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1.0 TITLE PAGE

PROJECT NO.: 20-VIN-0106

PROJECT REPORT

An Open Label, Balanced, Randomized, Single-Dose, Two-Treatment, Two-Sequence, Two-Period, Two-Way Crossover, Oral Bioequivalence Study of Pantoprazole Sodium delayed release tablet 40 mg of Graviti Pharmaceuticals Pvt. Ltd. India with PROTONIX (pantoprazole sodium) delayed-release tablets 40 mg of Wyeth Pharmaceuticals LLC, A subsidiary of Pfizer Inc, Philadelphia, PA, 19101 in Healthy, Adult, Human Subjects Under Fasting Condition.

Test Product (T) : Pantoprazole Sodium Delayed Release Tablets USP 40 mg
Reference product (R) : Protonix® (Pantoprazole Sodium) Delayed Release Tablets 40 mg

Report history			Protocol history		
Version No.	:	01	Version No.	:	01
Date	:	18 Mar 2021	Date	:	10 Jun 2020

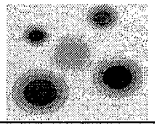
Clinical phase	Admission	Dosing	Discharge	Completion Date
Period 01	20 Jan 2021	21 Jan 2021	22 Jan 2021	22 Jan 2021
Period 02	26 Jan 2021	27 Jan 2021	28 Jan 2021	28 Jan 2021

PRINCIPAL INVESTIGATOR	NAME OF SPONSOR REPRESENTATIVE
Dr. Anand Jethwa, MBBS Site Address: Veeda Clinical Research Private Limited, Office no. 9, 10 & 11- 1st, 2nd and 3rd Floor, Radhe Palladium, Panchot, Mehsana, Gujarat- 384205, India Phone: +91-79-67773000 Fax: +91-79-30013010 Email: anand.jethwa@veedacr.com	C. Pradeep kumar Reddy, M. Pharm Senior General Manager Address: Graviti Pharmaceuticals Private Limited Survey No. 621/E & 621/EE, Isnapur Village, Patancheru Mandal, Sangareddy - 502 307 Telangana, India. Tel: +91-7680882447 EmaiI:pradeepkr@gravitipharma.com

Registered Office:
Veeda Clinical Research Pvt. Ltd.
Shivalik Plaza, Near I.I.M., Ambawadi
Ahmedabad – 380 015, India.

This study was performed in compliance with Good Clinical Practice (GCP); all essential documents pertaining to the study are available in the archive.

1.1 TABLE OF CONTENT

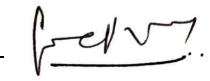


1.2 COMPLIANCE STATEMENT

We attest to the fact that the data presented here is accurate and reflects the raw data. The study was conducted as per IEC approved protocol and associated documents, all the requirements regarding the obligations of investigators and all other pertinent requirements of ICMR guidelines for National Ethical Guidelines for Biomedical and Health Research Involving Human Participants 2017, CDSCO guideline, New Drugs and Clinical Trials Rules, 2019, ICH E6 (R2) 'Guidance on Good Clinical Practice', Declaration of Helsinki (Brazil, October 2013), USFDA guidelines and procedures oriented to Good Laboratory Practice (OECD and Schedule L-I of D & C Rules 1945) and all other applicable regulatory requirements and SOPs of Veeda Clinical Research Pvt. Ltd. and we, on behalf of Veeda Clinical Research Pvt. Ltd., accept the responsibility for scientific correctness of the project and the validity of the data produced in this report.

Clinical Research	Dr. Anand Jethwa Principal Investigator
Signature	
Date	16 Mar 2021

I attest to the fact that the data presented here is accurate and reflects the raw data as per SOPs of Veeda Clinical Research Pvt. Ltd. and I, on behalf of Veeda Clinical Research Pvt. Ltd., accept the responsibility and ensure the validity of the data produced in this report.

Pharmacokinetics & Biostatistics	Dr. Ghanshyam Patel Lead Pharmacokinetics & Biostatistics
Signature	 Digitally signed by GHANSHYAMBHAI CHANDUBHAI PATEL Date: 2021.03.18 12:13:59 +05'30'
Date	

Quality Assurance Statement

The study was subjected to various quality assurance audits like the in-process as well as retrospective audits. Audits by the Quality Assurance department ensure that the study was conducted with full adherence to the IEC approved study protocol and associated document and SOPs. This is to certify that, to the best of my knowledge, this final report accurately describes the study methods and procedures used and the reported results accurately reflect the raw data. I, on behalf of Veeda clinical research Pvt. Ltd., release the study report.

Quality Assurance	Ms. Amee Kanuga Head, Quality Assurance
Signature	Amee Digitally signed by AMEE MILIND KANUGA Date: 2021.03.18 21:24:27 +05'30'
Date	

2.0 SYNOPSIS

- **Name of Sponsor:**

  Graviti Pharmaceuticals Private Limited
  Survey No. 621/E & 621/EE,
  Isnapur Village, Patancheru Mandal,
  Sangareddy - 502 307
  Telangana, India

- **Name of Finished Products:**

  Test Product (T): Pantoprazole Sodium Delayed Release Tablet USP 40 mg

  Reference Product (R): Protonix® (Pantoprazole Sodium) Delayed Release Tablets 40 mg

- **Name of Active Ingredient**: Pantoprazole Sodium

- **Title of the Study:**

  An Open Label, Balanced, Randomized, Single-Dose, Two-Treatment, Two-Sequence, Two-Period, Two-Way Crossover, Oral Bioequivalence Study of Pantoprazole Sodium delayed release tablet 40 mg of Graviti Pharmaceuticals Pvt. Ltd. India with PROTONIX (pantoprazole sodium) delayed-release tablets 40 mg of Wyeth Pharmaceuticals LLC, A subsidiary of Pfizer Inc, Philadelphia, PA, 19101 in Healthy, Adult, Human Subjects Under Fasting Condition.

- **Investigators:**

Principal Investigator	:	Dr. Anand Jethwa
Clinical Investigator	:	Dr. Purvangi Patel
Clinical Investigator	:	Dr. Mona Patel
Clinical Investigator	:	Dr. Sharvin Patel
Clinical Investigator	:	Dr. Axay Parth
Clinical Investigator	:	Dr. Gaurav Jansari
Clinical Investigator	:	Dr. Jayanit Shah
Head-Bioanalytical Research Department	:	Mr. Swati Guttikar
Lead Pharmacokinetics & Biostatistics	:	Dr. Ghanshyam Patel
Author of the report	:	Ms. Umangi Nayak

- **Study Centre:**

  Clinical center:

  Veeda Clinical Research Private Limited,
  Office no. 9, 10 & 11- 1st, 2nd and 3rd Floor,
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  Phone: +91-79-6777 3000,
  Fax: +91-79-3001 3010

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  Bioanalytical centre:

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  Nr. Grand Bhagvati Hotel,
  Sindhu Bhavan Road,
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  Fax: +91-79-3001 3010

- **Objective and Purpose:**

  To compare the rate and extent of absorption of Pantoprazole Sodium delayed release tablet 40 mg of Graviti Pharmaceuticals Pvt. Ltd. India with PROTONIX (pantoprazole sodium) delayed-release tablets 40 mg of Wyeth Pharmaceuticals LLC, A subsidiary of Pfizer Inc, Philadelphia, PA, 19101 in Healthy, Adult, Human subjects under fasting condition as well as to monitor the safety and tolerability of the subjects.

- **Study Design:**

  An Open Label, Balanced, Randomized, Single-Dose, Two-Treatment, Two-Sequence, Two-Period, Two-Way Crossover, Oral Bioequivalence Study in Healthy, Adult, Human Subjects Under Fasting Condition.

- **Ethics**

  Institutional/Independent Ethics Committee (IEC)

  Name of Institutional/Independent Ethics Committee: Shreenidhi Heart & Medical Hospital Ethics Committee

  Following documents were submitted to IEC along with IEC application form, Translation certificates, undertaking by the investigator, relevant literature, CV of investigators and other relevant documents for review/Expedited review and approval.

Name of document	Version and Date	Submission Date	Approval date
Protocol	Version 01 Dated 10 Jun 2020	04 Sep 2020	11 Sep 2020
Amendment 001 in Protocol Version 01 dated 10 Jun 2020	Dated 28 Nov 2020	07 Dec 2020	09 Dec 2020
Informed Consent Document (English, Gujarati and Hindi)	Version 02 Dated 27 Jun 2020	04 Sep 2020	11 Sep 2020
Amendment 001 in Informed Consent Document (English, Gujarati and Hindi) Version 02 Dated 27 Jun 2020	Dated 28 Nov 2020	07 Dec 2020	09 Dec 2020
Informed Consent Document for study-specific Tests/ procedure (English, Gujarati and Hindi)	Version 01 Dated 27 Jun 2020	04 Sep 2020	11 Sep 2020
Case Report Form	Version 01 Dated 31 Aug 2020	04 Sep 2020	11 Sep 2020
	Version 02 Dated 28 Nov 2020	07 Dec 2020	09 Dec 2020

  A 'list of IEC members' and a copy of 'Notification of Decision of the Independent Ethics Committee' is appended in **Appendix 5.3** and **5.4** respectively.

- **Methodology:**

  Treatments were allocated to subjects by carrying out randomization using SAS® software version 9.4.

Blood samples were drawn from before dosing and up to 24.00 hours after dosing in each study period.

The plasma concentrations of Pentoprazole were analyzed using a validated LC-ESI-MS-MS bioanalytical method.

Statistical Analysis of pharmacokinetic parameters of test and reference formulations using SAS®, version 9.4 was performed to assess bioequivalence.

- **Number of Subjects:**

Prior to start of the study, each subject was provided with a subject informed consent document, informed consent document for specific study/procedure, informed consent document for COVID 19 specific tests, informed consent document for processes to prevent spread of COVID 19 infection and checklist for evaluation risk of COVID 19 infection. The designated study personnel provided the volunteers with the information on the investigational drug, study procedures, potential risks of participating in the study and process to be followed in the study to prevent the spread of COVID 19 infection. Investigators discussed with volunteer about study related understanding and encouraged the volunteers for raising queries / questions related to any aspect of the study and resolved the same, up to his satisfaction. The entire informed consent process was documented via audio video recording while maintaining subject confidentiality. After that Investigator reviewed the signed and dated consent document before enrolling the subject in study. Checklist for evaluation risk of COVID 19 infection was filled by the study personnel for all subsequent visit of the subject to the study center.

A photocopy of the signed informed consent document & its related documents were given to all enrolled subjects who provided written informed consent. Copy of Informed Consent documents & it related documents (English, Gujarati and Hindi language) are appended in **Appendix 5.1**.

Informed consent document for processes to prevent spread of COVID 19 infection and checklist for evaluation risk of COVID 19 infection is part of our in-house SOP (VIN-CRD-129, 02) and SOP was approved by IEC on 01 Jul 2020. IEC approval letter for the SOP (VIN-CRD-129, 02) is appended in **Appendix 5.4**.

Sample copy of Informed consent document for processes to prevent spread of COVID 19 (English, Hindi and Gujarati language) infection and checklist for evaluation risk of COVID 19 infection (English) are appended in **Appendix 5.1.**

Details of number of volunteers reported and ICD presentation are given in below table:

Date of Reporting	20 Jan 2021
No. of volunteers reported	21
ICD presented to number of volunteers	21
No. of volunteers enrolled	16 (+02 extra male subjects up to period 01 dosing*)
No. of volunteer sent back with reason	03 volunteers (01-Unfit, 02-Sent back)

A total of 16 (+02 extra*) healthy, adult, male human subjects were enrolled in the study as per protocol.

*None of the subjects withdrew before period 01 dosing, hence extra subjects 01 and 02 were sent back without being dosed after dosing activity of period 01.

None of the subject was withdrawn during the study.

Therefore, 16 subjects completed the study as per protocol. Samples collected from 16 subjects were analyzed for Pentoprazole plasma concentrations.

- **Criteria for Inclusion:**

Healthy, willing, volunteers of age between 18 and 45 (including both) years, Body Mass Index 18.50 to 30.00 kg/m^2 (both inclusive) with minimum of 45 kg weight were selected on the basis of laboratory evaluations, medical history, clinical examination [vital signs (blood pressure, body temperature, radial pulse rate and respiratory rate), physical examination and systemic examination], chest X-ray (PA view)* and ECG recordings during screening.

*Considering COVID 19 situation and as per PI discretion, chest X-ray (PA view) was performed for all subject prior to start of the study.

Urine screen for drugs of abuse and urine alcohol test were performed on admission day of each period.

Demographic data of enrolled and completed subjects (N=16)

Demographic	Age (Years)	Height (cm)	Weight (Kg)	BMI (Kg/m²)
Mean	29.38	164.96	62.76	23.03
Standard Deviation	5.75	5.73	10.06	3.13
Median	30.00	164.25	59.50	22.54
Standard Error Mean	1.44	1.43	2.52	0.78

Maximum	44	177.00	86.70	29.79
Minimum	21	156.00	50.90	18.55

- **RESTRICTIONS**

Medication

Subjects were instructed not to consume any prescribed medicinal products and OTC medicinal products during the last 30 days prior to dosing in period 01 till the study was completed. None of the subject was given concomitant medication during the study.

Diet and Water

All subjects were fasted (overnight) for at least 10 hours before their schedule time of dosing. The subjects were received a standard meal at about 4.00, 8.00 and 12.00 hours after dosing in each period. During housing, all meal plans were identical for all the periods. In case, meal, vital signs measurement and blood sample collection start times coincide, blood sample collection and vital signs measurement were given the priority over meal.

Drinking water was not allowed from one hour before dosing till one hour post-dose (except for 240 ±2 mL of water given for dosing). Before and after that, drinking water was allowed at all times.

Posture

Subjects remained in sitting posture and were not allowed to lie down for at least 4.00 hours after administration of investigational product (except for any procedural requirements and using bathroom). Subjects were allowed to rise for brief periods under supervision (i.e. in order to use the washroom facilities or procedural requirements consisting of blood sample collection and vital signs measurements) during the restriction period. Thereafter, subjects were allowed to engage in normal activities while avoiding severe physical exertion.

Others

Subjects were instructed during screening to refrain from smoking, chewing tobacco, pan or pan masala, gutkha, masala (containing betel nut and tobacco) and from consuming any alcoholic products, xanthine-containing foods or beverages (like chocolate, tea, coffee or cola drinks) from 48 hours prior to dosing in Period 01 and until the last blood sample was collected in the study. Subjects were instructed during screening to refrain from consuming grape fruits or grapefruit juice from 72.00 hours prior to dosing of period 01 and until the last blood sample was collected in the study.

Subjects were not allowed to have the same from admission till discharge in each period.

Subjects were advised to use an approved form of birth control from period 01 dosing till end of the study and to continue for at least 30 days after the last dose of the study medication as a birth control restriction. Approved birth control methods (a double barrier method) during this period were:

- Condom with spermicide
- Condom with diaphragm

Subjects were instructed not to donate sperm during this time. Subjects were instructed to inform the study doctor incase their partner became pregnant during the study.

- **Investigational Products:**

Test Product (T):

Product Name	:	Pantoprazole Sodium Delayed Release Tablets USP 40 mg
Manufactured by	:	Graviti Pharmaceuticals Pvt. Ltd.
Batch No.	:	PAN-TD1-PB001
Manufacturing Date	:	Jan 2021
Expiry Date	:	Dec 2021
Mode of Administration	:	One tablet was administered orally at scheduled dosing time in sitting posture with 240±2 mL of water at ambient temperature followed by thorough mouth check using torch and disposable spatula immediately after dosing.

Reference Product (R):

Product Name	:	Protonix® (Pantoprazole Sodium) Delayed Release Tablets 40 mg
Distributed by	:	Wyeth Pharmaceuticals Inc., A subsidiary of Pfizer Inc, Philadelphia, PA 19101
Lot No.	:	411667N1
Manufacturing Date	:	NA
Expiry Date	:	Jan 2021
Mode of Administration	:	One tablet was administered orally at scheduled dosing time in sitting posture with 240±2 mL of water at ambient temperature followed by thorough mouth check using torch and disposable spatula immediately after dosing.

- **Duration of Treatment:**

  Total duration of the study was nine (09) days from the day of admission of first period till the end of second period.

  Upon entering into the study, subjects were housed in clinical facility of Veeda Clinical Research Pvt. Ltd. to ensure 10.00 hours overnight fasting before schedule time of dosing and continued to be housed in the facility till 24.00 hours post-dose blood sample in each period.

  A gap of six (06) days was kept as washout period between each dosing periods.

- **Blood Collection Times:**

  A total of 23 blood samples were collected during each period.

  The pre-dose (0.000 hr) blood sample of 3.0 mL was collected within one hour prior to dosing and the post-dose blood samples of 3.0 mL each were drawn at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00 and 24.00 hours following drug administration in each period.

  Blood samples were collected in pre-labeled (Project No., Subject No., Period, Sampling time point and Sample code) vacutainer containing K_3EDTA as anticoagulant.

  Blood sample that was collected placed on wet ice bath (below 10°C) from the point of collection until storage of plasma.

*A total of 46 blood samples were collected in the study. The total blood volume combining all the periods did not exceed 169.8 mL for male subjects as follows:		
For pharmacokinetic analysis	:	138.0 mL
For screening	:	10.0 mL (Up to)
Heparinised blood (0.3 mL of discarded heparinised blood prior to each in-house blood sample collected through cannula)	:	13.8 mL
For post study safety assessment	:	08.0 mL (Up to)
*The above criteria were followed for the subjects from whom all the blood samples were collected.		

- **Drug Analysis:**

  A validated LC-ESI-MS/MS bioanalytical method developed for the quantification of Pentoprazole in plasma was employed for subjects' sample analysis.

A calibration curve extending over the range from 10.000 ng/mL to 8000.000 ng/mL with a LLOQ of 10.000 ng/mL was used in subject sample analysis of Pentoprazole. The quality control samples showed % Bias (mean accuracy) and % CV as mentioned below.

QC Samples (LQC, MQC2, MQC1, HQC)	Precision (%CV)	(%Bias)
	2.82 to 3.38	-1.33 to 3.11

- **Pharmacokinetic Parameters:**

Employing the estimated concentration time profiles of Pantoprazole, primary pharmacokinetic parameters like $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$ and secondary pharmacokinetic parameters like T_{max}, $t_{1/2}$, K_{el} and AUC_%Extrap_obs were calculated using plasma concentration vs. time profile (Actual time of sample collection) data of all investigational products in individual subjects using non-compartmental model by using Phoenix WinNonlin® 8.2 (Pharsight Corporation, USA).

The individual and mean plasma concentration vs. time data of Reference (R) and Test (T) formulations are presented in Table 02 and Table 03 for Pantoprazole, respectively.

The individual and mean pharmacokinetic parameters of Reference (R) and Test (T) formulations are represented in Table 04 and Table 05 for Pantoprazole, respectively.

- **Statistical Methods:**

The statistical analysis plan mentioned in the protocol was used to analyze the data. Dataset for estimation of pharmacokinetic parameters C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $t_{1/2}$, $K_{el,}$ and AUC_%Extrap_obs were calculated for Pantoprazole using non-compartmental model by using Phoenix WinNonlin® 8.2 (Pharsight Corporation, USA).

Statistical analyses was performed on ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Pantoprazole using the SAS® package (SAS Institute Inc., Cary, NC, USA, Version 9.4).

For Pantoprazole, the ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were analyzed by analysis of variance (ANOVA) using PROC GLM in SAS® Software, Version 9.4.

The model statement of PROC GLM in SAS® was included the fixed effects of Sequence, Treatment, Period and random effect of Subject (Sequence). The Sequence effect was tested using the Subject (Sequence) effect as the error term.

The sequence effect was tested at the 0.10 level of significant and other main effects related to treatment and period was tested at the 0.05 level of significance.

Each analysis of variance was included calculation of least-square means, the difference between the adjusted formulation means and the standard error associated with the difference. The above analyses were done using procedure PROC GLM in SAS® version 9.4.

Intra-subject variability was calculated using mean square error of ANOVA for ln-transformed analysis of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Pantoprazole.

Power of test to detect at least 20% mean difference between formulations were calculated and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Pantoprazole.

Geometric least square means for test and reference formulations were obtained by taking the exponent of least square means of test and reference formulations for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Pantoprazole. Ratio analysis was performed by taking the ratio of geometric least square means of test to reference formulations for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The comparisons of interest were T vs. R, so the ratios determined was of the form T/R.
Where, T = Test product and R = Reference product

90% confidence intervals for the difference between least square means of test and reference formulations was calculated using mean square error, obtained in ANOVA, for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ data for Pantoprazole. 90% confidence interval for the geometric least squares mean ratio were obtained by taking the exponent of lower and upper limits of 90% confidence interval, obtained for the least square mean difference.

Two one-sided test, namely Schuirmann‟s test, was employed at 5% level of significance for the lower and upper limits of 90% confidence interval to check whether the 90% confidence interval for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ was entirely within the bioequivalence limits 0.80 – 1.25 (80.00% - 125.00%).

The conclusion of bioequivalence was based on the 90% confidence interval for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Pantoprazole.

- **Criteria for evaluation:**

  For Pantoprazole, based on the statistical results of 90% confidence intervals for the geometric least square mean ratio (T/R) for the pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, conclusions were drawn whether test formulation was bioequivalent to reference formulation under fasting condition. Acceptance range for bioequivalence was 80.00%-125.00% for 90% confidence intervals of the geometric least square means ratio for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

  (Where T = Test Product; R = Reference Product).

- **Summary Results:**

  The mean pharmacokinetic parameters of Pantoprazole estimated for the Reference (R) and Test (T) formulations are as follows:

  For Pantoprazole:

PK Parameters (Units)	Arithmetic Mean ± SD (%CV) (N = 16)	
	Reference product (R)	Test product (T)
C_{max} (ng/mL)	3032.238 ± 815.4567 (26.89%)	3209.373 ± 1057.1880 (32.94%)
#T_{max} (hr)	2.500 (1.00 - 3.67)	2.375 (1.67 - 4.50)
AUC_{0-t} (hr*ng/mL)	9571.113 ± 9882.7938 (103.26%)	9718.733 ± 11263.0997 (115.89%)
AUC_{0-inf} (hr*ng/mL)	10041.351 ± 10934.0673 (108.89%)	10328.329 ± 12893.9417 (124.84%)
$t_{½}$ (hr)	2.065 ± 1.9141 (92.71%)	2.014 ± 1.9739 (97.99%)
K_{el} (1/hr)	0.517 ± 0.2387 (46.20%)	0.523 ± 0.2307 (44.13%)
AUC_%Extrap_obs (%)	1.858 ± 2.9674 (159.73%)	1.941 ± 3.5074 (180.70%)

  # For T_{max} median (min – max)

  Linear and semi-logarithmic plot of mean plasma concentrations of Pantoprazole for Reference (R) and Test (T) formulations are presented in **Figure 01**.

  Linear and semi-logarithmic plots of individual plasma concentrations of Pantoprazole for Reference (R) and Test (T) formulations are presented in **Figure 02**.

  Summary report of statistical analysis using SAS® is appended in **Appendix 5.13** for Pantoprazole.

Statistical analysis:

For Pantoprazole, the statistical analysis was performed over 16 subjects. Analysis of Variance was carried out using PROC GLM of SAS® Version 9.4 (SAS Institute Inc., USA) for ln-transformed pharmacokinetic parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$. The least square means of test and reference formulations, its difference, intra-subject variability and power were computed for ln-transformed C_{max} , AUC_{0-t} and $AUC_{0-\infty}$. The geometric least square mean ratio and its 90% confidence interval were also computed for the pharmacokinetic parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$.

The geometric least squares mean of Test Formulation (T) and Reference Formulation (R), its ratio (T/R)%, intra-subject variability, Power and 90% confidence intervals of geometric least square mean ratio (T/R) are summarized in the following table:

For Pantoprazole:

PK Parameters (Units)	Geometric Least Squares Means and it's ratio (N = 16)			Intra-subject CV (%)	90% Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R) (%)			
C_{max} (ng/mL)	3078.489	2933.326	104.95	9.42	98.98% - 111.28%	99.99
AUC_{0-t} (hr*ng/mL)	6709.813	6749.344	99.41	9.47	93.73% - 105.44%	99.99
AUC_{0-inf} (hr*ng/mL)	6846.982	6880.200	99.52	9.76	93.66% - 105.74%	99.98

The statistical inference based on p-value derived from analysis of variance (ANOVA) for the assessment of the main effects like formulation, period and sequence is presented as follows (**Appendix 5.13**):

Main Effects	p-value for pharmacokinetic parameters		
	LnC_{max}	$LnAUC_{0-t}$	$LnAUC_{0-inf}$
Sequence	0.1022	0.1830	0.1803
Period	0.4762	*0.0063	*0.0061
Formulation	0.1682	0.8630	0.8903

* Statistical significant effect

Results:

For Pantoprazole:

PK Parameters (Units)	Acceptance Range of 90% Confidence Interval	Pantoprazole	
		90% Confidence Interval	Results
C_{max} (ng/mL)	80.00% - 125.00%	98.98% - 111.28%	BE Met
AUC_{0-t} (hr*ng /mL)	80.00% - 125.00%	93.73% - 105.44%	BE Met
AUC_{0-inf} (hr*ng/mL)	80.00% - 125.00%	93.66% - 105.74%	BE Met

- **Safety Analysis:**

Sitting blood pressure and radial pulse rate were measured for the subjects before dosing of investigational products (in the morning of the day of dosing) and at 1.00, 3.00, 6.00 and 13.00 hours after dosing in each period.

Post-dose sitting blood pressure and radial pulse rate were measured within ±45 minutes of the scheduled time.

Clinical examination [vital signs (sitting blood pressure, body temperature, radial pulse rate and respiratory rate), physical examination and systemic examination] was done on the day of admission and before discharge in each study period. Clinical examination before discharge was begun within 02.00 hours prior to the scheduled time of discharge of each subject in each study period.

Body temperature and COVID-19 related symptoms were measured at around every 8 hours (i.e. 8.00 and 16.00 hours) after dosing during housing. Body temperature and COVID-19 related symptoms were measured within ±45 minutes of the scheduled time.

Note: Body temperature of all in housed subjects was measured at pre-dose for safety purpose. (Refer file note copy ID M5863 appended in **Appendix 5.12**)

Subjects were questioned for well-being at the time of clinical examination, recording of sitting blood pressure, radial pulse rate and at the time of last in house blood sample in each study period.

Post study safety assessment (Hematology - Haemoglobin, Total and Differential Leukocyte Count, Platelet Count and biochemical parameters – SGOT, SGPT,

Bilirubin, Creatinine, ***Creatinine clearance*** and Urea) was done at the end of the study.

- **Adverse Events:**

  No adverse event was reported during the entire course of the study.

- **Individual clinically significant abnormalities:**

  Laboratory reports for all subjects at the time of post study examinations were studied by the Clinical Research Physician and found well within the clinically acceptable range.

- **Protocol deviations:**

  Sampling Deviations:

  Pre-dose blood sample was collected within one hour prior to dosing; post-dose in-house blood samples were collected within 2 minutes from the scheduled sampling time for all subjects except for below mentioned subject.

Sr. No.	Period	Date	Subject No.	Time Point (hr)	Scheduled Time	Actual Time	Actual Deviation (Min)	Reason for deviation*	Deviation as per protocol (Min)
01	01	21 Jan 2021	05	2.25	10:23	10:27	04	CB	02

*CB: Cannula blockage

The details are provided in **Appendix 5.11.**

Other deviation

None

3.0 CONCLUSION

Safety and Tolerability:

The test and reference products were well tolerated by the subjects. No adverse event, death or serious adverse event was reported during the conduct of the study.

Pharmacokinetic conclusion:

The Test Product (T) (Pantoprazole Sodium delayed release tablet 40 mg of Graviti Pharmaceuticals Pvt. Ltd. India) when compared with the Reference Product (R) (PROTONIX (pantoprazole sodium) delayed-release tablets 40 mg of Wyeth Pharmaceuticals LLC, A subsidiary of Pfizer Inc, Philadelphia, PA, 19101) meets the bioequivalence criteria in terms of rate and extent of absorption after administration of single dose as set in the protocol.

4.0 TABLES AND FIGURES

SR.NO.	DETAILS
Tables	
01	Subject's Demographic Profile
02	Individual and mean plasma concentrations of Pantoprazole after administration of Reference (R) formulation in Healthy, Adult, Human Subjects Under Fasting Condition
03	Individual and mean plasma concentrations of Pantoprazole after administration of Test (T) formulation in Healthy, Adult, Human Subjects Under Fasting Condition
04	Individual and mean pharmacokinetic parameters of Pantoprazole after administration of Reference (R) formulation in Healthy, Adult, Human Subjects Under Fasting Condition
05	Individual and mean pharmacokinetic parameters of Pantoprazole after administration of Test (T) formulation in Healthy, Adult, Human Subjects Under Fasting Condition
Figures	
01	Linear and semi-logarithmic plots of mean plasma concentrations versus time.
02	Linear and semi-logarithmic plots of individual plasma concentrations versus time.

5.0 APPENDICES

SR.NO.	DETAILS
5.1	Protocol and protocol amendment along with all appendices and ICD
5.2	Sample case report form
5.3	List of IEC members
5.4	IEC approval letter
5.5	List of investigators and other important participants with CVs
5.6	Randomization schedule
5.7	Investigational products accountability record
5.8	Adverse event listings (each subject)
5.9	Discontinued subjects
5.10	Protocol deviations
5.11	Sampling deviations
5.12	File Notes
5.13	Summary report of statistical analysis of ln-transformed C_{max}, AUC_{0-t} and AUC_{0-inf} using SAS® software