Redacted under Section 40, Section 41 and Section 43 of the Freedom of Information Act.

CLINICAL STUDY REPORT
Project Number: 068-20

An open-label, balanced, randomized, single-dose, two-sequence, four-period, fully-replicate, crossover study to evaluate the Dose-Proportionality of Glycopyrronium Bromide 1mg and 2mg Tablets manufactured for Kinedexe UK Limited, UK in healthy, adult, human subjects under fasting conditions.

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CLINICAL STDY REPORT
Project No.: 068-20

1.0 TITLE PAGE

An open-label, balanced, randomized, single-dose, two-sequence, four-period, fully-replicate, crossover study to evaluate the Dose-Proportionality of Glycopyrronium Bromide 1mg and 2mg Tablets manufactured for Kinedexe UK Limited, UK in healthy, adult, human subjects under fasting conditions.	
Test Product 1 (T1)	Glycopyrronium Bromide 1mg Tablets, manufactured for Kinedexe UK Limited, UK.
Test Product 2 (T2)	Glycopyrronium Bromide 2mg Tablets, manufactured for Kinedexe UK Limited, UK.
Phase of Development:	Dose-Proportionality Study
Study Design:	An Open label, balanced, randomized single-dose, two-sequence, four-period, fully replicate, crossover design under fasting conditions.
Clinical Phase:	Study initiation date [check-in of period 01]: 25Aug2020
	Study completion date [checkout of period 04]: 11Sep2020
Bioanalytical Phase:	Study initiation date (analysis start date): 12Sep2020
	Study completion date (analysis end date): 20Sep2020
Statistical Phase:	Statistical analysis start date: 23Sep2020
	Statistical analysis end date: 27Sep2020

Sponsor: Kinedexe UK Limited, Unit 15 Moorcroft, Harlington Road, Hillingdon, Middlesex UK UB8 3HD, United Kingdom Tel No: +442030967070-75 [redacted]	**Principal Investigator:** [redacted]

Version No.: 01
Date: 01Oct2020
Supersedes Version No.: None
Date: NA

SYNERGEN BIO PRIVATE LIMITED

[redacted]

2.0 SYNOPSIS

Name of Sponsor: Kinedexe UK Limited, UK.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	***(For National Authority Use only)***
Name of the Investigational Product: Glycopyrronium Bromide 1mg and 2mg		
Name of Active Ingredient: Glycopyrronium Bromide		

Title of the Study:

An open-label, balanced, randomized, single-dose, two-sequence, four-period, fully-replicate, crossover study to evaluate the Dose-Proportionality of Glycopyrronium Bromide 1mg and 2mg Tablets manufactured for Kinedexe UK Limited, UK in healthy, adult, human subjects under fasting conditions.

Investigators:

Principal Investigator :
Clinical Investigators :
:
*Bioanalytical Investigator :
Biostatistician :

[redacted] handed over responsibilities [redacted]

Center(s):

Clinical Research, Bioanalytical Research, Pharmacokinetics and Biostatistics and Quality Assurance Services: -

Synergen Bio Private Limited
[redacted]

Study Period:	**Clinical Phase:**	udy initiation date [check-in of period 01]: 25Aug2020
		Study completion date [checkout of period 04]: 11Sep2020
	Bioanalytical Phase:	Study initiation date (analysis start date): 12Sep2020
		Study completion date (analysis end date): 20Sep2020

Name of Sponsor: Kinedexe UK Limited, UK.		**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of the Investigational Product: Glycopyrronium Bromide 1mg and 2mg		**Volume:**	
Name of Active Ingredient: Glycopyrronium Bromide		**Page:**	
	Statistical Phase:	Statistical analysis start date: 23Sep2020	
		Statistical analysis end date: 27Sep2020	
Phase of Development: Dose-Proportionality Study			

Objectives:

Primary Objective

To evaluate the dose-proportionality of Glycopyrronium Bromide Tablets at doses of 1mg and 2mg in healthy, adult, human subjects under fasting conditions.

Secondary Objective

To monitor the safety and tolerability of a single dose of Glycopyrronium Bromide Tablets in healthy, adult, human subjects under fasting conditions.

Methodology:

All study related procedures, duration, dates and timings, information on the study treatments and confidentiality of the subjects' data were explained clearly to the subjects by clinical personnel during the informed consent procedure. Subjects who signed the consent form and showed their willingness to participate in the study were enrolled. Subjects who were eligible when assessed against the inclusion and exclusion criteria and who were found to be healthy on physical examination with laboratory investigation values within reference limits were considered for admission into the study. Subjects whose pre-study laboratory values were outside the reference range were also considered for participation provided these values were considered clinically non-significant by the investigators and clinical research physician. The eligible subjects reported to the study site on 25Aug2020 for period 01, 30Aug2020 for period 02, 04Sep2020 for period 03 and 09Sep2020 for period 04. Treatments were allocated to subjects as per the randomization schedule generated using statistical techniques with SAS® (SAS Institute Inc., USA) version 9.4. Blood samples were drawn before dosing (0.00 hour) and up to 24.00 hours after dosing in each period. The administration of each product was followed by a washout period of 05 days.

Plasma concentrations of Glycopyrronium were determined using validated analytical method developed at Synergen Bio Private Limited.

Name of Sponsor: Kinedexe UK Limited, UK. **Name of the Investigational Product:** Glycopyrronium Bromide 1mg and 2mg **Name of Active Ingredient:** Glycopyrronium Bromide	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	***(For National Authority Use only)***
Number of Subjects:	• Subjects planned: 16 • Subjects enrolled: 16 • Subjects dosed: Period 01: 16 Period 02: 16 Period 03: 16 Period 04: 16 • No. of subjects completing the study: 16 • No. of subjects withdrawn from the study: 00 • No. of subjects dropped out from the study: 00 • No. of subjects samples bio-analyzed: 16 • No. of subjects included in the pharmacokinetic and statistical analysis: 16 • No. of subjects included in safety evaluation: 16	
Diagnosis and Main Criteria for Inclusion: Healthy, non-smoking, willing, adult, human volunteers aged between 18 and 45 years (inclusive) were selected on the basis of laboratory evaluations during screening, demography (age, height, weight and BMI), medical history, clinical examination along with vital signs, chest X-ray (P/A view) and ECG recordings. A urine screen for drugs of abuse and an alcohol urine test were performed at the time of check-in in each period. An IgM and IgG rapid test were performed at the time of check-in in each period. No female volunteer were enrolled in the study.		
Investigational Products: **Test Product 1 (T1):** Glycopyrronium Bromide 1mg Tablets Manufactured for: Kinedexe UK Limited, UK. Dosage form/Route of administration: Tablets / Oral Dosage regimen: Single dose of 1 x 1mg Batch No. [redacted] Manufacturing Date: [redacted] Expiry Date: [redacted]		

Name of Sponsor: Kinedexe UK Limited, UK.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	***(For National Authority Use only)***
Name of the Investigational Product: Glycopyrronium Bromide 1mg and 2mg		
Name of Active Ingredient: Glycopyrronium Bromide		

Test Product 2 (T2): Glycopyrronium Bromide 2mg Tablets
Manufactured for: Kinedexe UK Limited, UK
Dosage form/Route of administration: Tablets / Oral
Dosage regimen: Single dose of 1 x 2mg
Batch No.: [redacted]
Manufacturing Date [redacted]
Expiry Date: [redacted]

Method of Administration: After an overnight fast of at least 10.00 hours, either Test product 1 (T1) or Test Product 2 (T2) tablet was administered orally to each subject while in sitting position with approximately 240 mL of water at ambient temperature as per randomization schedule in each period, followed by a thorough mouth check to ensure that the drug has been swallowed. The subject was instructed not to chew or crush the tablet but to swallow it whole.

Subject received T1 and T2 twice during the study.

Dosing was done under monochromatic light conditions.

Duration of Study:

The total duration of the study was 18 days from the day of check-in of the first period till the check-out of the fourth period.

Criteria for Evaluation:

Pharmacokinetic Parameters:

Employing the estimated plasma concentration-time profiles of Glycopyrronium, the following pharmacokinetic parameters were calculated using SAS (SAS Institute Inc., U.S.A.) version 9.4.

Primary pharmacokinetic parameters: AUC_{0-t} and $AUC_{0-\infty}$

Secondary pharmacokinetic parameters: C_{max}, T_{max}, $T_{1/2}$, K_{el} and extrapolated AUC.

The dose-normalized pharmacokinetic parameters of test product 2 (2 mg) were compared with those of the test product 1 (1 mg).

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Statistical Analysis:

Statistical analysis of the pharmacokinetic parameters were performed using SAS (SAS Institute Inc., U.S.A.) version 9.4.

Descriptive statistics were computed and reported for the pharmacokinetic parameters. The log-transformed pharmacokinetic parameters for Glycopyrronium was analysed using ANOVA.

The dose proportionality of Glycopyrronium over the dose range 1mg - 2mg was assessed by fitting a power model. The power model assumes a linear relationship between natural log-transformed pharmacokinetic exposure parameter (AUC_{0-t} and $AUC_{0-\infty}$) and natural log-**transformed dose; ln (PK) = β0 + β1* ln (dose). The proportionality constant (β1) and its** corresponding 90% confidence interval (CI) were compared with the modified acceptance range;

Modified acceptance range: lower limit as 1+(ln(0.8)/ln(r)) and upper limit as 1+(ln(1.25)/ln(r)),

$$1+(\ln(0.8)/\ln(r)) \quad <\beta 1> \quad 1+(\ln(1.25)/\ln(r))$$

Where r was the maximal dose ratio for the study.

In this study, the maximal dose ratio was 2 (2/1)

In addition to the power model, analysis of variance (ANOVA) model with factors for sequence, subject within sequence, period, and treatment was used to investigate the natural log-transformed, dose-normalized pharmacokinetic parameters including AUC_{0-t} and $AUC_{0-\infty}$. Differences between the periods of treatment and sequences of dosing was considered statistically significant if probability values of the respective effects (*p-values*) **are ≤0.05**.

Safety Assessment:

All subjects who had received at least one dose of investigational product were included in the safety evaluation. Safety assessment was based on clinical laboratory evaluation, chest X-ray (P/A view), post-study clinical laboratory safety evaluation. Laboratory assessments (hematology, biochemistry, serology and urine analysis), chest X-ray (P/A view) and ECG recordings were done at the time of screening. Clinical examination and vital signs (axillary

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Name of Active Ingredient: Glycopyrronium Bromide		

temperature, radial pulse rate, sitting blood pressure and respiratory rate) measurement were performed at the time of screening. Clinical examination and vital signs (axillary temperature, radial pulse rate, sitting blood pressure and respiratory rate) measurement were performed prior to check-in and check-out in each period of the study. Vital signs (axillary temperature, radial pulse rate and sitting blood pressure) and questioning for well-being were recorded within 2.50 hours prior to dosing in each period. Vital signs (sitting blood pressure and radial pulse rate) were measured and recorded at 1.00, 3.00 and 6.00 hours after dosing (within ± 40 minutes of the scheduled time, referring to the last recording) in each period. An urine screen for drugs of abuse and an alcohol urine test were performed at the time of check-in in each period. An IgM and IgG rapid test were performed at the time of check-in in each period. Subjects were questioned for well-being at the time of clinical examination and recording of vital signs. Clinical examination, measurement of vital signs and questioning for well-being was performed prior to check-out only for the subjects who were dosed.

A safety sample was collected for post-study safety assessment (hematology and biochemistry) from all dosed subjects at the end of the study.

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Results:

A) Pharmacokinetic and Statistical Evaluation:

Table A: Descriptive Statistics of Formulation Means for Glycopyrronium obtained by a Non-Compartmental Model (N=16)

Pharmacokinetic Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test Product 1 (T1)	Test Product 2 (T2)
Strength	**1 mg**	**2 mg**
C_{max} (pg/mL)	336.9115 ± 146.91040	740.6201 ± 378.89613
$C_{max\ normalized}$ (pg/mL)	336.9115 ± 146.91040	370.3101 ± 189.44806
AUC_{0-t} (pg.hr/mL)	1885.5873 ± 921.09903	4271.9833 ± 2287.45356
$AUC_{0-t\ normalized}$ (pg.hr/mL)	1885.5873 ± 921.09903	2135.9916 ± 1143.72678
$AUC_{0-\infty}$ (pg.hr/mL)	1976.3866 ± 953.98074	4447.8860 ± 2350.98317
$AUC_{0-\infty\ normalized}$ (pg.hr/mL)	1976.3866 ± 953.98074	2223.9430 ± 1175.49159
K_{el} (hr^{-1})	0.1153 ± 0.04012	0.1174 ± 0.03828
$t_{1/2}$ (hr)	6.5861 ±1.77301	6.4564 ± 1.84022
T_{max} (hr)	3.363 ± 1.0997	3.253 ± 1.3790
Extrapolated AUC (%)	4.844 ± 1.5519	4.064 ± 1.4421
	Median	
T_{max} (hr)	3.63 (1.33 - 4.67)	4.04 (1.00-4.67)

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Table B: Geometric Least Squares Mean, Ratio and Difference in Dose Adjusted Mean AUC (%) (N = 16)

PK Parameters (Unit)	Ln- transformed Geometric Least Squares Mean		Ratio (%)	Difference in dose adjusted mean AUC (%)
	Test Product 1 (T1)	Test Product 2 (T2)		
$AUC_{0-t\ normalized}$ (pg.hr/mL)	1660.612	1889.872	87.87	12.13
$AUC_{0-\infty\ normalized}$ (pg.hr/mL)	1745.375	1970.148	88.59	11.41

Table C: Slope and Modified acceptance range of AUC_{0-t} and $AUC_{0-\infty}$ (N=16)

PK Parameters	Slope	Modified acceptance range
AUC_{0-t}	1.18657	0.6781 – 1.3219
$AUC_{0-\infty}$	1.17477	0.6781 – 1.3219

Modified acceptance range: $1+\{\ln(0.8)/\ln(r)\}$, β, $1+\{\ln(1.25)/\ln(r)\}$; Where r is the maximal dose ratio for the study. In this study, the maximal dose ratio is 2 (2/1)

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D) Mean Plasma Concentrations Vs. Time Curve

Figure A: Linear Plot of Mean Plasma Concentrations of Glycopyrronium vs. Time for Test Product 1 (T1) and Test Product 2 (T2 (N = 16)

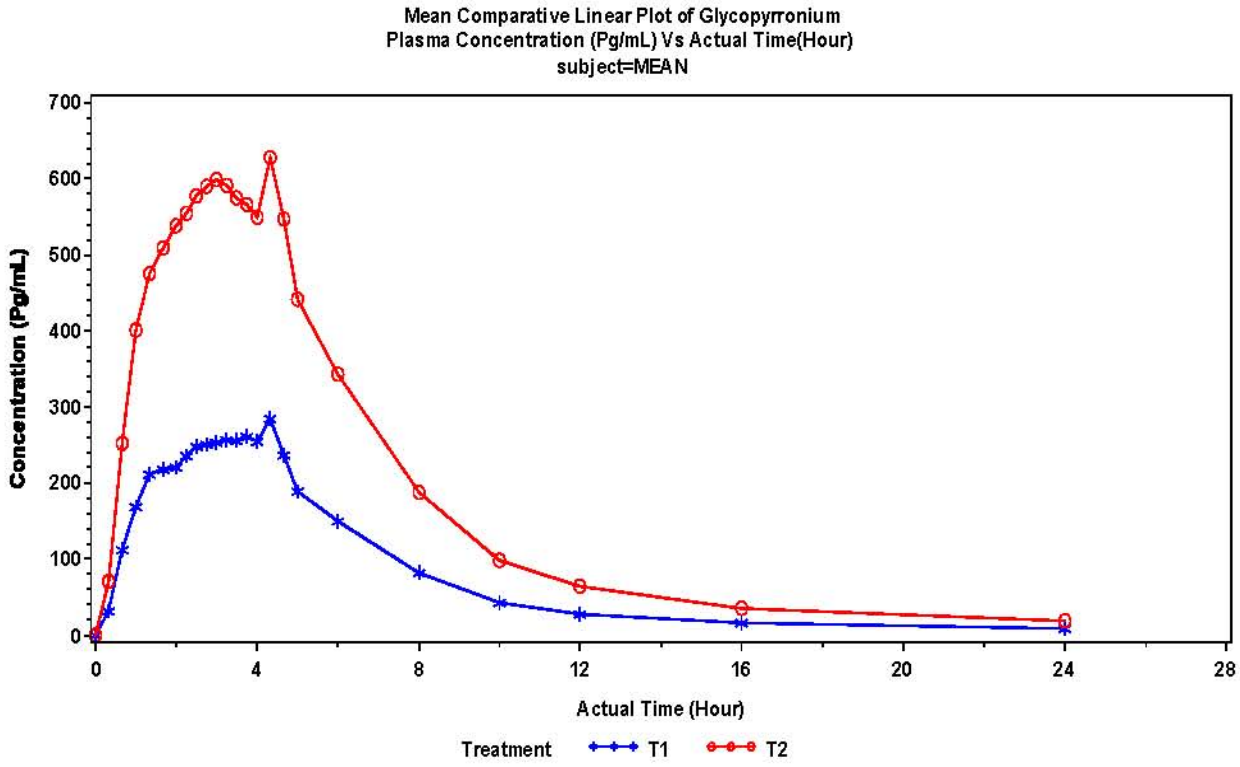

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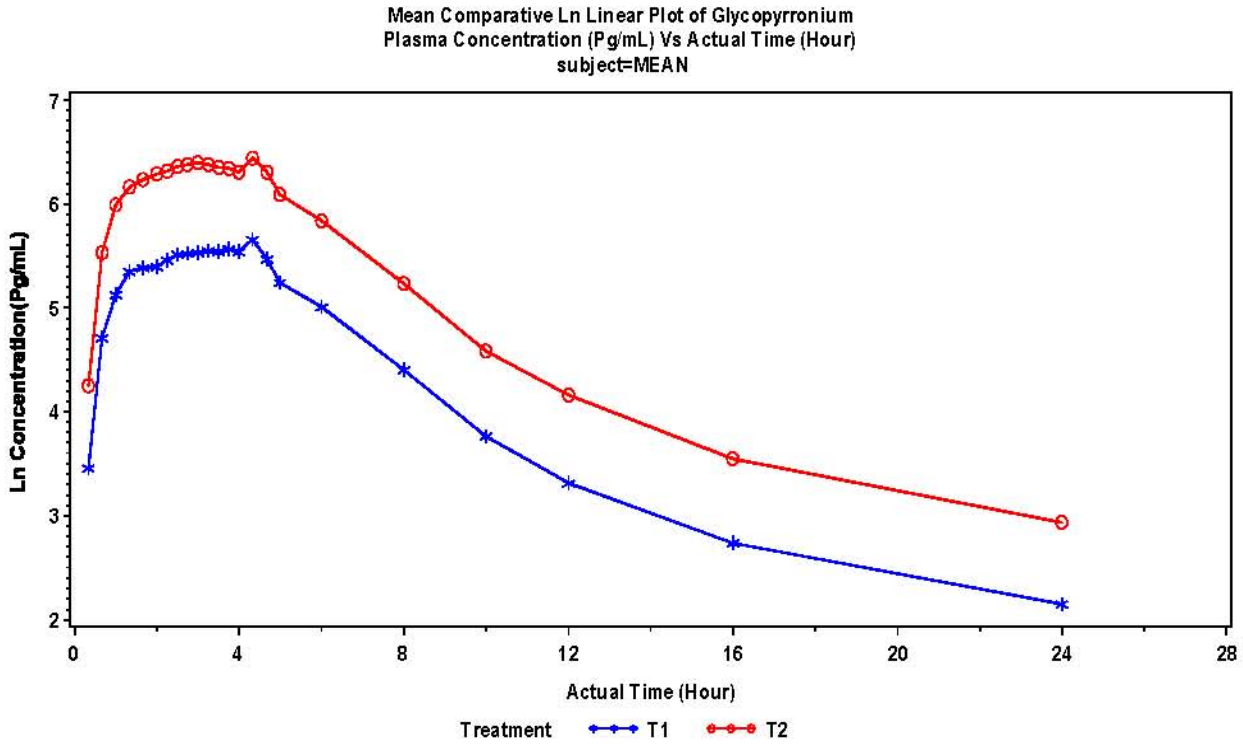
Figure B: Ln-Linear Plot of Mean Plasma Concentrations of Glycopyrronium vs. Time for Test Product 1 (T1) and Test Product 2 (T2 (N = 16)



E) Safety Evaluation:

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

Glycopyrronium Bromide 1mg and 2mg tablets were found to be safe and well tolerated upon single dose administration in healthy, adult, human subjects under fasting conditions.

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Conclusion:

As per GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE London, 20 January 2010 Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, pharmacokinetics is considered to be linear if the difference in dose-adjusted mean AUCs is no more than 25% when comparing the studied strength. In this study, the ratio of test product 1 (T1) and test product 2 (T2) for the Ln-transformed dose-normalized pharmacokinetic parameters AUC_{0-t} and $AUC_{0-\infty}$ for Glycopyrronium was found to be 87.87% and 88.59% respectively. This indicates that difference in dose adjusted mean AUC is 12.13% and 11.41% for AUC_{0-t} and $AUC_{0-\infty}$ respectively.

The slope calculated using the power model criteria for AUC_{0-t} and $AUC_{0-\infty}$ were 1.18657 and 1.17477 and were within modified acceptance range of 0.6781 – 1.3219 respectively.

The study results indicates that two strength formulations of Glycopyrronium Bromide tablets (1 mg and 2 mg) exhibited linear pharmacokinetics and that 1 mg and 2 mg of Glycopyrronium Bromide tablets were dose proportional in healthy subjects.

Date of Report: 01Oct2020

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FOLIO OF SIGNATURES

Prepared by:

I, the undersigned, declare that this report accurately reflects the methods employed and the raw data generated and has been prepared as per the relevant Standard Operating Procedures of Synergen Bio Pvt. Ltd.

[redacted]

Date: [redacted]

Reviewed by:

We, the undersigned, declare that we have thoroughly reviewed this report and supporting statistical evaluations for completeness, accuracy, compliance with the protocol, SOPs and GCP/ GLP, that we have documented any significant deviations from these requirements, and that we have critically evaluated the report for internal consistency. To the best of our knowledge, this report accurately reflects the methods used and the raw data generated.

[redacted]

Date: [redacted]

[redacted]

Date: [redacted]

[redacted]

[redacted]

Authorized by:

I, the undersigned declare that I have reviewed the data summaries, results and conclusions in this report and confirm that, to the best of my knowledge, the report is internally consistent, scientifically rational and accurately describes the conduct and results of the study.

[redacted]

[redacted]
Date:

4.0 LIST OF ABBREVIATIONS

%	Percentage
˚C	Degree Celsius
®	Registered Trademark
µL	Microlitre
AE	Adverse Event
ANOVA	Analysis of Variance
AUC	Area Under the Curve
$AUC_{0-\infty}$	Area under the concentration versus time curve from time zero to infinity
AUC_{0-t}	Area under the concentration versus time curve from time zero to the time of the last measurable concentration
BLOQ	Below Limit Of Quantification
BMI	Body Mass Index
BR	Bioanalytical Research Department
CI	Clinical Investigator
CI	Confidence Interval
Cm	Centimeter
C_{max}	Maximum observed drug concentration in plasma
COA	Certificate Of Analysis
CPMP	Committee For Proprietary Medicinal Products
CR	Clinical Research Department
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	Clinical Research Physician
CV	Curriculum Vitae
DCGI	Drug Controller General of India
dL	Decilitre
EC	Ethics Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
g or gm	Gram or grams
GCP	Good Clinical Practice
GLP	Good Laboratory Practices

GM	Geometric Mean
Hr	Hour/hours
i.e.	That is
ICD	Informed Consent Document
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMR	Indian Council of Medical Research
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
IP	Investigational Product
IU/ mL	International Units/ Millilitre
K_2EDTA	Di Potassium Ethylene Diamine Tetraacetic Acid
K_{el}	Elimination rate constant
Kg	Kilogram/kilograms
Kg/ m^2	Kilogram per meter square
L	Litre
L/ Kg	Litre per Kilogram
LC-MS/ MS	Liquid Chromatography – Mass Spectrometry/ Mass Spectrometry
Ln	Logarithmic Value to the Base e
M. Sc.	Master of Science
M.B.B.S.	Bachelor of Medicine, Bachelor of Surgery
Mg	Milligram
Min	Minute
mL or ML	Millilitre
Mm	Millimeter/millimeters
mM	Millimolar
mm of Hg	Millimeter of mercury
Mmol	Millimole
n or N	Number
NA	Not Applicable
NAV	Not Available
NE	Non Estimable
No.	Number

Nos./ nos.	Numbers
NV	Non Vegetarian
OTC	Over the Counter
P	Probability
P/A view	Posterior-Anterior View
pg	Pictogram
pg.hr/ mL	picogram.hour/millilitre
pg/ mL	picogram/millilitre
PI	Principal Investigator
QA	Quality Assurance
RBC	Red Blood Cells
Rpm	Revolutions per Minute
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard Deviation
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
T	Test Product
$t_{1/2}$	Plasma Half Life
T_{max}	Time taken to reach the Maximum Plasma Concentration
TMF	Trial Master File
UK	United Kingdom
USA	United States of America
V	Vegetarian
WMA	World Medical Association
Yr	Year

5.0 ETHICS

5.1 ETHICS COMMITTEE (EC)

The study protocol (version no.: 01 dated 30Jul2020) and the informed consent document in English (version no.: 01 dated 04Aug2020) and Marathi (version no.: 01 dated 13Aug2020) languages were used for obtaining written informed consent from each of the subjects were approved by the IECSSH (Institutional Ethics Committee Sai Sneh Hospital) on 20Aug2020, i.e., before commencement of the study.

The amendment to protocol (amendment no. 01 dated 18Aug2020) and amendment to informed consent document in English (version no.: 01 dated 20Aug2020) and Marathi (version no.: 01 dated 20Aug2020) were approved by the IECSSH (Institutional Ethics Committee Sai Sneh Hospital) on 21Aug2020, i.e., before commencement of the study.

The Informed Consent Document for Additional Information to Volunteer/ Subject (English) (Version no. 01 dated 24Aug2020) and The Informed Consent Document for Additional Information to Volunteer/ Subject (Marathi) (Version no. 01 dated 24Aug2020) were approved by the IECSSH (Institutional Ethics Committee Sai Sneh Hospital) on 25Aug2020, i.e., before commencement of the study.

The "Informed Consent for Screening" (English and Marathi versions) used during screening were reviewed and approved by the Royal Pune Independent Ethics Committee Pune (RPIEC), on 13Mar2020, i.e., prior to the start of the screening procedure.

The Ethics Committee was informed about the progress of each period during the course of the study.

A No Objection Letter for conducting this study from the Drug Controller General (India) was obtained on 21Aug2020. A notification to Drug Controller General (India) with regards to the Ethics Committee approved protocol and informed consent form was made on 24Aug2020.

A copy of the approved protocol is attached as Appendix 16.1.1.

A copy of the EC documents is attached as Appendix 16.1.3.

5.2 ETHICAL CONDUCT OF THE STUDY

The study was conducted 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 EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) effective date London, 20 January 2010.

The dose proportionality study (Project No.: 068-20) was conducted outside the European Union (in India) under ethical conditions which are equivalent to the ethical conditions laid down in Directive 2001/20/EC of the European Parliament and of the Council of 4th April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121 of 1.5.2001, p. 34).

5.3 SUBJECT INFORMATION AND CONSENT

General screening for participation in the study was done within the 21 days prior to dosing of period 01 after obtaining informed consent for screening from the subjects.

The principal investigator or designated study personnel informed the subjects (in English and/ or Marathi, whichever was best understood by the subject) before the initiation of the study through an oral presentation regarding the objective, purpose, procedures to be carried out, investigational products, potential hazards, restrictions, requirements of the study and rights of the study subjects. The subjects were encouraged to seek clarification of any questions and provided an opportunity to have any study-related issues resolved to their satisfaction. The subjects signified their willingness to participate in this study by reading, signing and dating the approved consent document and were included in the study on 25Aug2020. The subjects were required to understand and sign the ICD prior to check-in for the study and the signed ICDs were filed in the respective study file.

A photocopy of the signed ICD was provided to each subject at the time of check-in during period 01 and master copy of ICD approved by EC is attached in Appendix 16.1.3.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Principal Investigator :
Clinical Investigators :
:
Bioanalytical Investigator :

Biostatistician :
Incharge - Quality Assurance :

[redacted] handed over responsibilities [redacted]

STUDY ADMINISTRATIVE STRUCTURE

Clinical Research, Bioanalytical Research, Pharmacokinetics, Biostatistics and Quality Assurance Services	:	Synergen Bio Private Limited [redacted]
Clinical Laboratory Services	:	[redacted]
Radiological Services	:	
Ethics Committee	:	Institutional Ethics Committee Sai Sneh Hospital (IECSSH) Opposite PMT Bus Depot, Pune-Satara Road, Katraj, Pune, Maharashtra-411046, India. DCGI Registration No.: ECR/989/Inst/MH/2017

Emergency Hospital	:	[redacted]
Synergen Bio Pvt. Ltd.'s Medical Expert	:	[redacted]

Curriculum vitae (CVs) of principal study personnel are attached as Appendix 16.1.4.

Signatures of Principal and Coordinating Investigators are incorporated under the section 'Folio of Signatures' (refer to page no. 18 and 19).

7.0 INTRODUCTION

Rationale:

Kinedexe UK Limited, UK has developed two test formulations of Glycopyrronium Bromide Tablets of 1mg and 2mg (Test Product 1 and Test Product 2). Kinedexe UK Limited, UK have already demonstrated bioequivalence for 2mg Tablet. however, as per GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE London, 20 January 2010 Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **: If several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one or two strengths, depending on the proportionality in composition between the different strengths. The general requirements must met to get a waiver for additional strength(s) 1mg. Since over public domain there was no data available for dose-proportionality or linearity of pharmacokinetic of Glycopyrronium Bromide Tablets in healthy, adult, human subjects. This study was conducted to evaluate the dose-proportionality of Glycopyrronium Bromide Tablets in healthy, adult, human subjects under fasting conditions.

Sample Size:

Sixteen (16) healthy, adult, human subjects dosed in the study.

Test Product 1 (T1) - Glycopyrronium Bromide 1mg Tablets, manufactured for Kinedexe UK Limited, UK.

Test Product 2 (T2) - Glycopyrronium Bromide 2mg Tablets, manufactured for Kinedexe UK Limited, UK.

Duration of the Study:

The total duration of the study was 18 days from the day of check-in of the first period till the end of fourth period.

8.0 STUDY OBJECTIVES

Primary objective of this study was to evaluate the dose-proportionality of Glycopyrronium Bromide Tablets at doses of 1mg and 2mg in healthy, adult, human subjects under fasting conditions.

Secondary objective of this study was to monitor the safety and tolerability of a single dose of Glycopyrronium Bromide Tablets in healthy, adult, human subjects under fasting conditions.

9.0 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN - DESCRIPTION

Study Design:

This was an open label, balanced, randomized single-dose, two-sequence, four-period, fully-replicate, crossover design.

This study was being conducted to evaluate the dose-proportionality of two test formultions Glycopyrronium Bromide Tablets of 1mg and 2mg (Test Product 1 and Test Product 2) of Kinedexe UK Limited, UK in healthy, adult, human subjects under fasting conditions.

Blood samples were collected pre-dose (0.00 hour) and at intervals over 24.00 hours after dosing to allow measurement of plasma concentrations of Glycopyrronium.

Plasma concentrations of Glycopyrronium were determined using a LC-MS/ MS validated method at Synergen Bio Pvt. Ltd., [redacted], India. All analytical procedures were done under monochromatic conditions.

Statistical analysis was performed to compare the pharmacokinetic profiles of the test product (T1 and T2) using data from the subjects who completed the study according to the protocol.

Study data was collected on source documents. Completed case report forms (CRFs) were reviewed and signed by the investigators, project incharge and QC.

A sample copy of the CRF is attached as Appendix 16.1.2.

All study data and a copy of this report will be archived for the period of 15 years (as per sponsor agreement) and access will be given for audit/inspection purposes to duly authorized representative(s) of the sponsor, the EC and regulatory authorities.

Number of Subjects:

A total of 16 healthy, adult, human subjects were dosed in the study and all of them completed the study.

Method of Assignment:

The subjects, who were eligible when assessed against the inclusion and exclusion criteria for the study, were randomly assigned to the products. Randomization was carried out using the PROC PLAN procedure of SAS® (SAS Institute Inc., U.S.A.) version 9.4 in blocks such that the design was balanced. The order of receiving the test 1 and test 2 for each subject during the four periods of the study was determined according to the randomization schedule. Equal allocation of subjects to each sequence was ensured.

Duration of the Study:

The total duration of the study was 18 days from the day of check-in of the first period till the end of the fourth period. Upon entering into the study, subjects were confined to the clinical facility of Synergen Bio Pvt. Ltd. in order to ensure an overnight fast of at least 10.00 hours before dosing and to provide pre-dose blood samples. Subjects remained in the facility up to 24.00 hours after dosing in each period.

Washout Period:

The administration of each product was followed by a washout period of 05 days (i.e., at least five elimination half-lives), thus minimizing chances of measurable levels of drug being present before dosing in the following period.

Diet and Water:

All subjects were instructed to abstain from caffeine and /or xanthine-containing foods or beverages (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.), and consumption of grapefruit and/ or its juice and poppy containing foods for at least 48.00 hours prior to check-in of each period and throughout their stay in the facility.

All subjects were fasted (overnight) for at least 10.00 hours prior to dosing. The subjects received a standard meal on the day of check-in and at approximately 4.00, 8.00, 12.00 and 24.00 hours after dosing 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 (except approximately 240 mL of water given during dosing). Before and after that, drinking water was allowed at all times.

A copy of the meal menu is attached in Appendix 16.3.2.

Sitting Posture:

The study drug was administered to the subjects while in a sitting position and the subjects remained sitting upright for at least 4.00 hours after the administration of investigational product (except when the subjects needed to walk or natural exigencies). Thereafter, the subjects were allowed to engage in normal activities while avoiding severe physical exertion.

Housing:

Subjects were housed in the clinical facility from not less than 11.00 hours pre-dose. Subject left the facility 24.00 hours post-dose in each period. Restrictions outlined in the protocol were verified and maintained at check-in and during their stay in the facility.

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

Considering literature reported high intra subject variability for Glycopyrronium bromide, this dose-proportionality study was conducted using replicate design. Use of a crossover design is appropriate, since it enables comparison of treatments within the same subject thus improving the precision of treatment comparisons. The study was conducted on 16 subjects under fasting conditions. Based on the available data and elimination half-life of Glycopyrronium, a washout period of 05 days was kept in between each dose administration, thus minimising chances of residual drug being present in the following period. Multiple blood samples were collected according to the protocol to allow assessment of the dose-proportionality of test products (T1 and T2). As the study was of crossover design, every subject acted as his own control and no separate group of subjects was required to act as the control group.

9.3 SELECTION OF STUDY POPULATION

All subjects underwent a screening procedure comprising of demography (age, height, weight and BMI), clinical examination along with vital signs, physical examination, recording of electrocardiogram and laboratory investigations of blood and urine within 21 days prior to first dosing. A chest X-ray (P/A view) was taken not more than 365 days prior to the dosing of the first study period.

A copy of the normal reference ranges of clinical laboratory used in the study is attached in Appendix 16.3.2

A urine screen for drugs of abuse and an alcohol urine test were performed at the time of check-in in each period.

An IgM and IgG rapid test were performed at the time of check-in in each period.

Photocopies for urine screen for drug abuse and IgM/IgG test is attached in Appendix 16.3.2.

9.3.1 INCLUSION CRITERIA

Compliance with the following criteria was ensured for the inclusion of study subjects:

- Healthy, non-smoking human subjects (Male) aged between 18 and 45 years (inclusive).
- Male agreeing to use appropriate contraceptive measures like Double Barrier method (Condom+diaphragm, condom or diaphragm + spermicidal gel or foam), and should not donate sperm etc. during study and 07 days after completion of study.
- Subjects with a BMI between 18.50-30.00 kg/m^2 (inclusive of both) and body mass not less than 50.00 kg.
- Subjects in normal health as determined by personal medical history, clinical examination including vital signs and clinically acceptable results of laboratory examinations (including serological tests).
- Subjects having a normal or clinically not significant 12-lead electrocardiogram (ECG) recording.
- Subjects having a normal or clinically not significant chest X-Ray (P/A view).
- A negative urine screen result for drugs of abuse (including amphetamines, barbiturates, benzodiazepines, marijuana, cocaine and morphine).
- A negative alcohol urine test result.
- Subject able to communicate effectively and provide written informed consent.
- Subjects willing to adhere to the protocol requirements as evidenced by written informed consent approved by ethics committee.
- Subjects that can provide adequate evidence of their identity.
- Availability of volunteer for the entire study duration.
- Ability to fast for at least 14.00 hours and consume standard meals.

No females enrolled in this study.

9.3.2 EXCLUSION CRITERIA

Subjects meeting the following criteria were excluded from the study:

- Known hypersensitivity to Glycopyrronium Bromide or any component of this medication.
- Incapable of understanding the informed consent information.
- History or presence of significant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, immunological, dermatological, neurological or psychiatric disease or disorder.
- History or presence of alcoholism or drug abuse.
- History or presence of asthma, urticaria or other allergic reactions.
- History or presence of gastric and/or duodenal ulceration.
- History or presence of thyroid disease, adrenal dysfunction, organic intracranial lesion.
- History or presence of cancer.
- Difficulty with donating blood.
- Difficulty in swallowing solids like tablets.
- Use of any prescribed medication (including herbal remedies and vitamins) during the two weeks before the start of the study or OTC medicinal products (including herbal remedies and vitamins) during the week prior to study initiation and throughout the study.
- Use of any antimuscarinics during the two weeks before the start of the study and until the end of the study.
- Subject consumed pan or pan masala, gutkha, masala (containing beetle nut) for at least 48.00 hours prior to initiation of study and until the end of the study.
- Subject consumed caffeine and/or xanthine-containing foods or beverages (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) and grapefruit and/ or its juice and poppy containing foods for at least 48.00 hours prior to initiation of study and until the end of the study.
- Subject consumed tobacco/ tobacco containing products for at least 01 year prior to initiation of the study.
- Major illness during the 90 days before screening.
- Participation in a drug research study within 90 days of screening.
- Donation of blood within 90 days of screening.
- Positive screening test result for any one or more of the following: HIV, Hepatitis B, Hepatitis C and VDRL.
- History or presence of easy bruising or bleeding.
- Abnormal diet pattern for whatever reason (e.g. low sodium, fasting, and high protein diets) during the four weeks prior to initiation of study.
- Male volunteer unwilling to employ appropriate contraceptive measures to ensure that his partner will not get pregnant during the study till 07 days after the completion of study.
- Male volunteer willing to donate sperms during the study till 07 days after the completion of study.

  No females enrolled in this study.

9.3.3 REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

The subjects could have been withdrawn from the study for any of the following reasons:

- The subject suffered from significant inter-current illness or underwent surgery during the course of the study.
- The subject suffered from any other significant or serious adverse event.
- The subject was non-cooperative and undisciplined in the view of the Investigator.
- The subject was found to have entered the study in violation of protocol.
- If vomiting occurred at or before twice the median T_{max} of Glycopyrronium (3.00 h x 2 = 6.00 h). If vomiting occurred after this time, the subject might have been withdrawn at the Investigator's discretion, depending on the amount and contents of the vomitus and the health of the subject.
- Diarrhea[1] occurred at or before 3 times median T_{max} for Glycopyrronium Bromide (3.00 h x 3 = 9.00 h).
- The subject consumed any concomitant medication which might have interfered with the pharmacokinetics of the study medication.
- The subject violated any restrictions mentioned in the protocol.
- It was felt by the investigator that it was not in the subject's best interest to continue.
- The subject had a positive result from the alcohol urine test.
- The subject had one or more positive result from the urine screen for drugs of abuse.

Any subject that withdrew their consent would have been allowed to discontinue their participation without prejudice.

9.4 TREATMENTS

9.4.1 TREATMENTS ADMINISTERED

After an overnight fast of at least 10.00 hours, a single dose of the study drug Glycopyrronium Bromide 1mg Tablets [Test Pproduct 1 (T1)] or Glycopyrronium Bromide 2mg Tablets [Test Product 2 (T2)] was administered orally to each subject while in a sitting position with approximately 240 mL of water followed by a thorough mouth check to ensure that the drug has been swallowed. The subject was instructed not to chew or crush the tablet but to swallow it whole.

[1]Diarrhea is defined as 2 or more episodes of loose stool observed within hours, or one episode of loose stool accompanied by other gastro-intestinal symptoms, e.g. stomach pain, stomach cramps.

Subject received T1 and T2 twice during the study.

Dosing was done under monochromatic light conditions.

Period 01:

A single dose of either test product 1 [Glycopyrronium Bromide 1mg Tablets (T1)] or test product 2 [Glycopyrronium Bromide 2mg Tablets (T2)] was administered to each subject with approximately 240 mL of water as per the randomization schedule under fasting conditions.

Period 02:

Following a washout period of 05 days, a single dose of either the test product 1 [Glycopyrronium Bromide 1mg Tablets (T1)] or test product 2 [Glycopyrronium Bromide 2mg Tablets (T2)] was administered to each subject with approximately 240 mL of water as per the randomization schedule under fasting conditions.

Period 03:

Following a washout period of 05 days, a single dose of either the test product 1 [Glycopyrronium Bromide 1mg Tablets (T1)] or test product 2 [Glycopyrronium Bromide 2mg Tablets (T2)] was administered to each subject with approximately 240 mL of water as per the randomization schedule under fasting conditions.

Period 04:

Following a washout period of 05 days, a single dose of either the test product 1 [Glycopyrronium Bromide 1mg Tablets (T1)] or test product 2 [Glycopyrronium Bromide 2mg Tablets (T2)] was administered to each subject with approximately 240 mL of water as per the randomization schedule under fasting conditions.

9.4.2 IDENTITY OF INVESTIGATIONAL PRODUCT(S)

During the study, each subject received the test product 1 (T1) and test product 2 (T2) investigational products in random order as per the randomization schedule.

The details of the study investigational products are provided in Table 1 below.

Table 1: Identification of Test Investigational Products

	Test Product 1 (T1)	Test Product 2 (T2)
Investigational Product Name	Glycopyrronium Bromide 1mg Tablets	Glycopyrronium Bromide 2mg Tablets
Label Claim	Each tablets contains: Glycopyrronium Bromide 1mg	Each tablets contains: Glycopyrronium Bromide 2mg
Dosage Form	Tablets	Tablets
Route of administration	Oral	Oral
Manufactured for	Kinedexe UK Limited, UK.	Kinedexe UK Limited, UK.
Description	White round scored uncoated tablet engraved with "GP" and "1" on either side of score line and plain on the other.	White round scored uncoated tablet engraved with "GP" and "2" on either side of score line and plain on the other.
Batch Number	[redacted]	
Measured content(s) (% of label claim)	[redacted]	
Manufacturing Date	[redacted]	
Expiry date	[redacted]	
Location of Certificate of Analysis	_____ study report	_____ inical study report
This product was used in the trials:	068-20	068-20

Receipt, Dispensing and Handling of Investigational Products:

The sponsor supplied sufficient quantities of the investigational products for administration prior to the conduct of the study. The investigational products were received by the pharmacist as per the in-house SOP (Handling of Investigational Products). The Test Product 1 (T1) and Test Product 2 (T2) were supplied in container. Certificates of analysis (COA) and product details (product name, strength, no. of dosage units, manufacturer, batch number, manufacturing date, expiry date and storage condition etc.) were also provided.

The investigator and the personnel involved in dispensing of investigational products were accountable and ensured compliance with the randomization schedule. Accountability for the investigational products was documented in the respective "Logbook for IP Accountability" for the Test Product 1 (T1) and Test Product 2 (T2). The investigational products were stored in the pharmacy, accessible only to the pharmacy custodian and/ or authorized personnel. The Test Product 1 (T1) and Test

Product 2 (T2) were stored at 23±2°C and a relative humidity of 60±5% humidity chamber in the pharmacy. Records of the receipt and dispensing of study products were made to provide complete accountability of the disposition of all investigational products.

The pharmacy custodian dispensed sufficient quantities of the Test Product 1 (T1) and Test Product 2 (T2) for dosing of each period as per the randomization schedule and the remaining investigational products were kept in their original containers. The dispensed doses were transferred to the dispensing containers, pre-labeled "For clinical research use only", and with information about project no., period no., subject no. and product type (T1 and T2). The labels were verified by QA prior to dispensing. The pharmacy custodian carried out dispensing as per the randomization schedule in accordance with the current version of the dispensing SOP in the presence of QA personnel and designee.

All the activities related to handing of Investigational products including dispensing was done under monochromatic light conditions.

The investigational product accountability details are provided in Table 2.

Table 2: Investigational Product Accountability

Particulars	Test Product 1 (T1)	Test Product 2 (T2)
	Total Quantity Received = 60 Tablets	Total Quantity Received = 60 Tablets
Period 01	08	08
Period 02	08	08
Period 03	08	08
Period 04	08	08
Dispensed but undosed	04	04
Undispensed	23 + 01[#]	23 + 01[#]
Remaining**	28	28

[#]One tablet opened for description purpose.
**The dispensed but un-dosed investigational products and other remaining undispensed investigational products were stored in the pharmacy under controlled access to authorized persons only.

9.4.3 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

This was a randomized study. The order of receiving the test products (T1 and T2) for each subject in each period of the study was assigned according to a schedule generated by the biostatistician using the PROC PLAN procedure of SAS® version 9.4 and as per the in-house SOP. The subjects were numbered as 01 to 16. The randomization was balanced and the randomization schedule as well as the dispensing records of the investigational products were kept in the pharmacy under controlled access during the study and kept in the trial master file after completion of the study.

A copy of the randomization is attached as Appendix 16.1.7.

The study personnel involved in dispensing were accountable for ensuring compliance to randomization schedule.

9.4.4 SELECTION OF DOSES IN THE STUDY

As per the prescribing information, regulatory recommendations and literature of Glycopyrronium Bromide, a dose of 1 mg and 2 mg in tablet form was considered as safe, licensed dose to administer in healthy subjects and was expected to achieve sufficient plasma levels for characterization of the pharmacokinetic profile.

9.4.5 TIMING OF DOSE FOR EACH SUBJECT

Period 01:

Sixteen (16) subjects (subject nos. 01-16) were dosed the investigational products [test product 1 (T1) or test product 2 (T2) (as per the randomization schedule)] with approximately 240mL between 09:00 to 09:30 on 26Aug2020.

Period 02:

Sixteen (16) subjects (subject nos. 01-16) were dosed the investigational products [test product 1 (T1) or test product 2 (T2) (as per the randomization schedule)] with approximately 240mL between 09:00 to 09:30 on 31Aug2020.

Period 03:

Sixteen (16) subjects (subject nos. 01-16) were dosed the investigational products [test product 1 (T1) or test product 2 (T2) (as per the randomization schedule)] with approximately 240mL between 09:00 to 09:30 on 05Sep2020.

Period 04:

Sixteen (16) subjects (subject nos. 01-16) were dosed the investigational products [test product 1 (T1) or test product 2 (T2) (as per the randomization schedule)] with approximately 240mL between 09:00 to 09:30 on 10Sep2020.

9.4.6 BLINDING

This study followed a randomized, open-label design; however, the analytical staff was kept blind to the sequence of administration of test product 1 (T1) and test product 2 (T2).

9.4.7 PRIOR AND CONCOMITANT THERAPY

Subjects did not consume any prescribed medications (including herbal remedies and vitamins) for the two weeks prior to initiation of the study and/or any OTC medications during the week prior to initiation of the study. Also, subjects did not consume any prescribed medication (including herbal remedies and vitamins) and/or any OTC medications during and until end of the study.

None of the subjects reported taking any restricted medication within the time frames indicated.

9.4.8 TREATMENT COMPLIANCE

All subjects were dosed and monitored under the direct supervision of the principal investigator/CRP/CRA. Compliance for dosing was assessed by a thorough check of the oral cavity using a torch and spatula immediately after dosing by trained dosing personnel.

A duplicate of the label of the dosed container was pasted on the 'Dosing Log'. Drug dosing details were recorded in individual raw data forms. The dosing status of subjects in four periods is presented in Table 3.

Table 3: Subject No., Randomization Order, Date and Time of Dosing and Dosing Status

Subject No.	Randomization Order				Date and Time of Dosing				Dosing Status			
	Period 01	Period 02	Period 03	Period 04	Period 1 (26Aug2020)	Period 02 (31Aug2020)	Period 03 (05Sep2020)	Period 04 (10Sep2020)	Period 01	Period 02	Period 03	Period 04
[redacted]	T2	T1	T2	T1	[redacted]				Dosed	Dosed	Dosed	Dosed
	T1	T2	T1	T2					Dosed	Dosed	Dosed	Dosed
	T2	T1	T2	T1					Dosed	Dosed	Dosed	Dosed
	T1	T2	T1	T2					Dosed	Dosed	Dosed	Dosed
	T1	T2	T1	T2					Dosed	Dosed	Dosed	Dosed
	T2	T1	T2	T1					Dosed	Dosed	Dosed	Dosed
	T2	T1	T2	T1					Dosed	Dosed	Dosed	Dosed
	T1	T2	T1	T2					Dosed	Dosed	Dosed	Dosed
	T1	T2	T1	T2					Dosed	Dosed	Dosed	Dosed
	T2	T1	T2	T1					Dosed	Dosed	Dosed	Dosed
	T1	T2	T1	T2					Dosed	Dosed	Dosed	Dosed
	T2	T1	T2	T1					Dosed	Dosed	Dosed	Dosed
	T2	T1	T2	T1					Dosed	Dosed	Dosed	Dosed
	T1	T2	T1	T2					Dosed	Dosed	Dosed	Dosed
	T1	T2	T1	T2					Dosed	Dosed	Dosed	Dosed
	T2	T1	T2	T1					Dosed	Dosed	Dosed	Dosed

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 EFFICACY AND SAFETY MEASUREMENTS ASSESSED AND FLOW CHART

Efficacy:

A total of 16 subjects were dosed in the study as per the IECSSH (Institutional Ethics Committee Sai Sneh Hospital) approved protocol (version no.: 01 dated 30Jul2020) and all of them completed the study.

Samples from 16 subjects were analyzed in the bioanalytical laboratory to determine the concentrations of Glycopyrronium. Pharmacokinetic analysis of plasma concentration-time profiles of Glycopyrronium was performed on the data obtained. Sixteen (16) subjects were included in the pharmacokinetic and statistical analysis.

Actual sample collection times were used for the calculation of pharmacokinetic parameters.

The following pharmacokinetic parameters were computed for each formulation using SAS® version 9.4. Pharmacokinetic parameters C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $t_{1/2}$, K_{el} and Extrapolated AUC were calculated using plasma concentration-time profile data of the test products (T1 and T2) in individual subjects using SAS® version 9.4.

Primary Pharmacokinetic Parameters:

AUC_{0-t} : Area under the plasma concentration time curve measured to the last quantifiable concentration, using the Linear Trapezoidal rule.

$AUC_{0-\infty}$: AUC_{0-t} plus additional area extrapolated to infinity, calculated using the formula $AUC_{0-t}+C_t/K_{el}$, where C_t is the last measurable drug concentration and K_{el} is the elimination rate constant.

Secondary Pharmacokinetic Parameters:

C_{max} : Maximum observed drug concentration in plasma.

T_{max} : Time to the observed maximum drug concentration in plasma.

K_{el}	:	Apparent first – order terminal elimination rate constant calculated from a semi-log plot of the blood concentration versus time curve, using the method of least square regression.
$t_{1/2}$	:	Terminal half-life as determined by quotient $0.693/K_{el}$ [plasma concentration half-life]
Extrapolated AUC	:	The residual area in percentage determined by the formula, $[(AUC_{0-\infty} - AUC_{0-t})/ AUC_{0-\infty}] \times 100$

Plasma concentration-time data of subjects obtained from the bio-analysis of the pharmacokinetic samples were included in the final data (pharmacokinetic) analysis.

All concentration values below the limit of quantification (BLOQ) were set to zero for all pharmacokinetic and statistical calculations.

No subject had a pre-dose level of or in excess of 5% of the C_{max} value.

Safety Assessment:

The AEs and SAEs were identified as per the definitions below:

Adverse Events

An AE was any untoward medical occurrence in a subject after administration of a pharmaceutical product, which did not necessarily have a causal relationship with this treatment. An AE could be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an IMP, whether or not considered related to the IMP. Pre-existing conditions that worsened during the study were to be reported as AEs.

Any clinically significant abnormality in laboratory parameters, vital signs or ECG could have been reported as an AE according to the judgment of the PI/CI/CRP, taking into account any associated clinical signs and symptoms and pre-dose values.

Subjects were questioned and/or examined by the investigator or his/her designee for evidence of AEs. Each AE was recorded in the subject's adverse event report form, stating the date and time of onset, a description of the AE, duration, severity (mild, moderate, severe), action taken, outcome, and an Investigator's opinion on the relationship between

the study treatment and the event. A diagnosis and final opinion on the relationship (unrelated, possibly related, related) between the study treatment and the event was provided at the end of the study by the Investigator.

Serious Adverse Events

A serious adverse event (SAE) was any untoward medical occurrence or effect that, at any dose, resulted in death, was life-threatening, required or prolonged inpatient hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect or was recognized by the PI as an important medical event.

A suspected unexpected serious adverse reaction (SUSAR) was any unintended response to an IMP related to any dose, (i.e. a causal relationship between the IMP and the AE was at least a reasonable possibility) that was both serious and not consistent with the applicable product information.

Laboratory Parameters:

The laboratory assessments (hematology, biochemistry, serology and urinalysis) were performed at the time points specified in Table 05.

Safety measures analysis:

The safety analysis population included all subjects who received at least one dose of IMP.

The following measures were taken to monitor and assess the safety of the subjects during the study:

Safety assessment was based on clinical laboratory evaluation, chest X-ray (P/A view), ECG recordings, clinical examination and vital signs measurement and post-study clinical laboratory safety evaluation.

Laboratory assessments (hematology, biochemistry, serology and urine analysis), chest X-ray (P/A view) and ECG recordings were done at the time of screening.

Clinical examination along with vital signs (axillary temperature, radial pulse rate, sitting blood pressure and respiratory rate) were undertaken at the time of screening.

Clinical examination along with vital signs (axillary temperature, radial pulse rate, sitting blood pressure, respiratory rate) were undertaken during check-in and before check-out of each period.

Vital signs (axillary temperature, radial pulse rate, sitting blood pressure and respiratory rate) were recorded within 2.50 hours prior to dosing in each period.

Vital signs (sitting blood pressure and radial pulse rate) were measured and recorded at 1.00, 3.00 and 6.00 hours after dosing (within ± 40 minutes of the scheduled time, referring to the last recording) in each period.

Subjects were questioned for well-being at the time of clinical examination and recording of vital signs.

A urine screen for drugs of abuse and alcohol urine test were done during check-in of each period.

An IgM and IgG rapid test were performed at the time of check-in in each period.

A safety sample was collected for post-study safety assessment (hematology and biochemistry) from all dosed subjects at the end of the study.

This was done to identify any changes in those clinical laboratory parameters from the baseline for qualitative assessment of the safety of the investigational products.

Criteria for assessing the adverse events:

The severity of the adverse events was rated by the principal investigator or the clinical research physician.

A. The severity of the adverse event was determined based on the following:

Mild: Transient laboratory test alterations; discomfort noted but no disruption of daily activities; no therapy, or only symptomatic therapy required.

Moderate: Laboratory test alterations indicating injury without long-term risk; discomfort sufficient to modify normal daily activity; specific therapy required (i.e. more than symptomatic).

Severe: Laboratory test indicating a serious health threat or permanent injury; incapacity, inability to work, inability to perform normal daily activity; hospitalization required or prolonged; emergency treatment required; life-threatening events; death.

B. Causality Assessment of the Adverse Event to the Investigational Product (IP):

1. Certain

- Event or laboratory test abnormality, with a plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenological (i.e., it is an objective and specific medical disorder or a recognized pharmacological phenomenon)
- Rechallenge satisfactory, if necessary

2. Probable

- Event or laboratory test abnormality, with a reasonable time relationship to drug intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not required

3. Possible

- Event or laboratory test abnormality, with a reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal may be lacking or unclear

4. Unlikely

- Event or laboratory test abnormality, occurring at a time relative to drug intake that makes a relationship improbable (but not impossible)
- Disease or other drugs provide plausible explanations

5. Conditional

   - Event or laboratory test abnormality
   - More data for proper assessment needed, or
   - Additional data under examination

6. Unclassifiable

   - Report suggesting an adverse reaction
   - Cannot be judged because information is insufficient or contradictory
   - Data cannot be supplemented or verified

The schedule of assessments is summarized in Table 4 below.

Table 4: Schedule of Assessments

Activities	Screening	Period 01			Period 02			Period 03			Period 04		
Day	D-20 to D01	D01	D02	D03	D06	D07	D08	D11	D12	D13	D16	D17	D18
Screening consent document	*	-	-	-	-	-	-	-	-	-	-	-	-
Demographic data	*	-	-	-	-	-	-	-	-	-	-	-	-
Blood sample for hematology, biochemistry and serological Examination	*	-	-	-	-	-	-	-	-	-	-	-	-
Urine analysis	*	-	-	-	-	-	-	-	-	-	-	-	-
ECG	*	-	-	-	-	-	-	-	-	-	-	-	-
Clinical examination along with vital signs	*	*	-	*	*	-	*	*	-	*	*	-	*
Vital signs	-	-	*	-	-	*	-	-	*	-	-	*	-
Chest X ray (P/A view)**	*	-	-	-	-	-	-	-	-	-	-	-	-
Study informed consent document	-	*	-	-	-	-	-	-	-	-	-	-	-
Review against inclusion/ exclusion criteria	-	*	-	-	-	-	-	-	-	-	-	-	-
Urine sample for drugs of abuse	-	*	-	-	*	-	-	*	-	-	*	-	-
Alcohol urine test	-	*	-	-	*	-	-	*	-	-	*	-	-
IgM and IgG test	-	*	-	-	*	-	-	*	-	-	*	-	-
Check-in	-	*	-	-	*	-	-	*	-	-	*	-	-
Pre-dose sampling	-	-	*	-	-	*	-	-	*	-	-	*	-
Dosing	-	-	*	-	-	*	-	-	*	-	-	*	-
Post-dose sampling	-	-	*	*	-	*	*	-	*	*	-	*	*
Medical event monitoring	*	*	-	-	-	-	-	-	-	-	-	-	-
Adverse events monitoring	-	-	*	*	*	*	*	*	*	*	*	*	*
Post-study safety sample	-	-	-	-	-	-	-	-	-	-	-	-	*
Check-out	-	-		*	-	-	*	-	-	*	-	-	*

*Activity done on this day **Within 365 days prior to period 01 dosing.

9.5.2 APPROPRIATENESS OF MEASUREMENTS

The comparison of the dose adjusted pharmacokinetic parameters (AUC) of the test product 1 and test products 2 is the generally accepted methodology for determining dose proportionality.

The blood sampling points were chosen such that C_{max} could be accurately characterized. Serial blood samples 01 pre-dose (0.00 hours) samples and 23 post-dose samples up to 24.00 hours) were taken during each study period to obtain the bioavailability characteristics AUC_{0-t} and $AUC_{0-\infty}$ for dose-proportionality evaluation.

A 05 day (i.e., at least five elimination half-lives) washout period was kept between each investigational medicinal product (IMP) administration to ensure no significant carryover of the drug to the next administration.

Safety monitoring of the subjects was carried out at regular intervals during the course of the study. All safety assessments chosen were standard and widely used and were documented in the raw data sheets, which were subsequently transcribed in to the appropriate section of the Case Report Forms (CRFs).

9.5.3 EFFICACY VARIABLE(S)

Being a dose-proportionality study, no clinical efficacy assessment was done. However, the pharmacokinetic parameters AUC_{0-t} and $AUC_{0-\infty}$ of Glycopyrronium for each treatment (as surrogates for efficacy measures) were compared after log transformation. Other pharmacokinetic parameters C_{max}, T_{max}, $t_{1/2}$, K_{el} and extrapolated AUC of Glycopyrronium were obtained and reported for information purposes.

9.5.4 DRUG CONCENTRATION MEASUREMENTS

Sampling Schedule:

The sampling schedule was planned to provide an adequate estimation of C_{max} and to cover the plasma concentration-time curve long enough to provide a reliable estimate of the extent of absorption of Glycopyrronium.

A total of twenty-four (24) blood samples were collected from each subject in each period. Blood sample collection was done under monochromatic light conditions.

The pre-dose (0.00 hours) blood sample of 04 mL was collected not more than one hour prior to dosing in each period.

Further samples of 04 mL each were collected at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.33, 4.67, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00 and 24.00 hours post-dose in each period.

The subjects left the facility after the 24.00 hours housing.

If a meal and/or vital signs measurements and/or blood sample collection were scheduled for the same time, blood sample collection was given the highest priority.

Sampling Collection and Separation:

Blood samples was taken through an indwelling cannula placed in forearm vein using a disposable syringe, or alternatively through fresh venipunctures with disposable syringes and needles. The intravenous cannula was inserted into subject's arm for collection of blood samples before pre-dose blood sample collection.

Four (04) mL blood samples were collected into pre-labeled (Project No., Subject No., Period No., and Sampling time point) vacutainers containing K_2EDTA as anticoagulant. Samples drawn via the indwelling cannula were taken after discarding 0.4 mL of normal saline mixed blood. An intravenous indwelling cannula was kept in situ as long as possible during the 24.00 hours post-dose in each period. Cannula could be removed prior to 24.00 hours on subject's request.

After collection of blood samples from all subjects at a particular time point, the centrifugation under refrigeration was commenced within 01 hour of first blood sample collection. The samples were centrifuged at 3800 rpm for 10 minutes at 10°C to separate plasma. After centrifugation, the separated plasma was transferred to pre-labeled (Project No., Subject No., Period No., Sampling time point and Aliquot No.) polypropylene tubes in two aliquots, for all the samples.

Approximately 01 mL plasma was transferred into Aliquot 01 and rest of the plasma volume into Aliquot 02.

Polypropylene tubes were stored within 01 hour of centrifugation end time.

These polypropylene tubes were initially stored at -70 ± 10 °C in the clinical research department. At the end of the clinical phase of the study, Aliquot 01 and 02 samples were transferred to the bioanalytical research department of Synergen Bio Private Limited and stored at -70 ± 10 °C until analysis.

Samples were shipped frozen packed with sufficient quantities of dry ice to ensure that they remained frozen during shipment. A dedicated data logger monitoring temperature during shipment was placed.

Plasma separation was done under monochromatic light conditions.

The details of sample collection are provided in Table 5.

Table 5: Details of Sample Collection

<table>
<tr><td>Total no. of subjects, as per protocol</td><td colspan="4">16</td></tr>
<tr><td rowspan="2">Total no. of subjects dosed</td><td>Period 01</td><td>Period 02</td><td>Period 03</td><td>Period 04</td></tr>
<tr><td>16</td><td>16</td><td>16</td><td>16</td></tr>
<tr><td>Total no. of periods</td><td colspan="4">04</td></tr>
<tr><td>Total no. of sampling points</td><td colspan="4">24 samples / subject / period</td></tr>
<tr><td>Total no. of plasma samples to be collected, as per protocol</td><td colspan="4">1536 samples</td></tr>
<tr><td rowspan="4">Total no. of plasma samples collected</td><td colspan="2">Period 01 – 384</td><td colspan="2" rowspan="4">Total - 1536</td></tr>
<tr><td colspan="2">Period 02 – 384</td></tr>
<tr><td colspan="2">Period 03 – 384</td></tr>
<tr><td colspan="2">Period 04 – 384</td></tr>
<tr><td rowspan="4">Total no. of missing plasma samples</td><td colspan="2">Period 01 – 00</td><td colspan="2" rowspan="4">Total – 00</td></tr>
<tr><td colspan="2">Period 02 – 00</td></tr>
<tr><td colspan="2">Period 03 – 00</td></tr>
<tr><td colspan="2">Period 04 – 00</td></tr>
</table>

Blood Loss:

For each subject, combining the four periods, the total volume of blood drawn was 440.4 mL as follows.

	Blood volume for the samples for four periods (04 pre-dose samples of 04 mL each and 92 post-dose samples of 04 mL each)	:	384 mL
+	Discarded normal saline-containing blood for four periods (96 x 0.4 mL)	:	38.4 mL
+	Blood withdrawn for screening prior to study	:	10 mL
+	Blood sample collection for post-study safety assessment	:	08 mL
	Total blood loss for each subject	:	440.4 mL

Drug Analysis:

Plasma concentrations of Glycopyrronium were determined by a validated LC-MS/MS method in the Bioanalytical Research Department of Synergen Bio Pvt. Ltd, [redacted] India.

All analytical procedures were done under monochromatic conditions.

Analytical Methodology:

A validated LC-MS/MS method for estimation of Glycopyrronium in human plasma was validated over a calibration range of 4.002 pg/mL to 2028.838 pg/mL using Glycopyrronium D5 as an internal standard.

Project samples analysis for Glycopyrronium was carried out using a calibration range of 4.002 pg/mL to 2028.838 pg/mL.

For Method validation refer Appendix 16.5.3

9.6 DATA QUALITY ASSURANCE

9.6.1 QUALITY CONTROL

The principal investigator or his designate ensured that all the data from subject visits were entered in the CRFs as per the existing SOPs, approved protocol and applicable regulatory guidelines. The purpose of these quality control checks was to ensure that the data entered on all the CRFs was correct, complete and legible.

Quality control in the bioanalytical laboratory reflected relevant international guidelines with focus on the current guidance for industry on bioanalytical method validation.

Prior to submission of the data to QA for audit, individual departments like CR and BR performed quality control checks on the data and reports they had generated to ensure completeness and correctness of the data.

9.6.2 QUALITY ASSURANCE

To ensure the quality of the data, all source data records went through a random auditing process by the quality assurance department to confirm the accuracy of the transcription to the CRFs.

The quality assurance department assessed compliance of the study to the requirements of good clinical practice, good laboratory practice, standard operating procedures (SOPs), the study protocol and applicable regulatory guidelines.

Assessment of compliance was performed through in-process audits of various activities during the study conduct and retrospective audits of the generated data. During in-process audits, activities like reporting of volunteer/subject, ICD presentation, compliance check, dispensing of investigational drug products, dosing, phlebotomy, meal, clinical and vital examination and protocol (study) restrictions during the clinical phase of the study were audited.

During the bioanalytical phase, preparation of calibration curve standards and quality control samples and sample processing (subject samples) were audited on a random basis.

The raw data generated during the course of the study (clinical, analytical and pharmacokinetic) underwent quality assurance audit for conformance to the study protocol and all the governing SOPs by auditors from the quality assurance department of Synergen Bio Pvt. Ltd. The final report contains a statement of quality assurance duly signed by the In-charge Quality Assurance.

The audit certificate is attached as Appendix 16.1.8.

9.6.3 MONITORING

Monitor on the behalf of Kinedexe UK Limited, UK was present during conduct of the study and monitored the various study related activities like ICD presentation, dispensing, check-in, dosing procedure, blood sample collection, separation and vital signs

examination etc. Monitor reviewed documents like the trial master file (TMF), screening records, signed ICDs, CRFs, logbooks, etc.

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 STATISTICAL AND ANALYTICAL PLANS

A total of 16 subjects were dosed in the study and all of them completed the study. Sixteen (16) subjects were included in the pharmacokinetic analysis and statistical analysis.

Statistical analysis of pharmacokinetic parameters was performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, U.S.A.).

Descriptive statistics were computed and reported for the pharmacokinetic parameters. The log-transformed pharmacokinetic parameters for Glycopyrronium was analysed using ANOVA.

The dose proportionality of Glycopyrronium over the dose range 1mg - 2mg was assessed by fitting a power model. The power model assumes a linear relationship between natural log-transformed pharmacokinetic exposure parameter (AUC_{0-t} and $AUC_{0-\infty}$) and natural log-**transformed dose; ln (PK) = β0 + β1* ln (dose). The proportionality constant (β1) and** its corresponding 90% confidence interval (CI) was compared with the modified acceptance range;

Modified acceptance range: lower limit as 1+(ln(0.8)/ln(r)) and upper limit as 1+(ln(1.25)/ln(r)),

$$1+(\ln(0.8)/\ln(r)) \quad \mathbf{<\beta 1>} \quad \mathbf{1+(\ln(1.25)/\ln(r)}$$

Where r was the maximal dose ratio for the study.

In this study, the maximal dose ratio was 2 (2/1)

In addition to the power model, analysis of variance (ANOVA) model with factors for sequence, subject within sequence, period, and treatment was used to investigate the natural log-transformed, dose-normalized pharmacokinetic parameters including AUC_{0-t} and $AUC_{0-\infty}$. Differences between the periods of treatment and sequences of dosing was

considered statistically significant if probability values of the respective effects (p-values) **are ≤0.05.**

9.7.2 DETERMINATION OF SAMPLE SIZE

Since the study was conducted to assess the dose proportionality between 1mg and 2mg strengths of Glycopyrronium Bromide tablets, 16 subjects were considered sufficient to prove the dose proportionality.

As per GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE London, 20 January 2010 Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, "The number of evaluable subjects in a bioequivalence study should not be less than 12".

9.8 CHANGES IN CONDUCT OF THE STUDY OR PLANNED ANALYSES

There were no changes during conduct of the study.

10.0 STUDY SUBJECTS

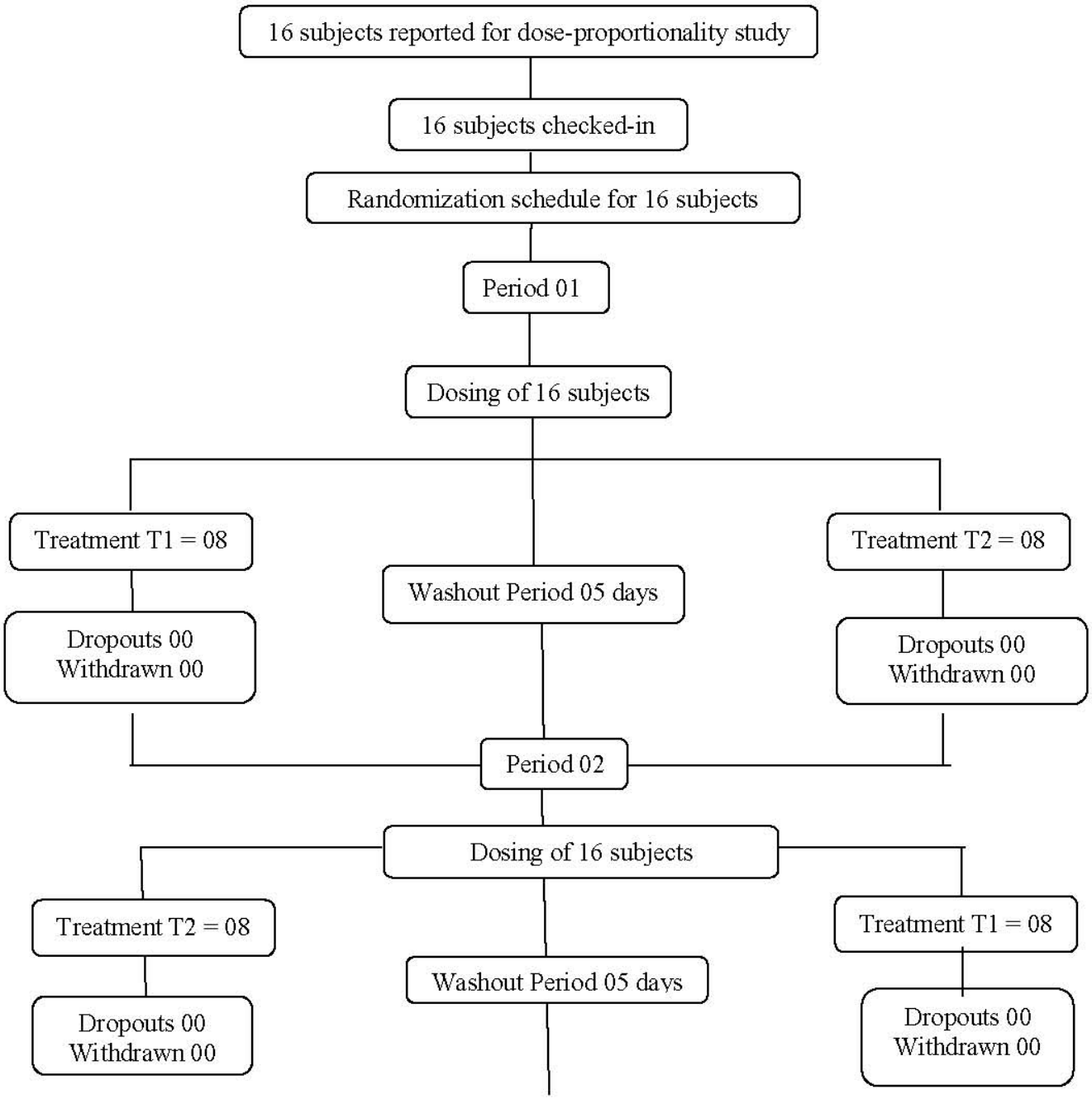
10.1 DISPOSITION OF SUBJECTS

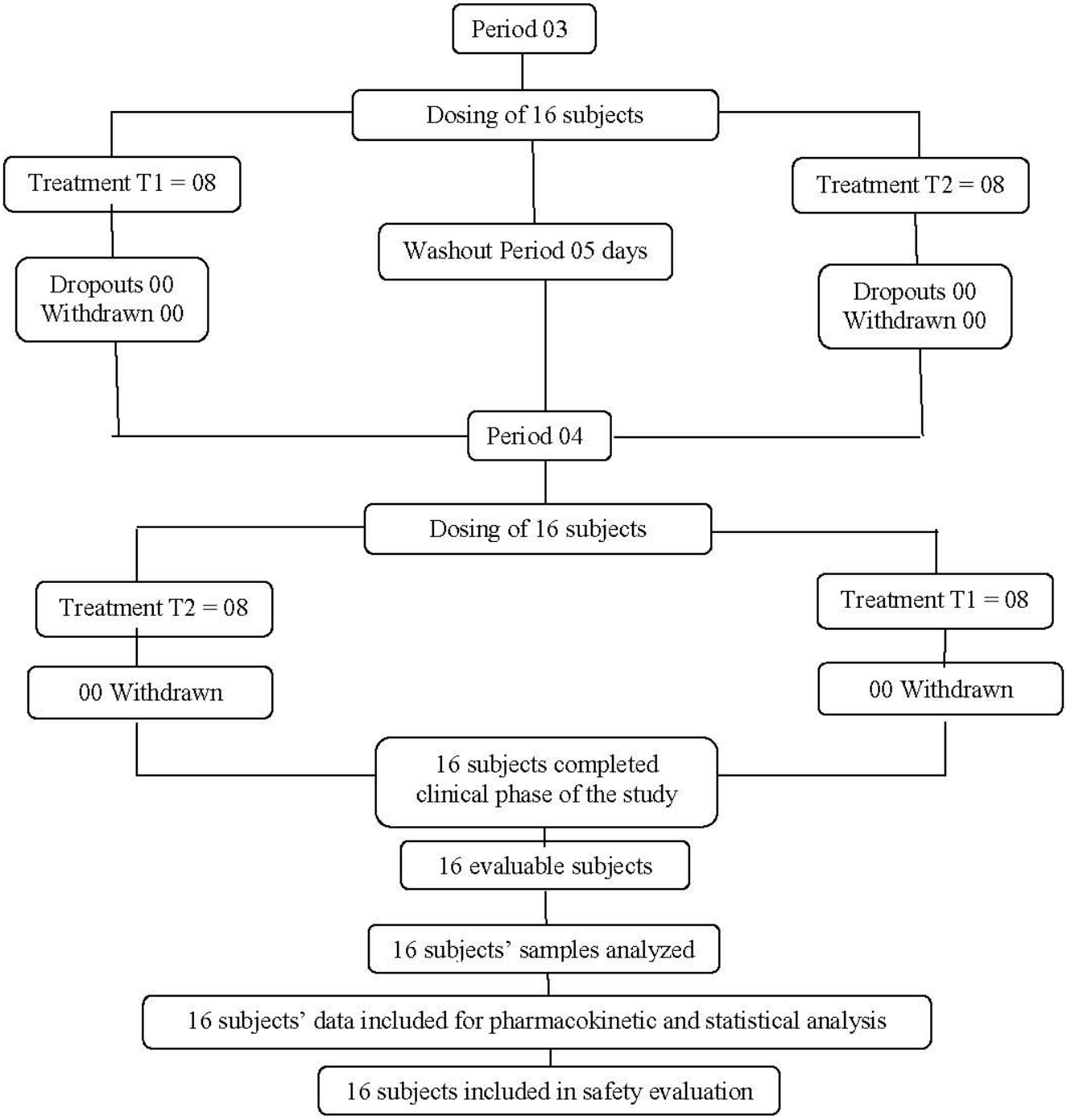
General screening within 21 days prior to dosing was carried out to select at least 16 healthy, adult, human, subjects as per the protocol. Sixteen (16) subjects were checked-in to the facility after obtaining study informed consent prior to the check-in of period 01; 16 subjects were dosed in period 01, period 02, period 03 and period 04. All subjects completed the study.

None of the subjects discontinued during conduct of the study.

The following flowchart summarizes the subjects' disposition:

Figure 1: Subjects' Disposition Flow Chart




Period 03
Dosing of 16 subjects
Treatment T1 = 08
Dropouts 00
Withdrawn 00
Washout Period 05 days
Treatment T2 = 08
Dropouts 00
Withdrawn 00
Period 04
Dosing of 16 subjects
Treatment T2 = 08
00 Withdrawn
Treatment T1 = 08
00 Withdrawn
16 subjects completed
clinical phase of the study
16 evaluable subjects
16 subjects' samples analyzed
16 subjects' data included for pharmacokinetic and statistical analysis
16 subjects included in safety evaluation

10.2 PROTOCOL DEVIATIONS

10.2.1 PHLEBOTOMY DEVIATION

As protocol section 11.6, the post-dose samples should be collected within 02 minutes of the scheduled sampling time.

However, for below mentioned subjects post-dose blood samples were not collected within 02 minutes of scheduled sampling time. The details are as follows:

Table 6: Phlebotomy Deviation

Subject No.	Time point (Hours)	Scheduled time	Actual Time	Deviation (Minutes)	Reason
Period 01					
[redacted]	[redacted]	[redacted]	[redacted]	+04	Difficulty in blood drawing
				+05	Cannula Blocked
				+04	Difficulty in blood drawing
				+05	Cannula Blocked
				+05	Cannula Blocked
				+07	Difficulty in blood drawing
Period 02					
[redacted]	[redacted]	[redacted]	[redacted]	+03	Cannula Blocked
				+03	Cannula Blocked
				+06	Cannula Blocked
				+04	Difficulty in blood drawing
Period 03					
[redacted]	[redacted]	[redacted]	[redacted]	+04	Difficulty in blood drawing

Subject No.	Time point (Hours)	Scheduled time	Actual Time	Deviation (Minutes)	Reason
Period 04					
[redacted]	[redacted]	[redacted]	[redacted]	+03	Difficulty in blood drawing
	[redacted]	[redacted]	[redacted]	+03	Cannula blocked, Difficulty in blood drawing
	[redacted]	[redacted]	[redacted]	+03	Difficulty in blood drawing
	[redacted]	[redacted]	[redacted]	+04	Cannula blocked , Difficulty in blood drawing
	[redacted]	[redacted]	[redacted]	+04	Difficulty in blood drawing
	[redacted]	[redacted]	[redacted]	+03	Difficulty in blood drawing
	[redacted]	[redacted]	[redacted]	+04	Difficulty in blood drawing
	[redacted]	[redacted]	[redacted]	+03	Difficulty in blood drawing

Impact: As actual time of sample collection was considered for the pharmacokinetic and statistical analysis calculations; hence, these deviations would not have any impact on study results and outcome.

Refer Appendix 16.2.2

11.0 EFFICACY EVALUATION

11.1 DATA SETS ANALYZED

A total of 16 subjects (subject nos. 01-16) were dosed in the study as per the IECSSH (Institutional Ethics Committee Sai Sneh Hospital) approved protocol (version no.: 01 dated 30Jul2020) and all of them completed the study.

The safety population consists of the 16 subjects that received at least one dose of study medication. Samples from 16 subjects were analyzed in the bioanalytical laboratory to determine the concentrations of Glycopyrronium.

The pharmacokinetic analysis and statistical analysis was performed on data from 16 subjects.

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The mean age, height, weight and BMI of the subjects who were dosed in the study were 29.8 years, 170.1 cms, 63.008 Kgs and 21.786 Kg/m^2 respectively. All subjects were of Asian origin. All subjects were non-smokers and non-alcoholic. Out of 16, 01 subject was vegetarian and 15 subjects were non-vegetarians.

Table 7: Overall Demographic Profile (N = 16)

Variable	Profile	Percentage
Race	Asian	100.00 %
	Others	0.00 %
Gender	Male	100.00 %
	Female	0.00 %
Diet	Non-Vegetarian	93.75 %
	Vegetarian	6.25 %
Smoking status	Non-smokers	100.00 %
	Smokers	0.00 %
Alcohol Consumption	Non alcoholics	100.00 %
	Alcoholics	0.00 %

	Mean	SD	Min	Max
Age (yr)	29.8	6.65	20	43
Height (cm)	170.1	5.64	162	182
Weight (Kg)	63.008	7.5278	52.40	77.70
BMI (Kg/m^2)	21.786	2.5341	18.54	26.57

For demographic details, refer Appendix 16.2.4

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

The individual subject drug concentration data for Glycopyrronium has been presented in Appendix 16.2.5.

11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL SUBJECT DATA

11.4.1 ANALYSIS OF EFFICACY

The pharmacokinetic parameters listed below were derived individually for each analyzed subject from the concentration vs. time profiles of Glycopyrronium in plasma. The dose-normalized pharmacokinetic parameters of test product 2 (2 mg) were compared with those of the test product 1 (1 mg). Actual times of sample collection were used for the estimation of pharmacokinetic parameters.

The mean pharmacokinetic parameters of Glycopyrronium for the test product 1 (T1) and test product 2 (T2) of 16 subjects who completed all periods and results of the comparisons of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ data are summarized in the following tables:

Pharmacokinetic and Statistical Evaluation:

Table 8: Descriptive Statistics of Formulation Means for Glycopyrronium obtained by a Non-Compartmental Model (N=16)

Pharmacokinetic Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test Product 1 (T1)	Test Product 2 (T2)
Strength	**1 mg**	**2 mg**
C_{max} (pg/mL)	336.9115 ± 146.91040	740.6201 ± 378.89613
$C_{max\ normalized}$ (pg/mL)	336.9115 ± 146.91040	370.3101 ± 189.44806
AUC_{0-t} (pg.hr/mL)	1885.5873 ± 921.09903	4271.9833 ± 2287.45356
$AUC_{0-t\ normalized}$ (pg.hr/mL)	1885.5873 ± 921.09903	2135.9916 ± 1143.72678
$AUC_{0-\infty}$ (pg.hr/mL)	1976.3866 ± 953.98074	4447.8860 ± 2350.98317
$AUC_{0-\infty\ normalized}$ (pg.hr/mL)	1976.3866 ± 953.98074	2223.9430 ± 1175.49159
K_{el} (hr^{-1})	0.1153 ± 0.04012	0.1174 ± 0.03828
$t_{1/2}$ (hr)	6.5861 ±1.77301	6.4564 ± 1.84022
T_{max} (hr)	3.363 ± 1.0997	3.253 ± 1.3790
Extrapolated AUC (%)	4.844 ± 1.5519	4.064 ± 1.4421
	Median	
T_{max} (hr)	3.63 (1.33 - 4.67)	4.04 (1.00-4.67)

Table 9: Geometric Least Squares Mean, Ratio and Difference in Dose Adjusted Mean AUC (%) (N = 16)

PK Parameters (Unit)	Ln- transformed		Ratio (%)	Difference in dose adjusted mean AUC (%)
	Geometric Least Squares Mean			
	Test Product 1 (T1)	Test Product 2 (T2)		
$AUC_{0-t\ normalized}$ (pg.hr/mL)	1660.612	1889.872	87.87	12.13
$AUC_{0-\infty\ normalized}$ (pg.hr/mL)	1745.375	1970.148	88.59	11.41

Table 10: Slope and Modified Acceptance Range of AUC_{0-t} and $AUC_{0-\infty}$ (N=16)

PK Parameters	Slope	Modified acceptance range
AUC_{0-t}	1.18657	0.6781 – 1.3219
$AUC_{0-\infty}$	1.17477	0.6781 – 1.3219

Modified acceptance range: 1+{ln(0.8)/ln(r)}, β,1+{ln(1.25)/ln(r)}; Where r is the maximal dose ratio for the study. In this study, the maximal dose ratio is 2 (2/1)

11.4.2 STATISTICAL/ ANALYTICAL ISSUES

Statistical analysis was performed using SAS® version 9.4. A total of 16 subjects were enrolled and dosed in the study. All of them completed the study. Statistical analysis was performed on data obtained from the all subjects who completed the study.

Detailed documentation of the individual subject graph is presented in Appendix 16.1.9.

11.4.2.1 Adjustments for Covariates

Not applicable.

11.4.2.2 Handling of Dropouts or Missing Data

Not applicable.

11.4.2.3 Interim Analyses and Data Monitoring

Not Applicable

11.4.2.4 Multicentre Studies

Not Applicable

11.4.2.5 Multiple Comparison/Multiplicity

Not Applicable

11.4.2.6 Use of an 'Efficacy Subset' of Subjects

Not Applicable

11.4.2.7 Active-Control Studies Intended to Show Equivalence

Not Applicable

11.4.2.8 Examination of Subgroups

Not Applicable

11.4.3 TABULATION OF INDIVIDUAL RESPONSE DATA

Refer to section 14.2 and Appendix 16.2.6.

11.4.4 DRUG DOSE, DRUG CONCENTRATION AND RELATIONSHIPS TO RESPONSE

In each period, subjects received either test product 1 (T1) Glycopyrronium Bromide 1mg Tablets of Kinedexe UK Limited, UK or test product 2 (T2) Glycopyrronium Bromide 2 mg Tablets of Kinedexe UK Limited, UK, orally after an overnight fast of at least 10.00 hours. The identity of the product administered was as indicated by the randomisation schedule.

For drug concentration data, refer to Appendix 16.2.5 and for pharmacokinetic and statistical data, refer to section 14.2.

11.4.5 DRUG-DRUG AND DRUG-DISEASE INTERACTIONS

No drug-drug or drug-disease interactions were investigated in this study.

11.4.6 BY-SUBJECT DISPLAYS

The individual plasma drug concentration - time profiles for Glycopyrronium were plotted in Appendix 16.2.5.

11.4.7 EFFICACY CONCLUSIONS

As per GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE London, 20 January 2010 Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, pharmacokinetics is considered to be linear if the difference in dose-adjusted mean AUCs is no more than 25% when comparing the studied strength. In this study, the ratio of test product 1 (T1) and test product 2 (T2) for the Ln-transformed dose-normalized pharmacokinetic parameters AUC_{0-t} and $AUC_{0-\infty}$ for Glycopyrronium was found to be 87.87% and 88.59% respectively. This indicates that difference in dose adjusted mean AUC is 12.13% and 11.41% for AUC_{0-t} and $AUC_{0-\infty}$ respectively.

The slope calculated using the power model criteria for AUC_{0-t} and $AUC_{0-\infty}$ were 1.18657 and 1.17477 and within modified acceptance range of 0.6781 - 1.3219 respectively.

The study results indicates that two strength formulations of Glycopyrronium Bromide tablets (1 mg and 2 mg) exhibited linear pharmacokinetics and that 1 mg and 2 mg of Glycopyrronium Bromide tablets were dose proportional in healthy subjects.

12.0 SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

Period 01:

Eight (08) subjects were given a single dose of Glycopyrronium Bromide 1mg Tablets (T1) of Kinedexe UK Limited, UK and eight (08) subjects were given a single dose of Glycopyrronium Bromide 2mg Tablets (T2) of Kinedexe UK Limited, UK.

Period 02:

Following a 05-day wash-out period, eight (08) subjects were given a single dose of Glycopyrronium Bromide 1mg Tablets (T1) of Kinedexe UK Limited, UK and eight (08) subjects were given a single dose of Glycopyrronium Bromide 2mg Tablets (T2) of Kinedexe UK Limited, UK.

Period 03:

Following a 05-day wash-out period, eight (08) subjects were given a single dose of Glycopyrronium Bromide 1mg Tablets (T1) of Kinedexe UK Limited, UK and eight (08) subjects were given a single dose of Glycopyrronium Bromide 2mg Tablets (T2) of Kinedexe UK Limited, UK.

Period 04:

Following a 05-day wash-out period, eight (08) subjects were given a single dose of Glycopyrronium Bromide 1mg Tablets (T1) of Kinedexe UK Limited, UK and eight (08) subjects were given a single dose of Glycopyrronium Bromide 2mg Tablets (T2) of Kinedexe UK Limited, UK.

12.2 ADVERSE EVENTS

12.2.1 BRIEF SUMMARY OF ADVERSE EVENTS

All subjects who had received at least one dose of investigational product were included in safety evaluation.

The subjects were monitored throughout the study for any adverse experiences. Subjects were encouraged to report signs, symptoms and any changes in health to the physician.

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

12.2.2 DISPLAY OF ADVERSE EVENTS

Not applicable.

12.2.3 ANALYSIS OF ADVERSE EVENTS

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

12.2.4 LISTING OF ADVERSE EVENTS BY SUBJECT

Refer to section 14.3.1.

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTSAND OTHER SIGNIFICANT ADVERSE EVENTS

There were no deaths or SAEs noted in this study.

12.3.1 LISTING OF DEATHS, OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

No deaths or significant adverse events or SAEs were noted in this study.

12.3.1.1 Deaths

No deaths were noted in this study.

12.3.1.2 Other Serious Adverse Events

No other serious adverse events were noted in this study.

12.3.1.3 Other Significant Adverse Events

Not applicable.

12.3.2 NARRATIVES OF DEATHS, OTHER SERIOUS ADVERSE EVENTS AND CERTAIN OTHER SIGNIFICANT ADVERSE EVENTS

No deaths or significant adverse events or serious adverse events were noted during the course of the study.

12.3.3 ANALYSIS AND DISCUSSION OF DEATHS, OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

No deaths or significant adverse events or SAEs adverse events were reported in this study.

12.4 CLINICAL LABORATORY EVALUATION

Clinical laboratory evaluation was carried out at screening and results were found within the relevant normal reference range or assessed as clinically non-significant.

A safety sample was collected for post-study safety assessment (hematology and biochemistry) from all dosed subjects.

All the subjects were found clinically a symptomatic and fit at the time of the check-out clinical examination.

All laboratory parameters results of each subject participated in the study are provided in Appendix 16.2.8.

12.4.1 LISTING OF INDIVIDUAL LABORATORY MEASUREMENTS BY SUBJECT AND EACH ABNORMAL LABORATORY VALUE (SECTION 14.3.4)

All the subjects underwent a pre-enrollment laboratory evaluation, including hematology, biochemistry, serology [(HIV (1 & 2) antibodies, HBsAg (Hepatitis B surface antigen), HCV antibodies and VDRL (RPR)] and urinalysis testing.

The laboratory reports were reviewed by the principal/clinical investigator/clinical research physician and were found clinically acceptable (including all the out of reference range reports).

The values of the laboratory parameters that were out of range are summarized in section 14.3.4.

12.4.2 EVALUATION OF EACH LABORATORY PARAMETER

All the laboratory parameters were measured in accordance with the SOPs and were reviewed by the pathologist. The laboratory parameters obtained during the course of the study were evaluated by the principal/clinical investigator.

12.4.2.1 Laboratory Values over Time

Not applicable.

12.4.2.2 Individual Subject Changes

Not applicable.

12.4.2.3 Individual Clinically Significant Abnormalities

Not applicable.

12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

All subjects who had received at least one dose of investigational product were included in the safety evaluation (N = 16).

No abnormality in vital signs or physical examination findings was reported during the conduct of the study.

Out of range laboratory parameter values that were considered clinically non-significant during the post-study safety evaluation have been summarized in section 14.3.4.

12.6 SAFETY CONCLUSIONS

Glycopyrronium Bromide 1mg and 2mg tablets were found to be safe and well tolerated upon single dose administration in healthy, adult, human subjects under fasting conditions.

13.0 DISCUSSION AND OVERALL CONCLUSIONS

13.1 DISCUSSION

As per GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE London, 20 January 2010 Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, pharmacokinetics is considered to be linear if the difference in dose-adjusted mean AUCs is no more than 25% when comparing the studied strength. In this study, the ratio of test product 1 (T1) and test product 2 (T2) for the Ln-transformed dose-normalized pharmacokinetic parameters AUC_{0-t} and $AUC_{0-\infty}$ for Glycopyrronium was found to be 87.87% and 88.59% respectively. This indicates that difference in dose adjusted mean AUC is 12.13% and 11.41% for AUC_{0-t} and $AUC_{0-\infty}$ respectively.

The slope calculated using the power model criteria for AUC_{0-t} and $AUC_{0-\infty}$ were 1.18657 and 1.17477 and within modified acceptance range of 0.6781 – 1.3219 respectively.

Safety Assessment:

No serious adverse events were reported during the study.

13.2 CONCLUSION

The study results indicates that two strength formulations of Glycopyrronium Bromide tablets (1 mg and 2 mg) exhibited linear pharmacokinetics and that 1 mg and 2 mg of Glycopyrronium Bromide tablets were dose proportional in healthy subjects.

14.0 TABLES, FIGURESAND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 DEMOGRAPHIC DATA

Table 11: Individual and Mean Demographic Data (N=16)

Subject No.	Age (Yr.)	Height (Cm)	Weight (Kg)	BMI (Kg/ m^2)	Diet	Gender	Race	Smoking Status
[redacted]					NV	Male	Asian	Non-smoker
					NV	Male	Asian	Non-smoker
					NV	Male	Asian	Non-smoker
					NV	Male	Asian	Non-smoker
					NV	Male	Asian	Non-smoker
					NV	Male	Asian	Non-smoker
					NV	Male	Asian	Non-smoker
					NV	Male	Asian	Non-smoker
					NV	Male	Asian	Non-smoker
					V	Male	Asian	Non-smoker
					NV	Male	Asian	Non-smoker
					NV	Male	Asian	Non-smoker
					NV	Male	Asian	Non-smoker
					NV	Male	Asian	Non-smoker
					NV	Male	Asian	Non-smoker
					NV	Male	Asian	Non-smoker
Mean	29.8	170.1	63.008	21.786				
SD	6.65	5.64	7.5278	2.5341				
Range	20-43	162-182	52.40 -77.70	18.54 – 26.57				

V- Vegetarian
NV - Non –Vegetarian,
SD - Standard Deviation,
BMI - Body Mass Index

14.2 PHARMACOKINETIC DATA

Table 12: Individual Pharmacokinetic Parameters of Glycopyrronium for Test Product 1 (T1)

Subject No.	Sequence	C_{max} (pg/mL)	T_{max} (hr)	AUC_{0-t} (pg.hr/mL)	$AUC_{0-\infty}$ (pg.hr/mL)	K_{el} $(hr)^{-1}$	$t_{1/2}$ (hr)	Extrapolated AUC (%)
[redacted]	T2T1T2T1	[redacted]						
	T2T1T2T1							
	T1T2T1T2							
	T1T2T1T2							
	T2T1T2T1							
	T2T1T2T1							
	T1T2T1T2							
	T1T2T1T2							
	T1T2T1T2							
	T1T2T1T2							
	T2T1T2T1							
	T2T1T2T1							
	T2T1T2T1							
	T2T1T2T1							
	T1T2T1T2							
	T1T2T1T2							
	T1T2T1T2							
	T1T2T1T2							

Subject No.	Sequence	C_{max} (pg/mL)	T_{max} (hr)	AUC_{0-t} (pg.hr/mL)	$AUC_{0-\infty}$ (pg.hr/mL)	K_{el} $(hr)^{-1}$	$t_{1/2}$ (hr)	Extrapolated AUC (%)
[redacted]	T2T1T2T1	[redacted]						
	T2T1T2T1							
	T1T2T1T2							
	T1T2T1T2							
	T2T1T2T1							
	T2T1T2T1							
	T2T1T2T1							
	T2T1T2T1							
	T1T2T1T2							
	T1T2T1T2							
	T1T2T1T2							
	T1T2T1T2							
	T2T1T2T1							
	T2T1T2T1							
N								
Mean		336.9115	3.363	1885.5873	1976.3866	0.1153	6.5861	4.844
SD		146.91040	1.0997	921.09903	953.98074	0.04012	1.77301	1.5519
Min		93.4270	1.330	421.2360	458.0220	0.0730	2.9640	2.790
Median		289.7625	3.625	1646.2800	1752.6730	0.1025	6.7615	4.610
Max		657.8720	4.670	4433.0750	4563.3990	0.2340	9.4450	8.030
CV%		43.6050	32.698	48.8495	48.2689	34.8141	26.9205	32.036

Table 13: Individual Pharmacokinetic Parameters of Glycopyrronium for Test Product 2 (T2)

Subject No.	Sequence	C_{max} (pg/mL)	T_{max} (hr)	AUC_{0-t} (pg.hr/mL)	$AUC_{0-\infty}$ (pg.hr/mL)	K_{el} $(hr)^{-1}$	$t_{1/2}$ (hr)	Extrapolated AUC (%)
[redacted]	T2T1T2T1	[redacted]						
	T2T1T2T1							
	T1T2T1T2							
	T1T2T1T2							
	T2T1T2T1							
	T2T1T2T1							
	T1T2T1T2							
	T1T2T1T2							
	T1T2T1T2							
	T1T2T1T2							
	T2T1T2T1							
	T2T1T2T1							
	T2T1T2T1							
	T2T1T2T1							
	T1T2T1T2							
	T1T2T1T2							
	T1T2T1T2							
	T1T2T1T2							
	T2T1T2T1							
	T2T1T2T1							

Subject No.	Sequence	C_{max} (pg/mL)	T_{max} (hr)	AUC_{0-t} (pg.hr/mL)	$AUC_{0-\infty}$ (pg.hr/mL)	K_{el} $(hr)^{-1}$	$t_{1/2}$ (hr)	Extrapolated AUC (%)
[redacted]	T1T2T1T2	[redacted]						
	T1T2T1T2							
	T2T1T2T1							
	T2T1T2T1							
	T2T1T2T1							
	T2T1T2T1							
	T1T2T1T2							
	T1T2T1T2							
	T1T2T1T2							
	T1T2T1T2							
	T2T1T2T1							
	T2T1T2T1							
N								
Mean		740.6201	3.253	4271.9833	4447.8860	0.1174	6.4564	4.064
SD		378.89613	1.3790	2287.45356	2350.98317	0.03828	1.84022	1.4421
Min		192.3390	1.000	1257.5170	1303.0380	0.0690	3.5660	2.050
Median		662.7685	4.040	3936.0815	4109.6750	0.1065	6.5225	3.870
Max		1868.4930	4.670	13074.0620	13347.3930	0.1940	10.0870	6.930
CV%		51.1593	42.390	53.5455	52.8562	32.5945	28.5022	35.487

Figure 2: Linear Plot of Mean Plasma Concentrations of Glycopyrronium vs. Time for Test Product 1 (T1) and Test Product 2 (T2) (N = 16)

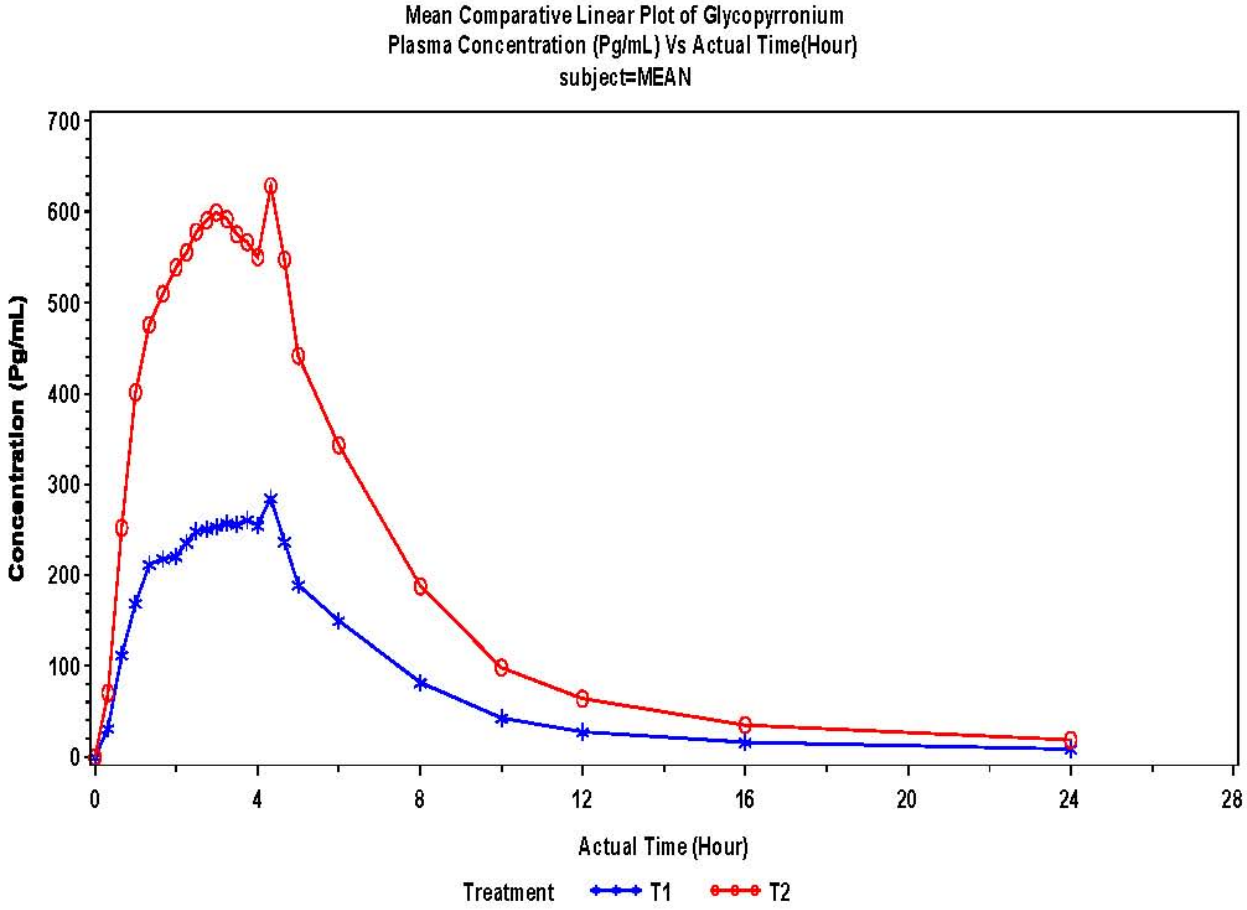
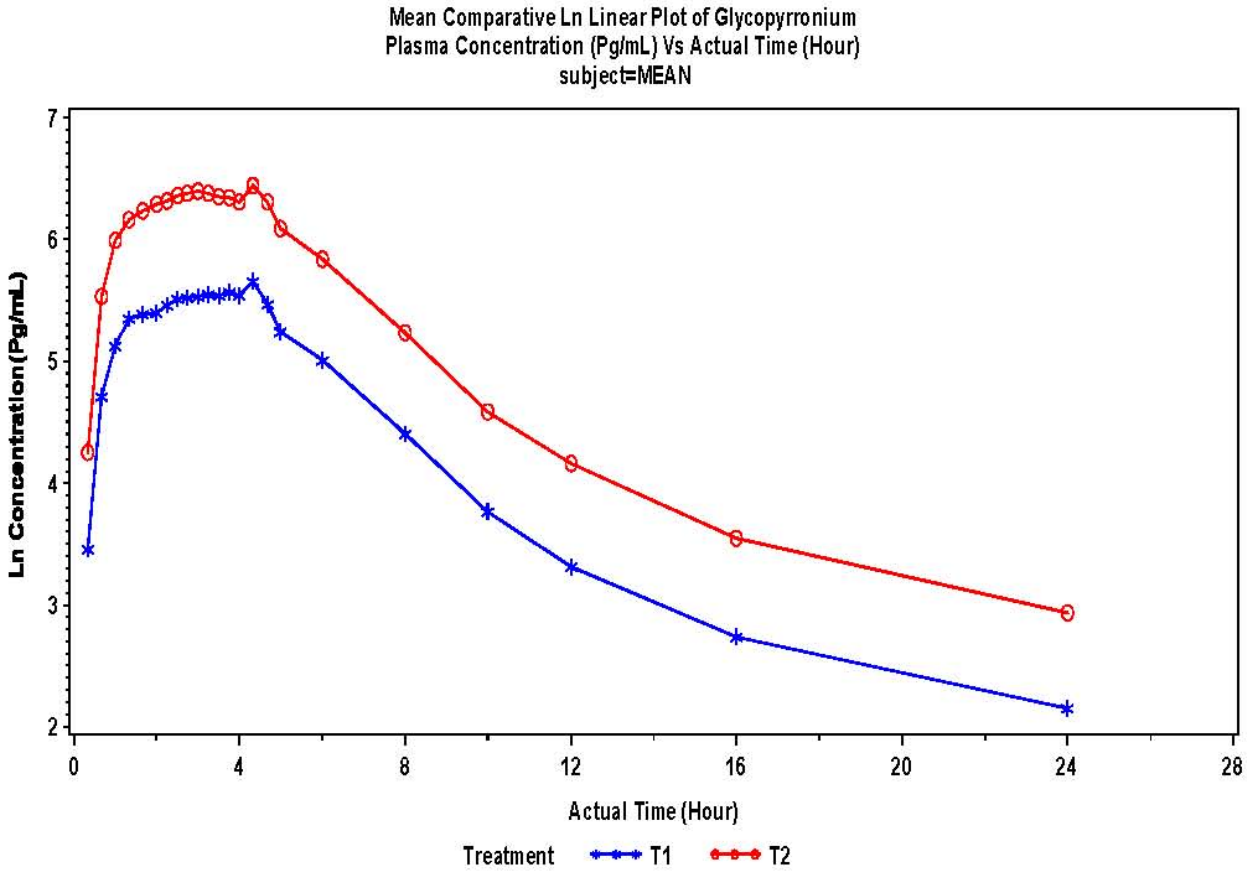


Figure 3: Ln Linear Plot of Mean Plasma Concentrations of Glycopyrronium vs. Time for Test Product 1 (T1) and Test Product 2 (T2) (N = 16)



14.3 SAFETY DATA

14.3.1 DISPLAY OF ADVRSE EVENTS

No adverse events occurred during the conduct of the study.

14.3.2 LISTINGS OF DEATHS, OTHER SERIOUS AND SIGNIFICANT ADVERSE EVENTS

No deaths or significant adverse events or SAEs were reported in the study.

14.3.3 NARRATIVES OF DEATHS, OTHER SERIOUS AND CERTAIN OTHER SIGNIFICANT ADVERSE EVENTS

No deaths or SAEs or other significant adverse were reported in the study.

14.3.4 ABNORMAL LABORATORY VALUE LISTING

Table 14: Post-Study Laboratory Assessments (Clinically Non-Significant Abnormal Laboratory Parameters)

Subject No.	Abnormal Lab Parameter	Baseline Value	Safety Assessment Value	Reference Range
[redacted]	Heamoglobin	12.1	11.8	13.0 - 18.0 gm/dL
	RBC	4.9	4.4	4.5-5.5 mil/µL
	Heamoglobin	12.3	12.1	13.0 - 18.0 gm/dL
	Heamoglobin	12.8	12.3	13.0 - 18.0 gm/dL
	Heamoglobin	13	12.6	13.0 - 18.0 gm/dL
	Heamoglobin	13.1	12.8	13.0 - 18.0 gm/dL

15.0 REFERENCE LIST

1. ICH (International Council for Harmonization) E3 'Structure and Contents of Clinical Study Report' 30 Nov 1995.

2. ICH (International Council for Harmonization) 'Guideline for Good Clinical Practice' E6 (R2) Step 4, dated 9 November 2016.

3. Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013).

4. National Ethical Guidelines for Biomedical and Health Research involving Human Participants, ICMR (Indian Council of Medical Research; 2017).

5. Notification of the Government of India, Ministry of Health and Family Welfare (Department of Health), G.S.R. 227(E) New Drugs and Clinical Trials Rules, 2019 effective from 19 Mar 2019.

6. EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 11 Corr**), effective date 20 Jan 2010.

16.0	**APPENDICES**
16.1	**STUDY INFORMATION**
16.1.1	Protocol and Protocol Amendments
16.1.2	Sample Case Report Form
16.1.3	List of IECs - Representative written information for Subject and Sample Consent Forms
16.1.4	List and Description of Investigators and other important participants in the study, including brief CVs or equivalent summaries of training and experience relevant to the performance of the clinical study
16.1.5	Signatures of Principal or Coordinating Investigators
16.1.6	Listing of Subjects Receiving Test Drug (s)/ Investigational Products
16.1.7	Randomization Schedule
16.1.8	Audit Certificate
16.1.9	Documentation of Statistical Methods
16.1.10	Documentation of Inter-Laboratory Standardization Methods
16.1.11	Publications Based on the Study
16.1.12	Important Publications Referred to in the Report
16.2	**SUBJECT DATA LISTINGS**
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16.2.2	Protocol Deviations
16.2.3	Subjects Excluded from the Efficacy Analysis
16.2.4	Demographic Data
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16.2.6	Individual Efficacy Response Data
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16.3.1	CRF's of Deaths, Other Serious Adverse Eventsand Withdrawals for AE
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16.5.5	Bioanalytical SOPs