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Phase I Randomized Crossover Bioequivalence Study of Nirmatrelvir and Ritonavir Tablets in Healthy Adult Volunteers Under Fasting Conditions

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Dr. M. Narender, Dr. K. Ramulu, Clinical Research, Hyderabad.

ABSTRACT:

This study was conducted to evaluate the bioequivalence of a test formulation of Nirmatrelvir 300 mg (2 × 150 mg tablets) combined with Ritonavir 100 mg compared with the reference product Paxlovid in healthy adult human subjects under fasting conditions. The study was an open-label, randomized, balanced, two-treatment, four-period, two-sequence, full replicate crossover design. A total of 44 healthy adult male subjects were enrolled and received a single oral dose of either the test or reference product. Pharmacokinetic parameters such as C_{max} and AUC_{0-t} were evaluated to determine bioequivalence. Safety and tolerability were also assessed during the study. The results demonstrated that the test product was bioequivalent to the reference product as the 90% confidence intervals for the primary pharmacokinetic parameters were within the accepted regulatory limits of 80.00%–125.00%.

Keywords: Nirmatrelvir and Ritonavir tables, antiviral, Fasting condition.

INTRODUCTION:

Bioequivalence studies are essential for comparing the pharmacokinetic characteristics of a generic formulation with a reference product. Nirmatrelvir in combination with Ritonavir is used as an antiviral therapy, and establishing bioequivalence ensures that the test formulation provides similar therapeutic effects as the reference drug.

This clinical study was conducted to assess the pharmacokinetic profile, safety, and tolerability of Nirmatrelvir and Ritonavir tablets manufactured by chromo labs Ltd., compared with the reference product Paxlovid. The study was conducted in compliance with Good Clinical Practice (GCP) guidelines and followed regulatory requirements for bioequivalence assessment

AIM AND OBJECTIVES

To evaluate the bioequivalence of the test product (Nirmatrelvir 300 mg + Ritonavir 100 mg) compared to the reference product in healthy adult human subjects under fasting conditions.

To assess the safety and tolerability of a single oral dose of the study drug in healthy adult participants.

MATERIALS AND METHODS

Study Design

This was an open-label, randomized, balanced, two-treatment, four-period, two-sequence, single-dose, full replicate crossover

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bioequivalence study conducted in healthy adult subjects. The study was performed at a clinical research facility in India and followed ICH E3 guidelines.

Study Population

A total of 44 healthy adult male subjects aged between 18 and 45 years with body mass index between 18.5 and 30.0 kg/m² were enrolled in the study after providing written informed consent.

Treatments

- Test product: Nirmatrelvir 300 mg (2 × 150 mg tablets) + Ritonavir 100 mg tablet
- Reference product: Paxlovid (Nirmatrelvir 300 mg + Ritonavir 100 mg).

Each subject received a single oral dose of either the test or reference product under fasting conditions with 240 mL of water according to the randomization schedule. A washout period of seven days was maintained between study periods.

Pharmacokinetic Sampling

Blood samples were collected at pre-dose and multiple post-dose time points up to 36 hours after drug administration to determine plasma concentrations of Nirmatrelvir and Ritonavir. Plasma samples were analyzed using a validated LC-MS/MS method.

Blood samples were collected at 0.00, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 24.00 & 36.00 hours. A total of 25 blood samples.

Pharmacokinetic and Statistical Analysis

Primary pharmacokinetic parameters included:

- Cmax (maximum plasma concentration)
- $AUC_{0–t}$ (area under the plasma concentration–time curve)

Bioequivalence was assessed using 90% confidence intervals of the log-transformed pharmacokinetic parameters. The acceptance criteria for bioequivalence were set between 80.00% and 125.00%.

Safety Assessment

Safety was evaluated through monitoring of adverse events, vital signs, laboratory investigations, electrocardiograms, and physical examinations throughout the study.

RESULTS

Study Participants

A total of 44 subjects were enrolled in the study, and 38 subjects completed all study periods. 07 subjects discontinued due to adverse events or protocol-related reasons.

Pharmacokinetic Results

For Nirmatrelvir:

- Mean Cmax was comparable between test and reference products.
- Mean $AUC_{0–t}$ values were similar for both treatments.

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Arithmetic Mean (SD) of Pharmacokinetic Parameters of Nirmatrelvir

PK Parameter (Units)	N	Treatment T (Test)	Treatment R (Reference)
Cmax (ng/mL)	83	3272.736 (822.517)	3262.272 (861.935)
AUC0-t (ng.hr/mL)	83	34638.009 (9970.573)	34890.137 (10350.773)
AUC0-∞ (ng.hr/mL)	83	36540.957 (10092.932)	36516.886 (10631.359)
*Tmax (hr)	83	3.000 (0.500,5.000)	3.000 (0.500,6.000)
t1/2(hr)	83	7.211 (2.317)	6.849 (2.055)
kel(1/hr)	83	0.106 (0.033)	0.110 (0.034)
AUC_%Extrap_obs	83	5.369 (4.476)	4.540 (3.427)
AUCRatio	83	94.631 (4.476)	95.460 (3.427)

*For Tmax, Median (Min, Max) are presented

For Ritonavir:

- Pharmacokinetic parameters such as Cmax and AUC₀–t were also comparable between the two formulations.

Arithmetic Mean (SD)of Pharmacokinetic Parameters of Ritonavir

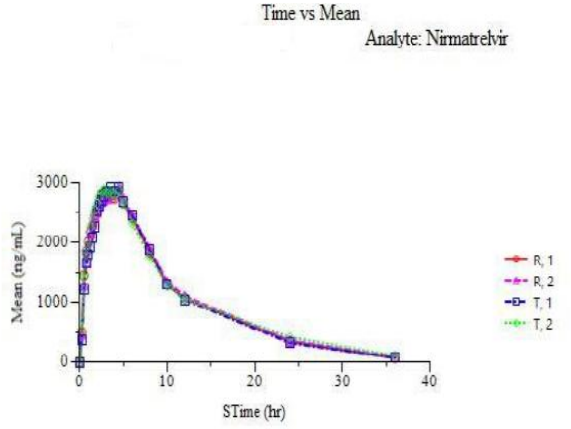
PK Parameter (Units)	N	Treatment T (Test)	Treatment R (Reference)
Cmax (ng/mL)	83	570.051 (301.445)	597.720 (246.547)
AUC0-t (ng.hr/mL)	83	5522.149 (2648.357)	5921.307 (2339.988)
AUC0-∞ (ng.hr/mL)	83	5870.927 (2723.809)	6210.179 (2466.314)
*Tmax (hr)	83	4.500 (1.500,8.000)	4.500 (1.500,6.000)
t1/2(hr)	83	7.397 (2.692)	6.906 (1.531)
kel(1/hr)	83	0.102 (0.026)	0.105 (0.023)
AUC_%Extrap_obs	83	7.260 (9.911)	4.726 (2.987)
AUCRatio	83	92.740 (9.911)	95.274 (2.987)

Statistical Analysis

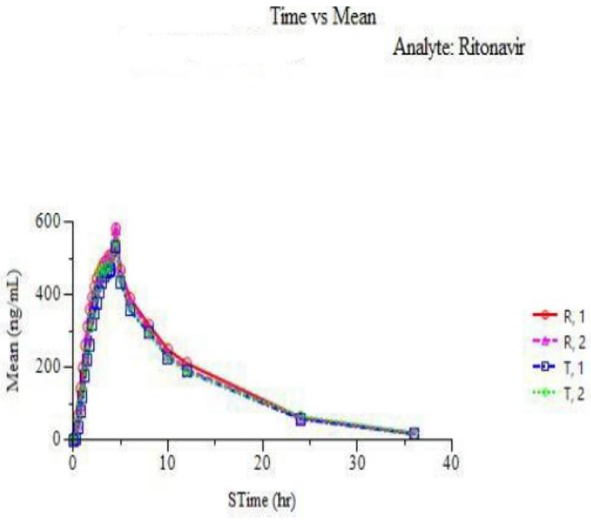
The statistical analysis showed that:

- The geometric mean ratio for Cmax and AUC₀–t of Nirmatrelvir and Ritonavir fell within the acceptable bioequivalence range.
- The 90% confidence intervals for the primary pharmacokinetic parameters were within the regulatory limits of 80.00%–125.00%.

Mean Plasma Nirmatrelvir Concentration Vs. Time Plots-Linear Scale



Mean Plasma Ritonavir Concentration Vs Time Plots-Log Linear Scale



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Statistical Results

Statistical Analysis Results for the Assessment of Bioequivalence Based on Average Bioequivalence approach for Nirmatrelvir

PK Parameter	ISCV	T/R Ratio	90% Confidence Interval	Power
Cmax	19.89%	100.46%	95.87%-105.28%	100.0%
AUC0-t	17.81%	99.40%	94.82%-104.19%	100.0%

Statistical Analysis Results for the Assessment of Bioequivalence Based on Average Bioequivalence approach for Ritonavir

PK Parameter	ISCV	T/R Ratio	90% Confidence Interval	Power
Cmax	27.98%	89.56%	81.19%-98.79%	97.8%
AUC0-t	38.61%	87.06%	79.04%-95.88%	98.1%

The within-subject coefficient of variation (CV%) for both Cmax and AUC_{0}–t of the reference Ritonavir product was ≤ 30%; therefore, bioequivalence for these pharmacokinetic parameters was evaluated using the average bioequivalence approach. The 90% confidence intervals for the geometric mean ratios of the ln-transformed Cmax values were within the accepted bioequivalence range of 80.00%–125.00%. However, the corresponding 90% confidence intervals for the ln-transformed AUC_{0}–t values fell outside the predefined bioequivalence limits of 80.00%–125.00%.

CONCLUSION

The study demonstrated that the test formulation of Nirmatrelvir 300 mg + Ritonavir 100 mg tablets is bioequivalent to the reference product Paxlovid under fasting conditions in healthy adult human subjects. Both formulations showed comparable pharmacokinetic profiles and were generally well tolerated. The results support the use of the test formulation as an alternative to the reference product.

REFERENCE:

1. Clinical Study Report: Bioequivalence Study of Nirmatrelvir 300 mg + Ritonavir 100 mg Tablets. Shanghai Desano Bio-Pharmaceutical Co., Ltd
2. International Council for Harmonisation (ICH) E3 Guidelines for Clinical Study Reports.
3. USFDA Prescribing Information of Paxlovid (Nirmatrelvir and Ritonavir) tablets.

Source of Support: Nil. **Conflicts of Interest:** None