted to establish a bridge to the EU/EEA reference medicinal product should be conducted against the EU/EEA reference medicinal product. The choice for a non-EU/EEA reference medicinal product as comparator in the pivotal study is not acceptable for hybrid applications pursuant to Article 10(3) of Directive 2001/83/EC **(MO).**

The applicant is invited to discuss the clinical relevance of differences in the shape of the plasma-concentration profiles **(OC)**.

A benefit/risk ratio comparable to the reference product can therefore not be concluded.

5.1. Conclusions

The overall benefit /risk balance of Asimtufii is negative.

5.2. Non clinical aspects

5.2.1. Major objections

None

5.2.2. Other concerns

1. **logKow:** The required study according to OECD 123 on the octanol-water partition coefficient of aripiprazole can be submitted as post-authorisation measure by Q3 2023 as already suggested by the applicant. A respective letter of agreement should be provided, including the anticipated time schedule. Depending on the result a bioaccumulation study may be required.

5.3. Clinical aspects

5.3.1. Major objections

Pharmacokinetics

2. In line with the requirements following from the selected legal basis (Article 10(3) of Directive 2001/83/EC), the pivotal study submitted to establish a bridge to the EU/EEA reference medicinal product should be conducted against the EU/EEA reference medicinal product. Therefore, the applicant is invited to provide results of a clinical study conducted against the EU/EEA reference medicinal product as part of the hybrid application pursuant to Article 10(3) of Directive 2001/83/EC.

5.3.2. Other concerns

Pharmacokinetics

3. The applicant is invited to discuss the clinical relevance of differences in the shape of the plasma-concentration profiles.

Safety

None

SPC

4. The proposed SmPC 4.6 minor update is noted. However the applicant is asked to implement changes in line with proposal below or else justify:

4.6 Fertility, pregnancy and lactation
Women of childbearing potential
Plasma exposure to aripiprazole after a single dose of ASIMTUFII is expected to remain for up to 34 weeks (see section 5.2). This should be taken into account when initiating treatment in women of childbearing potential, considering a possible future pregnancy or breast-feeding. ASIMTUFII should only be used in women planning to become pregnant if clearly necessary.
Pregnancy

There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity (see section 5.3).
Patients must be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. Prescribers need to be aware of the long-acting properties of ASIMTUFII. Aripiprazole has been detected in plasma in adult patients up to 34 weeks after a single-dose administration of ASIMTUFII.
New-born infants exposed to antipsychotics (including aripiprazole) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, new-born infants should be monitored carefully (see section 4.8).
Maternal exposure to ASIMTUFII before and during pregnancy may lead to adverse reactions in the newborn child. ASIMTUFII should not be used during pregnancy unless clearly necessary.
Breast-feeding
Aripiprazole/metabolites is excreted in the breast milk to such an extent that effects on the breast-fed infant are likely if ASIMTUFII is administered to breast-feeding women. Since a single dose of ASIMTUFII is expected to remain for up to 34 weeks in plasma (see section 5.2), breast-fed infants may be at risk even from ASIMTUFII administration long before breast-feeding. Patients currently under treatment or who have been treated in the past 34 weeks with ASIMTUFII should not breast feed.
Fertility
Aripiprazole did not impair fertility based on data from reproductive toxicity studies with aripiprazole.

5.2 Pharmacokinetic properties *(referred to from 4.6)*
Absorption / Distribution
Aripiprazole absorption into the systemic circulation is slow and prolonged following gluteal injection due to low solubility of aripiprazole particles. The release profile of aripiprazole from Asimtufii results in sustained plasma concentrations over 2 months following gluteal injection(s). The release of the active substance after a single dose of 2-monthly aripiprazole injectable starts day x and lasts for as long as xx months/weeks. Plasma concentrations have been studied up to x months/weeks after administration of ASIMTUFII.

5. The proposed justifications for similar safety in 1-month and 2-months formulations are noted. However the SmPC 4.2 should be revised into a general recommendation to start with a once monthly LAI, before initiating the 2-monthly Asimtufii. In the SmPC 4.2, for LAI initiation the highest strength 960 mg is recommended (720 mg for CYP2D6 poor metabolisers only). Further in 4.2: *"If there are adverse reactions with the 960 mg dose, reduction of the dose to 720 mg once every two months should be considered."* For those patients not tolerating the higher dose level 960 mg, onset of unfavourable effects could be expected from as early as during the initial peak concentration after first injection. If their first LAI is the 2-months product, their duration of continued exposure will be much longer than necessary. Once a LAI dose is injected, the very large total dose cannot be removed and its long duration of effects remains. Likely their duration of any intolerable effects would be equally longer for those when patients started on 2-months first LAI, than when on 1-months as first LAI. It should be taken into account here that only the higher dose 960 mg is recommended for starting LAI on the 2-months product. To further note in a harmonisation perspective, a recommendation to start injectable treatment on a 1-monthly product is in line with previously approved injectable products for this indication. Therefore, the general recommendation in 4.2 should be to start LAI treatment on a 1-month product.

5.4. Risk management plan

None

5.5. Pharmacovigilance

None

6. Recommended conditions for marketing authorisation and product information in case of a positive opinion

In view of the major objections it is premature to recommend any conditions for marketing authorisation and to propose changes in the product information (SmPC, Annex II, labelling, PL). The assessment of the user consultation or of the justification for not having them and any above risk minimisation questions should however be addressed.

6.1. Conditions for the marketing authorisation

*6.2. Proposed list of post-authorisation measures**

The proposed post-authorisation measures are subject to assessment of responses to the List of Questions:

6.3. Other conditions

6.4. Summary of product characteristics (SmPC)

6.5. Labelling

6.6. Package leaflet (PL)

User consultation

The results of the user consultation demonstrated that at least 90 % of the participants were able to find each point of information. The study also demonstrated that at least 90 % of those participants were able to understand the information. It can therefore be concluded that the leaflet meets the EU requirements for readability and usability.

Conclusion from the checklist for the review of user consultation

Quick Response (QR) code

The review of the QR code request submitted by the MAH is presented in a separate attachment to this report (checklist available for download here: Quick Response (QR) code).