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A Randomised, Open-Label, Multiple-Dose, Steady-State, Replicate, Crossover, Bioequivalence Study of Aripiprazole 400 Mg Powder and Solvent for Prolonged-Release Suspension for Injection in Adult Patients with Schizophrenia

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A B S T R A C T

Background: The objectives of this study were to demonstrate the bioequivalence and to evaluate the safety & tolerability of Aripiprazole 400 mg Powder and Solvent for Prolonged-Release Suspension for Injection of Sun Pharmaceutical Industries Limited and Abilify Maintena 400 mg Powder and Solvent for Prolonged-Release Suspension for Injection of Otsuka Pharmaceutical Europe Ltd. in schizophrenic patients under fasting condition according to the Europe guidelines.

Materials and methods: This was a randomised, open-label, two-treatment, two-period, two-sequence, multicentre, multiple-dose, steady-state, replicate, crossover study assessing the bioequivalence in 60 adult patients with schizophrenia under fasting condition. There was no washout between two periods. During the treatment period, eligible patients were randomized in a ratio of 1:1 to either of two sequences i.e., Test product (T) to Reference product (R), or Reference product (R) to Test product (T). Patients received six consecutive doses of 400 mg Test product or 400 mg Reference product of Aripiprazole Prolonged-Release Injectable Suspension 400 mg/vial (2.0 mL) at predefined injection site into the gluteal (buttock) muscle region by deep intramuscular route, 28 days apart in a crossover design, during the two periods (Period I and Period II). Safety, tolerability, and pharmacokinetics (PK) were evaluated throughout the study.

Safety assessments included measurement and monitoring of vital signs, physical examination including COVID-19 examination, weight/BMI examination, injection site reaction assessment, evaluation of severity of illness by assessing Clinical Global Impression – Severity of illness (CGI-S) scale, Suicidality Behavior, Neuroleptic Malignant Syndrome and any Extra Pyramidal Adverse Assessment, 12 lead ECG, Urine drug screen and alcohol urine test, prior and concomitant medication review, adverse events assessment and clinical laboratory assessment.

Primary PK endpoints were area under the concentration–time curve (AUC0-τ) at steady state from Day 0 to 28 post dose, maximum concentration (Cmax) and plasma concentration of aripiprazole at the end of dosing interval at steady state, C□ss (i.e. at 28 day) after the 5th & 6th dose of Test & Reference product.

Bioequivalence was assessed for Aripiprazole using 90% confidence intervals (CIs) of geometric mean ratios (GMRs) for AUC0-□, Cmaxss and C□ss.

Results: Total 69 patients were randomized in the study. Of these randomized 69 patients, 60 patients completed the study. Of the dosed 69 patients, 37 (53.62%) were male & 32 (46.38%) were female. All the 69 patients were of Asian origin having mean age of 40.3 years. The incidence of treatment-emergent adverse events (TEAEs) was similar between Test (31.82%) & Reference treatment (33.85%). The most frequently reported TEAEs were headache (Test: 4.55%; Reference: 4.62%) & pyrexia (Test: 3.03%; Reference: 4.62%).

The ratios of the least-squares geometric means of the Test to Reference product (T/R) for aripiprazole were 99.09% for AUC0-τ, 98.18 % for Cmaxss and 98.03 % for Cτss. Bioequivalence was concluded since the BE limits of the main pharmacokinetic parameters for aripiprazole were within the acceptable limits (80.00–125.00%).

Conclusions: Aripiprazole 400 mg Powder and Solvent for Prolonged-Release Suspension for Injection and Abilify Maintena 400 mg Powder and Solvent for Prolonged-Release Suspension for Injection were found to be bioequivalent and safe under steady state condition in schizophrenic patients.

Keywords: Aripiprazole, Abilify Maintena, Bioequivalence, Pharmacokinetic, Steady state condition, Schizophrenia

1. Introduction

Schizophrenia is a chronic, disabling, and progressive disease characterised by delusions, hallucinations, and cognitive impairment; symptoms and disease course differ across patients. Pharmacological therapy, which is used for relief of acute psychotic episodes and prevention of subsequent relapse, is essential for the effective management of schizophrenia. Aripiprazole is a quinolinone antipsychotic that is a partial agonist at the D2 and 5HT-1a receptors and an

antagonist at the 5HT-2a receptor. It has a high affinity for D2, D3, 5HT-1a, and 5HT2a receptors and moderate affinity for D4,5HT-2c, 5-HT7, alpha-1 adrenergic, and H1 receptors.

The study included a screening period within 21 days prior to the initiation of stabilization procedures (as applicable) OR within 21 days of the first IMP administration on Day 1 (in the absence of additional stabilisation requirements), stabilisation procedures (as applicable) for at least 3 months, treatment period of 48 weeks and an end of study visit on Day 337 of Period II.

Each patient received a total of 12 doses of Aripiprazole 400 mg Powder and Solvent for Prolonged-Release Suspension for Injection, at a dosing interval of 28 days.

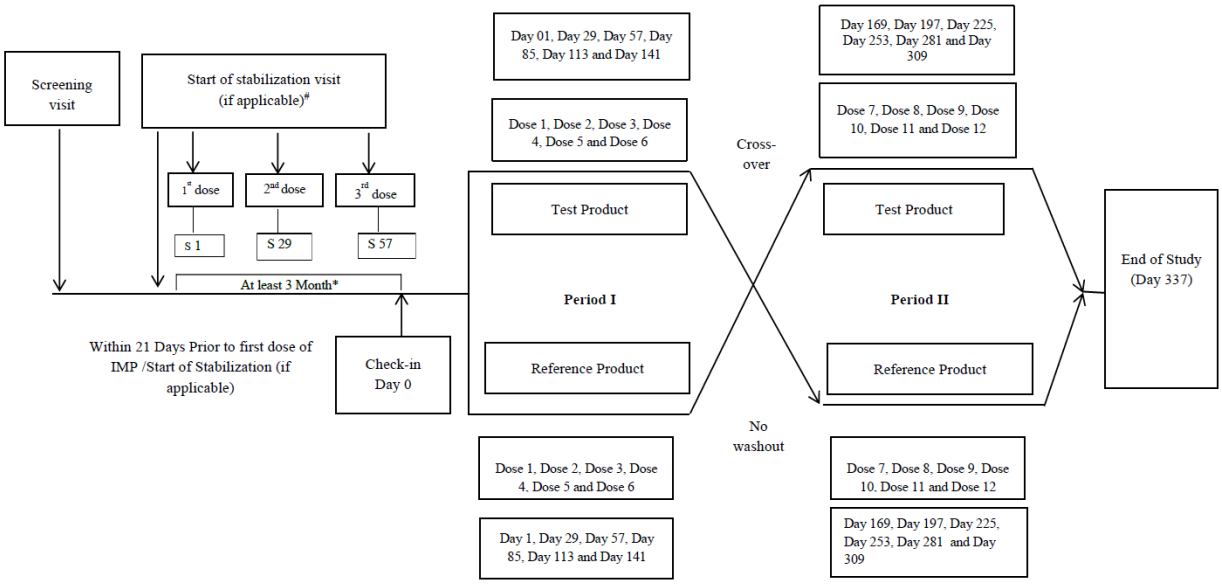

Figure 1. Study design. *Stabilisation period between screening and randomisation (Day 1) is applicable for all the patients who are not already under treatment with a stable regimen of Aripiprazole Prolonged/Extended Release Injectable Suspension for at least 3 doses via the intramuscular route.

For patients who have not taken oral aripiprazole, oral aripiprazole (10 mg to 20 mg) will be given for 3-14 days prior to initiating aripiprazole prolonged/extended release injectable suspension 400 mg to establish tolerability. If treatment is well tolerated, Aripiprazole Prolonged-Release Injectable Suspension 400 mg will be injected at dosing interval of 28 (±1) days into the gluteal muscle until 3 consecutive monthly doses.

2. Materials and methods

2.1 Study products

The study drugs (Test and Reference) were supplied by the sponsor (i.e. Sun Pharmaceutical Industries Limited, India). Characteristics of the study products are presented in Table 1.

Table 1. Characteristics of the study products.

	Test Product	**Reference Product**
Name:	Aripiprazole 400 mg Powder and Solvent for Prolonged-Release Suspension for Injection	Abilify Maintena (Aripiprazole) 400 mg Powder and Solvent for Prolonged-Release Suspension for Injection
Manufacturer	Sun Pharmaceutical Industries Limited.	Marketing authorisation holder: Otsuka Pharmaceutical Netherlands B.V. Herikerbergweg 292, 1101 CT, Amsterdam, Netherlands.
Product I.D.	Batch No.: HADE028B	Lot No.: 2705456
Manufacture Date:	03/2022	NA
Expiry Date:	02/2024	11/2023
Dosage form	Powder and Solvent for Prolonged-Release Suspension for Injection	Powder and Solvent for Prolonged-Release Suspension for Injection
Dose	Six doses, each dose of 400 mg at every 28 days into	Six doses, each dose of 400 mg at every 28 days into the gluteal
Mode of Administration:	Intramuscular injection	Intramuscular injection

2.2 Study design

This was a randomised, open-label, two-treatment, two-period, two-sequence, multicentre, multiple-dose, steady-state, replicate, crossover bioequivalence study. The study started on 26 May 2022 and was completed on 15 November 2023. Participants were enrolled into the study at 09 clinical sites**.** The study protocol and related documents were reviewed and approved by the Ethics Committee of respective site. The clinical study complied with the Declaration of Helsinki, Good Clinical Practice Guidelines of the ICH and the applicable EU regulations. Written informed consent was obtained from all the participants prior to the study.

The study included a screening period, stabilisation period (as applicable), treatment period and an end of study visit.

Screening period: Screening safety assessments were performed within 21 days prior to the initiation of stabilisation procedures OR within 21 days of the first Investigational Medicinal Product (IMP) administration on Day 1 (in the absence of additional stabilisation requirements).

Any screened patient who met eligibility criteria was categorized under one of the below four categories:

Category 1: Patients who were already on stable monthly regimen of Aripiprazole Prolonged/ Extended Release Injectable Suspension 400 mg for the treatment of schizophrenia and had received at least 3 consecutive monthly stable doses. These patients directly entered the treatment period after screening.

Category 2: Patients who were already on a monthly regimen of Aripiprazole Prolonged/ Extended Release Injectable Suspension 400 mg but had received a total of less than 3 consecutive monthly doses into the gluteal muscle at the time of screening, additional (one or two) required doses of Aripiprazole Prolonged/Extended Release Injectable Suspension 400 mg were continued at a dosing interval of 28 (±1) days until at least a minimum of three consecutive monthly doses were administered into the gluteal muscle as per investigator's discretion.

Category 3: Patients who were already on stable regimen of oral Aripiprazole 10-20 mg were switched to a monthly regimen of Aripiprazole Prolonged/Extended Release Injectable Suspension 400 mg based on clinical grounds as per investigator discretion. Patient who required chronic antipsychotic treatment and who benefited from initiating treatment with Aripiprazole Prolonged/Extended Release Injectable Suspension 400 mg were switched from their oral dose regimen to injectable dose regimen. Aripiprazole Prolonged/Extended Release Injectable Suspension 400 mg was injected at a dosing interval of 28 (±1) days into the gluteal muscle until 3 consecutive monthly doses. Aripiprazole oral therapy was continued for 14 days after the first injection to maintain the therapeutic concentration.

Category 4: For patients who had not taken oral aripiprazole, tolerability was established by giving oral aripiprazole (10 mg to 20 mg) for 3-14 days prior to initiating Aripiprazole Prolonged/Extended Release Injectable Suspension 400 mg. As the treatment was well tolerated, Aripiprazole Prolonged/Extended Release Injectable Suspension 400 mg was injected at dosing interval of 28 (±1) days into the gluteal muscle until 3 consecutive monthly doses. Aripiprazole oral therapy was given for 14 consecutive days after the first injection to maintain the therapeutic concentration.

Stabilisation period: Stabilisation period was applicable for patient falling under Category 2, 3 and 4.

Stabilisation of category 2 patients: Since category 2 patients had taken a total of less than 3 monthly doses of Aripiprazole Prolonged/Extended Release Injectable Suspension 400 mg, additional (one or two) required doses of Aripiprazole Prolonged/Extended Release Injectable Suspension 400 mg were injected into the gluteal muscle were continued at a dosing interval of 28 (±1) days until at least a minimum of 3 monthly doses were administered in a consecutive manner. Patient eligibility was confirmed prior to study randomisation.

Stabilisation of category 3 patients: Category 3 patients who were on a stable regimen of oral Aripiprazole therapy and met the study eligibility criteria as well as the criteria for treatment with Aripiprazole Prolonged/Extended Release Injectable Suspension 400 mg based on the judgement of the treating physician or investigator, received Aripiprazole Prolonged/Extended Release Injectable Suspension 400 mg administered into the gluteal muscle. In conjunction with first dose, patients were instructed to take concurrent oral aripiprazole (10 mg to 20 mg) for 14 consecutive days to maintain therapeutic concentration following the label of Aripiprazole Prolonged/Extended Release Injectable Suspension 400 mg.

Stabilisation of category 4 patients: Oral aripiprazole (10 mg to 20 mg) was given for 3-14 days prior to initiating aripiprazole prolonged/extended release injectable suspension 400 mg to establish tolerability. As the treatment was well tolerated, Aripiprazole Prolonged/Extended Release Injectable Suspension 400 mg was injected at dosing interval of 28 (±1) days into the gluteal muscle until 3 consecutive monthly doses. Aripiprazole oral therapy was given for 14 consecutive days after the first injection to maintain the therapeutic concentration.

Note: All injections administered no sooner than 26 days after the previous injection for Category 2, 3 & 4.

Patients administered 3 doses of Aripiprazole Prolonged/Extended Release Injectable Suspension 400 mg at Day 1, Day 29 (±1 day) and Day 57 (±1 day) into the gluteal site as per investigators discretion. These patients were also continued on the current oral Aripiprazole 10-20 mg (locally sourced) for the first 14 days after the first intramuscular injection of the stabilisation period in order to maintain adequate therapeutic plasma Aripiprazole concentrations.

After completion of 3 doses, these patients were eligible to randomize as long as they met all the other eligibility criteria and were determined as clinically stable by the Principal Investigator.

Duration of stabilisation period was increased based on investigator's judgement. If any noncompliance observed during dosage regimen of stabilisation period, the patient was screen failed as per investigator judgment. Injection was administered only by the principal investigator/sub-investigator/ designee (health care professional). Further, when the dosing was done by PI's designee, PI/ Sub-I supervised the dosing.

Treatment period: During the treatment period, patients were randomized in a ratio of 1:1 to either of two sequences i.e., Test product (T) to Reference product (R), or Reference product (R) to Test product (T). Patients received five consecutive doses of 400 mg Test product or 400 mg Reference product of Aripiprazole Prolonged-Release Injectable Suspension 400 mg/vial (2.0 mL) at predefined injection site into the gluteal (buttock) muscle region by deep intramuscular route, 28 days apart in a crossover design, during the two periods (Period I and Period II).

Investigational medicinal product was administered, according to the IMP manual, at 28 days intervals. A window period of ± 1 day was allowed for Dose 1 and Dose 2 in Period I. A total of 6 doses of the test or reference product were administered to each patient in each study period. There was no washout between two treatment periods.

Patients were housed in the clinical facility for at least 2 hours prior to each dose to at least 4 hours post dose for Dose 1 to Dose 4 of Period I and for Dose 7 to 10 of period II. Patients were housed in the clinical facility for at least 10 hours prior to dosing to at least 24 hours post dose for Dose 5 and 6 of Period I and dose 11 and 12 of Period II, after which the patients visited the site on ambulatory basis for the scheduled post-dose PK samples.

During the stabilisation period (as applicable), all patients were housed in the study centre on the day of injection for at least 2 hours before dosing to at least 4 hours after dosing.

2.3 Study Patients

The study was conducted in Asian population. Among 69 patients, 37 males (53.62%) and 32 females (46.38%) with schizophrenia meeting eligibility criteria were randomized in the study. The patients dosed in the study were within the age range of 18 to 58 years (mean age 40.3 years) and Body Mass Index (BMI) range of 18.33 to 29.60 kg/m^2 (mean BMI 24.708 kg/m^2).

Key inclusion criteria were: Male or non-pregnant, non-lactating female subjects between 18 and 60 years of age (both inclusive) with Body Mass Index (BMI) less than 30 kg/m_2 but greater than or equal to 18 kg/m^2 and weight not less than 50 kg, who had documented diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders – 5^{th} edition (DSM-V) or latest version criteria, and were clinically stable and had no hospitalization for exacerbation of psychiatric symptoms 3 months before screening and randomisation; stable on a regimen consisting of 400 mg of Aripiprazole Prolonged/Extended-Release Injectable Suspension via intramuscular route every four weeks for at least 12 weeks (i.e., at least 3 doses) as judged by the investigator prior to randomisation and with established tolerability for at least 14 days to oral Aripiprazole prior to screening, if not already on a stable regimen of 400 mg of Aripiprazole Prolonged/Extended-Release Injectable Suspension and patients who agreed to comply with the visit schedule and other study requirements were eligible for enrollment in the study.

Key exclusion criteria were: Patient on drugs known as inducer or inhibitor of CYP3A4 and CYP2D6 enzymes, Patient who was poor metaboliser of CYP2D6 enzyme, Patient with Clinical Global Impression – Severity of illness (CGI-S) score of 5 or more, Patient with a history of Neuroleptic Malignant Syndrome (NMS) or tardive dyskinesia while on treatment with atypical antipsychotics, Patient with a history of a corrected QT interval > 450 ms (Bazett's formula), Patient with history of alcohol or substance abuse during the 6-month period immediately prior to screening, Received Electroconvulsive Therapy (ECT) within the last 3 months prior to screening, Patient with suicidal ideation (score of 4 or 5 on the Columbia Suicide Severity Rating Scale [C-SSRS]) within the past 2 months or any suicidal behaviour occurring in the past year.

2.4 Drug administration

The order of dispensing the investigational medicinal product for each patient was determined according to a randomisation schedule. Patients were randomised to one of the two sequences: either TR or RT. Equal allocation of the sequence was ensured. The randomisation schedule was generated ensuring the treatment balance by using SAS® statistical software (Version: 9.4; SAS Institute Inc., USA). The randomisation schedule was generated by the biostatistician of Cliantha Research.

The randomisation schedule was maintained under controlled access. The personnel involved in the dispensing of investigational medicinal products were accountable for ensuring compliance to randomisation schedule. The randomisation schedule was not available to the Bio-analytical team of Sun Pharmaceutical Industries Limited, until the clinical and analytical phases of the study were completed.

Each patient was randomly assigned to receive test or reference product of Aripiprazole powder and solvent for Prolonged-Release Suspension for Injection 400 mg/vial (2.0 mL) at predefined injection site in the gluteal (buttock) region by deep intramuscular route, 28 days apart for consecutive six dosing (i.e. on Day-1, Day-29, Day-57, Day-85, Day-113, day-141 in Period I), as per randomisation schedule. Patients were then switched over to the other treatment arm for the next consecutive six doses (i.e. on Day-169, Day-197, Day-225, Day-253, Day-281 and Day-309 in Period II).

Investigational medicinal products were administered, according to the IMP manual, at 28 days intervals. Window period of ± 1 day was allowed for Dose 1 and Dose 2 in Period I. A total of six doses of the test or reference product were administered to each patient in each study period. The investigational medicinal products (test or reference) were administered using the appropriate enclosed safety needle.

When the patient underwent stabilisation period, the first randomisation dose was scheduled in such a way that it was given at 28 (±1) days from the actual date of administration of the last stabilisation dose.

The study design is shown in Figure 1.

2.5 Blood sample collection

Total 62 blood samples were collected including the pre-dose blood samples, throughout the whole study duration.

Detailed sampling point schedule and the window period for collection are presented in the below table 2:

Table 2: Blood sampling schedule

Period I				**Period II**			
Sample #	Day	Dose	Time point relative to dosing	Sample #	Day	Dose	Time point relative to dosing
1	57	3	-1344 hours	32	225	9	-1344 hours
2	85	4	-672 hours	33	253	10	-672 hours
3	113	5	0 hours	34	281	11	0 hours
4	114	5	+24 hours	35	282	11	+24 hours
5	115	5	+48 hours	36	283	11	+48 hours
6	116	5	+72 hours	37	284	11	+72 hours
7	117	5	+96 hours	38	285	11	+96 hours
8	118	5	+120 hours	39	286	11	+120 hours
9	119	5	+144 hours	40	287	11	+144 hours
10	120	5	+168 hours	41	288	11	+168 hours
11	121	5	+192 hours	42	289	11	+192 hours
12	122	5	+216 hours	43	290	11	+216 hours
13	124	5	+264 hours	44	292	11	+264 hours
14	127	5	+336 hours	45	295	11	+336 hours
15	130	5	+408 hours	46	298	11	+408 hours
16	134	5	+504 hours	47	302	11	+504 hours
17	141	5	+672 hours	48	309	11	+672 hours

Period I				**Period II**			
Sample #	Day	Dose	Time point relative to dosing	Sample #	Day	Dose	Time point relative to dosing
18	142	6	+24 hours	49	310	12	+24 hours
19	143	6	+48 hours	50	311	12	+48 hours
20	144	6	+72 hours	51	312	12	+72 hours
21	145	6	+96 hours	52	313	12	+96 hours
22	146	6	+120 hours	53	314	12	+120 hours
23	147	6	+144 hours	54	315	12	+144 hours
24	148	6	+168 hours	55	316	12	+168 hours
25	149	6	+192 hours	56	317	12	+192 hours
26	150	6	+216 hours	57	318	12	+216 hours
27	152	6	+264 hours	58	320	12	+264 hours
28	155	6	+336 hours	59	323	12	+336 hours
29	158	6	+408 hours	60	326	12	+408 hours
30	162	6	+504 hours	61	330	12	+504 hours
31	169	6	+672 hours	62	337	12	+672 hours

All samples were collected in K_2EDTA (Di-potassium salt of ethylene di-amine tetra acetic acid) vacutainers. After collection of blood samples from all the patients at each time-point, the sample tubes were placed upright in a wet ice bath (temperature of wet ice bath was maintained at 2-10°C & acknowledged) or other chilling device (temperature of chilling device was maintained at 2-10°C) until centrifugation.

Blood samples were centrifuged at 3300 RPM for 15 minutes under refrigeration (4°C ± 2°C) to separate plasma.

All the pre-dose and post dose plasma samples were divided into two aliquots and transferred to suitably labelled polypropylene tubes and re-checked to ensure transfer of plasma to the correct tube.

Safety assessments included measurement and monitoring of vital signs, physical examination including COVID-19 examination, weight/BMI examination, injection site reaction assessment, evaluation of severity of illness by assessing Clinical Global Impression – Severity of illness (CGI-S) scale, suicidality behavior, neuroleptic malignant syndrome and any extra pyramidal adverse assessment, 12 lead ECG, Urine drug screen (Marijuana-THC, amphetamine-AMP, barbiturates-BAR, cocaine-COC, benzodiazepines-BZD, and morphine-MOR) and alcohol urine test, prior and concomitant medication review, adverse events assessment and clinical laboratory assessment.

2.6 Pharmacokinetic analysis

Pharmacokinetic analysis was conducted only for samples from patient who completed both the periods of the study. Pharmacokinetic parameters were calculated for aripiprazole (after dose 5 & 6 of period-1 and after dose 11 & 12 of period-2) using Win-Nonlin® (Pharsight Corporation, Version 6.4) using non-compartmental analyses.

The aripiprazole plasma concentrations measured for each patient at each sampling time at steady state. The maximum plasma concentration after multiple dosing (C_{maxSS}) and the time to reach that peak concentration at steady state (T_{maxSS}) were determined for each subject and for each treatment. The area under the curve (AUC) from time 0 to time τ (tau = 672 hour) during a dosing interval at steady state ($AUC_{0-\tau}$) was calculated using the linear trapezoidal rule. Degree of fluctuation was calculated using formula $[(C_{max}ss-C_{min}ss)/C_{av}ss] \times 100$. $Cav_{ss} = AUC_{0-\tau} / \tau$ (τ or tau = Dosing interval).

2.7 Statistical analysis

For expected mean difference between Test and Reference formulation about ± 10% and based on anticipated intra-patient CV of around 33% for $C_{\tau ss}$, a sample size of 96 observations (48 patients) was considered sufficient to ensure 80% power for demonstrating bioequivalence for this replicate crossover study design.

- **Analysis for attainment of Steady State:**

To confirm the steady state attainment, a linear regression analysis was performed on three pre-dose concentrations (i.e. 3rd, 4th & 5th dose of Period-1 & 9th, 10th & 11th dose of Period-2) for each treatment using the SAS® package (SAS®, Version 9.4). Probability (p) value of the slope was calculated by

fitting "Linear Regression line" to the mean trough concentration values [i.e. trough concentration data on day 57, 85 & 113 of period-1 and on day 225, 253 & 281 of period-2)] and time data for Test treatment (T) and Reference treatment (R) individually. Attainment of steady state was to be concluded, if the slope of regression line was not statistically different from 0 ($p>0.05$).

- **Assessment of Bioequivalence:**

Statistical analyses were performed on individual pharmacokinetic parameters obtained at steady state for aripiprazole, using the SAS® package (SAS®, Version 9.4). All ANOVAs were performed with General Linear Model ANOVA procedure between Test and Reference. As this bio-study was conducted on patients with schizophrenia, based on availability, patients were dosed at different clinical site. Hence, each clinical site was considered as separate group and group term was included in the statistical model.

Analysis of variance was performed on Ln-transformed data of $C_{max}ss$, $C_{\tau}ss$ and $AUC_{0-\tau}$. The General Linear Model ANOVA was used to analyze Ln-transformed primary pharmacokinetic parameters ($C_{max}ss$, $C_{\tau}ss$ and $AUC_{0-\tau}$) that contain terms for Group, Day, Sequence, Group*Sequence, Period, Treatment and Patient (Group*Sequence) as fixed effects.

Probability (p) values were derived from Type III sums of squares. For Ln-transformed primary pharmacokinetic parameters (i.e. $C_{max}ss$, $C_{\tau}ss$ and $AUC_{0-\tau}$), the Sequence effect was tested at the 0.10 level of significance using the Patient nested within Group*Sequence mean square from the ANOVA as the error term. All other fixed effects (i.e. Group, Day, Group*Sequence, Period, Treatment) were tested at the 0.05 level of significance against the residual error (mean square error/MSE) from the ANOVA as the error term using Type-III sum of squares.

Difference of LSMs was calculated for Ln-transformed $AUC_{0-\tau}$, $C_{max}ss$ and $C_{\tau}ss$. The difference was of the form: Test-Reference. Ratios of means were expressed in percentage by taking the anti-log value of difference of LSM. Consistent with the two one-sided tests for bioequivalence, 90% confidence intervals for the difference between drug formulation least-square means (LSM) were calculated for the parameters $AUC_{0-\tau}$, $C_{max}ss$ and $C_{\tau}ss$ using Ln-transformed data. The confidence intervals were expressed as a percentage relative to the LSM of the reference formulation.

2.8 Safety assessment

The safety related laboratory tests like CYP2D6 genetic testing, hematology, blood biochemistry, electrolyte, urinalysis, and immunological tests (HIV-I & II, HBsAg, Anti-HCV, Syphilis [RPR/VDRL]) were performed during the screening period. All patients randomized in the study reported clinically acceptable laboratory values.

Hematology, blood biochemistry, and urinalysis were performed during stabilization period (as applicable) as per investigators' judgement. Patients with clinically acceptable levels were further considered for randomization.

Hematology, blood biochemistry, electrolyte (1st dose Period-I) and urinalysis were performed on the check-in of Period-I (Day 1, 29, 57, 85, 113 and 141) and on Day 169, 197, 225, 253, 281 and 309 of Period II. Hematology, blood biochemistry, electrolyte, and urinalysis were performed on Day 337 at the end of study.

Serum pregnancy test (for all females of childbearing potential) was performed at screening visit and Day 337 at the end of study and urine pregnancy test (for all females of childbearing potential) was performed during stabilization period, on the check-in of Period-I (Day 1, 29, 57, 85, 113 and 141) and on Day 169, 197, 225, 253, 281 and 309 of Period II. Urine drug screen (Marijuana-THC, amphetamine-AMP, barbiturates-BAR, cocaine-COC, benzodiazepines-BZD, and morphine-MOR) and alcohol urine test were performed on the day of screening, before each dose during stabilization period (as applicable) and treatment period.

Systolic and diastolic blood pressure values were evaluated for the clinical significance by Investigator or physician at screening visit, within 1 hour prior to each dose of stabilization and before check out during stabilization (as applicable), during treatment period, within 1 hour of PK sampling time point at ambulatory visits and end of study.

Orthostatic hypotension was measured during screening period and randomization visit.

Pulse rate, body temperature and respiratory rate were evaluated for the clinical significance by Investigator or physician at screening visit, within 1 hour prior to each dose of stabilization and before check-out during stabilization (as applicable), during treatment period, within 1 hour of PK sampling time point at ambulatory visits and end of study.

Physical examination including COVID-19 examination of the subject was conducted by Investigator or physician at the time of screening visit, stabilization period visit (as applicable), treatment period visits (Each dosing of Period I and II) and at end of study visit. Weight was measured at the screening visit, prior to each dose during stabilisation period (as applicable), treatment period and at end of study visit. 12-Lead ECG recording was performed at screening visit, Period I Day 1 (Dose 1), Period II Day 169 (Dose 7) and end of study.

Injection site reactions (e.g., redness, swelling, tenderness and induration) were evaluated by investigator/designee prior to each dose of stabilization (as applicable) and treatment period; before check-out during stabilization (as applicable) and treatment period; and at end of study.

CGI-S scale for severity of illness was recorded at the screening visit, prior to each dose on the day of dosing during stabilization period (as applicable), prior to each treatment period dosing and at the end of study visit.

Suicidal behavior (using C-SSRS scale), neuroleptic malignant syndrome and any extra pyramidal adverse event assessment were performed at the time of screening, prior to each dose during stabilization period (as applicable), prior to each dose during treatment period and at end of study visit by PI/designee.

3. Results

3.1 Subjects

A total of 96 patients underwent the screening assessments, of which 73 patients entered the stabilization phase and 69 patients were randomized in the study. Of these randomized 69 patients, 60 (86.96%) patients completed the study. A total of 09 subjects discontinued from the study. (Figure 2)

Of the dosed 69 patients, 37 (53.62%) were male & 32 (46.38%) were female. The age of the participants was 40.3 ± 10.51 years (range: 18–58 years); body weight, 64.29 ± 10.349 kg (range: 50.3 - 95.0 kg); height, 161.12 ± 8.034 cm (range: 140.0 - 181.5 cm); and body mass index, 24.708 ± 3.0518kg/m^2 (range: 18.33 - 29.60 kg/m^2). (Table 3)

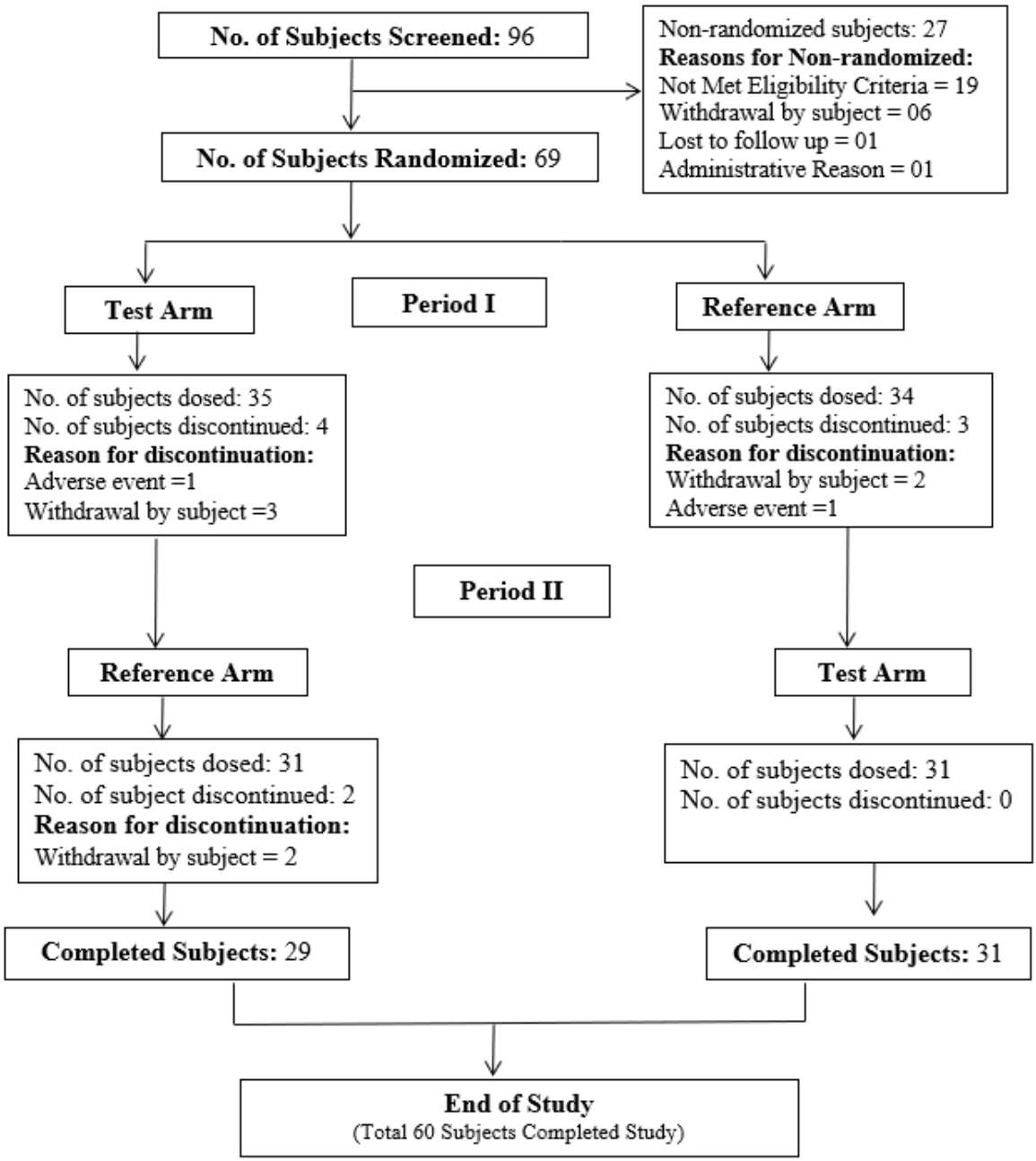

Figure 2. Flow diagram of patients for the clinical study.

Table 3: Demographic characteristics

		Dosed (N=69)	**Completed (N=60)**
Age (Years)	Mean ± SD	40.3 ± 10.51	40.8 ± 10.26
	Range	18 - 58	18 - 58
	Median	40.0	40.5
Age Group, n (%)	< 18	0	0
	18 - 40	36 (52.17%)	30 (50.00%)
	41 - 64	33 (47.83%)	30 (50.00%)
	65 - 75	0	0
	> 75	0	0
Sex, n (%)	Male	37 (53.62%)	32 (53.33%)
	Female	32 (46.38%)	28 (46.67%)
Race, n (%)	American Indian or Alaska Native	0	0
	Asian	69 (100%)	60 (100%)
	Caucasian	0	0
	Black or African American	0	0
	Native Hawaiian or other Pacific Islander	0	0
	White	0	0
	Other	0	0
Ethnicity, n (%)	Hispanic or Latino	0	0
	Not-Hispanic or Latino	69 (100%)	60 (100%)
	Other	0	0
CYP2D6 Genetic Testing	Intermediate Metabolizer	15 (21.74%)	12 (20.00%)
	Extensive Metabolizer	54 (78.26%)	48 (80.00%)
	Poor Metabolizer	0	0
Height (cm)	Mean ± SD	161.12 ± 8.034	160.54 ± 7.354
	Range	140.0 - 181.5	140.0 - 175.0
	Median	161.00	161.00
Weight (kg)	Mean ± SD	64.29 ± 10.349	63.73 ± 9.633
	Range	50.3 - 95.0	50.3 - 88.5
	Median	64.00	63.25
BMI (kg/m^2)	Mean ± SD	24.708 ± 3.0518	24.688 ± 2.9909
	Range	18.33 - 29.60	18.33 - 29.60
	Median	24.700	24.800

Abbreviations: BMI: Body Mass Index, cm: Centimeter, kg: Kilogram, m: Meter, N=Number of patients in the specified group, n=Number of patients in the specified category.

3.2 Confirmation of steady state attainment

Probability (p) value of the slope for test treatment (T) was 0.8369 (p>0.05) and for reference treatment (R) was 0.9671 (p>0.05), which is non-significant for both test and reference treatment. Hence, it is concluded that steady state has been reached for both Test and reference treatments.

3.3 Pharmacokinetics

Aripiprazole plasma concentrations following the 5th & 6th administration of Test and Reference treatment are presented in Figure 3. Table 4 shows the pharmacokinetic parameters of Aripiprazole. Mean Aripiprazole exposure ($AUC_{0-\tau}$) was similar after the 5th & 6th dose of Test (5th dose: 241721 ng.h/mL; 6th dose: 236897 ng.h/mL) & Reference treatment (5th dose: 238795 ng.h/mL; 6th dose: 237504 ng.h/mL). [Table 4], indicating aripiprazole exposure remained consistent over the entire dosing interval. C_{maxSS} and $C_{\tau SS}$ were comparable for both treatment groups (Table 4).

Table 4. Aripiprazole PK parameters after dose 5 & 6 of Test and Reference treatment (n=60).

	Aripiprazole 400 mg Powder and Solvent for Prolonged-Release Suspension for Injection (T)		**Abilify Maintena (Aripiprazole) 400 mg Powder and Solvent for Prolonged-Release Suspension for injection (R)**	
PK Parameters (Mean±SD)	**Day 113 (Dose 5)**	**Day 141 (Dose 6)**	**Day 113 (Dose 5)**	**Day 141 (Dose 6)**
$AUC_{0-\tau}$ (ng.h/mL)	241721.23 ± 93799.94	236896.75 ± 94471.17	238795.11 ± 92052.95	237503.63 ± 83333.09
C_{maxSS} (ng/mL)	451.20 ± 181.15	432.57 ± 185.09	455.15 ± 233.15	435.45 ± 151.37
$C_{\tau SS}$ (ng/mL)	314.81 ± 128.58	310.57 ± 130.27	304.73 ± 111.46	316.61 ± 116.14
C_{avSS} (ng/mL)	359.71 ± 139.58	352.53 ± 140.58	355.35 ± 136.98	353.43 ± 124.01
T_{maxSS}*(h)	144 (0-672)	120 (0-672)	166.4 (0-672)	168 (24 – 672)
Fluctuation (h)	50.89 ± 39.16	47.34 ± 27.92	49.83 ± 33.29	47.31 ± 24.47

*Median values (range) are presented.

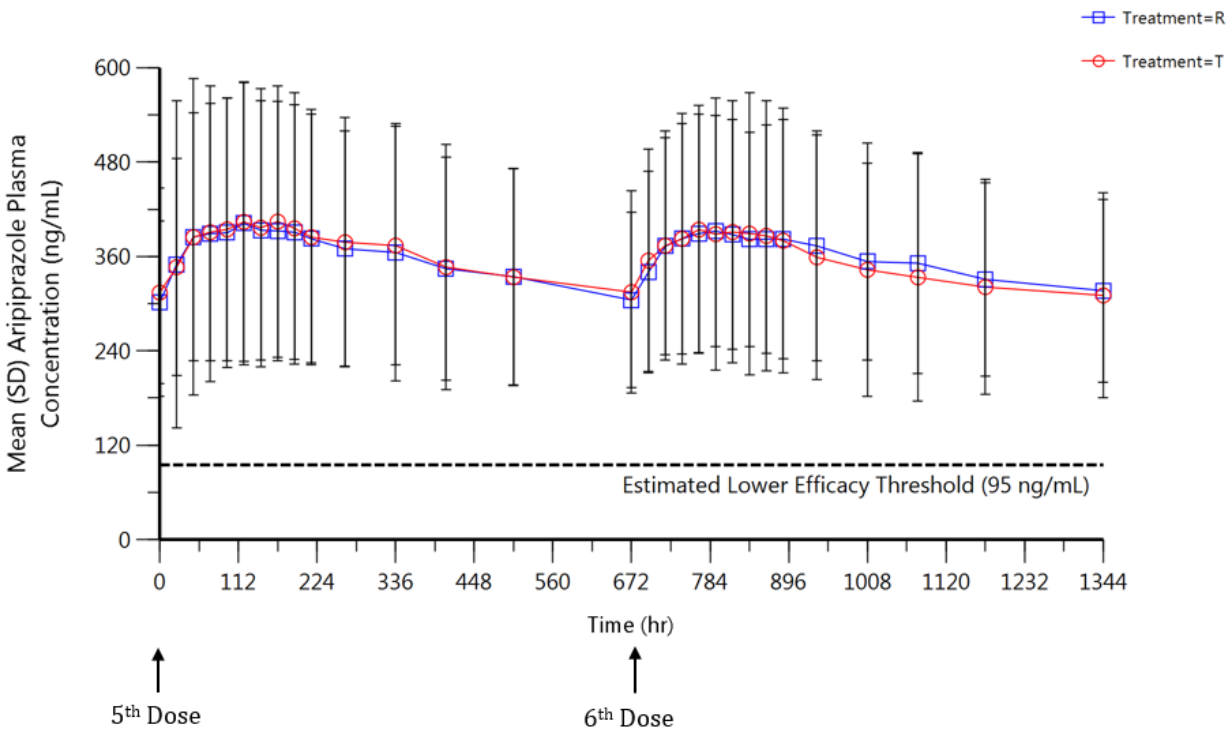

Figure 3 Mean (SD) aripiprazole plasma concentrations after the 5th & 6th dose of Test & Reference treatment

3.4 Bioequivalence assessment

Table 5 shows the bioequivalence analysis results for Aripiprazole. The ratios of the least-squares geometric means of the Test to Reference product (T/R) for aripiprazole were 99.09 % for $AUC_{0-\tau}$, 98.18 % for $C_{max}ss$ and 98.03 % for $C_{\tau}ss$. Since the 90% CIs of the main pharmacokinetic parameters of Aripiprazole were within the acceptable limits (80.00–125.00%), we conclude that the test and reference formulations were bioequivalent when administered under steady state condition.

Table 5. Bioequivalence analysis of generic Aripiprazole 400 mg Powder and Solvent for Prolonged-Release Suspension for Injection and Abilify Maintena (Aripiprazole) 400 mg Powder and Solvent for Prolonged-Release Suspension for injection in schizophrenic patients (n=60) after Multiple-Dose administration at Steady State.

Pharmacokinetic Parameters	Geometric mean value and ratio			p-value
	T	R	T/R (%)	
$AUC_{0-\tau}$ (ng.h/mL)	220440.15	222459.16	99.09	0.6937
C_{maxSS} (ng/mL)	406.46	413.99	98.18	0.5866
$C_{\tau SS}$ (ng/mL)	283.85	289.56	98.03	0.4689

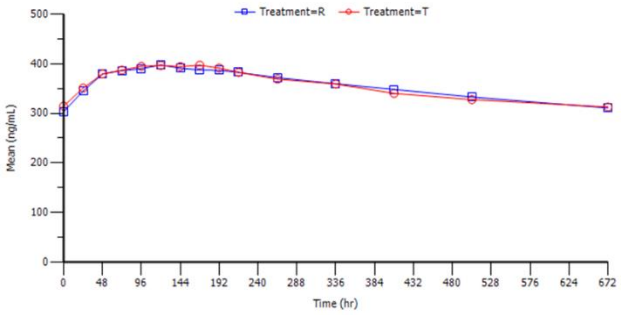

Figure 4. Linear plot of mean (N=60) plasma concentration profile of Aripiprazole

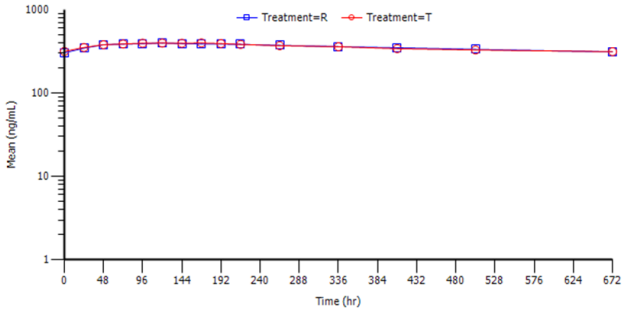

Figure 5. Semi Logarithmic plot of mean (N=60) plasma concentration profile of Aripiprazole

3.5 Safety and tolerability

All 69 randomized patients received at least one study drug dose and were included in the safety analyses. No deaths or serious adverse events (SAEs) occurred in this study. A total of 72 AEs were reported by 43 subjects in the study. Out of them, 15 AEs were reported in 13 subjects prior to the randomization and 57 AEs were reported by 36 subjects after the randomization which were considered as treatment emergent adverse events (TEAEs). Among them, 28 TEAEs were reported in 21 subjects (31.82%) receiving the test treatment and 29 TEAEs were reported in 22 subjects (33.85%) receiving the reference treatment. All the TEAEs were mild to moderate in severity. Most of the TEAEs were resolved/ recovered.

Two subjects were discontinued from the study due to TEAEs (i.e., patient with hypertriglyceridaemia and blood glucose increased; and patient with akathisia). A summary of TEAEs is presented in Table 6.

The most frequently reported TEAEs were headache (Test: 4.55%; Reference: 4.62%) & pyrexia (Test: 3.03%; Reference: 4.62%). Injection-site pain was experienced by only 2 (3.03%) patients after administration of Test treatment whereas no patient experienced Injection-site pain after administration of Reference treatment. Both the events of injection-site pain were rated by the investigators as ‘mild’ in intensity.

There was no suicidal behavior observed in any of the patients during the study. Signs and symptoms of neuroleptic malignant syndrome were not observed in any of the patients during the study. Akathisia and tremors were reported during the conduct of study. One patient reported tremor after receiving reference treatment and this AE was resolved/recovered. One patient reported akathisia after receiving reference treatment and one subject reported akathisia after receiving test treatment. These AEs were resolved/recovered with treatment.

Overall, both the study treatments (test and reference) were safe and well tolerated by the study patients.

Table 6. Summary of Treatment Emergent Adverse Events by SOC, PT - Safety Population

System Organ Class / Preferred Term	**Treatment T (N=66) n (%)**	**Treatment R (N=65) n (%)**
Number of subjects with at least one TEAE	21 (31.82)	22 (33.85)
Blood And Lymphatic System Disorders	1 (1.52)	2 (3.08)
Anaemia	1 (1.52)	2 (3.08)
Gastrointestinal Disorders	4 (6.06)	1 (1.54)
Diarrhoea	0	1 (1.54)
Dyspepsia	1 (1.52)	0
Nausea	2 (3.03)	0
Vomiting	1 (1.52)	0
General Disorders And Administration Site Conditions	7 (10.61)	5 (7.69)
Asthenia	0	1 (1.54)
Chills	1 (1.52)	0
Injection Site Pain	2 (3.03)	0
Pain	2 (3.03)	1 (1.54)
Pyrexia	2 (3.03)	3 (4.62)
Infections And Infestations	3 (4.55)	2 (3.08)
Conjunctivitis	0	1 (1.54)
Nasopharyngitis	1 (1.52)	1 (1.54)
Urinary Tract Infection	2 (3.03)	0
Investigations	0	2 (3.08)
Blood Glucose Increased	0	1 (1.54)
Weight Increased	0	1 (1.54)
Metabolism And Nutrition Disorders	3 (4.55)	5 (7.69)
Glucose Tolerance Impaired	0	1 (1.54)
Hyperglycaemia	1 (1.52)	1 (1.54)
Hypertriglyceridaemia	1 (1.52)	2 (3.08)
Type 2 Diabetes Mellitus	1 (1.52)	1 (1.54)
Musculoskeletal And Connective Tissue Disorders	1 (1.52)	1 (1.54)
Back Pain	1 (1.52)	1 (1.54)
Nervous System Disorders	5 (7.58)	5 (7.69)
Akathisia	1 (1.52)	1 (1.54)
Dizziness	1 (1.52)	0
Headache	3 (4.55)	3 (4.62)
Tremor	0	1 (1.54)
Psychiatric Disorders	3 (4.55)	2 (3.08)
Insomnia	1 (1.52)	0

System Organ Class / Preferred Term	**Treatment T (N=66) n (%)**	**Treatment R (N=65) n (%)**
Obsessive-Compulsive Disorder	1 (1.52)	0
Sleep Disorder	1 (1.52)	2 (3.08)
Reproductive System And Breast Disorders	0	1 (1.54)
Amenorrhoea	0	1 (1.54)
Respiratory, Thoracic And Mediastinal Disorders	0	2 (3.08)
Cough	0	2 (3.08)

Abbreviations: TEAE=Treatment Emergent Adverse Event, SOC=System Organ Class, PT=Preferred Term, N=Number of subjects in the specified treatment group, n=Number of subjects in the specified category.

Treatment T: Aripiprazole 400 mg Powder and Solvent For Prolonged-Release Suspension For Injection

Treatment R: Abilify Maintena (Aripiprazole) 400 mg Powder and Solvent for Prolonged-Release Suspension for Injection

Medical Dictionary used: MedDRA Version 25.0

4. Discussion

Total sixty-nine (69) patients were randomized and dosed in the study. Out of these 69 patients, sixty (60) patients had completed both the periods of the study.

Pharmacokinetic:

The ratios of the least-squares geometric means of the Test to Reference product (T/R) for aripiprazole were 99.09 % for $AUC_{0-\tau}$, 98.18 % for C_{maxss} and 98.03 % for $C_{\tau ss}$. From the above data of aripiprazole, it can be concluded that the $AUC_{0-\tau}$, C_{maxss} and $C_{\tau ss}$ results were within the acceptable limits of 80.00% to 125.00%.

Safety:

A total of 72 AEs were reported by 43 subjects in the study. Out of them, 15 AEs were reported prior to the randomization and 57 AEs were reported after the randomization which were considered as TEAEs. No death or SAE was reported in the study. A total of 57 TEAEs were reported by 36 subjects over the course of the study.

Test Product:

A total of 28 TEAEs were reported by 21 subjects (31.82%) receiving the test treatment. One patient was discontinued after receipt of the test treatment due to TEAE (i.e., akathisia). Two (02) TEAEs reported by 02 subjects were certainly related, 03 TEAEs reported by 03 subjects were probably and 06 TEAEs reported by 04 subjects were possibly related to the study drug. The remaining 17 TEAEs reported by 15 subjects were unlikely related to the study drug.

Reference product:

A total of 29 TEAEs were reported by 22 subjects (33.85%) receiving the reference treatment. One patient was discontinued after receipt of the reference treatment due to TEAEs (i.e., hypertriglyceridemia and blood glucose increased). Two (02) TEAEs reported by 01 subject were certainly related, 03 TEAEs reported by 03 subjects were probably related, 08 TEAEs reported by 06 subjects were possibly related to the study drug. The remaining 16 TEAEs reported by 13 subjects were unlikely related to the study drug.

The reported TEAEs were comparable in both treatments and were mild or moderate in severity. Overall, both the study treatments (test and reference) were safe and well tolerated as evidenced by its 3% discontinuation rate.

5. Conclusions

Aripiprazole 400 mg Powder and Solvent for Prolonged-Release Suspension for Injection and Abilify Maintena 400 mg Powder and Solvent for Prolonged-Release Suspension for Injection were declared as bioequivalent and safe under steady state condition in schizophrenic patients.

During the entire study period, mean aripiprazole plasma concentrations for both test and reference treatments remained above the efficacy threshold of ≥ 95 ng/mL[6]. By maintaining aripiprazole plasma concentrations above this threshold reducing the risk of impending relapse. All patients in both treatment arms remained clinically stable after the completion of the study.

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Ethical approval

Written informed consent was obtained from all the participants prior to the study. The study protocol and related documents were reviewed and approved by the Institutional Ethics Committee of respective site.

Author contributions

Krunalkumar Patel drafted the article. Pinkesh Patel reviewed it critically for intellectual content. Amresh Chakra approved the final version to be published and agree to be accountable for all aspects of the work.

Disclosure statement

Krunalkumar Patel, Pinkesh Patel & Amresh Chakra are employees of Sun Pharmaceutical Industries Limited. No potential conflict of interest was reported by the author(s). None of the authors had any financial or other substantive conflicts of interest that may be construed to influence the results or interpretation of the manuscript.

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