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Oral Bioequivalence Study of Lumateperone Capsule 42 Mg In Healthy Indian Subjects Under Fasting Conditions

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Abstract

Objective: To compare the rate and extent of absorption and also to monitor the safety and tolerability of a single dose of Lumateperone Capsule 42 mg of Test drug with Reference Product CAPLYTA® (Lumateperone) 42 mg capsule.

Design: Open label, balanced, randomized single-dose, two-treatment, two-sequence, two-period two-way Crossover design.

Setting: Clinical, Bioanalytical and Quality Assurance Services, Jindal Life Science Private Limited, Jaipur, India.

Participants: Twenty-four (24) Healthy, Adult, Human Subjects Under Fasting Conditions.

Method: Twenty-three (23) subjects were dosed with the investigational product [test (T) or reference (R) (as per the randomization schedule)] with approximately 240±02 mL of water at ambient temperature were dosed. Plasma concentrations of Lumateperone were determined using a LC-MS/MS method developed at Jindal Life Sciences Private Limited, Jaipur, India. Intra-subject variability of the pharmacokinetic parameters C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of Lumateperone was estimated using the root mean square error obtained after carrying out an analysis of variance for bioequivalence assessment. Also, the relative bioavailability was evaluated by calculating least squares mean ratios for Cmax, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ for Lumateperone to Lumateperone (reference). The 90% confidence intervals for the ratios of least squares means between drug formulations were calculated for the Ln-transformed data of both C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of Lumateperone. Additionally, the power of the test to detect a 20% difference between the test product (T) and reference product (R) was computed and reported for Lumateperone.

Results: The geometric least squares mean ratios (test/reference) for the ln-transformed pharmacokinetic parameters of lumateperone were 97.87% for C_{max}, 85.54% for AUC_0–t, and 90.08% for AUC_0–∞. The corresponding 90% confidence intervals were 97.57%–110.82%, 85.54%–109.85%, and 90.08%–116.76%, respectively, all of which were within the predefined bioequivalence acceptance range of 80.00%–125.00%. Both formulations were well tolerated, and no adverse events were reported.

Conclusion: The 90% confidence intervals of the differences of least squares means for the Ln-transformed pharmacokinetic parameters C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of Lumateperone were within the

bioequivalence acceptance limits of 80.00 - 125.00% and thus the test product (T) Lumateperone Capsule 42 mg and reference product (R) CAPLYTA® (Lumateperone) capsule 42 mg were found bioequivalent with respect to rate and extent of absorption. The 42 mg oral dose of Lumateperone was well tolerated and was found safe.

Introduction

Bioequivalence studies are conducted to establish therapeutic equivalence between a test formulation and its reference product through comparative evaluation of primary pharmacokinetic parameters, including Cmax and AUC. (European Medicines Agency, 2010). For orally administered drugs, a randomized, open-label, two-treatment, two-period, two-sequence crossover design is generally recommended because it minimizes inter-subject variability and allows each subject to serve as their own control (European Medicines Agency, 2010). Adequate washout periods, typically corresponding to at least five elimination half-lives of the drug, are required to ensure the absence of carryover effects between study periods (European Medicines Agency, 2010).

Schizophrenia is a chronic and severe psychiatric disorder characterized by disturbances in perception, cognition, emotional regulation, and behavior, and it affects millions of individuals worldwide (Syed & Brašić, 2021). The disorder is associated with significant functional impairment, increased morbidity, and reduced life expectancy, even when optimal therapeutic interventions are employed (Longo et al., 2023). Pharmacological treatment with antipsychotic agents remains the cornerstone of schizophrenia management and is effective in controlling positive symptoms such as hallucinations and delusions, although negative symptoms and cognitive deficits are often less responsive (Maini et al., 2021).

Lumateperone tosylate is a second-generation antipsychotic approved by the United States Food and Drug Administration for the treatment of schizophrenia in adults and, subsequently, for bipolar depression (Maini et al., 2021; Tarzian et al., 2023). Unlike conventional antipsychotics, lumateperone exhibits a unique pharmacological profile involving concurrent modulation of serotonergic, dopaminergic, and glutamatergic neurotransmission systems (Syed & Brašić, 2021). Specifically, lumateperone demonstrates high affinity antagonism at serotonin 5-HT2A receptors, moderate affinity at dopamine D2 receptors, and indirect modulation of glutamatergic signaling through NMDA receptor pathways (Sowa-Kućma et al., 2024).

Clinical trials have demonstrated that lumateperone is effective in reducing schizophrenia symptom severity while maintaining a favorable safety and tolerability profile compared with other second-generation antipsychotics (Maini et al., 2021). Commonly reported adverse events, such as somnolence and fatigue, are generally mild in severity, and lumateperone has been associated with minimal extrapyramidal symptoms and limited metabolic disturbances (Tarzian et al., 2023; Peng et al., 2024). The recommended therapeutic dose of lumateperone is 42 mg administered once daily, without the need for dose titration (Maini et al., 2021).

Despite its established clinical efficacy, lumateperone exhibits low absolute oral bioavailability and substantial inter-subject pharmacokinetic variability, underscoring the importance of rigorous bioequivalence evaluation for generic formulations (Metabolic Profiling Study, 2024). Demonstrating bioequivalence ensures that a generic lumateperone formulation delivers systemic exposure comparable to that of the reference product, thereby supporting therapeutic interchangeability (European Medicines Agency, 2010).

The present study was therefore designed to evaluate the bioequivalence of a test formulation of Lumateperone Capsule 42 mg with the reference product, CAPLYTA® (lumateperone) 42 mg capsules, under fasting conditions in healthy adult Indian subjects. The primary objective was to compare key pharmacokinetic parameters, including maximum plasma concentration (Cmax) and area under the plasma concentration–time curve (AUC), in accordance with regulatory guidelines for bioequivalence assessment (European Medicines Agency, 2010).

Materials and Methods Study Drugs:

Lumateperone Capsules were supplied and manufactured by Exemed Pharmaceuticals (Vapi, Gujarat, 396195, India) for oral administration (42 mg). Reference Product CAPLYTA® (lumateperone) 42mg capsules Manufactured by: Intra-Cellular Therapies, Inc. New York, NY10016, USA, The study drugs were stored at 22 °C and a relative humidity of 60±5%.

Study Designs:

The study was an open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period two-way crossover at a single site in India (Jindal Life Sciences, Jaipur). The study investigated the safety, tolerability, and Pharmacokinetics of Lumateperone after oral dosing in fasting, healthy human adults.

The single-dose oral bioequivalence study divided into two periods:

In period 01, twelve (12) subjects were given a single dose of test drug Lumateperone Capsule 42 mg of Exemed Pharmaceuticals in Gujarat, India, and twelve (12) subjects were given a single dose of reference drug CAPLYTA® (lumateperone) 42mg capsules Intra-Cellular Therapies, Inc. New York. The subjects fasted for 24 hours following the administration of the study drug.

In a period 02, Following a 09-day washout period, the subjects received the alternate formulation to that they were given in period 01 (12 received the test product and 12 received the reference product) under identical conditions. In Period 02 Subject no. 04 did not report to facility for period II check in, hence he was considered dropped out for the study on 16JAN2025 at 20:35.

The subjects fasted overnight for at least 10.00 hours prior to drug administration. All safety and tolerability data and available PK data at the TPD dose were reviewed by the clinical investigator.

Ethical Considerations

The study was approved by the Manglam Medicity Hospital Institutional Ethics Committee on December 23, 2024. Written informed consent was given by all participants. The study was carried out in accordance with the EC approved protocol and clinical research guidelines established by the basic principles defined in the ICH-GCP guidelines, the ICMR Ethical Guidelines for Biomedical Research on Human Subjects (2017), the Declaration of Helsinki (Fortaleza, Brazil, October 2013), G.S.R. 227(E) New Drugs and Clinical Trials Rules, 2019, and Guidelines for Bioavailability and Bioequivalence Studies, Central Drugs Standard Control Organization, March 2016

Study Populations:

In the study, all subjects eligible for enrollment were in good health based on medical history, clinical examination, along with vital signs, recording of electrocardiogram and laboratory test results, tested negative for drugs of abuse and were able to provide written informed consent Subjects who were aged between 18 -45 years with a body mass index (BMI) between 18.50- 30.00 kg/m^2 (inclusive of both) and body weight not less than 50.00 kg and agreeing to use appropriate contraceptive measures.

Randomization

Subjects were assigned to either of the treatments using computer generated randomization schedules.

Study Procedures:

Subjects were checked in on 07JAN2025 for period 01 and on 16JAN2025 for period 02. The total duration of the study was 09 days from the day of check-in of the first period till the end of the second period. Extra subjects E1 and E2 were enrolled in the study on the day of period 01 check-in. Subject E1 and E2 checked-out from the facility after dosing of the required number of subjects.

The study was conducted in two periods, after overnight fasting of at least 10.00 hours, A single dose of either test product (T) or reference product (R) was administered orally to the subjects in sitting posture with approximately 240 ± 02 mL of water at ambient temperature in period 01, whereas in period 02, Following a washout period of 09 days, a single dose of the alternate product to that of used in period 01 was dosed to each subject.

Serial blood samples (01 pre-dose (0.00 hour) sample and 21 post-dose samples in each period up to 48.00 hours) were taken during each study period.

Blood samples were collected through an indwelling cannula placed in a forearm vein using a disposable syringe or alternatively through venipuncture with disposable syringes and needles in the case of cannula blockage. An intravenous indwelling cannula was kept *in situ* as long as possible during the 24.00 hours post-dose in-house stay in each period. Normal saline solution was injected to keep the cannula patent, and blood samples were drawn after discarding the first 0.5 mL of normal saline mixed blood from the cannula (except ambulatory samples). Ambulatory samples were collected by fresh venipuncture. Five (05) mL of blood was collected in pre-labelled (Study No., Subject No., Period No., Time Point) polypropylene tubes (initially stored at -70 ± 10°C) containing K2EDTA anticoagulant at each sampling time point.

Blood samples were collected at the following time points during treatment periods in Studies.

00.000 hour (pre dose) 00.250, 00.500, 00.750, 01.000, 01.250, 01.500, 01.750, 02.000, 2.333, 2.667, 03.000, 04.000, 05.000, 06.000, 08.000, 10.000, 12.000, 16.000, 24.000, 36.000, 48.000. The blood samples at 36.000- and 48.000- hours post-dose were collected on ambulatory basis (i.e., on separate visit).

After collection of blood samples from all subjects at a particular time point, the processing and storage of blood sample was commenced within 01 hour of blood sample collection.

The subjects received a standard meal on the day of check-in and at approximately 4.00, 8.00, and 12.00-hours post-dose in each period. During housing, the meal menu was identical in terms of content and quantity for all periods. Drinking water was not allowed from one hour before until one hour after dosing in each period (except for approximately 240 ± 02 mL of water given during dosing).

Safety Assessment:

All subjects who had received at least one dose of the investigational product were included in the safety evaluation. A duty physician was available within the facility throughout the subjects' housing (from check-in to check-out).

A) Vital signs sitting blood pressure, pulse rate and body temperature was measured during check-in and prior to check-out in each period. Sitting blood pressure, pulse rate and body temperature was measured prior to dosing (within 120 minutes) in each period. Supine position blood pressure and pulse rate was measured at 1.00, 3.00, and 5.00 hours (=40 minutes) post dose and as per physician / investigator opinion in each period.

Note: *Subject was remain supine position for initial 08 hours post-dose, all the post dose blood samples was collected bedside till posture restriction 08.00 hours post dose.*

Physical examination (clinical examination) of the subject was conducted by a qualified medical Designate personnel during check-in and prior to check-out in each period.

B) Well-being assessment: Subjects was advised to report any AE that may occur during the study and was specifically asked for these by trained study personnel in a non-leading manner at the time of physical examination (clinical examinations), during vital signs recording, at about 16.0, 36.0and 48.0 hours post dose and as per physician / investigator opinion in each period. Adverse events was managed and recorded as appropriate by the investigator or available physician. All dosed study subjects was assessed for their well-being by a physical examination (clinical examination) which was include vital signs measurement (sitting blood pressure, pulse rate, and body temperature).

Pharmacokinetics:

PK analysis was performed to characterize the pharmacokinetic profile of the test product in comparison to the reference product. Plasma concentrations of Lumateperone were determined using a LC-MS/MS method developed & Validated at Jindal Life Science Pvt. Ltd. India.

Primary Pharmacokinetic Parameters: Cmax, $AUC_{o\text{-}t}$, $AUC_{o\text{-}inf}$

Secondary Pharmacokinetic Parameters: Tmax, Kel, $T_{1/2el}$, TLIN, LQCT

The 90% confidence intervals (CI) was calculated for the Ln-transformed values for the pharmacokinetic parameters Cmax, $AUC_{o\text{-}t}$ and $AUC_{o\text{-}inf}$ of test (T) and reference (R) formulations. The power of a test to detect 20% difference between each test (T) and reference (R) formulation for the pharmacokinetic parameters Cmax, $AUC_{o\text{-}t}$ and $AUC_{o\text{-}inf}$ was computed and reported for Lumateperone. Ratio of geometric least square means of test (T) and reference (R) formulations was calculated and reported in percentage for Ln-transformed Cmax, AUCo-t and $AUC_{o\text{-}inf}$ for Lumateperone. The inter-subject and intra-subject variability was computed and reported for Ln-transformed pharmacokinetic parameters Cmax, $AUC_{o\text{-}t}$ and $AUC_{o\text{-}inf}$ for Lumateperone. If any subjects experience emesis at any time during the labeled dosing interval, samples of such subject would be analyzed but would not be considered for pharmacokinetic and statistical analysis.

OBSERVATIONS AND RESULTS

1. Demographic And Other Baseline Characteristics:

Table 1: Demographic and other baseline characteristics of study participants (N = 24)

Variable	Profile	Percentage
Race	Asian	100.00 %
	Others	0.00 %
Gender	Male	100.00 %

		Female		0.00 %
Diet		Non-Vegetarian		83.33 %
		Vegetarian		16.67 %
Smoking status		Non-smokers		100.00 %
		Smokers		0.00 %
Alcohol Consumption		Non alcoholics		100.00 %
		Alcoholics		0.00 %
	Mean	**SD**	**Min**	**Max**
Age (yr)	29.88	4.88	22.00	42.0
Height (cm)	170.32	5.60	161.00	178.20
Weight (Kg)	68.28	7.44	55.40	83.00
BMI (Kg/m^2)	23.53	2.25	18.70	28.10

The mean of age, height, weight and BMI of the subjects who received the dose in the study were 29.88 ±4.88years, 170.32±5.44 cms, 68.28±7.44 Kgs and 23.53±2.25 Kg/m2 respectively. All subjects were of Asian origin, non-smokers and non-alcohol. Out of the 24 subjects, 20 were non-vegetarians, while 4 was a vegetarian.

2. PHARMACOKINETIC AND STATISTICAL EVALUATION:

Table 2: Descriptive Statistics of Pharmacokinetic Parameters of Test Product (T) for Lumateperone (N = 23)

Parameter	Treatment	N	Mean	Std Dev	Minimum	Median	Maximum	%CV
AUC0-∞	T	23	207.1611	89.85997	10.773	197.8753	362.391	43.38
AUCo-t	T	23	167.5005	69.32188	9.322	161.5557	278.240	41.39
Cmax	T	23	23.4708	5.45394	4.338	24.8990	31.066	23.24
Kel	T	23	0.055	0.0814	0.02	0.030	0.37	147.01
t1/2	T	23	22.366	9.8794	1.86	10.273	45.93	44.17
Tmax	T	23	1.326	0.2315	1.00	1.250	1.75	17.46
TLIN	T	23	15.884	7.7444	2.33	16.000	24.00	48.76
LQCT	T	23	44.609	11.2724	6.00	48.000	48.00	25.27

Table 3: Descriptive Statistics of Pharmacokinetic Parameters of Reference Product (T) for Lumateperone (N = 23)

Parameter	Treatment	N	Mean	Std Dev	Minimum	Median	Maximum	%CV
AUC0-∞	R	23	193.4944	80.21524	39.844	183.1164	358.138	41.46
AUCo-t	R	23	167.1405	70.79203	37.922	166.9842	335.057	42.35
Cmax	R	23	23.3881	4.52576	14.771	23.6460	31.220	19.35
Kel	R	23	0.057	0.0621	0.02	0.038	0.25	109.65
t1/2	R	23	19.063	8.6193	2.78	18.401	36.62	45.21

Tmax	R	23	1.326	0.2763	0.75	1.500	1.75	20.83
TLIN	R	23	12.761	7.6954	1.75	12.000	24.00	60.30
LQCT	R	23	44.696	10.9480	10.00	48.000	48.00	24.49

Table 4: Geometric Least Squares Means, Ratios, 90% Confidence Intervals, ISCV and Power for Pharmacokinetic Parameters (Cmax, AUC0-t and AUC0-∞) of Lumateperone (N = 23)

Parameter	GLSMT	GLSMR	(T/R) Ratio	90% CI Lower	90% CI Upper	Power	ISCV	BE
Cmax	22.4036	22.8915	97.87%	97.57%	110.82%	90.73%	24.84%	YES
AUCt	144.2723	148.8319	85.54%	98.82%	109.85%	90.43%	25.00%	YES
AUC0-∞	176.1268	171.7374	90.08%	98.71%	116.76%	88.56%	25.96%	YES

Geometric Least Squares Means of Cmax for test drug was 22.4036 and that of reference drug was 22.8915 which showed T/R ratio of 97.87% (90%CI 97.57%-110.82%) and ISCV of 24.84% suggesting that the test drug was bioequivalent.

Geometric Least Squares Means of AUCt for test drug was 144.2723 and that of reference drug was 148.8319 which showed T/R ratio of 85.54% (90%CI 98.82%-109.85%) and ISCV of 25.00% suggesting that the test drug was bioequivalent.

Geometric Least Squares Means of AUC0-∞ for test drug was 176.1268 and that of reference drug was 171.7374 which showed T/R ratio of 90.08% (90%CI 98.71%-116.76%) and ISCV of 25.96% suggesting that the test drug was bioequivalent.

Figure 1: Linear Plot of Mean Plasma Concentrations of Lumateperone vs. Actual Time for Test Product (T) and Reference Product (R) (N = 23)

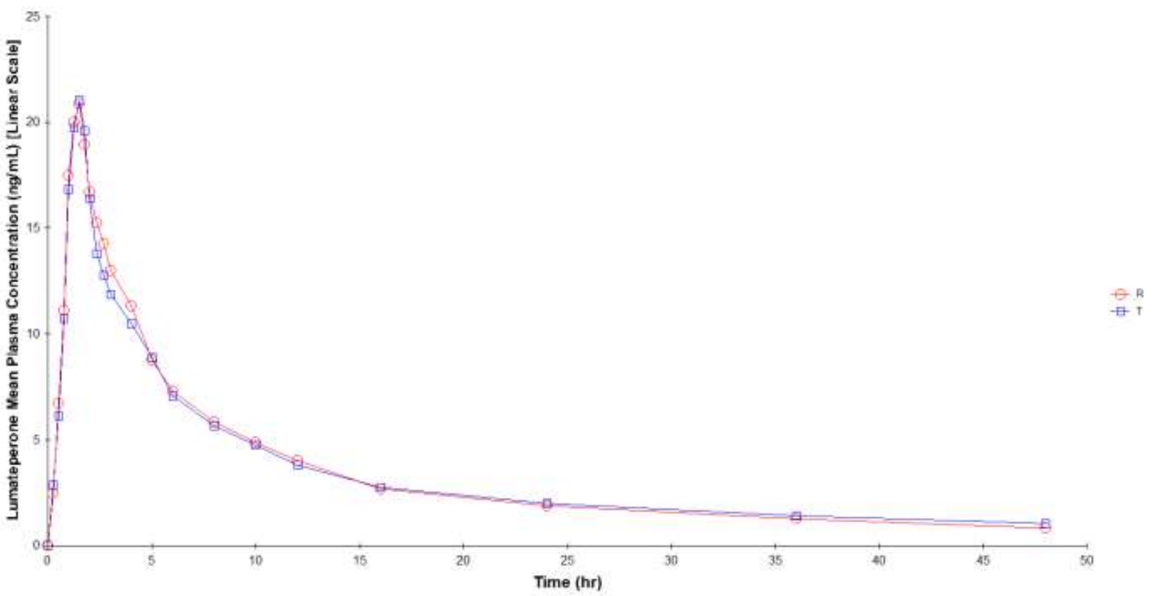
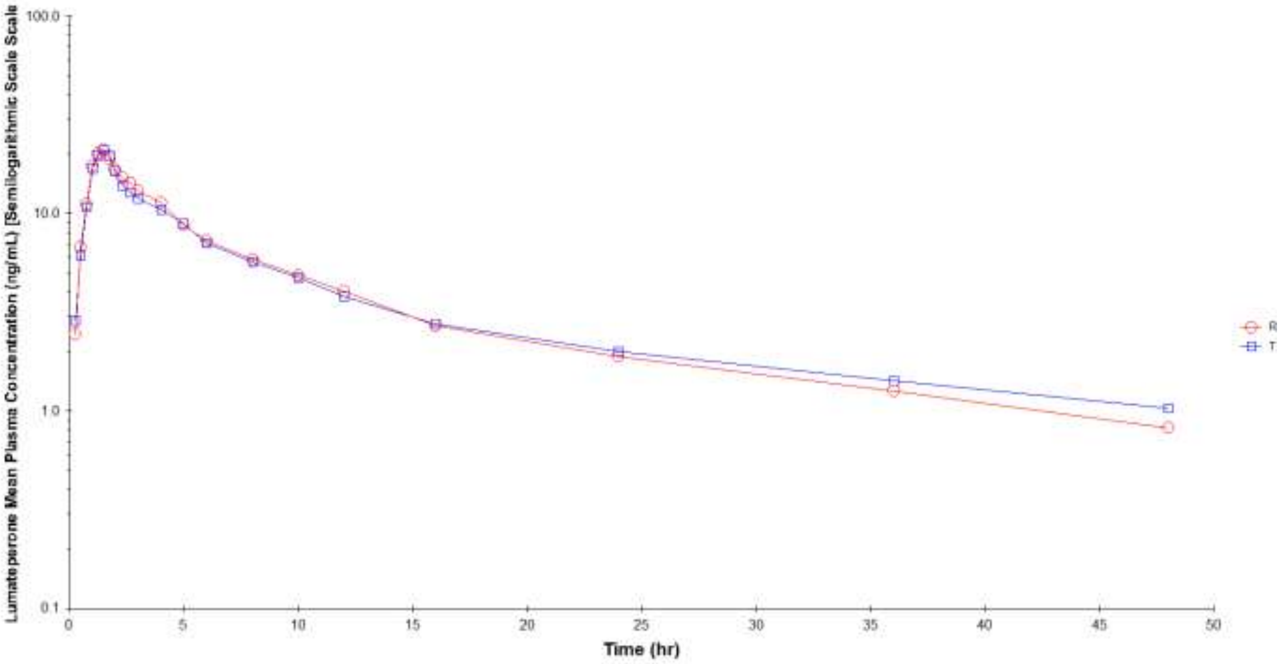


Figure 2: Ln Linear Plot of Mean Plasma Concentrations of Lumateperone vs. Actual Time for Test Product (T) and Reference Product (R) (N = 23)



3. SAFETY:

The test and reference products were comparable in their safety and tolerability in healthy, adult, human male subjects under fasting conditions.

4. ADVERSE EVENTS:

No mild, moderate, severe, serious or life-threatening adverse events were reported during the course of the study.

5. DISCUSSION:

Bioequivalence studies are essential for demonstrating therapeutic interchangeability between generic and reference pharmaceutical products by comparing their pharmacokinetic characteristics under standardized conditions (European Medicines Agency, 2010). In the present study, a test formulation of Lumateperone Capsule 42 mg was evaluated for bioequivalence against the reference product, CAPLYTA® (lumateperone) 42 mg capsules, following single-dose oral administration under fasting conditions in healthy adult male subjects.

The primary pharmacokinetic parameters used for bioequivalence assessment—maximum plasma concentration (Cmax), area under the plasma concentration–time curve from time zero to the last measurable concentration (AUC_0–t), and area under the plasma concentration–time curve extrapolated to infinity (AUC_0–∞)—met the regulatory acceptance criteria. The geometric least squares mean ratios and corresponding 90% confidence intervals for all three parameters were within the predefined bioequivalence range of 80.00% to 125.00%, indicating comparable rates and extents of absorption between the test and reference formulations (European Medicines Agency, 2010).

Lumateperone is known to exhibit low absolute oral bioavailability and inter-subject pharmacokinetic variability due to extensive first-pass metabolism (Metabolic Profiling Study, 2024). Despite these characteristics, the present study demonstrated consistent pharmacokinetic performance across

formulations. Secondary parameters, including Tmax and elimination half-life, were also similar, further supporting pharmacokinetic equivalence.
Both formulations were well tolerated, with no adverse events or clinically significant safety findings observed during the study. This outcome is consistent with previously reported clinical data indicating that lumateperone is generally safe and well tolerated at the recommended dose of 42 mg (Maini et al., 2021; Tarzian et al., 2023).

6. CONCLUSION:

The present bioequivalence study demonstrated that the test formulation of Lumateperone Capsule 42 mg is pharmacokinetically equivalent to the reference product, CAPLYTA® (lumateperone) 42 mg capsules, with respect to both the rate and extent of absorption under fasting conditions. The 90% confidence intervals for Cmax, AUC_0–t, and AUC_0–∞ were within the accepted bioequivalence limits, and both formulations were well tolerated. These results support the therapeutic interchangeability of the test and reference products.

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