

1.0 Title Page

Study Title: A Single-Dose, Randomized, Open-Label, Crossover, Pivotal, Comparative Bioavailability Study of Aripiprazole 10 mg Tablets (J. Uriach y Compañía S.A.) and ABILIFY® 10 mg Tablets (MAH: Otsuka Pharmaceutical Europe Ltd.) in Healthy Male and Female Volunteers under Fasting Conditions

Study Drugs: Aripiprazole 10 mg Tablets;
Lot No: H003;
(J. Uriach y Compañía S.A.)

ABILIFY® 10 mg Tablets;
Lot No: 2L69769;
(MAH: Otsuka Pharmaceutical Europe Ltd.)

Indication Studied: N/A

Description: This study is an evaluation of the comparative bioavailability between Aripiprazole 10 mg Tablets (J. Uriach y Compañía S.A.) and ABILIFY® 10 mg Tablets (MAH: Otsuka Pharmaceutical Europe Ltd.)

Name of Sponsor: J. Uriach y Compañía S.A.,
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Study Number: 1563
Protocol Version Number: 1.0
Protocol Version Date: July 04, 2013

J. Uriach Study Code: GE/12/ARI/1/13

Phase of Development: Bioequivalence

Study Initiation: August 08, 2013

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Study Completion: September 16, 2013

Principal Investigator: Dr. Esmat Dessouki, M.D., F.R.C.S.(C)

Sponsor Signatory: Iñaki Izquierdo
Head of Clinical Development Department
J. Uriach y Compañía S.A.

GCP Compliance: The clinical conduct of this study (1563) was performed
in compliance with Good Clinical Practice (GCP).

Date of Report (Final): November 19, 2013

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2.0 Synopsis

Name of Sponsor: J. Uriach y Compañía S.A.	Volume:	(For National Authority Use Only)
Name of Finished Product: Aripiprazole 10 mg Tablets		
Name of Active Ingredient: Aripiprazole		
Page:		
Title of Study: A Single-Dose, Randomized, Open-Label, Crossover, Pivotal, Comparative Bioavailability Study of Aripiprazole 10 mg Tablets (J. Uriach y Compañía S.A.) and ABILIFY® 10 mg Tablets (MAH: Otsuka Pharmaceutical Europe Ltd.) in Healthy Male and Female Volunteers under Fasting Conditions		
Investigators: Dr. Esmat Dessouki, M.D., F.R.C.S.(C) Dr. Asif Khan, M.D. Dr. Ola Kassim, M.D. Dr. Reza Behjati, M.D. Dr. Janice Faulknor, M.D.		
Study Center(s):		
Clinical Facility:	Bio Pharma Services Inc. 4000 Weston Road Toronto, Ontario, Canada, M9L 3A2	
Clinical Laboratory:	Gamma-Dynacare Medical Laboratories 115 Midair Court Brampton, Ontario, Canada, L6T 5M3	
Analytical Laboratory:	inVentiv Health Clinique inc. 2500 rue Einstein, Québec, QC, Canada G1P 0A2	
Pharmacokinetic, Statistical and Report Issuing Facility:	Bio Pharma Services Inc. 4000 Weston Road Toronto, Ontario, Canada, M9L 3A2	
Dosing Dates: Period 1: August 09, 2013 Period 2: September 13, 2013		Phase of Development: Bioequivalence
Objectives: The objective of this pivotal study was to compare the bioavailability of aripiprazole from Aripiprazole 10 mg Tablets (J. Uriach y Compañía S.A.) and ABILIFY® 10 mg Tablets (MAH: Otsuka Pharmaceutical Europe Ltd.) in healthy, non-smoking, male and female volunteers under fasting conditions. This study is intended for submission to the European Medicines Agency (EMA).		

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Name of Sponsor: J. Uriach y Compañía S.A.	Volume:	(For National Authority Use Only)
Name of Finished Product: Aripiprazole 10 mg Tablets		
Name of Active Ingredient: Aripiprazole		
Page:		

Methodology:
This was a pivotal, single-dose, randomized, open-label, two-period, two-sequence, two-treatment, single-centre, crossover study designed to evaluate the comparative bioavailability of aripiprazole from Aripiprazole 10 mg Tablets (J. Uriach y Compañía S.A.) and ABILIFY® 10 mg Tablets (MAH: Otsuka Pharmaceutical Europe Ltd.) administered to healthy male and female subjects under fasting conditions. Subjects were randomly assigned to one of the two dosing sequences.

The concentration of aripiprazole was measured from plasma samples collected over a 72-hour interval after dosing in each period. Pharmacokinetic parameters C_{max}, T_{max}, and AUC₇₂ were estimated based on aripiprazole plasma levels for subjects included in the statistical analysis.

Blood Sampling Schedule
Blood samples were taken at the following time points: pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hours after dosing.

Number of Subjects (planned and analyzed):
Thirty (30) subjects were enrolled and dosed in Period 1.
Twenty-four (24) subjects completed the study in its entirety.
Data from 30 subjects were analyzed by the bioanalytical laboratory.
Data from 24 subjects were included in the pharmacokinetic and statistical analysis.

Diagnosis and main criteria for inclusion:
Subjects met the following inclusion criteria within 30 days prior to Period 1 dosing:

1. Healthy, non-smoking (for at least 6 months prior to first drug administration), male and female volunteers, 45 years of age or older.
2. BMI that is within 18.5-30.0 kg/m², inclusive.
3. Healthy, according to the medical history, ECG, vital signs, laboratory results and physical examination as determined by the Principal Investigator/Sub-Investigator.
4. QTc interval < 430 milliseconds for males and < 450 milliseconds for females, unless deemed otherwise by the Principal Investigator/Sub-Investigator.
5. Systolic blood pressure between 100-140 mmHg, inclusive, and diastolic blood pressure between 65-90 mmHg, inclusive, and heart rate between 50-100 bpm, inclusive, unless deemed otherwise by the Principal Investigator/Sub-Investigator.
6. Clinical laboratory values within BPSI's acceptable range, unless values are deemed by the Principal Investigator/Sub-Investigator as "Not Clinically Significant".
7. Ability to comprehend and be informed of the nature of the study, as assessed by BPSI staff. Capable of giving written informed consent prior to receiving any study medication. Must be able to communicate effectively with clinic staff.
8. Ability to fast for at least 14 hours and consume standard meals.
9. Availability to volunteer for the entire study duration and willing to adhere to all protocol requirements.

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Name of Finished Product: Aripiprazole 10 mg Tablets		
Name of Active Ingredient: Aripiprazole	Page:	
10. Agree not to have a tattoo or body piercing until the end of the study. 11. Agree not to drive or operate heavy machinery if feeling dizzy or drowsy following drug administration until full mental alertness is regained. 12. Female subjects must fulfill at least one of the following: • Be surgically sterile for a minimum of 6 months; • Post-menopausal for a minimum of 1 year; • Agree to avoid pregnancy and use medically acceptable method of contraception from at least 30 days prior to the study until 30 days after the study has ended (last study procedure). Medically acceptable methods of contraception include non-hormonal intrauterine device or double barrier method (condom with foam or vaginal spermicidal suppository, diaphragm with spermicide). Complete abstinence alone can be used as a method of contraception.		
Test product, dose and mode of administration, batch number: Test Product (Treatment A): Aripiprazole 10 mg Tablets; Lot No: H003; (J. Uriach y Compañía S.A.) Dose: 1 x 10 mg Mode of Administration: Oral under fasting conditions		
Reference Product (Treatment B): ABILIFY® 10 mg Tablets; Lot No: 2L69769; (MAH: Otsuka Pharmaceutical Europe Ltd.) Dose: 1 x 10 mg Mode of Administration: Oral under fasting conditions		
Duration of treatment: The study consisted of two study periods. Each study period included a single-dose drug administration of either the Test product or the Reference product. There was a washout period of 35 days between each drug administration. Subjects were confined to the clinic the day prior to dosing until approximately 72 hours post-dose.		
Criteria for Evaluation: Bioequivalence: To establish bioequivalence, the calculated 90% CI for the ratio of geometric means for AUC₇₂ and C_{max} for aripiprazole should fall within 80.00%-125.00%.		
Safety: Safety was evaluated by vital signs measurement, clinical laboratory tests (including hematology, urine analysis, serum chemistry and serum hCG [females only] tests), physical examinations and adverse events reported by subjects who received a drug treatment.		

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Name of Finished Product: Aripiprazole 10 mg Tablets																												
Name of Active Ingredient: Aripiprazole																												
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Statistical Methods: Descriptive statistics (min, max, median, mean, standard deviation and coefficient of variability) of all pharmacokinetic parameters were provided for the test and reference products. ANOVA including sequence, subjects nested within sequence, period and treatment was performed on the ln-transformed data for AUC₇₂ and C_{max}, and on the un-transformed data for T_{max}. T_{max} was analyzed using an additional non-parametric test. The 90% confidence intervals (CI) of the Test/Reference ratios of geometric means for AUC₇₂ and C_{max} were calculated based on the least square means (LSMEANS) and ESTIMATE of the ANOVA.																												
Bioequivalence Results: Aripiprazole: (N=24)																												
Bioequivalence Analysis Results For Plasma Aripiprazole TREATMENT A vs TREATMENT B <table border="1"> <thead> <tr> <th rowspan="2">Parameter (N/N)</th> <th colspan="2">Geometric Means Arithmetic Means (CV %)</th> <th rowspan="2">Ratio of Geometric Means</th> <th rowspan="2">90% Confidence Interval</th> <th rowspan="2">Intra- Subject CV (%)</th> </tr> <tr> <th>TRT A</th> <th>TRT B</th> </tr> </thead> <tbody> <tr> <td>AUC₇₂ (ng.h/mL) (24 /24)</td> <td>1400.01 1436.55 (23.25)</td> <td>1321.85 1357.25 (24.90)</td> <td>105.91</td> <td>101.44 - 110.59</td> <td>8.74</td> </tr> <tr> <td>C_{MAX} (ng/mL) (24 /24)</td> <td>41.81 44.95 (37.45)</td> <td>38.40 40.80 (43.35)</td> <td>108.89</td> <td>97.49 - 121.61</td> <td>22.62</td> </tr> <tr> <td>T_{max}* (h) (24 /24)</td> <td>2.26 (1.00 - 36.00)</td> <td>3.28 (1.50 - 5.00)</td> <td></td> <td></td> <td></td> </tr> </tbody> </table> * Presented as median and range			Parameter (N/N)	Geometric Means Arithmetic Means (CV %)		Ratio of Geometric Means	90% Confidence Interval	Intra- Subject CV (%)	TRT A	TRT B	AUC ₇₂ (ng.h/mL) (24 /24)	1400.01 1436.55 (23.25)	1321.85 1357.25 (24.90)	105.91	101.44 - 110.59	8.74	C _{MAX} (ng/mL) (24 /24)	41.81 44.95 (37.45)	38.40 40.80 (43.35)	108.89	97.49 - 121.61	22.62	T _{max} * (h) (24 /24)	2.26 (1.00 - 36.00)	3.28 (1.50 - 5.00)			
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TRT A: Aripiprazole 10 mg Tablets; Lot No: H003; (J. Uriach y Compañía S.A.) TRT B: ABILIFY® 10 mg Tablets; Lot No: 2L69769; (MAH: Otsuka Pharmaceutical Europe Ltd.)																												
SUMMARY – CONCLUSIONS																												
Bioequivalence Results: The calculated 90% confidence interval for the ratio of geometric means for the ln-transformed AUC₇₂ and C_{max} parameters were entirely contained within the acceptance range of 80.00% to 125.00%. Therefore, in this study, bioequivalence was demonstrated between Aripiprazole 10 mg Tablets (J. Uriach y Compañía S.A.) and ABILIFY® 10 mg Tablets (MAH: Otsuka Pharmaceutical Europe Ltd.) in normal, healthy, male and female volunteers under fasting conditions.																												
Safety Results: A total of 29 mild and 8 moderate AEs were experienced by the subjects after taking the Test product.																												

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4.0 List of Abbreviations and Definitions of Terms

AE:	Adverse Event
ALT:	Alanine Aminotransferase
AST:	Aspartate Aminotransferase
AUC ₇₂ , AUC72:	Area under the concentration-time curve from time zero to 72 hours.
BLQ or BQL:	Below the Limit Of Quantitation
BMI:	Body Mass Index (kg/m ²)
BP:	Blood Pressure
BPM:	Beats Per Minute
BPSI:	Bio Pharma Services Inc.
CI:	Confidence Interval
C _{max} , Cmax, CMAX:	The maximal observed plasma concentration.
CRF:	Case Report Form
CYP450:	Cytochrome P450
ECG:	Electrocardiogram
EMA:	European Medicines Agency
FDA:	Food and Drug Administration
hCG:	Human Chorionic Gonadotropin
GCP:	Good Clinical Practice
HIV:	Human Immunodeficiency Virus
HR:	Heart Rate
hr:	Hour
ICF:	Informed Consent Form
ICH:	International Conference on Harmonization

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IRB:	Institutional Review Board
MedDRA:	Medical Dictionary for Regulatory Activities
mmHg:	Millimeter of Mercury
N/A or NA:	Not applicable, Not Available
PK:	Pharmacokinetic
QA:	Quality Assurance
RBC:	Red Blood Cell
RPM:	Revolutions Per Minute
SOP:	Standard Operating Procedure
TP:	Time Point
TRT:	Treatment
T _{max} , Tmax, TMAX:	Time when the maximal plasma concentration is observed.
UBG:	Urobilinogen
WBC:	White Blood Cell

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5.0 Ethics

5.1 Institutional Review Board (IRB)

The Institutional Review Board, Optimum Clinical Research Inc., reviewed the Protocol and ICF on July 10, 2013, and approved:

- Protocol No.: 1563, Version Number: 1.0, Version Date: July 04, 2013

Changes were made to the ICF at the request of the IRB. The Chair reviewed the revised ICF on July 11, 2013, and approved:

- Informed Consent Form (ICF), Version Date: July 10, 2013

A notification (Dated: August 07, 2013) was generated to clarify the post-dosing posture restrictions in Section 11.7 Physical Activity of the protocol (Version 1.0, Dated July 04, 2013). The Chair acknowledged the notification on August 09, 2013.

5.2 Ethical Conduct of the Study

This study was conducted in accordance with the current EMA guidance documents¹, Good Clinical Practice, as established by the International Conference on Harmonization (ICH), the basic principles defined in Division 5 of the Canadian Food and Drug Regulations, the Belmont Report, the European Directive EC/2001, and the principles enunciated in the World Medical Association Declaration of Helsinki (Seoul, Korea, 2008).

This study was also conducted in adherence to the SOP's of BPSI and the protocol provided in Appendix [16.1.1 Protocol and Protocol Amendments](#).

5.3 Subject Information and Consent

The IRB approved the Informed Consent for Medical Screening on September 05, 2012, Version Dated: September 05, 2012.

The Informed Consent Form (ICF) was approved on July 11, 2013, Version Dated: July 10, 2013.

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Subjects signed an Informed Consent for Medical Screening prior to starting any screening procedures and an ICF was signed prior to study procedures at Period 1 check-in. ICF was read and explained to subjects by staff. Subjects were given time to read and understand the ICF. Subjects were then interviewed on a one on one basis in private and any questions and concerns were addressed prior to signing of the ICF.

A copy of the Informed Consent for Medical Screening and ICF can be found in Appendix [16.1.3 List of IRB and Representative Written Information for Subject and Sample Consent Forms](#).

Please refer to Appendix [16.1.3 List of IRB and Representative Written Information for Subject and Sample Consent Forms](#) for the IRB approval documentation and a list of IRB members in attendance at the approval meeting.

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6.0 Investigators and Study Administrative Structure

Principal Investigator:	Dr. Esmat Dessouki, M.D., F.R.C.S.(C)
Sub-Investigators:	Dr. Asif Khan, M.D. Dr. Ola Kassim, M.D. Dr. Reza Behjati, M.D. Dr. Janice Faulknor, M.D.
Director, Clinical Operations:	Justin Vilafana, B.Sc., C.C.R.P.
Clinical Research Coordinator:	Lucia Son, B.MSc, CCRP
Vice-President of Scientific Affairs:	Fethi Trabelsi, Ph.D.
Senior Director, Biopharmaceutics:	Juan He, M.Sc. Phm, B.Sc. Phm
Supervisor, Biostatistics:	Yu Ding, M.Sc. Statistics
Medical Writer:	Ivan Kasule, B.Sc. (Hon)
Institutional Review Board:	Optimum Clinical Research Inc. 604 Taunton Road West Oshawa, ON, Canada, L1H 7K4 Tel: 905-723-4694; Fax: 905-723-7590
Clinical Facility:	Bio Pharma Services Inc. 4000 Weston Road Toronto, Ontario, Canada, M9L 3A2 Tel: 416-747-8484; Fax: 416-747-8480
Clinical Laboratory:	Gamma-Dynacare Medical Laboratories 115 Midair Court Brampton, Ontario, Canada, L6T 5M3 Tel: 905-790-3000; Fax: 905-790-3055
Analytical Laboratory:	inVentiv Health Clinique inc. 2500 rue Einstein, Québec, QC, Canada G1P 0A2 Tel: (418) 527-3067
Pharmacokinetic, Statistical & Report Issuing Facility:	Bio Pharma Services Inc. 4000 Weston Road Toronto, Ontario, Canada, M9L 3A2 Tel: 416-747-8484; Fax: 416-747-8480
Refer to Appendix 16.1.4 List and Description of Investigators for Investigators' qualifications.	

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7.0 Introduction¹

Absorption

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution

Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 L/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and dehydro-aripiprazole are greater than 99% bound to serum proteins, binding primarily to albumin.

Metabolism

Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Elimination

The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolizers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 mL/min/kg, which is primarily hepatic.

Following a single oral dose of [¹⁴C]-labelled aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the faeces. Less than 1% of unchanged aripiprazole was excreted in the urine and

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approximately 18% was recovered unchanged in the faeces.

Elderly:

There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

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8.0 Study Objective

The objective of this pivotal study was to compare the bioavailability of aripiprazole from Aripiprazole 10 mg Tablets (J. Uriach y Compañía S.A.) and ABILIFY® 10 mg Tablets (MAH: Otsuka Pharmaceutical Europe Ltd.) in healthy, non-smoking, male and female volunteers under fasting conditions.

This study is intended for submission to the EMA.

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9.0 Investigational Plan

9.1 Overall Study Design and Plan: Description

This was a pivotal, single-dose, randomized, open-label, two-period, two-sequence, two-treatment, single-centre, crossover, comparative bioavailability study of Aripiprazole 10 mg Tablets (J. Uriach y Compañía S.A.) and ABILIFY® 10 mg Tablets (MAH: Otsuka Pharmaceutical Europe Ltd.). The products were studied using a crossover design with 30 healthy male and female non-smoking volunteers being administered an oral dose of 1×10 mg tablets under fasting conditions.

9.2 Discussion of Study Design

For this trial, the measure of therapeutic equivalence was planned to be demonstrated through pharmacokinetic means, thus the comparison of the bioavailability of the two study drugs.

This approach is generally considered appropriate to investigate pharmacokinetic properties and detect possible bioavailability differences of the tested products.

Subjects who met the eligibility criteria were to be randomly assigned to receive the study drugs according to one of the two dosing sequences A-B or B-A. A total of 15 subjects were planned to receive treatment sequence A-B and 15 subjects were planned to receive sequence B-A. Subjects randomized to the A-B sequence were to receive the Test product (Treatment A) in Period 1, and then following a minimum 35-day washout period, were to receive the Reference product (Treatment B) in Period 2. Subjects randomized to the B-A sequence were to receive the Reference product (Treatment B) in Period 1, and then following a minimum 35-day washout period, were to receive the Test product (Treatment A) in Period 2. The washout period of 35 days was estimated to be adequate in avoiding carry-over effects of the preceding treatments.

Subjects were to receive either a single dose of the Test product [Treatment A – Aripiprazole 10 mg Tablets (J. Uriach y Compañía S.A.)] or a single dose of the Reference product [Treatment B – ABILIFY® 10 mg Tablets (MAH: Otsuka Pharmaceutical Europe Ltd.)] on Day 1 of each study period. The trial was to be

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performed as an open-label study as the pharmacokinetic profile was not expected to be affected by having the knowledge of which study drug was administered; blinding of the investigator/clinic staff and subjects was therefore not necessary.

The concentration of aripiprazole was to be measured from the plasma samples collected over a 72-hour interval after dosing in each study period.

9.3 Selection of Study Population

The following screening procedures were conducted on each potential subject prior to consideration for inclusion into the study:

- Obtain written informed consent for screening as evidenced by potential subject's signing an Informed Consent for Medical Screening (Screening Informed Consent Form [ICF]).
- Record medical/medication history and demographic information based on the interview with the potential subject.
- Review of Inclusion/Exclusion criteria for each potential subject.
- Obtain height and body weight to calculate BMI.
- Obtain Vital Signs (temperature, respiratory rate [RR], pulse as well as seated BP) and perform an electrocardiogram (ECG).
- Collect blood and urine samples for hematology, chemistry, serology, urinalysis, screening for drugs of abuse and cotinine. Perform breath alcohol test. For a complete listing of all tests to be performed, please refer to Section [11.2 Demographic and Other Baseline Characteristics](#).
- Perform a physical examination.
- Principal Investigator's/Sub-Investigator's review of Inclusion/Exclusion criteria and all screening results/data to assess eligibility of each potential subject.

Screening procedures were conducted within thirty (30) days prior to dosing in Period 1 (Day -30 to Day -1).

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9.3.1 Inclusion Criteria

Subjects met all of the following inclusion criteria within 30 days prior to the first drug administration.

1. Healthy, non-smoking (for at least 6 months prior to first drug administration), male and female volunteers, 45 years of age or older.
2. BMI that is within 18.5-30.0 kg/m², inclusive.
3. Healthy, according to the medical history, ECG, vital signs, laboratory results and physical examination as determined by the Principal Investigator/Sub-Investigator.
4. QTc interval < 430 milliseconds for males and < 450 milliseconds for females, unless deemed otherwise by the Principal Investigator/Sub-Investigator.
5. Systolic blood pressure between 100-140 mmHg, inclusive, and diastolic blood pressure between 65-90 mmHg, inclusive, and heart rate between 50-100 bpm, inclusive, unless deemed otherwise by the Principal Investigator/Sub-Investigator.
6. Clinical laboratory values within BPSI's acceptable range, unless values are deemed by the Principal Investigator/Sub-Investigator as "Not Clinically Significant".
7. Ability to comprehend and be informed of the nature of the study, as assessed by BPSI staff. Capable of giving written informed consent prior to receiving any study medication. Must be able to communicate effectively with clinic staff.
8. Ability to fast for at least 14 hours and consume standard meals.
9. Availability to volunteer for the entire study duration and willing to adhere to all protocol requirements.
10. Agree not to have a tattoo or body piercing until the end of the study.

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11. Agree not to drive or operate heavy machinery if feeling dizzy or drowsy following drug administration until full mental alertness is regained.
12. Female subjects must fulfill at least one of the following:
 - Be surgically sterile for a minimum of 6 months;
 - Post-menopausal for a minimum of 1 year;
 - Agree to avoid pregnancy and use medically acceptable method of contraception from at least 30 days prior to the study until 30 days after the study has ended (last study procedure).

Medically acceptable methods of contraception include non-hormonal intrauterine device or double barrier method (condom with foam or vaginal spermicidal suppository, diaphragm with spermicide). Complete abstinence alone can be used as a method of contraception.

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9.3.2 Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study.

1. Known history or presence of any clinically significant hepatic, renal/genitourinary, gastrointestinal (e.g. dysphagia), cardiovascular (e.g. myocardial infarction, ischemic heart disease, heart failure, conduction abnormalities, hypertension, QT prolongation, tachycardia, bradycardia, venous thromboembolisms), cerebrovascular, pulmonary (e.g. aspiration pneumonia), endocrine (e.g. hyperglycaemia, diabetes mellitus, thyroid disorder, pituitary adenoma), immunological, musculoskeletal, neurological (e.g. Neuroleptic Malignant Syndrome, seizures, tardive dyskinesia, dystonia), psychiatric (e.g. suicidal ideation and behavior, depression, psychosis, pathological gambling), dermatological or hematological (e.g. blood clots) disease or condition unless determined as not clinically significant by the Principal Investigator/Sub-Investigator.
2. Clinically significant history or presence of any clinically significant gastrointestinal pathology (e.g. chronic diarrhea, inflammatory bowel disease), unresolved gastrointestinal symptoms (e.g. diarrhea, vomiting), or other conditions known to interfere with the absorption, distribution, metabolism or excretion of the drug experienced within 7 days prior to first drug administration, as determined by the Principal Investigator/Sub-Investigator.
3. Presence of any clinically significant illness within 30 days prior to first dosing, as determined by the Principal Investigator/Sub-Investigator.
4. Presence of any significant physical or organ abnormality as determined by the Principal Investigator/Sub-Investigator.
5. A positive test result for any of the following: HIV, Hepatitis B surface antigen, Hepatitis C, drugs of abuse (marijuana, amphetamines, barbiturates, cocaine, opiates, phencyclidine and benzodiazepines), breath alcohol test and cotinine. Positive pregnancy test for female subjects.

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6. Known history or presence of:
 - Alcohol abuse or dependence within one year prior to first drug administration;
 - Drug abuse or dependence;
 - Hypersensitivity or idiosyncratic reaction to aripiprazole, its excipients, and/or related substances;
 - Lactose intolerance, galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption;
 - Food allergies and/or presence of any dietary restrictions;
 - Severe allergic reactions (e.g. anaphylactic reactions, angioedema).
7. Intolerance to and/or difficulty with blood sampling through venipuncture.
8. Abnormal diet patterns (for any reason) during the four weeks preceding the study, including fasting, high protein diets etc.
9. Individuals who have donated, in the days prior to first drug administration:
 - 50-499 mL of blood in the previous 30 days
 - 500 mL or more in the previous 56 days
10. Donation of plasma by plasmapheresis within 7 days prior to first drug administration.
11. Individuals who have participated in another clinical trial or who received an investigational drug within 30 days prior to first drug administration.
12. Consumption of food or beverages containing caffeine/methylxanthines, poppy seeds and/or alcohol within 48 hours before dosing and containing grapefruit and/or pomelo within 10 days prior to first drug administration.
13. Use of any prescription medication within 14 days prior to first drug administration

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14. Use of any enzyme-modifying drugs, including strong inhibitors of cytochrome P450 (CYP) enzymes (e.g. cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem and HIV antivirals) and strong inducers of CYP enzymes (e.g. barbiturates, carbamazepine, glucocorticoids, phenytoin and rifampin) in the previous 30 days before first drug administration.
15. Use of any over-the-counter medications (including oral multivitamins, herbal and/or dietary supplements and/or teas) within 14 days prior to first drug administration (except for spermicidal/barrier contraceptive products).
16. Use of any antihypertensive agents (e.g. beta blockers, diuretics), other CNS medicinal products (e.g. CNS stimulants), medicinal products known to cause QT prolongation or electrolyte imbalance, famotidine, St. John's Wort, within 30 days prior to first drug administration.
17. Females taking oral or transdermal hormonal contraceptives within 30 days prior to first drug administration.
18. Females having used implanted, injected, intravaginal, or intrauterine hormonal contraceptive within 6 months prior to first drug administration.
19. Individuals having undergone any major surgery within 6 months prior to the start of the study, unless deemed otherwise by Principal Investigator/Sub-Investigator.
20. Difficulty with swallowing whole tablets.
21. Women who are pregnant or lactating.
22. Unable or unwilling to provide informed consent.
23. Have had a tattoo or body piercing within 30 days prior to first drug administration.

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9.3.3 Removal of Subjects from Therapy or Assessment

Subjects whose participation in the study was discontinued (for any reason) were not to be replaced.

A subject was free to withdraw at any time, for any reason. A subject may also have been removed, if necessary, to protect their health or the integrity of the study. This determination was to be made by the Principal Investigator/Sub-Investigator. Every attempt was to be made to record reasons for withdrawal. Removal of a subject from the study was only to be permitted prior to commencement of bioanalysis.

If a subject's participation was terminated prematurely, the cause for the early termination was to be documented on the source documents and in the final study report.

Subjects who experienced emesis within 10 hours were to be dismissed from the study. Any subjects who experienced diarrhea were to be evaluated on a case by case basis.

Withdrawn and dismissed subjects were not required to adhere to the study specific procedures (e.g. food and fluid restrictions, sample collections). If withdrawn or dismissed following drug administration, these subjects were asked to adhere to the study restrictions in regards to the safety, prescription medication, over-the-counter medication, dietary and/or herbal supplements and/or teas for the expected duration of the restriction relevant to the study period the subject withdrew or was dismissed from (where that period becomes the subject's last study period). Female subjects were asked to adhere to the requirements of not becoming pregnant and using a medically acceptable method of contraception for 30 days after discontinuation in the study (if applicable).

If a subject withdrew or was dismissed from the study, a post-study physical examination and post-study testing were to be completed, where possible.

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9.4 Treatments

9.4.1 Treatments Administered

The study drugs were dispensed into unit dose packages according to the randomization scheme prior to each study period.

In each study period, subjects were dosed according to the randomization scheme with one of the following treatments:

Treatment A: 1 × 10 mg Aripiprazole Tablets
(J. Uriach y Compañía S.A.)

Treatment B: 1 × 10 mg ABILIFY® Tablets
(MAH: Otsuka Pharmaceutical Europe Ltd.)

Subjects were randomized equally into one of the following two sequence groups:

	Period 1	Period 2
Sequence 1	A	B
Sequence 2	B	A

Each subject was scheduled to receive a total of two treatments by the end of the study. The washout interval between drug administrations was 35 days.

9.4.2 Identity of Investigational Product

The following table presents information on the study drugs:

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Treatment Code	A	B
Drug Name:	Aripiprazole	ABILIFY®
Lot No.:	H003	2L69769
Strength:	10 mg	10 mg
Dosage Form:	Tablets	Tablets
Manufacturer:	J. Uriach y Compañía S.A.	MAH: Otsuka Pharmaceutical Europe Ltd.
Potency:	99.5%	98.9%
Manufacturing Date:	05-2013 (07-05-2013 as per Certificate of Analysis)	06/2012 (As per Certificate of Analysis)
Re-test Date	11-2014	N/A
Expiry Date:	N/A	06-2015
Dose:	1 x 10 mg	1 x 10 mg

For Certificates of Analysis please refer to Appendix [16.1.13 Certificates of Analysis](#).

9.4.3 Method of Assigning Subjects to Treatment Groups

In this study, the assignment of treatment groups was generated by a computer program designed internally by the IT (Information Technology) Department of the Sponsor producing a balanced random allocation of subjects into treatment sequences known as the randomization scheme. Subjects were assigned consecutive subject numbers in an ascending order. The randomization scheme provided by the Sponsor used 4-digit numbers (e.g., 0001); however, study source documents used 2-digit numbers (e.g., 01). This number identified the subject and determined the treatment sequence the subject was to undergo. Further, the randomization scheme provided by the Sponsor used Number 1 and Number 2 to assign the treatments to the subjects. The Sponsor clarified that number 1 represented Treatment A and number 2 represented Treatment B. For additional details, see Appendix [16.1.7 Randomization Scheme](#).

9.4.4 Selection of Doses in the Study

A 1 x 10 mg dose was used for this bioequivalence study, as requested by the Sponsor.

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9.4.5 Selection and Timing of Dose for each Subject

Subjects were dosed consecutively according to the randomization scheme beginning at 07:01 on:

- August 09, 2013 for Period 1 and
- September 13, 2013 for Period 2.

Subjects took their assigned formulation, designated by the randomization scheme, after at least a 10-hour fast with 240 mL of ambient temperature water at their scheduled timepoint.

Subjects were instructed not to touch, chew, bite or break the study drug. If a subject chewed, bit or broke the study drug, that subject was to be removed from the study.

A hand and mouth check was conducted by clinic staff immediately following dosing.

9.4.6 Blinding

This study was an open-label trial and, as such, the subjects, staff and Investigators were not blinded as to the identity of the study medication. A member of BioPharma Services Inc. verified the unit-dose packaging of the medication prior to administration to the subjects.

The analytical laboratory did not have access to the randomization scheme until the bioanalytical analysis was complete.

9.4.7 Prior and Concomitant Therapy

The following table presents the restrictions that subjects were to comply with prior to, during and after study conduct:

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Restriction Period	Item Restricted	Examples
6 months prior to first drug administration until the last blood draw in the final study period.	Females: implanted, injected, intravaginal, or intrauterine hormonal contraceptive	
30 days prior to first drug administration until the last blood draw in the final study period.	Enzyme-modifying drugs	Strong inhibitors of CYP enzymes (e.g. Cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem and HIV antivirals); Strong inducers of CYP enzymes (e.g. Barbiturates, carbamazepine, glucocorticoids, phenytoin and rifampin)
	antihypertensive agents	beta blockers, diuretics
	other CNS medicinal products	CNS stimulants
	medicinal products known to cause QT prolongation or electrolyte imbalance	
	famotidine	
	St. John's Wort	
	Females: oral or transdermal hormonal contraceptives	
14 days prior to first drug administration until the last blood draw in the final study period.	Prescription medication	Prescription pills, topical systemic creams, inhalants, sprays.
	Over-the-counter medication, dietary and/or herbal supplements and/or teas	Acetaminophen, Ricola, oral multivitamins
	Note: Spermicidal/barrier contraceptive products may be permitted.	

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Restriction Period	Item Restricted	Examples
10 days prior to first drug administration until the last blood draw in the final study period	Foods and/or beverages containing grapefruit and/or pomelo	Grapefruit, grapefruit juice, grapefruit candies, pomelo, etc.
48 hours prior to drug administration until after the last blood draw in each study period.	Products containing caffeine/methylxanthines	Coffee, tea, chocolate, caffeine-containing soft drinks (e.g. Coke, Pepsi, Red Bull)
	Alcohol of any kind	Wine, beer, liquor, cocktails
	Poppy seeds	Poppy seed cake, cookies, bagels

If any subject did not comply with the aforementioned restrictions, at any time prior to or during the study, or if a restricted item was found with the subject's belongings at check-in, continued participation was to be re-assessed by the Principal Investigator/Sub-Investigator.

Any concomitant medication (prescription or over-the-counter, except for spermicidal/barrier contraceptive products), any herbal formulation or any dietary supplement was not permitted during the study unless deemed otherwise by Principal Investigator/Sub-Investigator.

No concomitant medication or drug use was reported by subjects during the conduct of this study.

9.4.8 Treatment Compliance

Subjects were 100% compliant with the study treatments as they were confined to the clinic for each drug administration. Dosing was performed by one member of the BPSI clinical staff and was supervised by another member. The Investigator was present approximately 30 minutes prior to dosing and until at least 6 hours after the last subject was dosed. The Investigator remained on-call throughout the

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duration of the study.

Clinic staff and source documents confirmed that the study drugs were administered according to the randomization scheme through direct observation of the dosing procedures and recording any events on applicable source documents. Subjects were confined to the clinical facility and their activities were monitored by clinic staff throughout the duration of the confinement period.

Subjects remained awake in a supine position for the first 8 hours following drug administration (starting no longer than 15 minutes after each dose), and were allowed to rise under supervision only for brief periods of time, in order to comply with study-related activities and to use the washroom, after which they were allowed to ambulate freely within the clinic. However, if a medical event (i.e. AE) occurred, subjects may have been placed in an appropriate position at any time. Subjects were required to abstain from strenuous activities for the duration of study period(s).

For 1 hour after each study drug administration, subject visits to the washroom were monitored and recorded by clinic staff. Subjects were restricted from flushing the toilet to allow staff to inspect the content during this time.

Subjects were confined to BPSI clinical facility from at least 10 hours prior to each drug administration until after the 72-hour blood sample collection in each study period.

In each period, an optional snack was provided to each subject after check-in and prior to the fasting period. Subjects fasted overnight for at least 10 hours prior to each drug administration and then subjects fasted for at least 4 hours following each drug administration.

Following a fasting period of at least 4-hours after dosing, subjects were given standardized meals and caffeine/methylxanthine-free beverages at scheduled times. In this study, meals were served at approximately 4.5, 9.5, 13.5, 24.5, 28.5, 33.5, 37.5, 48.5, 52.5, 57.5, 61.5 hours after dosing. Meals and beverages during confinement were identical between each study period.

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With the exception of the water ingested during drug administration, water was not permitted from 1 hour prior to drug administration until 1 hour post-dose, after which water was permitted *ad libitum*.

9.5 Bioequivalence and Safety Variables

9.5.1 Bioequivalence and Safety Measurements Assessed and Flow Chart

Procedure/Activity	Time points				
	Screening	Each Period Check-in	Period 1	Period 2	Post-Study
Screening ICF	X				
ICF		X ^a			
Drugs of Abuse	X	X ^b			
Breath Alcohol	X	X ^b			
Urine Cotinine	X	X ^b			
Serum hCG (females only)	X				
Urine hCG (females only)		X			
BP	X		X ^c	X ^c	X
HR	X		X ^c	X ^c	X
RR	X				X
Temperature	X				X
Laboratory Testing	X				X
Medical History	X				
BMI	X				
ECG	X		X ^d	X ^d	
Inclusion/Exclusion Assessment	X				
Restrictions Compliance Check		X	X ^e	X ^e	
Physical Exam	X				X
Dosing			X	X	
PK Sampling			X ^f	X ^f	
Adverse Event Reporting		X ^g	X ^e	X ^e	X
Meals		X	X	X	

^a- At Period 1 check-in only.

^b- On all subjects.

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- ^c- Vital signs measurements (BP and HR) were obtained at pre-dose, and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 24, 36, 48, 60 and 72 hours after dosing in each study period.
- ^d- ECGs were obtained at pre-dose and at 4 ($\pm$ 1 hour) and 10 ($\pm$ 2 hours) hours after dosing in each study period.
- ^e- Confirmed at each ambulatory blood draw, if applicable.
- ^f- PK sampling - pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hours after dosing in each study period.
- ^g- Pre-dose conditions at Period 1 check-in.

Subject safety was assessed via continuous health monitoring and scheduled recording of safety measurements throughout the study. Staff monitored vital signs (BP and HR) at pre-dose (within 12 hours prior to drug administration), and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 24, 36, 48, 60 and 72 hours after dosing in each study period.

Subjects were instructed to inform clinic personnel of any untoward medical symptoms and/or events that arose during the course of the study. Prior to Period 2, subjects were questioned concerning unusual symptoms that may have occurred after the previous administration of the study drug(s).

The Principal Investigator/Sub-Investigator evaluated the relationship of all adverse events to the study drugs. Each adverse event was assessed as Mild, Moderate or Severe as defined in the protocol. The Principal Investigator/Sub-Investigator also approved the subjects for subsequent dosing.

Post-clinical laboratory tests (hematology, serum chemistry, and urinalysis) and a post-study physical examination including vital sign measurements (blood pressure, pulse rate, temperature and respiration rate) were performed.

9.5.2 Appropriateness of Measurements

According to the EMA guidance¹, the determination of bioavailability is dependent on the reliable, precise and accurate measurement of the concentration levels of the active ingredient of the drug product in blood, plasma, serum or other biological matrices. In this study, plasma samples were assayed for aripiprazole using a validated analytical method. Based on these concentration levels, the C_{max} , T_{max} , and AUC_{72} were estimated in order to characterize the pharmacokinetics of

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the study drugs.

9.5.3 Primary Efficacy Variables (N/A)

Not Applicable.

9.5.4 Drug Concentration Measurements

Blood samples were taken at the following time points: pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hours after dosing.

Blood sampling time adjustments are presented in Appendix [16.2.2 Protocol Deviations](#).

Blood samples were collected from 22 time points in each study period by direct venipuncture or by indwelling catheter into pre-chilled 3 mL K₂EDTA Vacutainer[®] tubes. Samples were centrifuged within 60 minutes from the time of collection at 3000 revolutions per minute (RPM) for 10 minutes under refrigerated (approximately 4°C) conditions.

After centrifugation, the plasma was aspirated and aliquoted into 2 ambient clear polypropylene tubes. A minimum of 0.5 mL plasma was transferred to the first tube, and remaining plasma (if any) was aliquoted into a second tube. Polypropylene tubes were ambient and pre-labeled with Timepoint, Study Number, Study Period, Aliquot Number, Matrix and Subject Number. The samples were stored at -20°C (-15°C or colder) in a freezer pending shipment. Samples were placed in the freezer within 70 minutes from the start of centrifugation.

Throughout sample collection and following centrifugation, the samples were maintained in an ice-bath until stored in the freezer.

All plasma samples were shipped by courier, frozen in dry ice, and were received frozen and in good condition.

Plasma samples were received by the bioanalytical facility (inVentiv Health Clinique inc.) on:

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Periods 1 and 2 Aliquot 1	Periods 1 and 2 Aliquot 2
September 17, 2013	October 01, 2013

9.6 Data Quality Assurance

Quality Assurance (QA) audits were performed throughout the study. After an audit of the report, a QA statement was issued.

Please refer to Appendix [16.1.8 Audit Certificate](#) for the Quality Assurance Statement.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

9.7.1.1 Pharmacokinetic Parameters

The following pharmacokinetic parameters were to be estimated (where possible) for aripiprazole and included in the pharmacokinetic and statistical analysis for the subjects in the final data set:

$C_{\max}$:	The maximal observed plasma concentration.
$T_{\max}$:	Time when the maximal plasma concentration is observed.
AUC_{72} :	Area under the concentration-time curve from time zero to 72 hours.

If a subject's pre-dose concentration was less than or equal to 5% of the $C_{\max}$ value for that subject in the given period, then the subject's data without any adjustments could be included in all pharmacokinetic measurements and calculations. If the pre-dose value was greater than 5% of the $C_{\max}$, data from that subject was to be dropped from the pharmacokinetic and statistical analysis. Data for subjects dropped due to higher than 5% of $C_{\max}$ pre-dose concentrations were to be included in a separate appendix in the final study

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report.

During pharmacokinetic and statistical analyses, drug concentrations below the lower limit of quantitation (BLQ) of an assay were to be considered as zero except when they occurred between two non-BLQ concentrations where they were to be considered as missing during pharmacokinetic calculations and estimations.

Missed samples and non-reportable concentrations (e.g. quantity not sufficient) from the analytical laboratory were to be treated in the pharmacokinetic analysis as if they had not been scheduled for collection.

Data from subjects with lack of any measurable concentrations or only very low plasma concentrations for the reference medicinal product were to be excluded from the analysis. A subject was considered to have very low plasma concentrations if their AUC was less than 5% of the reference medicinal product geometric mean AUC (which should have been calculated without inclusion of data from the outlying subject).

The AUC₇₂ parameter was not to be estimated for plasma concentration-time profiles where the 72 hour blood sample was not available (ie: missing).

9.7.1.2 Statistical Analysis

The data from the following subjects was to be included in the final pharmacokinetic and statistical analysis:

1. Subjects who completed all study periods.
2. Subjects who had missed samples that were pre-determined prior to the start of bioanalytical analysis to not significantly impact the overall outcome of the study.

Data from subjects who were dismissed or who withdrew for any reason were not to be included in the pharmacokinetic and statistical analysis. The data for these subjects was to be presented separately.

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Any decision for excluding data from the final data set was to be provided with a detailed explanation and was to be properly recorded and dated.

The final data set was to be defined prior to sample analysis.

Pharmacokinetic and statistical analysis was to be performed on all data from all subjects in the final data set.

The pharmacokinetic and/or statistical analyses outlined in the protocol may have been altered with appropriate justification.

Pharmacokinetic and statistical analysis was performed by BPSI.

Descriptive statistics (min, max, median, mean, standard deviation and coefficient of variability) of all pharmacokinetic parameters were to be provided for aripiprazole for the Test and Reference products.

ANOVA including sequence, subjects nested within sequence, period and treatment was to be performed on the ln-transformed data for AUC_{72} and C_{max} and on the un-transformed data for T_{max} . T_{max} was to be analyzed using an additional non-parametric test (Wilcoxon test).

The 90% confidence intervals (CI) of the Test/Reference ratios of geometric means for AUC_{72} and C_{max} were to be calculated based on the least square means (LSMEANS) and ESTIMATE of the ANOVA.

Additional statistical and alternate tests may have been performed if necessary.

The pharmacokinetic and statistical analyses were to be performed using SAS[®] Version 9.1.

9.7.2 Determination of Sample Size

A sample size of 30 subjects (which included a moderate buffer for withdrawals and/or dismissals) was estimated to attain at least 80% statistical power to demonstrate bioequivalence between the Test and Reference products, assuming the mean Test to Reference difference was within 5%, based on an estimated

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intrasubject variability of approximately 23%. Subjects who were dosed (and were withdrawn or dismissed) were not replaced.

9.8 Changes in the Conduct of the Study or Planned Analyses

The entire study was conducted as described in the protocol; except for those actions presented as protocol deviations (refer to Appendix [16.2.2 Protocol Deviations](#)). No other changes were made in the conduct of the study or the planned analyses of the samples.

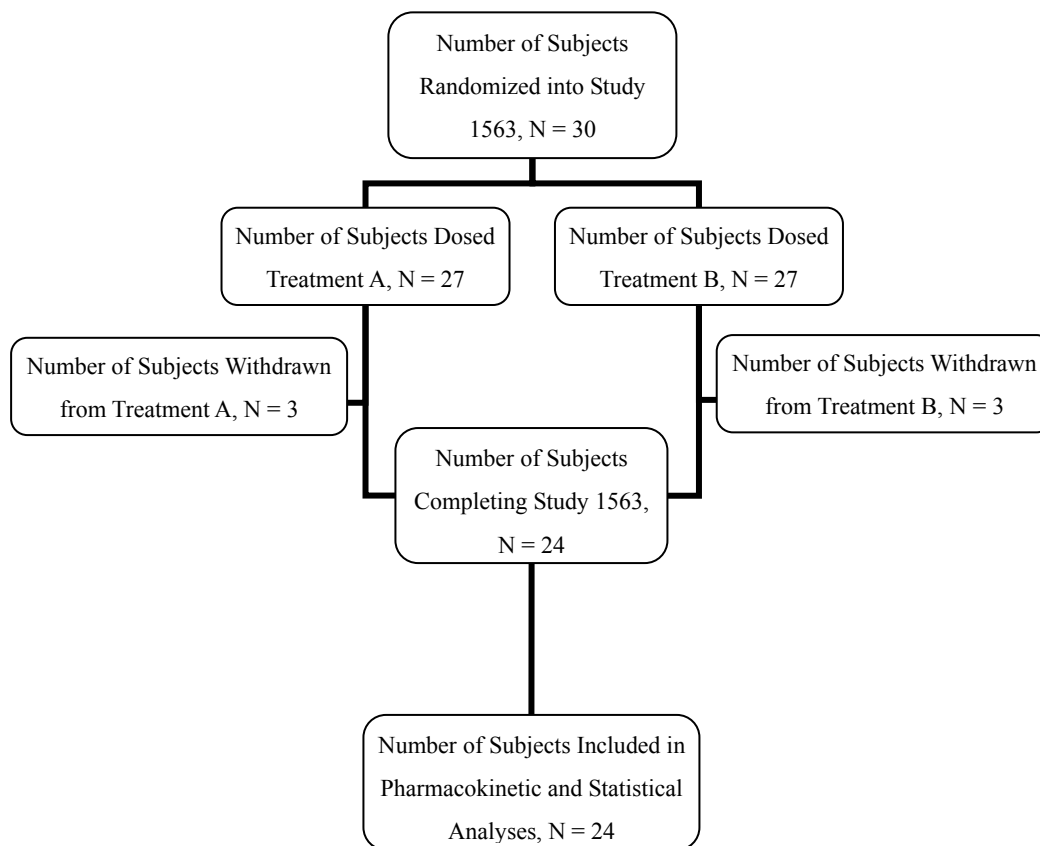
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10.0 Study Subjects

10.1 Disposition of Subjects

Subjects who were selected for this study met the inclusion criteria and did not fulfill any of the exclusion criteria described in the study protocol.



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The following subjects did not complete the study for the following reasons:

Subject	Last Treatment Administered	Reason	Phase of Dropout
01	B	Dismissed due to vomiting as per protocol	During Period 1
02	B	Dismissed due to vomiting as per protocol	During Period 1
05	A	Dismissed due to vomiting as per protocol	During Period 1
12	B	Dismissed due to vomiting as per protocol	During Period 1
16	A	Dismissed due to vomiting as per protocol	During Period 1
22	A	Withdrew due to AEs (dizziness, nausea, and heart rate decreased) experienced in Period 1	Prior to Period 2

Subjects who withdrew or were dismissed were not replaced.

10.2 Protocol Deviations

The following protocol deviations were reported during the conduct of this study:

- The vital signs measurement time is inconclusive for the following:
 - Period 1, Subject 09, Time Point 4hr, BP – due to late correction
 - Period 1, Subject 21, Time Point 24 hr, BP – due to overwriting
 - Period 1, Subject 23, Time Point 6 hr, HR – due to overwriting
- Ongoing AEs were missed to be followed up for 2 weeks after the subjects completed the study for the following:
 - Subject 01 – Burning sensation at upper abdomen area
 - Subject 04 – Nausea
 - Subject 28 – Nausea

Each subject was contacted immediately to follow up on unresolved AE.

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Blood sampling time adjustments greater than or equal to 1 minute and a summary of all protocol deviations are presented in Appendix [16.2.2 Protocol Deviations](#). Sampling times were adjusted using the recorded blood sampling times in the pharmacokinetic analysis in order to more accurately reflect the temporal collection of samples.

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11.0 Bioequivalence Evaluations

11.1 Data Sets Analyzed

Thirty (30) subjects were enrolled in the study. Twenty-four (24) subjects completed the study in its entirety.

Subject 01, Subject 02, Subject 05, Subject 12 and Subject 16 were all dismissed from the study as they experienced emesis within 10 hours following dosing in Period 1.

Subject 22 withdrew prior to Period 2 dosing due to an adverse event (dizziness, nausea, and heart rate decreased) experienced in Period 1.

Overall, samples from thirty (30) subjects were analyzed by the bioanalytical laboratory and data from twenty-four (24) subjects was included in the pharmacokinetic and statistical analyses.

11.2 Demographic and Other Baseline Characteristics

Refer to Appendix [16.2.4 Demographic Data](#) for all subjects enrolled in this study. The following table is for the 24 subjects included in the data set. There were 13 males and 11 females.

	Age	Height		Weight		BMI	Race/Ethnicity	
		(cm)	(in)	(kg)	(lb)			
Mean	53	165.8	65.3	72.9	160.6	26.5	White	10
+/- SD	5	8.8	3.5	8.4	18.6	2.2	Black	4
Median	54	165.8	65.3	73.9	162.8	26.6	Asian	6
							Native	0
Range	45-64	148.8-184.0	58.6-72.4	57.2-87.3	126.1-192.5	21.8-29.5	Hispanic/Latino	4

Subjects enrolled in the study were healthy based upon a medical history assessment, physical examination, vital signs, 12-lead ECG, and clinical laboratory tests (hematology, serum chemistry urinalysis, HIV, Hepatitis B surface antigen, Hepatitis C antibody and serum hCG [females only]), which were performed during screening within 30 days prior to the first drug administration.

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The following laboratory tests were performed:

TYPE OF TEST	COMPONENTS			
Hematology	• Hemoglobin • Hematocrit	• RBC • Platelet count	• WBC and differential • Peripheral blood smear	
Serum Chemistry	• Glucose • Calcium • Sodium • Chloride	• Albumin • Protein • Bilirubin • Lactate Dehydrogenase	• AST • ALT • Potassium • Alkaline Phosphatase	• Urea • Uric Acid • Creatinine • Creatine Kinase
Urinalysis	• Bilirubin • Blood • Glucose	• pH • Ketones • Leukocytes	• Nitrites • Protein	• Specific Gravity • UBG
Additional Tests	Serology (HIV, Hepatitis B surface antigen, Hepatitis C antibody)		Breath alcohol test Urine Cotinine Serum hCG (females only at Screening)	
Urine Tests for Drugs of Abuse	Marijuana, Amphetamines, Phencyclidine, Barbiturates, Cocaine, Opiates, Benzodiazepines			

Urine tests for drugs of abuse (marijuana, amphetamines, phencyclidine, barbiturates, cocaine, opiates and benzodiazepines), cotinine, and a breath alcohol test were performed in-house during screening. All test results at screening for drugs of abuse, cotinine, and breath alcohol were negative.

There were no screening laboratory results outside of normal range that were deemed Clinically Significant by the Investigator.

11.3 Measurements of Treatment Compliance (N/A)

Not Applicable.

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11.4 Bioequivalence Results and Tabulations of Individual Subject Data

11.4.1 Analysis of Bioequivalence

The bioavailability of aripiprazole was estimated for the Test and Reference products. All pharmacokinetic parameters were derived from the plasma concentrations of aripiprazole. Plasma concentrations were measured using a validated analytical method.

Results of the ANOVA are presented in Appendix [16.1.9.1](#), and summarized in Appendices [16.1.9.2](#), [16.1.9.3](#), [16.1.9.4](#), and [16.1.9.5](#). Results of the non-parametric test performed on T_{max} are presented in Appendix [16.1.9.6](#).

To establish bioequivalence, the calculated 90% confidence interval for the ratio of geometric means for AUC_{72} and C_{max} for aripiprazole should fall within 80.00%-125.00%.

11.4.2 Statistical/Analytical Issues

The average bioequivalence analysis was performed using PROC GLM in SAS[®], with SEQ, SUBJECT(SEQ), PERIOD, and TREATMENT as the independent variables and the pharmacokinetic parameters as the dependent variables. All main effects were tested against the mean square error term except where sequence effect was tested against the error term of SUBJECT(SEQ). Least square means (LSMEANS) and the standard errors (ESTIMATE) for the treatment and the differences between treatment means and the standard errors associated with these differences were calculated.

The 90% confidence intervals of the Test/Reference ratios for AUC_{72} and C_{max} were calculated. The confidence intervals are presented for the Test/Reference ratios for the geometric means (obtained from data transformed to their natural logarithms). Power for treatment comparisons for the pharmacokinetic parameters was calculated as the probability (type I error fixed at the 5% level) of detecting a difference at least equal to 20% of the reference treatment mean.

SAS[®] Version 9.1 was used for the statistical analysis and for plotting the data.

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All values below the lower limit of quantitation (BLQ) were considered as zero during the statistical analysis except when they occurred between two non-BLQ concentrations where they were to be considered as missing during pharmacokinetic calculations and estimations.

Actual sampling times were used for the pharmacokinetic calculations and plotting of data to account for adjustment from the scheduled sampling times.

11.4.2.1 Adjustments of Covariates (N/A)

Not Applicable.

11.4.2.2 Handling of Dropouts or Missing Data

Thirty (30) subjects were enrolled in the study. Twenty-four (24) subjects completed the study in its entirety.

Subject 01, Subject 02, Subject 05, Subject 12 and Subject 16 were all dismissed from the study as they experienced emesis within 10 hours following dosing in Period 1. Samples from these subjects were analyzed by the bioanalytical laboratory.

Subject 22 withdrew prior to Period 2 dosing due to an adverse event (dizziness, nausea, and heart rate decreased) experienced in Period 1. Samples from this subject were analyzed by the bioanalytical laboratory.

Data for Subject 01, Subject 02, Subject 05, Subject 12, Subject 16 and Subject 22 are reported in Appendix [16.2.5.4 Data for Subjects Not Included in Analysis](#). Data for these subjects was not included in the pharmacokinetic and statistical analyses.

Overall, samples from thirty (30) subjects were analyzed by the bioanalytical laboratory and data from twenty-four (24) subjects was included in the pharmacokinetic and statistical analyses.

Please refer to Appendix [16.2.1 Discontinued Subjects](#) for a list of discontinued subjects.

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pharmacokinetic analysis as missing.

11.4.2.3 Interim Analysis and Data Monitoring (N/A)

Not Applicable.

11.4.2.4 Multicentre Studies (N/A)

Not Applicable.

11.4.2.5 Multiple Comparison/Multiplicity (N/A)

Not Applicable.

11.4.2.6 Use of an “Efficacy Subset” of Subjects (N/A)

Not Applicable.

11.4.2.7 Active-Control Studies Intended to Show Equivalence (N/A)

Not Applicable.

11.4.2.8 Examination of Subgroups (N/A)

Not Applicable.

11.4.3 Tabulation of Individual Response Data

Individual plasma aripiprazole concentrations reported by the analytical laboratory are tabulated in Appendix [16.2.6.1](#). Results are presented separately for each formulation. Appendix [16.2.6.2](#) contains the summary descriptive statistics of plasma concentrations at each time point for each of the tested formulations, including the minimum, maximum, mean, standard deviation, and coefficient of variation. Individual pharmacokinetic parameters calculated on un-transformed data for AUC_{72} , C_{max} and T_{max} and also on AUC_{72} and C_{max} transformed to their natural logarithms are presented by treatment in Appendix [16.2.6.3](#). Descriptive statistics of the pharmacokinetic parameters are presented by formulation in Appendix [16.2.6.4](#). Ratios of the Test/Reference products for the pharmacokinetic parameters AUC_{72} and C_{max} are presented in Appendix [16.2.6.5](#).

Individual aripiprazole plasma concentrations were plotted against the actual

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sampling times using both linear and semi-logarithmic scales. Mean and individual graphs are presented in Appendix [16.2.6.6](#). The mean graphs are also presented in Section [14.2](#), where Figures 1 and 2 illustrate the mean aripiprazole plasma concentrations for the Test and Reference formulations in linear and semi-logarithmic scales, respectively.

11.4.4 Drug Dose, Drug Concentration, and Relationships to Response (N/A)

Not Applicable.

11.4.5 Drug-Drug and Drug-Disease Interaction (N/A)

Not Applicable.

11.4.6 By-Subject Displays (N/A)

Not Applicable.

11.4.7 Bioequivalence Conclusions

The Test/Reference ratios of geometric means, the corresponding 90% confidence intervals and the intra-subject variability for AUC₇₂ and C_{max} for aripiprazole were as follows:

Pharmacokinetic Parameter	Test/Reference Ratio of Geometric Means (90% Confidence Interval)	Intra-Subject CV (%)
AUC ₇₂	105.91% (101.44% – 110.59%)	8.74%
C _{max}	108.89% (97.49% – 121.61%)	22.62%

The calculated 90% confidence interval for the ratio of geometric means for the ln-transformed AUC₇₂ and C_{max} parameters were entirely contained within the acceptance range of 80.00% to 125.00%.

Therefore, in this study, bioequivalence was demonstrated between Aripiprazole 10 mg Tablets (J. Uriach y Compañía S.A.) and ABILIFY® 10 mg Tablets (MAH: Otsuka Pharmaceutical Europe Ltd.) in normal, healthy, male and female volunteers under fasting conditions.

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A statistically significant treatment effect was observed for the ln-transformed AUC₇₂ parameter. The 90% confidence interval for the ratio of geometric means for the ln-transformed AUC₇₂ parameter was entirely contained within the acceptance range of 80.00% to 125.00%, therefore, it is possible that the statistically significant treatment effect observed is due to low variability. A significant effect for treatment can simply be ignored.

The non-parametric analysis of T_{max} for aripiprazole did not detect a significant difference in T_{max} between the Test and Reference products [Wilcoxon two-sample test, two-sided normal (Z) approximation].

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12.0 Safety Evaluations

12.1 Extent of Exposure (N/A)

Not Applicable.

12.2 Adverse Events

12.2.1 Brief Summary of Adverse Events

There were 79 adverse events involving 30 subjects in this study.

No serious AEs were reported during the conduct of this study.

There were 37 AEs associated with 20 subjects who received Treatment A, which consisted of (in MedDRA Preferred Terminology (PT)):

- Somnolence (14)
- Heart rate decreased (4)
- Nausea (4)
- Headache (3)
- Vomiting (3)
- Diarrhoea (2)
- Dizziness (2)
- Abdominal pain (1)
- Blood pressure decreased (1)
- Catheter site swelling (1)
- Constipation (1)
- Excoriation (1)

Subject 04 had 1 instance each of vomiting and diarrhoea after drug administration with Treatment A in Period 1. For additional details see Section [12.3.1.3 Other Significant Adverse Events](#).

Subject 05 experienced 1 instance of vomiting after drug administration with Treatment A in Period 1. The subject was dismissed from the study due to this AE. For additional details see Section [12.3.1.3 Other Significant Adverse Events](#).

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Subject 16 experienced 1 instance of vomiting after drug administration with Treatment A in Period 1. The subject was dismissed from the study due to this AE. For additional details see Section [12.3.1.3 Other Significant Adverse Events](#).

Subject 25 had 1 instance of diarrhoea after drug administration with Treatment A in Period 1. For additional details see Section [12.3.1.3 Other Significant Adverse Events](#).

Subject 22 experienced 1 instance each of dizziness, nausea, and heart rate decreased after drug administration with Treatment A in Period 1. The subject withdrew from the study due to these AEs. For additional details see Section [12.3.1.3 Other Significant Adverse Events](#).

There were 37 AEs associated with 24 subjects who received Treatment B, which consisted of (in MedDRA Preferred Terminology (PT)):

- Somnolence (20)
- Blood pressure decreased (3)
- Vomiting (3)
- Heart rate decreased (3)
- Nausea (3)
- Dizziness (2)
- Blood pressure increased (1)
- Abdominal pain upper (1)
- Abdominal discomfort (1)

Subject 01 experienced 1 instance of vomiting after drug administration with Treatment B in Period 1. The subject was dismissed from the study due to this AE. For additional details see Section [12.3.1.3 Other Significant Adverse Events](#).

Subject 02 experienced 1 instance of vomiting after drug administration with Treatment B in Period 1. The subject was dismissed from the study due to this AE. For additional details see Section [12.3.1.3 Other Significant Adverse Events](#).

Subject 12 experienced 1 instance of vomiting after drug administration with Treatment B in Period 1. The subject was dismissed from the study due to this AE. For additional details see Section [12.3.1.3 Other Significant Adverse Events](#).

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There were 5 AEs associated with 3 subjects at post-study, which consisted of (in MedDRA Preferred Terminology (PT)):

- Blood lactate dehydrogenase increased (1)
- Blood potassium increased (1)
- Eosinophil count increased (1)
- Neutrophil count decreased (1)
- White blood cell count decreased (1)

12.2.2 Display of Adverse Events

All adverse events are summarized in Appendix [14.3.1 Displays of Adverse Events](#).

12.2.3 Analysis of Adverse Events

The table below presents severity, relationship to study drug and action taken for adverse events reported in this study per treatment.

Treatment Group	Severity			Relationship to Drug				Intervention		
	Mild	Moderate	Severe	Unrelated	Unlikely	Possible	Probable	Pharmacologic	Other	None
A	29	8	0	2	6	3	26	0	5	32
B	32	5	0	3	4	5	25	0	3	34
N/A	5	0	0	0	3	2	0	0	0	5
Total	66	13	0	5	13	10	51	0	8	71

12.2.4 Listing of Adverse Events by Subject

Refer to Appendix [16.2.7 Adverse Event Listings](#).

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other Serious Adverse Events and Other Significant Adverse Events (N/A)

Not Applicable.

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12.3.1.1 Deaths (N/A)

Not Applicable.

12.3.1.2 Other Serious Adverse Events (N/A)

Not Applicable.

12.3.1.3 Other Significant Adverse Events

Subject 01 experienced 1 instance of vomiting at 1.08 hours after drug administration with Treatment B in Period 1. The AE was documented as moderate in severity and was deemed probably related to the study drug by the Investigator. The AE was considered resolved at 2.67 hours after onset with no action taken. The subject was dismissed from the study due to this AE.

Subject 02 experienced 1 instance of vomiting at 5.08 hours after drug administration with Treatment B in Period 1. The AE was documented as moderate in severity and was deemed probably related to the study drug by the Investigator. The AE was considered resolved at approximately 30 seconds after onset with no action taken. The subject was dismissed from the study due to this AE.

Subject 04 had the following AEs after drug administration with Treatment A in Period 1:

- 1 instance of vomiting at 16.02 hours after drug administration. This AE was documented as moderate in severity and was deemed as probably related to the study drug by the Investigator. The AE was considered resolved at 0.03 hours (approximately 2 minutes) after onset with no action taken.
- 1 instance of diarrhoea at 12.13 hours after drug administration. This AE was documented as moderate in severity and was deemed as unlikely related to the study drug by the Investigator. The AE was considered resolved at 0.05 hours (approximately 3 minutes) after onset with no action taken.

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Subject 05 experienced 1 instance of vomiting at 2.35 hours after drug administration with Treatment A in Period 1. The AE was documented as moderate in severity and was deemed probably related to the study drug by the Investigator. The AE was considered resolved at 0.03 hours (approximately 2 minutes) after onset with no action taken. The subject was dismissed from the study due to this AE.

Subject 12 experienced 1 instance of vomiting at 3.48 hours after drug administration with Treatment B in Period 1. The AE was documented as moderate in severity and was deemed probably related to the study drug by the Investigator. The AE was considered resolved at 0.02 hours (approximately 1 minute) after onset with no action taken. The subject was dismissed from the study due to this AE.

Subject 16 experienced 1 instance of vomiting at 2.13 hours after drug administration with Treatment A in Period 1. The AE was documented as moderate in severity and was deemed probably related to the study drug by the Investigator. The AE was considered resolved at 1.00 hour after onset with no action taken. The subject was dismissed from the study due to this AE.

Subject 22 experienced the following AEs after drug administration with Treatment A in Period 1. The subject withdrew from the study due to these AEs:

- 1 instance of dizziness at 4.78 hours after drug administration. The AE was documented as moderate in severity and was deemed probably related to the study drug by the Investigator. The AE was considered resolved at 0.33 hours after onset following the elevation of the subject's legs.
- 1 instance nausea at 4.70 hours after drug administration. The AE was documented as mild in severity and was deemed probably related to the study drug by the Investigator. The AE was considered resolved at 17.58 hours after onset with no action taken.

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- 1 instance of heart rate decreased at 5.33 hour after drug administration. The AE was documented as mild in severity and was deemed unlikely related to the study drug by the Investigator. The AE was considered resolved at 1.22 hours after onset with no action taken.

Subject 25 experienced 1 instance of diarrhoea at 27.18 hours after drug administration with Treatment A in Period 1. The AE was documented as moderate in severity and was deemed as unlikely related to the study drug by the Investigator. The AE was considered resolved at 5.50 hours after onset with no action taken.

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events (N/A)

Not Applicable.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events (N/A)

Not Applicable.

12.4 Clinical Laboratory Evaluations

All subjects underwent urine tests for drugs of abuse, cotinine, and an alcohol breath test at check-in for each study period. All female subjects underwent a urine hCG test at check-in for each study period. All test results at check-in for drugs of abuse, cotinine, breath alcohol and pregnancy were negative.

The clinical laboratory tests (hematology, serum chemistry and urinalysis) were repeated prior to discharge at the end of the study or after termination of subjects from the study.

12.4.1 Abnormal Laboratory Value(s)

Subject 08 had the following laboratory tests outside of normal range at post-study: decreased white blood cell count and decreased neutrophil count. These findings were documented as mild AEs and were deemed unlikely related to the study drug by the Investigator. Upon repeat testing for each parameter, results

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returned to normal. Both AEs were considered resolved at 196.88 hours (approximately 8 days) after onset with no action taken.

Subject 10 had the following laboratory tests outside of normal range at post-study: increased blood lactate dehydrogenase and increased eosinophil count. These findings were documented as mild in severity. One instance of blood lactate dehydrogenase increased was deemed unlikely related to the study drugs and one instance of eosinophil count increased was deemed possibly related to the study drugs by the Investigator. Upon repeat testing for blood lactate dehydrogenase increased, results returned to normal. Upon repeat testing for eosinophil count increased, results remained out of acceptable range and were deemed not clinically significant by the Investigator. Both AEs were considered resolved at 218.30 hours (approximately 9 days) after onset with no action taken.

Subject 26 had the following laboratory test outside normal range at post-study: increased blood potassium. This finding was documented as a mild AE and was deemed possibly related to the study drugs by the Investigator. Upon repeat testing, results remained outside of acceptable range and were deemed not clinically significant by the Investigator. The AE was considered resolved at 193.33 hours (approximately 8 days) after onset with no action taken.

There were no screening or other post-study laboratory results outside of normal range that were deemed Clinically Significant by the Investigator.

12.4.2 Evaluations of Each Laboratory Parameter (N/A)

Not Applicable.

12.4.2.1 Laboratory Values Over Time (N/A)

Not Applicable.

12.4.2.2 Individual Subject Changes (N/A)

Not Applicable.

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12.4.2.3 Individual Clinically Significant Abnormalities (N/A)

Not Applicable.

12.5 Vital Signs, Physical Findings and other Observations Related to Safety

During the conduct of the study, several subjects experienced AEs related to vital sign measurements. Figure 1 details the subjects who had vital sign measurement AEs, along with the number of episodes associated with the last treatment they were administered.

Figure 1

Adverse Event	Subject Number	Treatment A		Treatment B	
		No. of Occurrences	Relationship to Study Drug	No. of Occurrences	Relationship to Study Drug
Blood pressure decreased	01	--	--	1	Probable
	04	1	Possible	--	--
	30	--	--	1	Possible
	30	--	--	1	Unrelated
Blood pressure increased	23	--	--	1	Possible
Heart rate decreased	07	1	Unlikely	--	--
	09	1	Unlikely	--	--
	14	--	--	1	Unlikely
	15	--	--	1	Unlikely
	22	1	Unlikely	--	--
	27	1	Unlikely	1	Unlikely

The subjects who experienced AEs related to vital sign measurements were monitored until resolution. Details of the AEs associated with vital sign measurements such as Severity, time from dosing AE occurred etc., are listed in Section [16.2.7 Adverse Event Listings](#).

All other vital signs measurements were within normal range, returned to normal after repeated measurements, or were deemed Not Clinically Significant by the Investigator.

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All AEs were followed until resolution, regardless of whether the subject was still participating in the study or not.

12.6 Safety Conclusions

No serious AEs were reported during the conduct of this study. Both study drugs were well tolerated by all subjects.

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13.0 Discussion and Overall Conclusions

No serious AEs were reported during the conduct of this study. Both the test product and reference product were relatively well tolerated by all subjects.

The calculated 90% confidence interval for the ratio of geometric means for the ln-transformed AUC_{72} and C_{max} parameters were entirely contained within the acceptance range of 80.00% to 125.00%.

Therefore, in this study, bioequivalence was demonstrated between Aripiprazole 10 mg Tablets (J. Uriach y Compañía S.A.) and ABILIFY® 10 mg Tablets (MAH: Otsuka Pharmaceutical Europe Ltd.) in normal, healthy, male and female volunteers under fasting conditions.

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14.0 Tables, Figures and Graphs Referred To But Not Included in the Text

14.1 Demographic Data Summary figures and tables

14.1.1 Summary of Demographic Characteristics

The table below presents the demographics for all subjects enrolled in this study (subjects receiving at least one treatment) and for all subjects completing the study in its entirety (subjects that did not withdraw or were dismissed). Demographics for all subjects included in the final data set are presented in Section [11.2 Demographic and Other Baseline Characteristics](#).

Characteristic	Statistic	Completed	Enrolled
Age (years)	Number of Subjects	24	30
	Mean	53	54
	SD	5	6
	Median	54	54
	Range	45-64	45-64
Gender	Number of Subjects n (%)	24	30
	Female	11 (45.83%)	15 (50%)
	Male	13 (54.17%)	15 (50%)
Ethnicity-Race	Number of Subjects n (%)	24	30
	White	10 (41.67%)	15 (50%)
	Black	4 (16.67%)	4 (13.33%)
	Asian	6 (25%)	6 (20%)
	Native	0 (0%)	0 (0%)
	Hispanic/Latino	4 (16.67%)	5 (16.67%)
	Other	0 (0%)	0 (0%)
BMI (Kg/m²)	Number of Subjects	24	30
	Mean	26.5	26.5
	SD	2.2	2.1
	Median	26.6	26.6
	Range	21.8-29.5	21.8-29.5
Height (cm)	Number of Subjects	24	30
	Mean	165.8	164.7
	SD	8.8	9.4
	Median	165.8	164.9
	Range	148.8-184.0	146.0-184.0

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Characteristic	Statistic	Completed	Enrolled
Weight (Kg)	Number of Subjects	24	30
	Mean	72.9	72.0
	SD	8.4	9.4
	Median	73.9	73.2
	Range	57.2-87.3	51.7-87.3

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14.1.2 Treatment Groups Demographics

The table below presents the demographics for all subjects enrolled in this study, summarized by treatment group. Demographics for all subjects who received at least one treatment are included in this table, regardless of whether or not the subject completed the study in its entirety (i.e. withdrew or was dismissed) or was included in the final data set.

	TRT A N = 27	TRT B N = 27
Age (years)		
Mean $\pm$ SD	54 $\pm$ 6	54 $\pm$ 5
Range	45-64	45-64
Age Groups		
< 18	0 (0%)	0 (0%)
18 – 40	0 (0%)	0 (0%)
41 – 64	27 (100%)	27 (100%)
65 – 75	0 (0%)	0 (0%)
> 75	0 (0%)	0 (0%)
Sex		
Female	13 (48%)	13 (48%)
Male	14 (52%)	14 (52%)
Race		
Asian	6 (22%)	6 (22%)
Black	4 (15%)	4 (15%)
White	13 (48%)	12 (44%)
Native	0 (0%)	0 (0%)
Hispanic/Latino	4 (15%)	5 (19%)
Other	0 (0%)	0 (0%)
BMI		
Mean $\pm$ SD	26.5 $\pm$ 2.1	26.4 $\pm$ 2.1
Range	21.8-29.5	21.8-29.5

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14.2 Bioequivalence Data

Statistical Methods:

Descriptive statistics (min, max, median, mean, standard deviation and coefficient of variability) of all pharmacokinetic parameters were provided for the test and reference products.

ANOVA including sequence, subjects nested within sequence, period and treatment was performed on the ln-transformed data for AUC₇₂ and C_{max}, and on the un-transformed data for T_{max}. T_{max} was analyzed using an additional non-parametric test.

The 90% confidence intervals (CI) of the Test/Reference ratios of geometric means for AUC₇₂ and C_{max} were calculated based on the least square means (LSMEANS) and ESTIMATE of the ANOVA.

Bioequivalence Results:

Aripiprazole: (N=24)

Bioequivalence Analysis Results For Plasma Aripiprazole							
TREATMENT A vs TREATMENT B							
Parameter (N/N)	Geometric Means Arithmetic Means (CV %)				Ratio of Geometric Means	90% Confidence Interval	Intra- Subject CV (%)
	TRT A		TRT B				
AUC72 (ng.h/mL) (24 /24)	1400.01 1436.55	(23.25)	1321.85 1357.25	(24.90)	105.91	101.44 - 110.59	8.74
C _{MAX} (ng/mL) (24 /24)	41.81 44.95	(37.45)	38.40 40.80	(43.35)	108.89	97.49 - 121.61	22.62
T _{max} * (h) (24 /24)	2.26 (1.00 - 36.00)		3.28 (1.50 - 5.00)				

* Presented as median and range

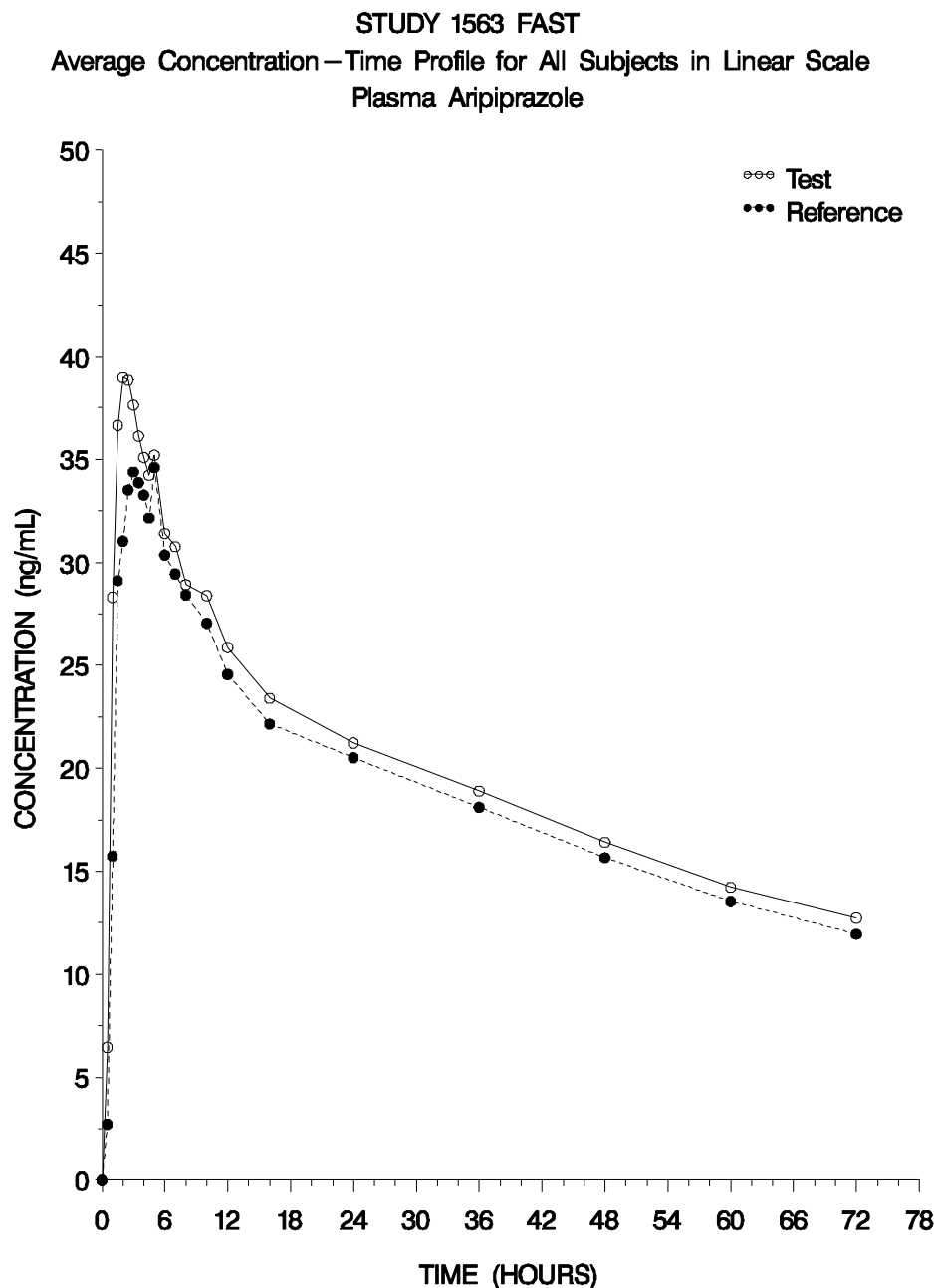
TRT A: Aripiprazole 10 mg Tablets; Lot No: H003; (J. Uriach y Compañía S.A.)

TRT B: ABILIFY® 10 mg Tablets; Lot No: 2L69769; (MAH: Otsuka Pharmaceutical Europe Ltd.)

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Figure 1: The mean plasma concentration profile for aripiprazole in linear scale plot

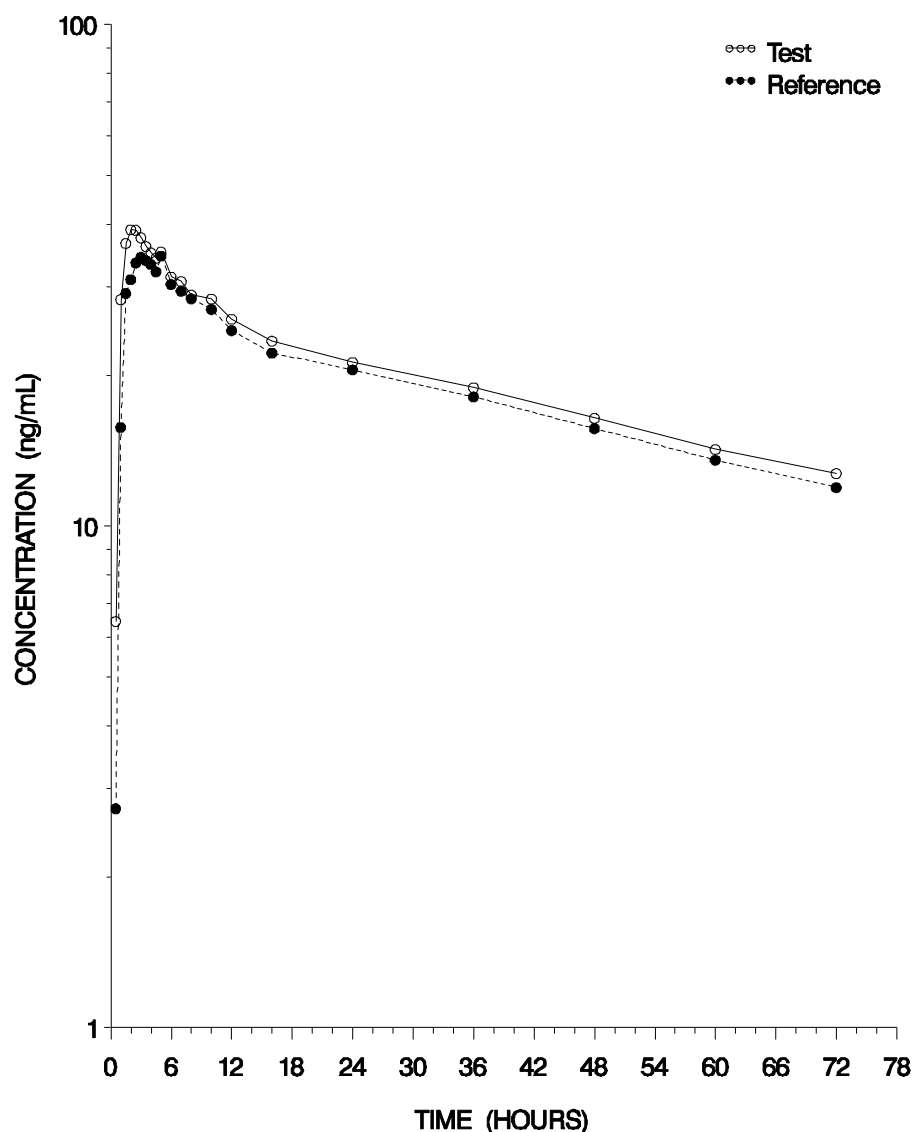


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Figure 2: The mean plasma concentration profile for aripiprazole in semi-log scale plot

STUDY 1563 FAST
Average Concentration–Time Profile for All Subjects in Semi–logarithmic Scale
Plasma Aripiprazole



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14.3 Safety Data

14.3.1 Displays of Adverse Events

The adverse events were coded using MedDRA terminologies and summarized below by treatment group. Adverse events are presented as a percentage of the total number of subjects who received that treatment.

Adverse events occurring at post-study related to clinical laboratory tests were not associated with a treatment and are presented in a separate table below. Please refer to Appendix [16.2.7 Adverse Event Listings](#) for detailed listings.

System Organ Classification/ Preferred Term (PT)	Reported Incidence by Treatment Group	
	TRT A (N = 27)	TRT B (N = 27)
Investigations		
Blood pressure decreased	1 (3.7%)	3 (11.1%)
Heart rate decreased	4 (14.8%)	3 (11.1%)
Blood pressure increased	0 (0.0%)	1 (3.7%)
Gastrointestinal disorders		
Vomiting	3 (11.1%)	3 (11.1%)
Diarrhoea	2 (7.4%)	0 (0.0%)
Abdominal pain	1 (3.7%)	0 (0.0%)
Constipation	1 (3.7%)	0 (0.0%)
Abdominal pain upper	0 (0.0%)	1 (3.7%)
Abdominal discomfort	0 (0.0%)	1 (3.7%)
Nausea	4 (14.8%)	3 (11.1%)
Nervous system disorders		
Headache	3 (11.1%)	0 (0.0%)
Somnolence	14 (51.9%)	20 (74.1%)
Dizziness	2 (7.4%)	2 (7.4%)
Skin and subcutaneous tissue disorders		
Excoriation	1 (3.7%)	0 (0.0%)
General disorders and administration site conditions		
Catheter site swelling	1 (3.7%)	0 (0.0%)
Total	37 (137.0%)	37 (137.0%)

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System Organ Classification/ Preferred Term (PT)	Reported Incidence at Post-Study (N = 30)
Investigations	
White blood cell count decreased	1 (3.3%)
Neutrophil count decreased	1 (3.3%)
Blood lactate dehydrogenase increased	1 (3.3%)
Eosinophil count increased	1 (3.3%)
Blood potassium increased	1 (3.3%)
Total	5 (16.7%)

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events (N/A)

Not Applicable.

14.3.3 Narratives of Deaths, Other Serious and Certain other Adverse Events (N/A)

Not Applicable.

14.3.4 Abnormal Laboratory Value Listing

Subject 08 had the following laboratory tests outside of normal range at post-study: decreased white blood cell count and decreased neutrophil count. These findings were documented as mild AEs and were deemed unlikely related to the study drug by the Investigator. Upon repeat testing for each parameter, results returned to normal. Both AEs were considered resolved at 196.88 hours (approximately 8 days) after onset with no action taken.

Subject 10 had the following laboratory tests outside of normal range at post-study: increased blood lactate dehydrogenase and increased eosinophil count. These findings were documented as mild in severity. One instance of blood lactate dehydrogenase increased was deemed unlikely related to the study drugs and one instance of eosinophil count increased was deemed possibly related to the study drugs by the Investigator. Upon repeat testing for blood lactate dehydrogenase increased, results returned to normal. Upon repeat testing for eosinophil count increased, results remained out of acceptable range and were deemed not clinically significant by the Investigator. Both AEs were considered resolved at 218.30 hours (approximately 9 days) after onset with no action taken.

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Subject 26 had the following laboratory test outside normal range at post-study: increased blood potassium. This finding was documented as a mild AE and was deemed possibly related to the study drugs by the Investigator. Upon repeat testing, results remained outside of acceptable range and were deemed not clinically significant by the Investigator. The AE was considered resolved at 193.33 hours (approximately 8 days) after onset with no action taken.

There were no screening or other post-study laboratory results outside of normal range that were deemed Clinically Significant by the Investigator.

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15.0 Reference List

1. Guidance for Industry – Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Consider. Center for Drug Evaluation and Research (CDER), Food and Drug Administration. March 2003.
2. ABILIFY[®] Product Information

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