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CLINICAL STUDY REPORT
(STUDY NO.: 934-19)

1.0 TITLE PAGE

Study Title:

An open-label, balanced, randomized, single dose, two-treatment, two-sequence, four-period, fully replicate cross over, oral bioequivalence study comparing Glycopyrronium Bromide 2mg Tablets manufactured for Kinedexe UK Limited, UK with Cuvposa® oral solution 1 mg/5mL of Glycopyrrolate as 1 mg/5mL of Glycopyrronium Bromide (dose of 10 mL equivalent to 2 mg of Glycopyrronium Bromide) manufactured for Merz Pharmaceuticals, LLC in healthy, adult, human subjects under fasting conditions.

Test Product	:	Glycopyrronium Bromide 2 mg Tablets M.A Holder: Kinedexe UK Limited, Unit 15 Moorcroft, Harlington Road, Uxbridge. UB8 3HD, UK.
Reference Product	:	Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL [redacted] Manufactured For: Merz North America, Inc.
Sponsor	:	Kinedexe UK Limited, Unit 15, Moorcroft Harlington Road, Hillingdon Middlesex, UB8 3HD, UK Phone No.: +44 20 3096 7070-75
Principal Investigator	:	[redacted]

Sponsor"s Representative	:	[redacted]
GCP/GLP Compliance	:	This study was conducted in compliance with International council for Harmonisation - Good Clinical Practices (ICH–GCP) and Good Laboratory Practices.
Protocol Identification (Code or No.)	:	934-19, Version No. 00, Dated 19-Nov-2019 Amendment Number: 01, Dated 02-Mar-2020 Amendment Number: 02, Dated 06-May-2020
Phase of Development	:	Bioequivalence Study
Study Initiation Date (Check-in for Period I)	:	Group-I: 21-May-2020 Group-II: 24-May-2020 Group-III: 29-May-2020
Study Completion Date (Last blood sample collection of Period IV)	:	Group-I: 07-Jun-2020 Group-II: 10-Jun-2020 Group-III: 15-Jun-2020
Report Version No	:	00
Date of the Report	:	10-Aug-2020
Supersedes Version No	:	None
Date	:	Not Applicable
Study Center	:	VerGo Pharma Research Pvt. Ltd, (Division - VerGo Clinicals) [redacted]

2.0 SYNOPSIS

Name of Sponsor / Company: Kinedexe UK Limited	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: Glycopyrronium Bromide 2mg Tablets		
Name of Active Ingredient: Glycopyrronium		

Title of Study:

An open-label, balanced, randomized, single dose, two-treatment, two-sequence, four-period, fully replicate cross over, oral bioequivalence study comparing Glycopyrronium Bromide 2mg Tablets manufactured for Kinedexe UK Limited, UK with Cuvposa® oral solution 1mg/5mL of Glycopyrrolate as 1mg/5mL of Glycopyrronium Bromide (dose of 10 mL equivalent to 2 mg of Glycopyrronium Bromide) manufactured for Merz Pharmaceuticals, LLC in healthy, adult, human subjects under fasting conditions.

Investigators:

Principal Investigator: [redacted]

Clinical Investigator (s):

Bioanalytical Investigator

Statistical Investigator:

Study Centre (s):

Clinical Facility:

VerGo Pharma Research Pvt. Ltd.

(Division - VerGo Clinicals),

[redacted]

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Name of Finished Product: Glycopyrronium Bromide 2mg Tablets		
Name of Active Ingredient: Glycopyrronium		

Bio analytical Facility:

VerGo Pharma Research Pvt. Ltd.

(Division - VerGo Clinicals),

[redacted]

Pharmacokinetics and Statistical Management:

VerGo Pharma Research Pvt. Ltd.

(Division - VerGo Clinicals),

[redacted]

Diagnostic Facility:

VerGo Pharma Research Pvt. Ltd.

(Division - VerGo Pathology Centre),

[redacted]

Emergency care Hospital:

[redacted]

Name of Sponsor / Company: Kinedexe UK Limited	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Glycopyrronium Bromide 2mg Tablets	Volume:	
Name of Active Ingredient: Glycopyrronium	Page:	
Publication (reference): Not applicable		
Study Duration	**Initiation date**	**Completion date**
Period I		
Group I	21-May-2020	23-May-2020
Group II	24-May-2020	26-May-2020
Group III	29-May-2020	31-May-2020
Period II		
Group I	26-May-2020	28-May-2020
Group II	29-May-2020	31-May-2020
Group III	03-Jun-2020	05-Jun-2020
Period III		
Group I	31-May-2020	02-Jun-2020
Group II	03-Jun-2020	05-Jun-2020
Group III	08-Jun-2020	10-Jun-2020
Period IV		
Group I	05-Jun-2020	07-Jun-2020
Group II	08-Jun-2020	10-Jun-2020
Group III	13-Jun-2020	15-Jun-2020
Clinical Phase Completion Date (Last blood sample collection of Period IV)	Group-I: 07-Jun-2020 Group-II: 10-Jun-2020 Group-III: 15-Jun-2020	
Analytical Phase	15-Jun-2020	09-Jul-2020
Statistical Phase	15-Jul-2020	27-Jul-2020

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Objective:

The bioequivalence study presented here was carried out with the following objective:

Primary objective: To compare the rate and extent of absorption of single dose of Glycopyrronium Bromide 2mg Tablets manufactured for Kinedexe UK Limited, UK with Cuvposa® oral solution 1mg/5mL of Glycopyrrolate as 1mg/5mL of Glycopyrronium Bromide (dose of 10 mL equivalent to 2 mg of Glycopyrronium Bromide) manufactured for Merz Pharmaceuticals, LLC administered under fasting conditions in healthy, adult, human subjects in a randomized cross over study.

Secondary objective: To evaluate the safety and tolerability of a single dose of Glycopyrronium Bromide 2mg Tablets when administered orally in healthy, adult, human subjects under fasting conditions.

Methodology:

The study was an open-label, balanced, randomized, single dose, two-treatment, two-sequence, four-period, fully replicate cross over, oral bioequivalence study comparing Glycopyrronium Bromide 2mg Tablets manufactured for Kinedexe UK Limited, UK with Cuvposa® oral solution 1mg/5mL of Glycopyrrolate as 1mg/5mL of Glycopyrronium Bromide (dose of 10 mL equivalent to 2 mg of Glycopyrronium Bromide) manufactured for Merz Pharmaceuticals, LLC in healthy, adult, human subjects under fasting conditions with a washout period 5 days between two consecutive dosing days. Treatments were allocated to subjects by carrying out randomization using SAS® software (SAS® Software Version 9.3).

Before the subject‟s voluntary participation in the study, written informed consent was obtained from all the willing volunteers. Subjects underwent a screening procedure to determine their eligibility to participate in the study.

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Total 72 healthy willing adult, human volunteers who given written informed consent for the study participation and who complied with the inclusion and exclusion criteria were enrolled in the study. Subjects checked-in the clinical facility at 11.00 hours before administration of the investigational product (IP) and continued to remain in clinical facility for 24.00 hours after dosing in each period of the study.

In each study period after an overnight fasting of 10.00 hours, as per the randomization schedule one tablet of Test product (T) - Glycopyrronium Bromide 2 mg Tablets or 10 mL oral solution of Reference product (R) - Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL (10 mL containing 2 mg of Glycopyrronium Bromide) was administered at ambient temperature to each subject in sitting position by trained personnel. Refer below details procedure for test and reference product administration.

Administration of Test Product (T): One tablet of test product Glycopyrronium Bromide 2 mg Tablet was administered orally with 240 mL of drinking water at ambient temperature to each subject in sitting position. Subjects were instructed not to chew or crush the tablet but to consume it as a whole.

Administration of Reference Product (R): 10 ml of oral solution of reference product (R) - Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL of Glycopyrrolate as 1mg/5mL of Glycopyrronium Bromide (10 mL containing 2 mg of Glycopyrronium Bromide) was administered orally using a syringe at ambient temperature to each subject in sitting position. After administration, the syringe was rinsed twice with 05 mL of drinking water taken in each rinse and both rinsing were administered to the subject to ensure complete consumption of the solution. The water used for rinsing was taken from 240 mL drinking water and the remaining water was then

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administered. The total amount of water given for dosing was 240 mL.

In this study, in each period, a total of 24 blood samples were collected from each subject in K_2EDTA vacutainers (containing K_2EDTA as an anticoagulant). Pre dose sample 08 mL (-02.00 to 00.00 hours) was withdrawn before dosing (in the morning on the day of dosing) and the post dose samples of 04 mL were collected at 00.33, 00.67, 01.00, 01.33, 01.67, 02.00, 02.25, 02.50, 02.75, 03.00, 03.25, 03.50, 03.75, 04.00, 04.33, 04.67, 05.00, 06.00, 08.00, 10.00, 12.00, 16.00 and 24.00 hours after dosing in each period. All blood samples were collected as in-house samples.

In-house post-dose blood samples were collected on scheduled time with allowed deviation of +02 minutes. Any deviations greater than +02 minutes were recorded as protocol deviation and appropriate time corrections, for the actual time of sample collection were incorporated at the time of pharmacokinetic analysis.

Subjects were received standard dinner on the day of check-in after which they were fasted for at least 10 hours prior to dosing. Being a fasting study, subjects were not served breakfast on dosing day. The subjects received standard meals at 04.00 (lunch), 08.00 (snacks) and 12.00 (dinner) hours after dosing in each period.

Note: Post dose meals were provided with a window period of ± 30 minutes to the scheduled time except post dose lunch on dosing day. For lunch, on dosing day +30 minutes of window period was allowed..

All blood samples were collected in pre-labelled K_2EDTA vacutainers via an indwelling intravenous cannula placed in the one of the forearm vein of the subject. The vacutainers prelabelled with Study no., Sub. No., Period No., Sampling time point and Serial No. The

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vacutainers were immediately inverted manually to ensure proper mixing of blood with anticoagulant and placed upright in a rack kept in wet ice bath until centrifugation and during separation.

Heparin-lock technique (about 0.5 mL of 05 IU/ mL heparin in normal saline solution was injected into the cannula after each sample collection) was used to prevent clotting of the blood in the indwelling cannula. When blood samples were collected from intravenous cannula in which heparinized saline was injected previously, initial 0.5 mL of blood drawn was discarded. Then the required volume of blood was collected. In case of difficulty in blood withdrawal due to partial cannula blockage, alternatively blood samples were drawn by a fresh venipuncture.

Indwelling intravenous cannula kept in place up to 16.00 hours after dosing. Cannula was removed after 16.00 hours blood sample collection and the cannulations site was evaluated. The blood samples at 24.00 hours was collected via a direct venipuncture.

For post study safety assessment sample of 06 mL of blood sample was collected for Hematology and Biochemistry test as safety sample from each subject.

Blood samples were centrifuged in a refrigerated centrifuge machine set at 4000 rpm for 10 minutes at 5 ± 2°C within 45 minutes of sample collection. The plasma sample stored within 60 minutes from the blood sample collection. Both activities were carried out with respect to last sample collection of that time sequence. Samples were kept in wet ice bath during separation until storage.

The separated plasma samples were transferred to pre-labelled polypropylene tubes labelled with Study no., Sub. No., Period No., Sampling time point, Aliquot No. and Serial No. in two aliquots.

For pre dose sample 02 mL of plasma was transferred in aliquot I and the remaining in aliquot II

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using a Pasteur pipette.

For post dose samples 1.2 mL of plasma was transferred in aliquot I and the remaining in aliquot II using a Pasteur pipette.

The aliquots were stored upright in a clinical site deep freezer set at -30 ± 10ºC. Samples were transferred to the bioanalytical department of VerGo Clinicals under controlled temperature conditions at the end of the clinical phase of the study. Samples in the bioanalytical department stored at -70 ± 15ºC deep freezer till analysis. After completion of bioanalysis samples were stored at-20 ± 05ºC.

The total volume of blood withdrawn from each subject during the study was 452 mL combining all the periods. (During screening 08 mL blood sample was withdrawn for routine blood test of hematology biochemistry and serology test).

Note: IP dosing, blood sample collection, sample processing, segregation of samples and bioanalysis were done under sodium vapour lamp light conditions.

Glycopyrronium in plasma samples were quantified under sodium vapour lamp light conditions used a validated bioanalytical LC-MS/MS method.

Pharmacokinetic parameters and descriptive statistics were evaluated for Glycopyrronium used Phoenix WinNonlin professional Software Version 6.3 (Pharsight Corporation, USA).

Number of Subjects (planned and analyzed):

Total 72 healthy, adult, human subjects were enrolled in the study as per the IEC approved protocol amendment 01 and 02.

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- No. of subjects planned: 72
- No. of subjects enrolled: 72
  - Group I: 36 (Subject No. [redacted])
  - Group II: 24 (Subject No. [redacted])
  - Group III: 12 (Subject No. [redacted])
- No. of subjects dosed:
  - Period I:

    Group I: 36 (Subject No. [redacted])

    Group II: 24 (Subject No. [redacted])

    Group III: 12 (Subject No. [redacted])
  - Period II:

    Group I: 34 (Subject No. [redacted])

    Group II: 21 (Subject No. [redacted])

    Group III: 11 (Subject No. [redacted])
  - Period III:

    Group I: 34 (Subject No. [redacted])

    Group II: 17 (Subject No. [redacted])

    Group III: 11 (Subject No. [redacted])
  - Period IV:

    Group I: 34 (Subject No. [redacted])

    Group II: 17 (Subject No. [redacted])

    Group III: 11 (Subject No. [redacted])

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- No. of subjects withdrawn: 00
- No. of subjects dropped out: 10 (Subject No. [redacted])

  Subject no. [redacted] were considered as dropout for the study, as they did not report for period II, III and IV check-in.

  Subject no. [redacted] they were withdrawn their consent after check out of period II due to their personal reasons (they were leaving to their native place). Hence, considered as dropout. (Both the subjects completed period II and their post study safety assessment were done after period II check-out on 31-May-2020. Hence, these subjects were not applicable for period III and IV)

  Subject No. [redacted] was withdrawn [redacted] consent on own accord on the day of check-in of period II due to [redacted] personal reason. Hence, considered as dropout for period II (Subjects no. [redacted] post study safety was done on 03-Jun-2020, Hence, this subject not applicable for period III and IV).

  Subject no. [redacted] was withdrawn [redacted] consent on own accord before dosing of period III due to [redacted] personal reasons. Hence, considered as dropout for period III.

  Subject no. [redacted] did not report to the facility for period IV check-in. Hence, considered as dropout for period IV.

  Subject no. [redacted] was considered as dropout for the study, as [redacted] did not report for period, III and IV check-in.
- No. of subjects analyzed: [redacted]

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- No. of subjects included in pharmacokinetic analysis and bioequivalence evaluation: [redacted] (Except the subject no. [redacted], [redacted], [redacted] [redacted] [redacted] and [redacted] they were not completed two periods of the study)
- No. of subject included in within-subject standard deviation of reference product: [redacted] (Except subject no. [redacted], [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] and [redacted] they were not completed two period of reference formulation)
- No. of subjects included in safety evaluation: 72 (Subject no. [redacted])

[Note: Subject no. [redacted] was withdrawn consent on [redacted] own accord after check-in of period-I. Hence, another volunteer was enrolled [redacted] and allotted as same subject [redacted]

Main Criteria for Inclusion:

Healthy, willing subjects of age 18 to 45 years (both years inclusive) were selected on the basis of laboratory evaluations including demography [age, height, weight (not less than 50 kg) and Body Mass Index (BMI) between 18.50 and 30.00 Kg / m^2], medical history (present and past, Surgical history, Family history, including habits of smoking, tobacco chewing, alcohol consumption, addiction to recreational drugs, history of blood donation), general clinical examination, Participation in clinical research studies, Allergies, Drug allergy/reaction, Medication history, physical examination, clinical examination along with vital signs, ECG were recorded during screening, absence of significant disease. Normal or within acceptable biochemical, hematological and urinary parameters. Urine screen for drugs of abuse and breath test for alcohol consumption were performed on the day of check-in of each period.

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Name of Active Ingredient: Glycopyrronium		

Investigational Product Details:

Test product (T):

Glycopyrronium Bromide 2 mg Tablets

M.A Holder: Kinedexe UK Limited, Unit 15 Moorcroft, Harlington Road, Uxbridge. UB8 3HD, UK.

Lot No: [redacted]

Manufactured date: [redacted]

Expiry date: [redacted]

Dose and route of administration: 2mg (01 Tablet × 2 mg) Tablet Orally.

Reference product (R):

Product name: Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL

[redacted]

Manufactured For: Merz North, America, Inc

Lot No: [redacted]

Manufactured date: [redacted]

Expiry date: [redacted]

Dose and route of administration: 10 mL of Cuvposa® oral solution 1mg/5mL = Total 2mg/ 10 mL of Glycopyrrolate as Glycopyrronium Bromide Orally.

Duration of Treatment:

Total duration of the study was 18 days from the day of check-in of period I (Group I, II, III) to the last blood sample collection of Period-IV (Group I, II and III).

Single oral dose of the test (T) or reference (R) product was administered for period I on 22-May-2020 (Group-I), 25-May-2020 (Group-II), 30-May-2020 (Group-III), for period II on 27-May-2020

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(Group-I), 30-May-2020 (Group-II), 04-Jun-2020 (Group-III), for period III on 01-Jun-2020 (Group-I), 04-Jun-2020 (Group-II), 09-Jun-2020 (Group-III), for period IV on 06-Jun-2020 (Group-I), 09-Jun-2020 (Group-II) and 14-Jun-2020 (Group-III) separated by a washout period of 5 days for group I, II and III between two dosing days.

Criteria for Evaluation:

To establish bioequivalence, 90% confidence interval (CI) for the ratios of the geometric least square means of the Ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for Glycopyrronium.

For C_{max}:

Case 1 (Within-subject variability of the reference formulation (S_{WR}) is> 30% for C_{max}):

The reference-scaled procedure will be applied if the within subject variability of the C_{max} of the Glycopyrronium found to be more than 30% for the reference product data and in that case a widened BE acceptance range will be employed, as referred in the below table.

Within-subject CV (%)*	Lower Limit	Upper Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

* $CV(\%) = 100\ \sqrt{(\exp(S^2_{WR}) - 1)}$.

The log transformed PK parameter values of C_{max} of the Glycopyrronium will be subjected to ANOVA procedure.

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The extent of the widening is defined based upon the within-subject variability seen in this bioequivalence study using scaled-average bioequivalence according to [U, L] = exp [±k.S_{WR}], Where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and S_{WR} is the within-subject standard deviation of the log transformed values of C_{max} of the reference product.

Based on the above table the 90% confidence limits will be considered for C_{max} based on the derived S_{WR} value, however the ratios should fall within 80.00% to 125.00%.

Case 2 (Within-subject variability of the reference formulation (S_{WR}) is< 30% for C_{max}):
The test product is considered as bioequivalent to the reference product, if the 90% Confidence Intervals for geometric least square mean ratios of log transformed parameters C_{max} of Glycopyrronium should fall within the acceptance range of 80.00-125.00%.

For AUC_{0-t}:
The test product is considered as bioequivalent to the reference product, if the 90% Confidence Intervals for geometric least square mean ratios of Ln-transformed parameter AUC_{0-t} for Glycopyrronium fall within the acceptance range of 80.00-125.00%.

Pharmacokinetic Parameters:
The following pharmacokinetic parameters were calculated using Phoenix WinNonlin® software version 6.3 for Glycopyrronium.

Primary PK parameters: C_{max} and AUC_{0-t}
Secondary PK parameters: AUC_{0-inf}, T_{max}, $T_{1/2}$, K_{el} and $AUC\_{\%Extrap.}$

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Statistical Methods:

Statistical analysis was performed on the primary pharmacokinetic parameters using SAS® 9.3. The analysis included data from subjects who completed two periods (T and R) of the study. Summary statistics, ANOVA, ratio analysis, power, intra subject variability, two one-sided test and 90% confidence interval were calculated for the log transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for Glycopyrronium.

A total of 66 subjects who completed two periods (one test and one reference) of the study were included in the statistical analysis.

Handling of Outlier

Outliers in a data set was defined as observations that appear to be inconsistent in Test/Reference ratios with remaining data. They identified as the values that completely distort descriptive statistics. Subjects who exhibit extremely high or low Test/Reference values was detected using statistical method namely Studentized residual test (using statistical package SAS® 9.3 .version). The outlier test was performed by using the Lund"s method for detection of outlier for pk parameter C_{max} and $AUC_{0-t.}$

Outlier test was performed during statistical analysis and it was observed that there is no outlier in the Glycopyrronium data set. Decision was taken on the basis of studentized residual values greater than the range of ± 3.

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Efficacy Results:

A. Pharmacokinetic Evaluation:

Table 1: Mean and Standard Deviation of Pharmacokinetic Parameters for Glycopyrronium after administration of Test product (T) and Reference Product (R) (Test N=128 and Reference N = 128).

PK Parameters (Units)	Glycopyrronium (Mean ± SD)	
	Test (T)	Reference (R)
C_{max} (pg/mL)	642.9620 ± 433.33620	581.0435 ± 316.38537
AUC_{0-t} (hr*pg/mL)	3221.2630 ± 1872.20509	3065.6417 ± 1650.85661
AUC_{0-inf} (hr*pg/mL)	3349.5189 ± 1936.31928	3202.5926 ± 1698.57406
$AUC_{\_\%Extrap}$	3.871 ± 1.9097	4.550 ± 2.3007
T_{max} (hr)	3.641 ± 1.1221	3.840 ± 1.0461
$T_{1/2}$ (hr)	6.583 ± 2.1412	6.840 ± 2.2831
K_{el} (1/hr)	0.12004 ± 0.051305	0.11799 ± 0.055562
Glycopyrronium (Median (Min - Max))		
T_{max} (hr)	4.330 (1.00 - 4.67)	4.330 (1.33 - 8.00)
$T_{1/2}$ (hr)	6.642 (2.36 - 15.45)	7.027 (2.18 - 11.83)

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B. Statistical Evaluation:

Table 2: Within-subject standard deviation of the log-transfermed value of C_{max} of the Reference Formulation for Glycopyrronium (N=62)

PK Parameter	DF	S^2_{WR}	S_{WR}	CV_{WR}	Lower_Limit	Upper_Limit
Ln (C_{max}) (pg/mL)	60	0.097586	0.31239	32.02	78.8664	126.797

Table 3: Least Square Means, Geometric Least Square Means, Ratio, 90% confidence intervals, Intra subject Variability and Power for the Log transformed C_{max} and AUC_{0-t} for Glycopyrronium (N = 66).

Parameters (units)	Least Square Means		Geometric Least Square Means		Ratio (%) (T Vs R)	90% Confidence Intervals (%)	Intra Subject CV (%)	Power (T Vs R) (%)
	T	R	T	R				
Ln (C_{max}) (pg/mL)	6.2971	6.2351	542.982	510.332	106.40	98.52 - 114.91	38.52	99.90
Ln (AUC_{0-t}) (hr *pg/mL)	7.8807	7.8340	2645.737	2524.977	104.78	97.37 -112.76	32.77	99.96

The Linear Plot of Mean Glycopyrronium Plasma Concentration Vs Time Profile is presented in Figure 01 for period I, Figure 02 for period II, Figure 03 for period III and Figure 04 for period IV while Semi-Log Plot of Mean Glycopyrronium Plasma Concentration Vs Time Profile presented in Figure 05 for period I, Figure 06 for period II, Figure 07 for period III and Figure 08 for period IV.

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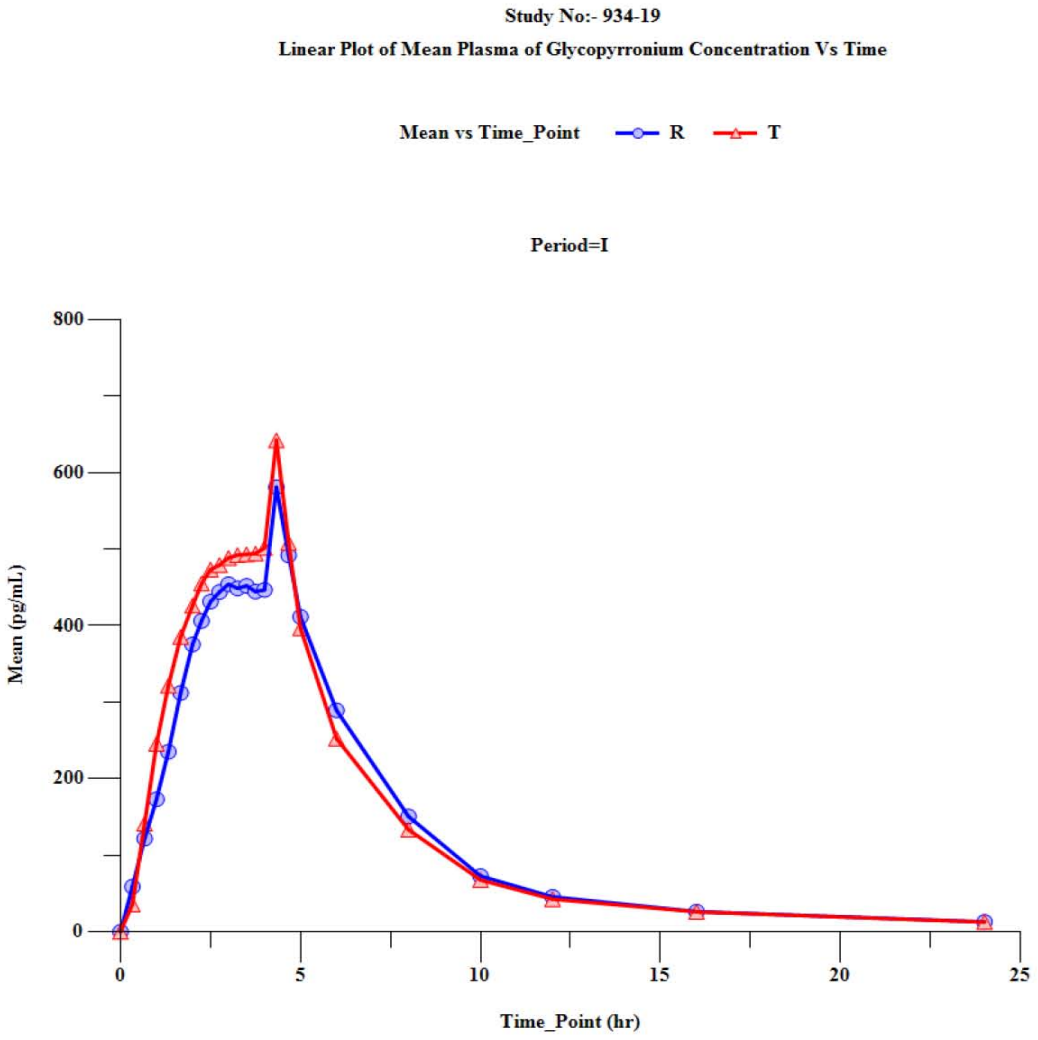
Figure 1: Linear Plot of Mean Glycopyrronium Plasma Concentrations Vs Time of Period- I



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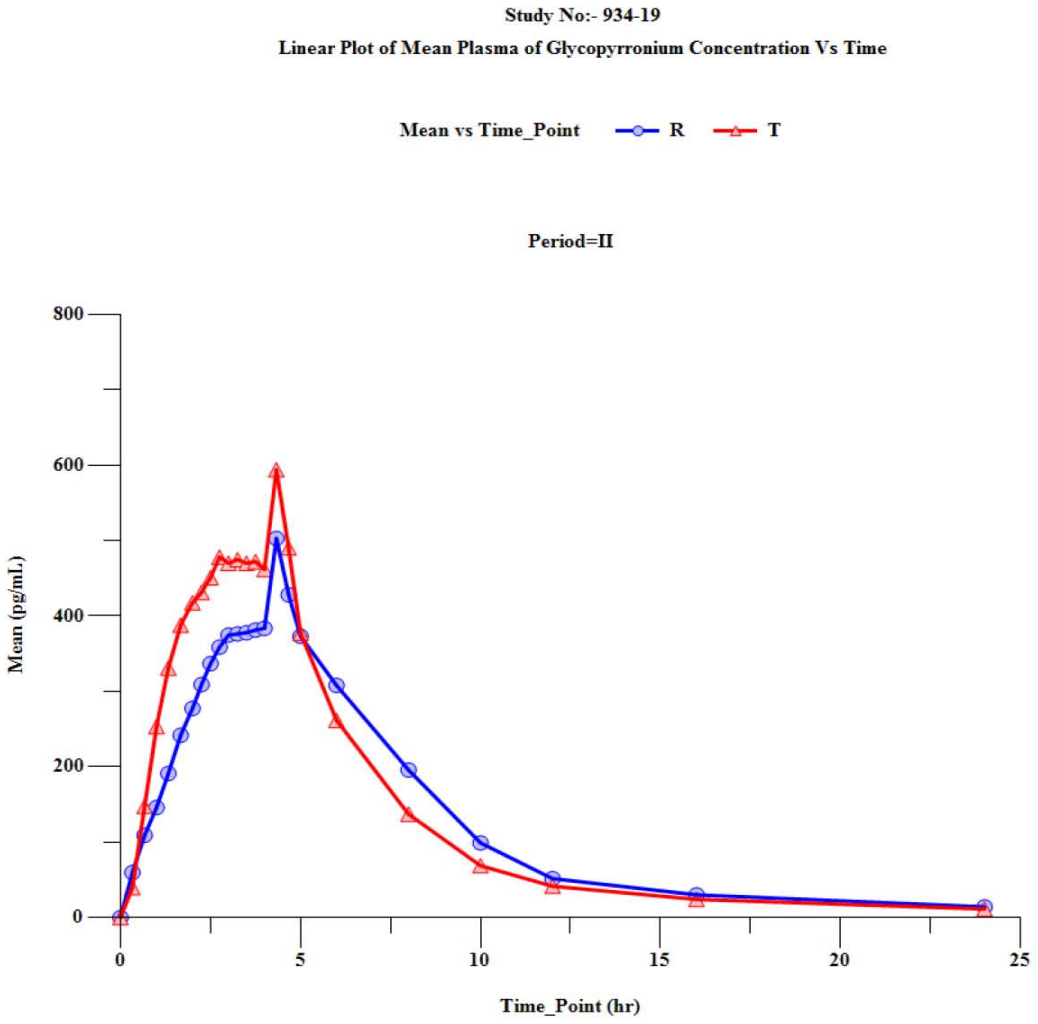
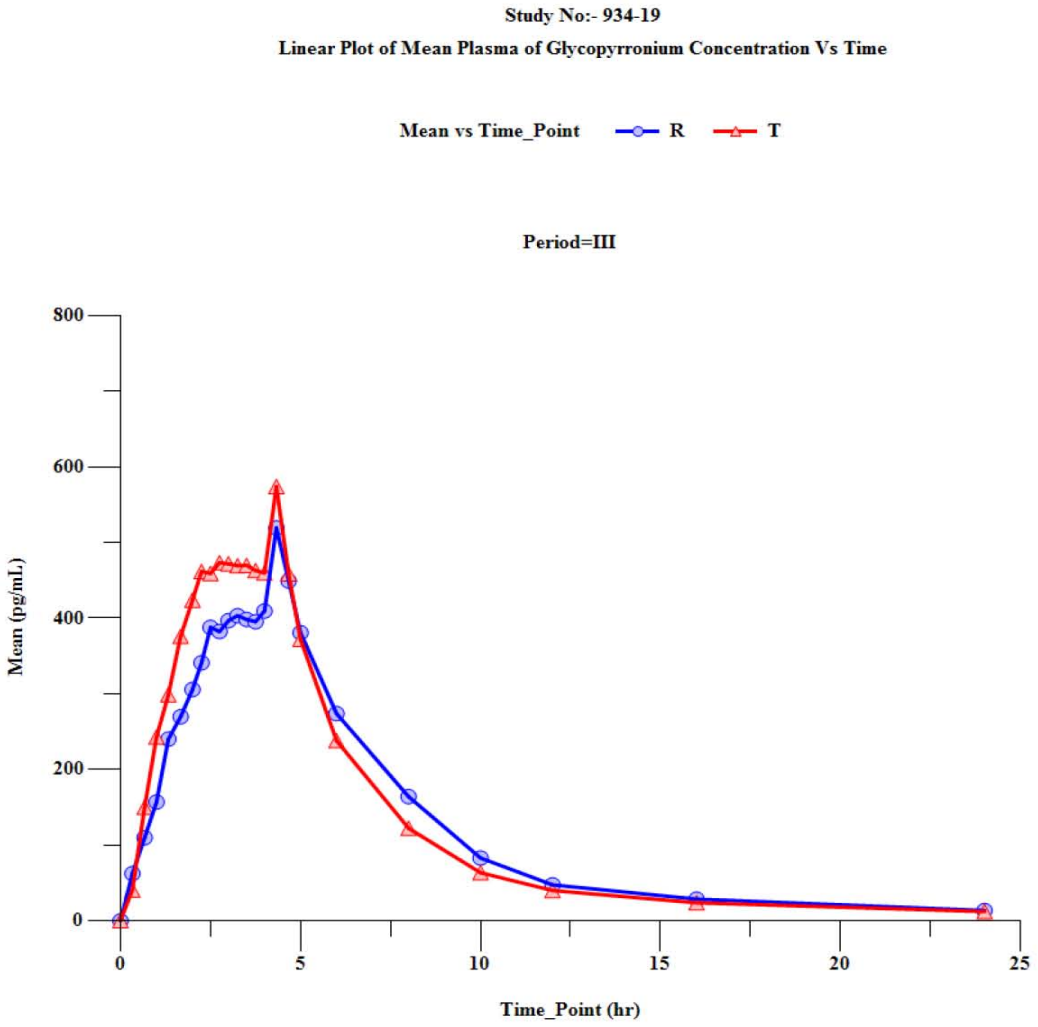
Name of Active Ingredient: Glycopyrronium		

Figure 2: Linear Plot of Mean Glycopyrronium Plasma Concentrations Vs Time of Period -II



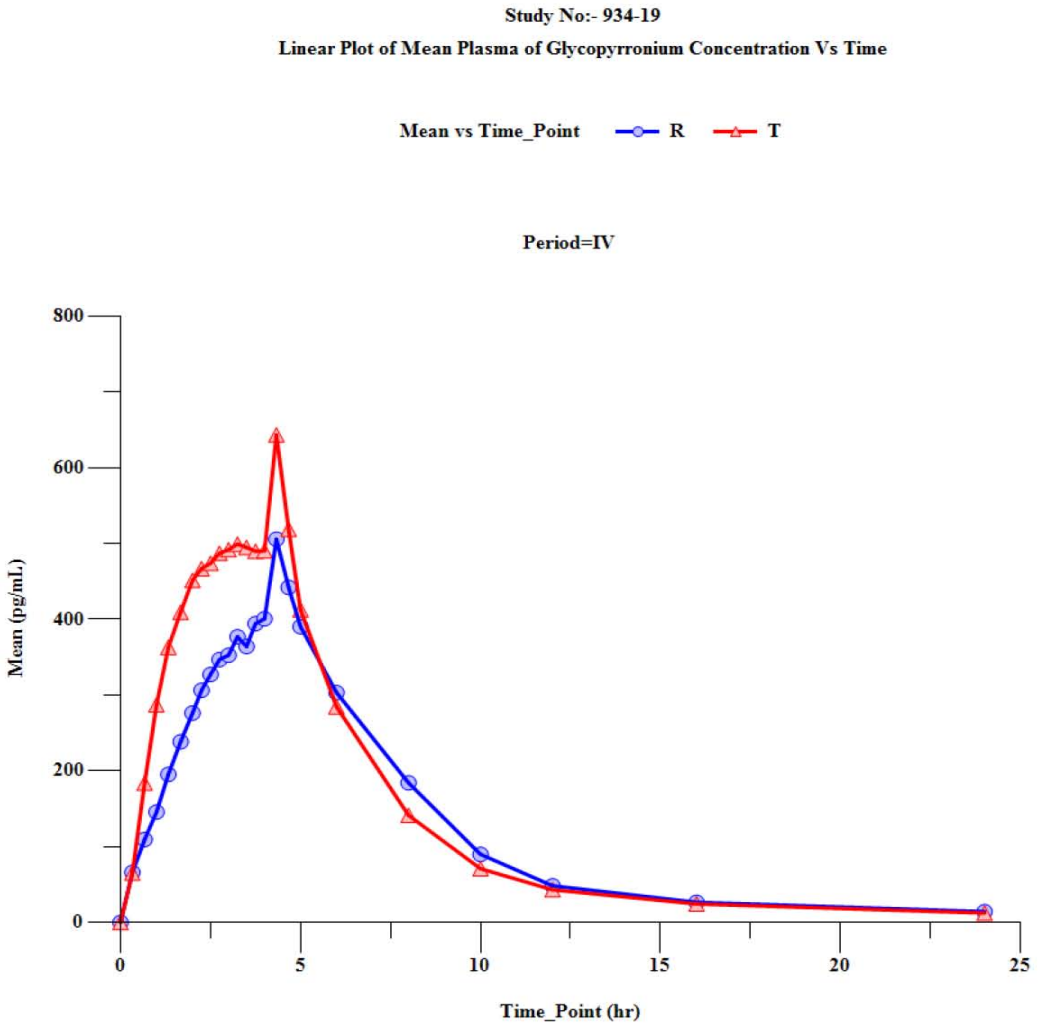
Name of Sponsor / Company: Kinedexe UK Limited	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: Glycopyrronium Bromide 2mg Tablets		
Name of Active Ingredient: Glycopyrronium		

Figure 3: Linear Plot of Mean Glycopyrronium Plasma Concentrations Vs Time of Period -III



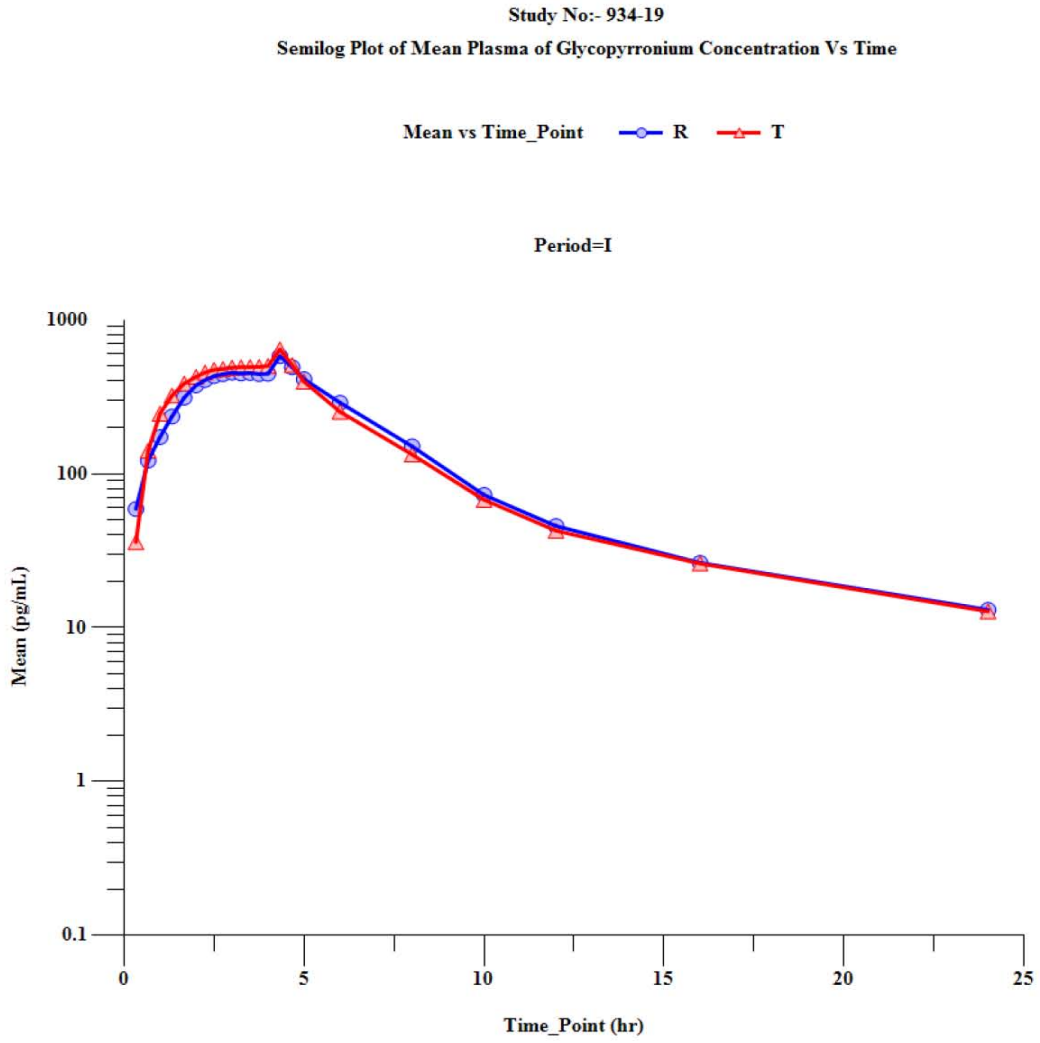
Name of Sponsor / Company: Kinedexe UK Limited	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: Glycopyrronium Bromide 2mg Tablets		
Name of Active Ingredient: Glycopyrronium		

Figure 4: Linear Plot of Mean Glycopyrronium Plasma Concentrations Vs Time of Period -IV



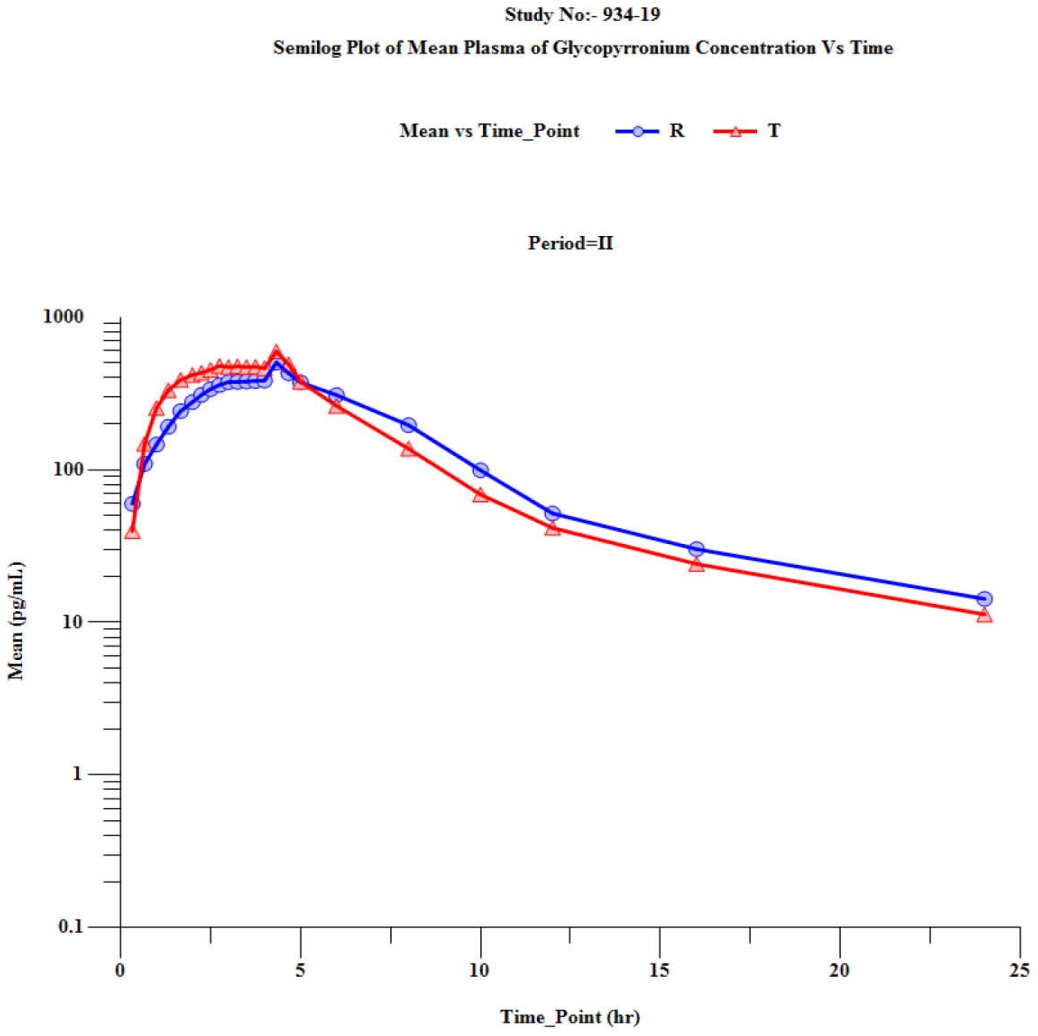
Name of Sponsor / Company: Kinedexe UK Limited	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: Glycopyrronium Bromide 2mg Tablets		
Name of Active Ingredient: Glycopyrronium		

Figure 5: Semi logarithm Plot of Mean Glycopyrronium Plasma Concentrations Vs Time of Period-I



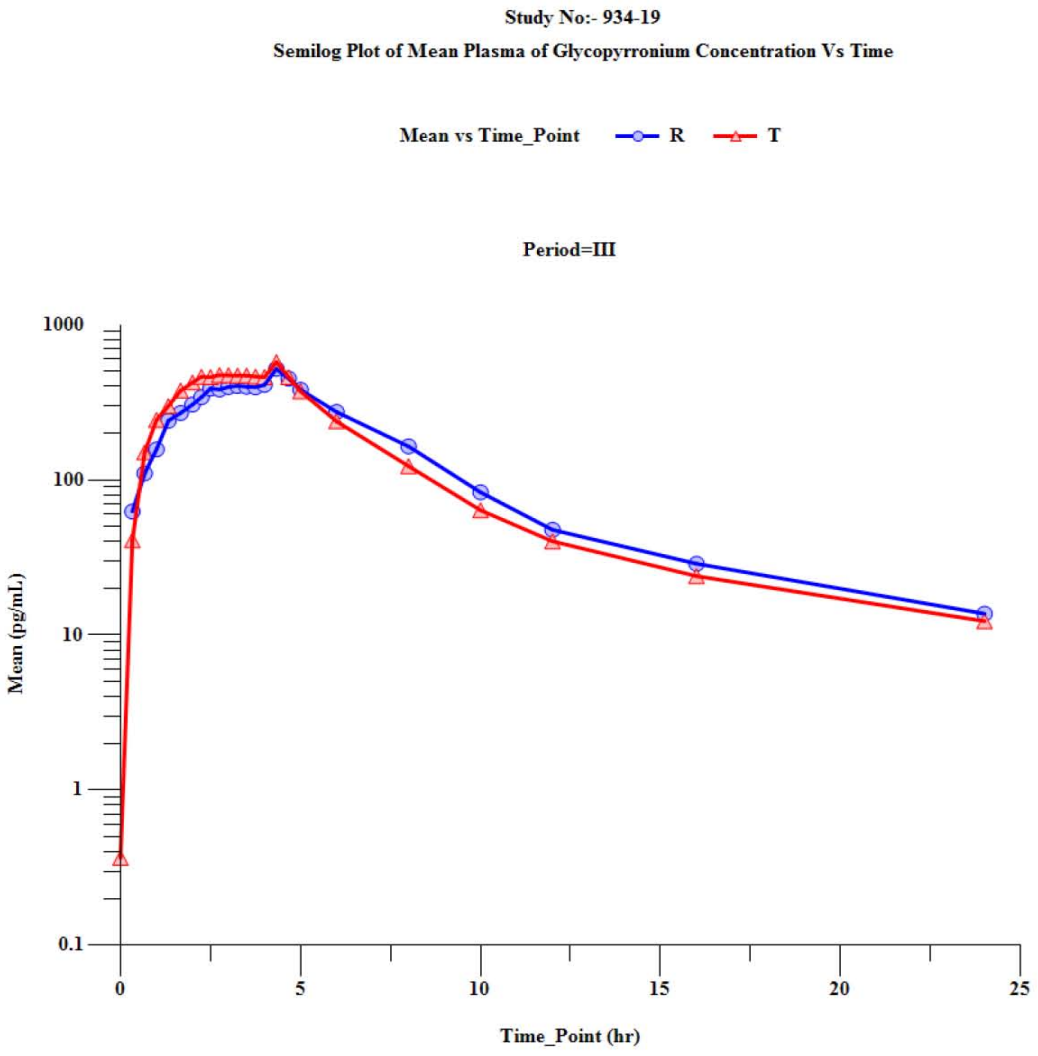
Name of Sponsor / Company: Kinedexe UK Limited	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: Glycopyrronium Bromide 2mg Tablets		
Name of Active Ingredient: Glycopyrronium		

Figure 6: Semi logarithm Plot of Mean Glycopyrronium Plasma Concentrations Vs Time of Period-II



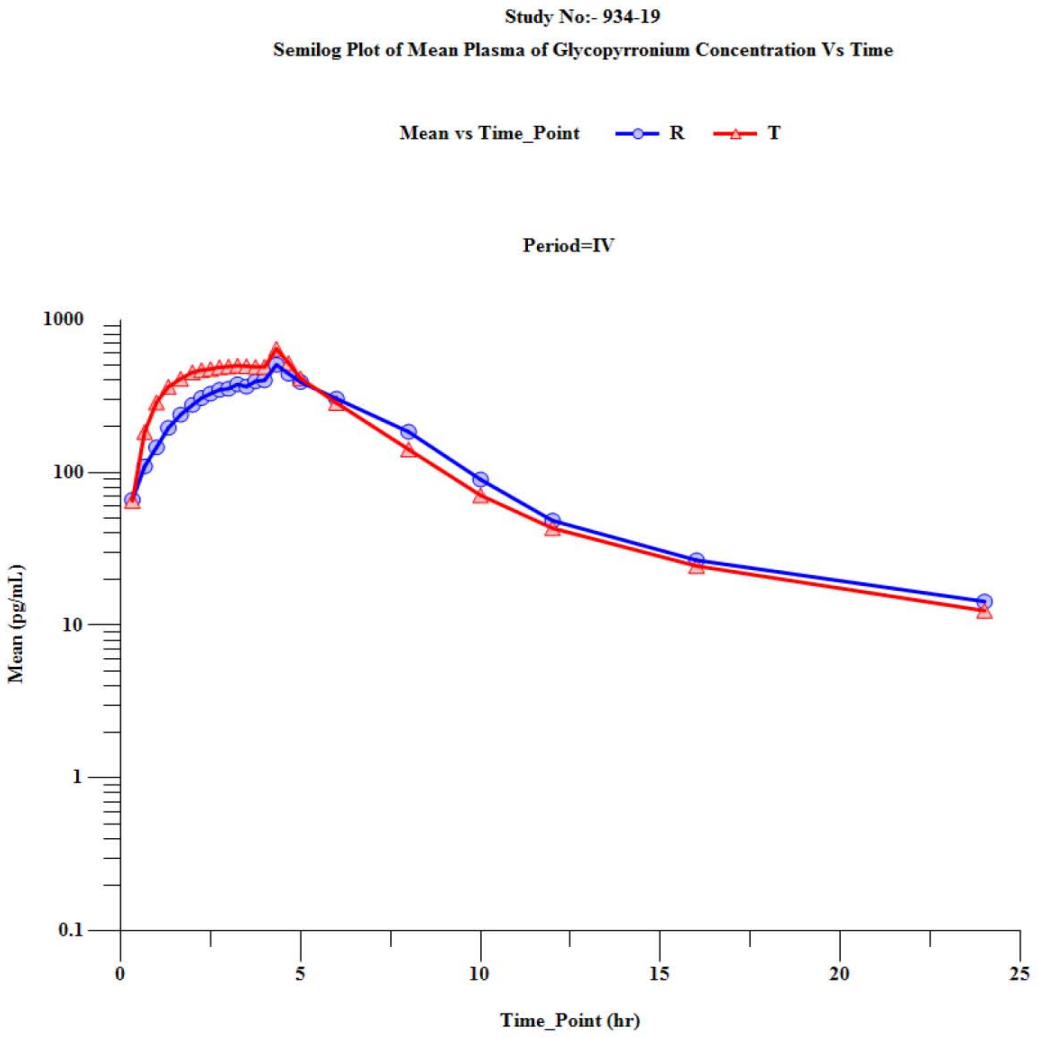
Name of Sponsor / Company: Kinedexe UK Limited	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: Glycopyrronium Bromide 2mg Tablets		
Name of Active Ingredient: Glycopyrronium		

Figure 7: Semi logarithm Plot of Mean Glycopyrronium Plasma Concentrations Vs Time of Period-III



Name of Sponsor / Company: Kinedexe UK Limited	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: Glycopyrronium Bromide 2mg Tablets		
Name of Active Ingredient: Glycopyrronium		

Figure 8: Semi logarithm Plot of Mean Glycopyrronium Plasma Concentrations Vs Time of Period-IV



Name of Sponsor / Company: Kinedexe UK Limited	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: Glycopyrronium Bromide 2mg Tablets		
Name of Active Ingredient: Glycopyrronium		

Safety Results:

A total of 72 healthy, adult, human subjects were enrolled and included in safety assessment. Safety assessment was carried out at the time of screening, during the course of the study and at the end of study by conducting medical examination, recording of vital signs and enquiring about the well-being, laboratory assessments and ECG.

During study from check-in of period I (Group-I, II and III) till last PK sample in period IV (Group-I, II and III)) total 22 adverse events were occurred. Out of 22 AEs, 11 AEs were occurred after administration of test product and 11 AEs were occurred after administration of reference product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving test formulation (T) in period I (Group-I). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving reference formulation (R) in period I (Group-I). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving reference formulation (R) in period I (Group-I). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving test formulation (T) in period I (Group-I). The adverse event was mild in nature, expected and definitely related to the investigational product.

Name of Sponsor / Company: Kinedexe UK Limited	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Glycopyrronium Bromide 2mg Tablets	Volume:	
Name of Active Ingredient: Glycopyrronium	Page:	

Subject no. [redacted] was reported an adverse event of dry mouth after receiving reference formulation (R) in period I (Group-I). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving reference formulation (R) in period I (Group-I). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving reference formulation (R) in period I (Group-II). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving test formulation (T) in period I (Group-II). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving test formulation (T) in period I (Group-III). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving reference formulation (R) in period II (Group-I). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving test formulation (T) in period II (Group-I). The adverse event was mild in nature, expected and definitely related to the investigational product.

Name of Sponsor / Company: Kinedexe UK Limited	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Glycopyrronium Bromide 2mg Tablets	Volume:	
Name of Active Ingredient: Glycopyrronium	Page:	

Subject no. [redacted] was reported an adverse event of dry mouth after receiving test formulation (T) in period II (Group-I). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving reference formulation (R) in period II (Group-I). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no [redacted] was reported an adverse event of dry mouth after receiving reference formulation (R) in period II (Group-II). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving test formulation (T) in period III (Group-I). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving reference formulation (R) in period III (Group-I). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving test formulation (T) in period III (Group-II). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving test formulation (T) in period III (Group-II). The adverse event was mild in nature, expected and definitely related to the investigational product.

Name of Sponsor / Company: Kinedexe UK Limited	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Glycopyrronium Bromide 2mg Tablets	Volume:	
Name of Active Ingredient: Glycopyrronium	Page:	

Subject no. [redacted] was reported an adverse event of dry mouth after receiving test formulation (T) in period IV (Group-I). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving reference formulation (R) in period IV (Group-I). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving test formulation (T) in period IV (Group-II). The adverse event was mild in nature, expected and definitely related to the investigational product.

Subject no. [redacted] was reported an adverse event of dry mouth after receiving reference formulation (R) in period IV (Group-II). The adverse event was mild in nature, expected and definitely related to the investigational product.

During post study safety assessment, values of the laboratory parameters tested were found to be within acceptable limit and clinically insignificant for all subjects, except subject numbe[redacted] and [redacted]

Subject no. [redacted] had adverse event of increased Eosinophils count.

Subject no. [redacted] had adverse event of increased Eosinophils count.

Subject no. [redacted] had adverse event of increased Eosinophils count.

Subject no. [redacted] had adverse event of increased Eosinophils count.

Subject no. [redacted] had adverse event of increased Eosinophils count.

Subject no. [redacted] had adverse event of increased Eosinophils count.

Subject no. [redacted] had adverse event of increased Eosinophils count.

Name of Sponsor / Company: Kinedexe UK Limited	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: Glycopyrronium Bromide 2mg Tablets		
Name of Active Ingredient: Glycopyrronium		

Subject no. [redacted] had adverse event of increased ALT level.

Subject no. [redacted] had adverse event of increased ALT level.

Subject no. [redacted] had adverse event of increased Eosinophils count.

All reported adverse events were resolved completely without any sequelae except subject no. [redacted], [redacted] and [redacted] (subject did not report to the facility for post study safety assessment follow-up. Hence, considered to be lost to follow-up).

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

The test and reference products were comparable in their safety and tolerability. Hence the test product was found to be safe and well tolerated upon single dose administration in healthy, adult, human, subjects under fasting conditions.

CONCLUSION:

The 90% confidence intervals for the test/reference ratios of the geometric least squares means between test and reference formulations calculated for primary pharmacokinetic parameter C_{max} and AUC_{0-t} were within the bioequivalence range of 78.86% – 126.79 and 80.00% – 125.00% respectively, for Glycopyrronium.

Based on the results obtained, it is concluded that Glycopyrronium Bromide 2mg Tablets manufactured for Kinedexe UK Limited, UK, is bioequivalent Cuvposa® oral solution 1 mg/5mL of Glycopyrrolate as 1 mg/5mL of Glycopyrronium Bromide (dose of 10 mL equivalent to 2 mg of Glycopyrronium Bromide) manufactured for Merz Pharmaceuticals, LLC in Healthy, Adult, Human Subjects Under Fasting Conditions.

Date of the Report: 10-Aug-2020

3.0 TABLE OF CONTENTS

List of Tables

List of Figures

Folio of Signatures

Prepared by:

I, the undersigned, declare that this report accurately reflects the method employed and the raw data generated and has been prepared as per the relevant standard operating procedures of VerGo Pharma Research Pvt. Ltd (Division - VerGo Clinicals).

[redacted]

Reviewed by:

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

[redacted]

Approved 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, accurately describes the conduct and results of the study.

4.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

%	:	Percentage
=	:	Is Equal to
±	:	Plus or Minus
®	:	Registered Trade Mark
°C	:	Degree Celsius
Ach	:	Acetylcholine
AE(s)	:	Adverse Event(s)
ALT	:	Alanine transaminase
AMP	:	Amphetamines
ANOVA	:	Analysis of Variance
&		And
AST	:	Aspartate Aminotransferase
AUC	:	Area Under the Curve
$AUC_{0\text{-}inf}$	:	Area under the concentration versus time curve from zero to infinity
$AUC_{0\text{-}t}$	:	Area under the concentration versus time curve from time zero to the last measurable concentration
$AUC_{\_\%Extrap}/AUC_{Extra}$	:	Residual area in percentage
BA	:	Bioavailability
BAR	:	Barbiturates
BE	:	Bioequivalence
BMI	:	Body Mass Index
BP	:	Blood Pressure
BZO	:	Benzodiazepines
CDSCO	:	Central Drugs Standard Control Organization
CI	:	Confidence Interval
CV	:	Coefficient Of Variation
CV_{WR}	:	Intrasubject variability of the reference product
C_{max} / C_{max}	:	Maximum measured plasma concentration following each „treatment“
COA	:	Certificate of Analysis
COC	:	Cocaine
CR	:	Clinical Research
CRF(s)	:	Case Report Form(s)
CRO	:	Contract Research Organization
CV / C.V.	:	Coefficient of variation
DCGI	:	Drug Control General of India
D.F	:	Degree of freedom
Dr	:	Doctor
e.g.	:	Example

ECG	:	Electrocardiogram
EMEA	:	European Medicines Agency
GMP	:	Good Manufacturing Practices
HIV	:	Human Immunodeficiency Virus
Hr(s)	:	Hour(s)
ICD	:	Informed Consent Document
ICF	:	Informed Consent Form
ICH	:	International Council for Harmonization
ICMR	:	Indian Council of Medical Research
IEC	:	Independent Ethics Committee
IP		Investigational Product
IU	:	International Unit
K_2 EDTA	:	Ethylene Diamine Tetra Acetic acid Di-potassium Salt
K_{el}	:	Terminal elimination rate constant
Kg	:	Kilograms
L	:	Liter
LC-MS/MS	:	Liquid Chromatography–Tandem Mass Spectrometry
Ltd	:	Limited
m^2	:	Meter Square
Mg	:	Milligrams
min.	:	Minutes
mL / ml	:	Milliliter
Mm	:	Millimeters
mmHg	:	Millimeters of Mercury
ME	:	Medical Examination
MHRA	:	Medicines and Healthcare Products Regulatory Agency
MO	:	Medical Officer
NR	:	Not Reported
n / No.(s)	:	Number(s)
OTC	:	Over The Counter
OPI	:	Opiate
PCV	:	Packed Cell Volume
Pg	:	Picogram
Ph	:	Phone
PI	:	Principal Investigator
PK	:	Pharmacokinetic
Pvt		Private
QA	:	Quality Assurance
R	:	Reference
RBC	:	Red Blood Cell

Rpm	:	Revolutions Per Minute
Rs	:	Rupees
SAE(s)	:	Serious Adverse Event(s)
SAP	:	Statistical Analysis Plan
SAS	:	Statistical Analysis System
SIS	:	Subject Information Sheet
SOP(s)	:	Standard Operating Procedure(s)
SD	:	Standard Deviation
SGOT	:	Serum Glutamic Oxaloacetic Transaminase
SGPT	:	Serum Glutamic Pyruvic Transaminase
S_{WR}	:	Within the subject of standard deviation of reference formulation of log value.
T	:	Test
$T_{1/2}$ / $t_{1/2}$ / T_{half}	:	Terminal Half- life
T_{max}	:	Time of maximum measured plasma concentration
THC	:	Tetrahydrocannabinol (Marijuana)
USA	:	United States of America
UK	:	United Kingdom
WMA	:	World Medical Association
Yr(s)	:	Year(s)

5.0 ETHICS

5.1 Independent Ethics Committee (IEC):

Proposal of the BE study of Glycopyrronium Bromide 2mg Tablets, Protocol no. 934-19 along with ICDs (English, Hindi and Marathi) (Version No. 00: dated 19-Nov-2019) were sent to Aavishkar Ethics Committee (AEC) on 10-Dec-2019 which were reviewed in meeting held on 14-Dec-2019 and the IEC (Aavishkar Ethics Committee) provided the approvals for protocol no. 934-19 and ICDs (English, Hindi and Marathi) (Version No. 00: dated 19-Nov-2019) on 16-Dec-2019. Informed consent documents were used for obtaining written informed consent from each of the subject.

Amendment no. 01 to the protocol and ICDs (Dated: 02-Mar-2020) was sent to Aavishkar Ethics Committee (AEC) on 04-Mar-2020 which were reviewed in meeting held on 04-Mar-2020 and the IEC (Aavishkar Ethics Committee) provided the approvals for Amendment no. 01 on 04-Mar-2020.

Amendment no. 02 to the protocol and ICDs (Dated: 06-May-2020) was sent to Aavishkar Ethics Committee (AEC) on 13-May-2020 which were reviewed in meeting held on 13-May-2020 and the IEC (Aavishkar Ethics Committee) provided the approvals for Amendment no. 02 on 13-May-2020.

Erratum to protocol amendment 02 were sent to IEC (Aavishkar Ethics Committee) on 14-Jul-2020 for review and acknowledgement received to Erratum from IEC (Aavishkar Ethics Committee) on same date. A copy of the erratum is attached in Appendix 16.1.3.

A copy of the IEC approved protocol and protocol amendments to the ICDs are attached in Appendix 16.1.1 and a copy of IEC Documents (IEC Submission, Attendance and IEC decision, Approval letter and Composition of IEC member) and Sample Informed Consent Form (English, Hindi and Marathi) are attached in Appendix 16.1.3 and_Sample copy of case report form is attached in Appendix 16.1.2.

5.2 Ethical Conduct of the Study

The study was conducted in accordance with the IEC approved protocol and protocol amendments to comply with all the obligations of investigator and all other pertinent

requirements of "ICH Guidelines for Good Clinical Practices E6 (R2) 2016", "New Drugs and Clinical Trial Rules, 2019, "Drugs and Cosmetics Act, 1940", "ICMR National Ethical Guidelines For Biomedical And Health Research Involving Human Participants, 2017", "CDSCO Guidelines for BA/BE Studies, March 2005", The principles enunciated in the Declaration of Helsinki (64th WMA General Assembly, Brazil 2013), Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products, EMEA "Guideline on the Investigation of Bioequivalence, Jan 2010" and with procedures oriented to Good Laboratory Practice and other applicable guidelines.

5.3 Subject Information and Consent

Before the subject"s voluntary participation in the study, written informed consent was obtained from all the willing volunteers. Subjects underwent a screening procedure to determine their eligibility to participate in the study.

General screening of volunteers for participation in the study were done on 11-May-2020, 12-May-2020, 13-May-2020, 15-May-2020, 16-May-2020, 18-May-2020, 19-May-2020, 20-May-2020, 21-May-2020, 22-May-2020, 23-May-2020, 24-May-2020 and 27-May-2020 within 21 days prior to first dosing of period I. Refer section 9.3.

The Principal Investigator/ Clinical Investigator / MO/ designated CR personnel provided information to the study subject through informed consent process regarding the essential elements of the study including the purpose, procedures to be carried out, potential hazards and rights of the subjects including right to claim compensation in case of study-related injury or death. Study investigator informed the subject or his nominee (s) of their right to contact the sponsor for the purpose of making claims in case of study-related injury or death.

Each subject had a one-to-one discussion with the Principal Investigator/ Clinical Investigator /MO/ designated CR personnel during the informed consent process to address any individual concern/query (s). The IEC approved, study-specific informed consent document was written in a language that is understandable to the subject and was presented to the subject prior to study participation. The subjects were given ample time

to read, understand and sign the informed consent document prior to study participation which summarized the discussion prior to check-in for the study in period I (Group-I, II and III).

The whole informed consent process was captured through audio-video recording as per in house SOP(s). Copies of the ICD"s (English, Hindi and Marathi language versions) were used for obtaining consent for participation in the study is appended in Appendix 16.1.3.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The Clinical phase, Bio-analytical phase and Statistical phases were conducted in VerGo Pharma Research Pvt. Ltd (Division - VerGo Clinicals), [redacted] The following study personnel were responsible for protocol development, study conduct, clinical monitoring and reporting data of the study in compliance with the protocol, SOPs and regulatory requirements.

Principal Investigator	:	[redacted]
Clinical Investigator(s)	:	
	:	
	:	
Bioanalytical Investigator	:	
Statistical Investigator	:	
Curriculum vitae (CVs) of study investigators are attached in Appendix 16.1.4. The signatures of the principal investigators or other coordinating investigators are included in the Appendix 16.1.5.		

Facilities utilized for the study as follows:

Clinical Facility:

VerGo Pharma Research Pvt. Ltd

(Division - VerGo Clinicals),

[redacted]

Bio analytical Facility:

VerGo Pharma Research Pvt. Ltd

(Division - VerGo Clinicals),

[redacted]

Pharmacokinetics and Statistical Management:

VerGo Pharma Research Pvt. Ltd

(Division - VerGo Clinicals),

[redacted]

Diagnostic Facility:

VerGo Pharma Research Pvt. Ltd.

(Division - VerGo Pathology Centre),

[redacted]

Emergency care Hospital:

[redacted]

7.0 INTRODUCTION

Multisource pharmaceutical products need to confirm to the same standards of quality, efficacy and safety as required of the originator's (comparator/reference) product. Specifically, the multisource product should be therapeutically equivalent and interchangeable with the reference product. Testing the bioequivalence between a test product (pharmaceutically equivalent or a pharmaceutical alternative) and a suitable reference product in a pharmacokinetic study with a limited number of subjects is one way of demonstrating therapeutic equivalence without having to perform a clinical trial involving many subjects.

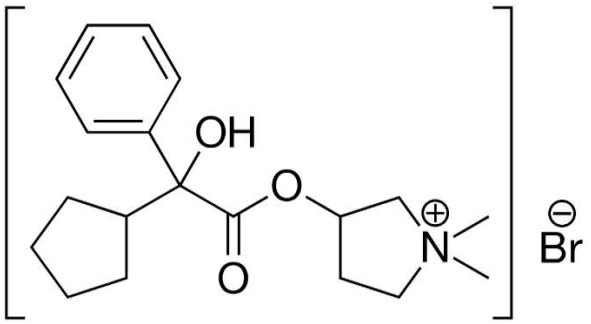
Kinedexe UK Limited has developed a generic version of Glycopyrronium Bromide 2 mg Tablets. It is intended to show bioequivalence of test formulations Glycopyrronium Bromide 2 mg Tablets M.A Holder Kinedexe UK Limited, Unit 15 Moorcroft, Harlington Road, Uxbridge. UB8 3HD, UK with that of reference formulation with Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL of Glycopyrrolate as 1 mg/5mL of Glycopyrronium Bromide (10 mL containing 2 mg of Glycopyrronium Bromide) [redacted] Manufactured For Merz North America in healthy, adult, human subjects under fasting condition.

In this study, the bioequivalence of single oral dose of test product Glycopyrronium Bromide 2 mg Tablets M.A Holder Kinedexe UK Limited, Unit 15 Moorcroft, Harlington Road, Uxbridge. UB8 3HD, UK was assessed with the reference product Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL of Glycopyrrolate as 1 mg/5mL of Glycopyrronium Bromide (10 mL containing 2 mg of Glycopyrronium Bromide) [redacted] Manufactured For Merz North America, administered under fasting conditions in healthy, adult, human subjects. Protocol was designed with adequate blood sampling points (24 time points / period), duration of the study was 18 days and washout period (5 days) were planned between the four periods of the study so that the drug concentration in the biological fluid could be characterized accurately for this bioequivalence study.

Test Product (T):	Glycopyrronium Bromide 2 mg Tablets M.A Holder: Kinedexe UK Limited, Unit 15 Moorcroft, Harlington Road, Uxbridge. UB8 3HD, UK.
Reference Product (R):	Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL [redacted] Manufactured For: Merz North America, Inc.

Description of the Investigational Products:

Glycopyrronium (as the bromide salt glycopyrrolate) is an anticholinergic agent with a quaternary ammonium structure, a muscarinic competitive antagonist used as an antispasmodic, in some disorders of the gastrointestinal tract, and to reduce salivation with some anesthetics.



Molecular Formula of Glycopyrronium Bromide: $C_{19}H_{28}BrNO_3$

Molecular Weight of Glycopyrronium Bromide: 398.355 g/mol

Clinical Pharmacology

Mechanism of Action:

Glycopyrronium Bromide is a muscarinic anticholinergic agent that binds competitively to the muscarinic acetylcholine receptor. Like other anticholinergic (antimuscarinic) agents, it inhibits the action of acetylcholine on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sinoatrial node, the atrioventricular node,

exocrine glands and, to a limited degree, in the autonomic ganglia. Thus, it diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal, and bronchial secretions. Aside from differences in the CNS actions, the spectrum of pharmacological actions by Glycopyrronium Bromide is qualitatively similar to that of the naturally occurring alkaloids atropine and scopolamine, but differs with regard to duration and intensity. Within the peripheral nervous system, Glycopyrronium Bromide acts as a potent competitive antagonist at muscarinic receptors and attenuates physiological processes regulated by the parasympathetic nervous system, including predictable actions within the respiratory tract, gastrointestinal system, and heart. The highly polar quaternary ammonium group of Glycopyrronium Bromide limits its passage across lipid membranes, such as the blood-brain barrier.

Pharmacokinetics

Absorption:

Glycopyrronium Bromide is poorly absorbed from the gastrointestinal tract. Oral Glycopyrronium Bromide has low oral bioavailability; a mean of approximately 3% is found in plasma. Mean absolute oral bioavailability of glycopyrronium comparing a single 50 µg/kg oral dose and a single 5 µg/kg i.v. dose was low at approximately 3% (range 1.3–13.3%) in children aged 7–14 years undergoing intraocular surgery (n = 6) due to the medicinal product's low lipid solubility. Data from sparse PK sampling in children suggests dose proportional PK. Oral Glycopyrronium Bromide produces low plasma concentrations (Cmax 0.318 ± 0.190 pg/mL) lasting up to 12 hours.

Food effect data indicate that the mean C_{max} under fed high fat meal conditions is about 74% lower than the C_{max} observed under fasting conditions.

Distribution:

Co-administration with food results in a marked decrease in systemic glycopyrronium exposure.

Following administration of 3H-labelled glycopyrronium more than 90% of the radiolabel disappeared from the plasma in 5 minutes, and almost 100% within 30

minutes, reflecting rapid distribution. Analyses of population pharmacokinetic data from healthy adults and children with cerebral palsy-associated chronic moderate to severe drooling who received glycopyrronium (route of administration and dosages not specified) did not demonstrate linear pharmacokinetics of the medicinal product.
The volume of distribution, 0.64 ± 0.29 L/kg in adults is similar to that of total body water. Volume of distribution is somewhat higher in the paediatric population(s), in the range 1.31 to 1.83 L/kg.

In most paediatric subjects, plasma glycopyrronium vs. time plots are reported to show a triexponential curve; adults generally show a biexponential curve. Modest changes in volume of distribution (Vss) and clearance (Cl) have been observed in children between 1 and 3 years of age, leading to a statistically significant shorter elimination half-life ($t_{½, z}$) than that observed in younger (<1 year of age; p = 0.037) or older (>3 years of age; p = 0.042) groups.

In a study in healthy adults, a 2000 µg single dose of Glycopyrronium Bromide resulted in an AUC of 2.39 µg.h/L (fasted). An $AUC_{0\text{-}6\ h}$ of 8.64 µg.h/L was observed after 6 µg/kg i.v. Glycopyrronium Bromide.

Based upon theoretical physicochemical considerations, the quaternary ammonium compound glycopyrronium would be expected to have low central bioavailability. The primary route of elimination of glycopyrronium is via renal excretion, mainly as unchanged medicinal product. Approximately 65% of an i.v. dose is renally excreted within the first 24 hours. A small proportion (~5%) is eliminated in the bile.
The elimination half-life of glycopyrronium Bromide appears in the region of 2.5 - 4 h after oral (solution) administration, though again this was highly variable. It is possible that prolonged absorption after oral administration translates into elimination being faster than absorption (known as flip-flop kinetics, characterized by Ka < Ke).

The total body clearance of the medicinal product following an i.v. dose is relatively high at between 0.54 ± 0.14 L/h/kg and 1.14 ± 0.31 L/h/kg. As this exceeds the glomerular filtration rate and it appears that more than 50% of the dose is excreted unchanged in the

urine, it is probable that the renal elimination of glycopyrronium involves both glomerular filtration and proximal tubular secretion by the base secretory mechanism.

A mean increase in total systemic exposure (AUClast) of up to 1.4 fold was seen in adult subjects with mild and moderate renal impairment (GFR ≥30mL/min/1.73m2) and up to 2.2 fold in subjects with severe renal impairment or end stage renal disease (estimated GFR <30 mL/min/1.73m2). A 30% dose reduction is required for patients with mild to moderate renal impairment. Glycopyrronium is contraindicated in patients with severe renal impairment.

Baseline characteristics (age, weight, gender and race) do not affect the pharmacokinetics of glycopyrronium.

Glycopyrronium Bromide penetrates the blood-brain barrier poorly. Glycopyrronium Bromide crosses the placenta to a limited extent; and is not known whether it is distributed into milk.

Elimination:

Urinary radioactivity was highest in the first 3 hours and 85% was excreted in the urine within 48 hours. Paper chromatography showed 80% of the radioactivity in bile and urine corresponding to unchanged glycopyrronium. Following oral administration to mice, 7.6% was excreted in the urine and about 79% in the faeces.

Impaired hepatic function is not expected to affect the pharmacokinetics of glycopyrronium since the majority of the medicinal product is eliminated through the kidneys.

Indications

Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders.

For use as a preoperative antimuscarinic to reduce salivary, tracheobronchial, and pharyngeal secretions, to reduce the volume and free acidity of gastric secretions and to block cardiac vagal inhibitory reflexes during induction of anesthesia and intubation. Also used to treat chronic obstructive pulmonary disease (COPD).

8.0 STUDY OBJECTIVES

Primary objective:

To compare the rate and extent of absorption of single dose of Glycopyrronium Bromide 2mg Tablets manufactured for Kinedexe UK Limited, UK with Cuvposa® oral solution 1 mg/5mL of Glycopyrrolate as 1 mg/5mL of Glycopyrronium Bromide (dose of 10 mL equivalent to 2 mg of Glycopyrronium Bromide) manufactured for Merz Pharmaceuticals, LLC administered under fasting conditions in healthy, adult, human subjects in a randomized cross over study.

Secondary objective:

To evaluate the safety and tolerability of a single dose of Glycopyrronium Bromide 2mg Tablets when administered orally in healthy, adult, human subjects under fasting conditions.

9.0 INVESTIGATIONAL PLAN

The Clinical phase, Bio-analytical phase and Pharmacokinetic & Statistical analysis were conducted at VerGo Pharma Research Pvt. Ltd (Division - VerGo Clinicals), [redacted] India under the Study No. 934-19.

9.1 Overall Study Design and Plan

Study Design:

An open-label, balanced, randomized, single dose, two-treatment, two-sequence, four-period, fully replicate cross over, oral bioequivalence study in healthy, adult, human subjects under fasting conditions.

Number of Subjects:

A total of 72 healthy, adult, human subjects who met the inclusion and exclusion criteria as described in the protocol were enrolled into the study (refer section 9.3.1 & 9.3.2). Total 72 subjects were dosed in period-I, 66 subjects were dosed in period II and 62 subjects were dosed in period III and IV. Total 62 subjects completed all four periods of the study.

Subject no. [redacted] and [redacted] were considered as dropout for the study, as they did not report for period II, III and IV check-in.

Subject no. [redacted] and [redacted] they were withdrawn their consent after check out of period II due to their personal reasons (they were leaving to their native place). Hence, considered as dropout. (Both the subjects completed period II and their post study safety assessment were done after period II check-out on 31-May-2020. Hence, these subjects were not applicable for period III and IV).

Subject No. [redacted] was withdrawn [redacted] consent on own accord on the day of check-in of period II due to [redacted] personal reason. Hence, considered as dropout for period II (Subjects no. 63 [redacted] post study safety was done on 03-Jun-2020, Hence, this subject not applicable for period III and IV).

Subject no. [redacted] was withdrawn [redacted] consent on own accord before dosing of period III due to [redacted] personal reasons. Hence, considered as dropout for period III.

Subject no. [redacted] did not report to the facility for period IV check-in. Hence, considered as dropout for period IV.

Subject no. [redacted] was considered as dropout for the study, as [redacted] did not report for period, III and IV check-in.

Test Product (T):	Glycopyrronium Bromide 2 mg Tablets M.A Holder: Kinedexe UK Limited, Unit 15 Moorcroft, Harlington Road, Uxbridge. UB8 3HD, UK.
Reference Product (R):	Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL [redacted]. Manufactured For: Merz North America, Inc.

Method of Blinding:

This study was comprised of a randomized open label design. However, study personnel"s involved in the sample analysis were kept blinded from the randomization code till the completion of the bio analytical phase of the study.

Method of Assignment to treatment:

The subjects were randomly assigned to one of the possible sequences of the test or reference product in consecutive order following the randomization code provided by VerGo Pharma Research Pvt. Ltd (Division – VerGo Clinicals) according to SAS® (version 9.3) generated randomization.

The test or the reference drugs were administered to 72 subjects in period-I, 66 subjects were dosed in period II, 62 subjects in period III and IV as per the randomization schedule.

Randomization:

The eligible subjects, who fulfilled the inclusion and exclusion criteria for the study, were randomly assigned to one of the following sequence by using SAS software (version 9.3).

	Period I	Period II	Period III	Period IV
Treatment I	T	R	T	R
Treatment II	R	T	R	T

The randomization was balanced and the randomization schedules as well as the dispensing records were kept in the pharmacy under controlled access.

Sequence and Duration of Study Periods:

An open-label, balanced, randomized, single dose, two-treatment, two-sequence, four-period, fully replicate cross over, oral bioequivalence study in healthy, adult, human subjects under fasting conditions. Total duration of the study was 18 days from the day of check-in of period I (Group I, II, III) to the last blood sample collection of Period-IV (Group I, II and III).

Sitting Posture:

Administration of investigational products were carried out while the subjects were in sitting posture and they were instructed to remain supine for first four hours after dosing in each period except when clinically indicated to change the posture or in case of natural exigency. Postural changes were also allowed while recording vitals and sample collection. Thereafter the subjects were allowed to engage in normal activities while avoiding physical exertion.

Housing

Subjects were housed in the clinical facility at 11.00 hours prior to dosing and continued to remain in the clinical facility for at 24.00 hours after dosing in each period.

The protocol and sample case report form have been attached as Appendix 16.1.1 and Appendix 16.1.2 respectively.

9.2 Discussion of Study Design, Including the Choice of Control Groups

The study was conducted to establish the bioequivalence between test formulation-Glycopyrronium Bromide 2 mg Tablets M.A Holder Kinedexe UK Limited, Unit 15 Moorcroft, Harlington Road, Uxbridge UB8 3HD, UK with reference formulation Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL [redacted]

[redacted] Manufactured For Merz North America, Inc in healthy, adult, human subjects under fasting conditions.

A single-center design was chosen for this trial to standardize the trial conditions and reduce variability. This trial was performed as an open-label trial. This was not considered to introduce bias, because the main assessment criteria were based on pharmacokinetic parameters.

In consideration with half-life of drug are usually about Glycopyrronium Bromide 2 mg tablet (Approx 3.3 hours) and Glycopyrronium Bromide 1mg/5 mL oral solution (2.5 to 4 hours) and the sampling schedule up to 24.00 hours was sufficient to characterize pharmacokinetic profile.

A total of 72 healthy, adult, human subjects who met the inclusion and exclusion criteria as described in the protocol and amendment were enrolled into the study in three groups (For details, refer to Section 9.3.1 and 9.3.2). Total 72 subjects were dosed in period-I, 66 subjects were dosed in period II, 62 subjects were dosed in period III and IV. Total 62 subjects completed all four periods of the study (For details, refer to Section 10.1).

Subjects were housed in the clinical facility at 11.00 hours prior to dosing and continued to remain in the clinical facility for at 24.00 hours after dosing in each period.

Period I:

Group I: 36 subjects (Subject No. [redacted]) were dosed on 22-May-2020 and were housed in the clinical facility. Subjects were checked out on 23-May-2020.

Group II: 24 subjects (Subject No. [redacted]) were dosed on 25-May-2020 and were housed in the clinical facility. Subjects were checked out on 26-May-2020.

Group III: 12 subjects (Subject No. [redacted]) were dosed on 30-May-2020 and were housed in the clinical facility. Subjects were checked out on 31-May-2020.

Period II:

Group I: 34 subjects (Subject No. [redacted]) were dosed on 27-May-2020 and were housed in the clinical facility. Subjects were checked out on 28-May-2020.

Group II: 21 subjects (Subject No. [redacted] were dosed on 30-May-2020 and were housed in the clinical facility. Subjects were checked out on 31-May-2020.

Group III: 11 subjects (Subject No. [redacted] were dosed on 04-Jun-2020 and were housed in the clinical facility. Subjects were checked out on 05-Jun-2020.

Period III:

Group I: 34 subjects (Subject No. [redacted]) were dosed on 01-Jun-2020 and were housed in the clinical facility. Subjects were checked out on 02-Jun-2020.

Group II: 17 subjects (Subject No. [redacted]) were dosed on 04-Jun-2020 and were housed in the clinical facility. Subjects were checked out on 05-Jun-2020.

Group III: 11 subjects (Subject No. [redacted] were dosed on 09-Jun-2020 and were housed in the clinical facility. Subjects were checked out on 10-Jun-2020.

Period IV:

Group I: 34 subjects (Subject No. [redacted] were dosed on 06-Jun-2020 and were housed in the clinical facility. Subjects were checked out on 07-Jun-2020.

Group II: 17 subjects (Subject No. [redacted]) were dosed on 09-Jun-2020 and were housed in the clinical facility. Subjects were checked out on 10-Jun-2020.

Group III: 11 subjects (Subject No. [redacted] were dosed on 14-Jun-2020 and were housed in the clinical facility. Subjects were checked out on 15-Jun-2020.

Total 62 subjects (Subject no. [redacted]) completed all four periods of the study. Total duration of the study was 18 days from the day of check-in of period I (Group I, II, III) to the last blood sample collection of Period-IV (Group I, II and III). Separated by a washout period of 5 days between two dosing days.

During study from period I check-in (Group-I, II and III) till last PK sample in period IV (Group-I, II and III)) total 22 adverse events were occurred and 10 adverse events were observed during the post study evaluation and details provided in Section 12.2.1.

Duration of dosing is described in Section 9.4.5 „Selection and Timing of Dose for Each Subject".

Blood samples were collected and processed as described in Section 9.5.4 „Drug Concentration Measurements" of the report.

During the study, safety parameters -vital signs, clinical examination, tests of Urine screen for drugs of abuse and breath test for alcohol consumption (performed on the day of check-in of each period). The adverse event monitoring was done throughout the study. The ECG was recorded at the time of screening. Laboratory parameters of hematology and biochemistry were repeated at the end of the study *i.e.* 24.00 hours post dose of Period IV (Group-I, II and III). Safety parameters of vital signs, clinical examination and medical history are discussed in Section 9.5.1. Efficacy and safety measurements assessed and flow Chart" of the report. Laboratory measurements conducted in the study are discussed in Appendix 16.2.8.

Total 72 subjects were dosed in period-I, 66 subjects were dosed in period II, 62 subjects were dosed in period III and IV. Total 62 subjects completed all four periods of the study. Samples of 72 subjects were used in bio analytical analysis. Data from 66 subjects were used in the pharmacokinetic analysis (these subjects were completed two periods *i.e.* one test treatment and one reference treatment or two reference treatment), The data of 62 subjects were used in within subject standard deviation of reference formulation (these subjects were completed two reference treatment) and the data of 62 subjects were used for bioequivalence evaluation (these subjects received one test treatment and one reference treatment), according to the protocol. Bioequivalence was determined by statistical analysis of log-transformed data of C_{max} and AUC_{0-t} of Glycopyrronium for the test and reference products.

9.3 Selection of Study Population

All subjects underwent a screening procedure (performed within 21 days prior to first dosing). Demographics (Height, weight, BMI, ethnic origin), Medical history (present and past, Surgical history, Family history, Personal history including habits of smoking, tobacco chewing, alcohol consumption, addiction to recreational drugs, history of blood donation), physical examination and Systemic examination, General Examination, Participation in clinical research studies, Allergies, Drug allergy/reaction and Medication history. Clinical laboratory tests [hematology, biochemistry parameters, urine analysis (Routine & Microscopy) and serology] at baseline were assessed, The ECG was recorded at the time of screening, Further at the time of check-in for all periods of the study, the subjects underwent of breath test for alcohol consumption and Urine screen for drugs of abuse. Only those subjects who were found negative for these tests were checked-in for the study periods. The subjects were selected on the basis of following inclusion and exclusion criteria.

9.3.1 Inclusion Criteria

Subjects who were enrolled in the study met all of the following criteria:

- Subjects should be 18 to 45 years of age (both years inclusive).
- Capable and willing to give informed written consent and to adhere to the study requirements.
- Subjects able to read and write and able to communicate effectively.
- Body Mass Index (BMI) between 18.50–30.00 Kg / m^2 and body weight not less than 50 kg.
- Healthy individuals as evaluated by personal history, medical history and general clinical examination.
- Absence of significant disease
- Normal or within acceptable biochemical, hematological and urinary parameters performed within 21 days prior to first dosing for the first period of the study.
- Have a normal 12 lead ECG

- Negative HIV 1 & 2 antibodies, Hepatitis B surface antigen, Hepatitis C antibody and Syphilis.
- Negative urine test for drugs of abuse for Marijuana-THC, Amphetamine-AMP, Barbiturates-BAR, Cocaine-COC, Benzodiazepines-BZO and Opiates (OPI)-Morphine (MOR) (to be performed on the day of check-in during each period).
- Negative breath alcohol test (to be performed on the day of check-in during each period).
- Subject should preferably be a nonsmoker and without a history of alcohol or drug abuse.

9.3.2 Exclusion Criteria

Subjects were excluded for any one of the following reasons:

- Subjects incapable of understanding the informed consent.
- History of any major surgical procedure in the past 3 months.
- History of diabetes mellitus, tuberculosis and systemic hypertension.
- History suggestive of cardiac, gastrointestinal, respiratory, hepatic, renal, endocrine, metabolic, psychiatric, neurological or hematological systems, judged to be clinically significant.
- Recent history of dehydration from diarrhoea, vomiting or any other reason within a period of 24 hours prior to the study
- History of dysphasia.
- History of any medical disorder that is of significance in the investigator‟s opinion.
- Alcohol consumers and found positive in breath alcohol test during check-in of each period.
- History of any drug abuse.
- History of hypersensitivity to study medications and related drugs e.g., Sulpha drugs, Heparin or excipients in the formulation (if the excipients are known).
- History of allergy to vegetables and / or food substances and / or any other manifestations suggestive of hypersensitivity reactions.

- Present or past history of intake of drugs* which potentially modify kinetics / dynamics of study medications or any other medication judged to be clinically significant by the investigator.
- Consumption of grapefruit juice and /or grapefruit at least 48-hours prior to Period I check-in to the last PK sample collection of the last Period of the study.
- Intake of any prescription medications within 14 days prior to check-in and throughout the study, and/or over-the counter (OTC) & herbal drugs within 7 days prior to check-in and / or intake of any drug* in the past that could affect the kinetics or dynamics of study medications in view of investigator.
- Subjects with clinically significant abnormal values of laboratory parameters.
- Subjects who had participated in any other clinical study or who had bled in the past 90 days from the date of start of study either for blood donation or for any other reason.
- Consumption of caffeine and /or xanthine products, cigarettes and tobacco containing products within 24 hrs prior to check-in and inability to withhold the intake during the - in house - stay.
- Difficulty in swallowing tablets/oral solution.
- An unusual diet for whatever reason e.g. low sodium diet, for four weeks prior to study initiation and throughout subject"s participation in the study.
- Had a depot injection or an implant of any drug 3 months prior to the commencement of this study.
- Known hypersensitivity or idiosyncratic reaction to Glycopyrronium Bromide, its excipients or similar classes of drugs.

* Drugs that can potentially affect the hepatic metabolism of other drugs are as listed below (not limited to the following).

Hepatic microsomal enzyme inducers (which can reduce the systemic bioavailability):- Barbiturates, Carbamazepine, Ethanol (chronic), Inhalational anaesthetics, Griseofulvin, Phenytoin, Phenobarbital, Primidone, Rifampicin. Mefloquine

Hepatic microsomal enzyme inhibitors (which can increase the systemic bioavailability):- Amiodarone, Cimetidine, Ciprofloxacin, Dextropropoxyphene, Ethanol (acute), Etomidate, Erythromycin, Fluconazole, Ketoconazole, Metronidazole and Felbamate.

9.3.3 Removal of Subjects from Assessment

The Principal Investigator considered the following criteria for withdrawal of the subject from the study:

- The subject withdrew consent.
- Development of intolerable adverse event due to study participation as determined by the Principal investigator and / or subject.
- If any subject experienced emesis at or before two times median T_{max}, or significant diarrhea in any period, decision of withdrawal at the discretion of Principal Investigator.
- Development of an intercurrent illness or condition for which the subject required concomitant medications which had interfered with the kinetics of the study medication.
- Discovery that the subject entered the study in violation of the protocol or occurrence of a significant protocol violation during the study.
- The investigator felt that in the best interest of the subject‟s health, the subject to be withdrawn from the study.
- Data which not been known before starting the trial was available and raised concern about the safety of the study drug so that continuation had posed potential risk to any particular subject.
- If the subject was non cooperative and / or undisciplined.
- If subject was not reported for check-in of any of the study periods due to own accord, then the subject was considered as dropout from that particular period and allowed to continue his participation in subsequent periods as per investigator‟s discretion.

Any such subject withdrawals were reported for the following.

- Reasons for withdrawal (if any) and date and time of withdrawal which was adequately documented in the CRF and reported to the Sponsor and IEC.
- Medical examination of the subject was done at the time of withdrawal, if a subject withdrew during the in-house stay at VerGo Pharma Research Pvt. Ltd, (Division - VerGo Clinicals).
- Laboratory investigations at the time of withdrawal or after completion of the study.
- Any other reason which affected the trial outcome and safety of the subjects.
- Subjects who were withdrawn from the study were declared to be medically fit by Principal Investigator /Clinical Investigator/MO prior to their final study check-out.

9.4 Treatments

9.4.1 Treatments Administered

In each study period after an overnight fasting of 10.00 hours, as per the randomization schedule one tablet of Test product - Glycopyrronium Bromide 2 mg Tablets or 10 mL oral solution of Reference product (R) - Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL (10 mL containing 2 mg of Glycopyrronium Bromide) was administered at ambient temperature to each subject in sitting position by trained personnel. Refer below details procedure of test and reference product administration.

Administration of Test Product (T): One tablet of test product Glycopyrronium Bromide 2 mg Tablets M.A Holder Kinedexe UK Limited, Unit 15 Moorcroft, Harlington Road, Uxbridge. UB8 3HD, UK was administered orally with 240 mL of drinking water at ambient temperature to each subject in sitting position. Subjects were instructed not to chew or crush the tablet but to consume it as a whole.

Administration of Reference Product (R): 10 ml of oral solution of reference product (R) - Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL of Glycopyrrolate as 1 mg/5mL of Glycopyrronium Bromide (10 mL containing 2 mg of Glycopyrronium Bromide) [redacted] Manufactured For Merz North America, Inc was administered orally using a syringe at ambient temperature to each subject in sitting position. After administration, the syringe was rinsed twice with 05 mL

of drinking water taken in each rinse and both rinsing were administered to the subject to ensure complete consumption of the solution. The water used for rinsing was taken from 240 mL drinking water and the remaining water was then administered. The total amount of water given for dosing was 240 mL.

Administration of IPs were done by trained personnel in the presence of Principal Investigator/Clinical Investigator, sponsor monitor and QA personnel. Subjects were instructed to remain in supine position for first four hours after dosing in each period except when clinically indicated to change the posture or in case of natural exigency. Postural changes allowed while recording vitals and sample collection. Thereafter the subject allowed engaging in normal activities while avoiding severe physical exertion. Ensure the subject had swallowed the IP, Subjects" oral cavity (mouth check) was checked by trained study personnel using torch and tongue depressor under the tongue, under the lips, in the corners of the mouth and between the gums and cheeks immediately after dosing.

Subjects were dosed in two stations in period I, II, III, and IV (Group I and II) and subject were dosed in one station in period I, II, III, and IV (Group III) as mentioned below:

Period I:

Group I: 36 subjects were dosed in two stations [Subject no. [redacted] were dosed in station I at [redacted] and subjects no. [redacted] were dosed in station II at [redacted] on 22-May-2020].

Group II: 24 subjects were dosed in two stations [Subject no. [redacted] were dosed in station I at [redacted] and subjects no. [redacted] were dosed in station II at [redacted] on 25-May-2020].

Group III: 12 subjects were dosed in one station [Subject no. [redacted] were dosed in station I at [redacted] on 30-May-2020].

Period II:

Group I: 34 subjects were dosed in two stations [Subject no. [redacted] were dosed in station I at [redacted] and subjects no. [redacted] were dosed in station II at [redacted] and [redacted] on 27-May-2020].

Group II: 21 subjects were dosed in two stations [Subject no. [redacted] were dosed in station I at [redacted] and [redacted] and subject no. [redacted] and [redacted] were dosed in station II at [redacted] and [redacted] hours on 30-May-2020].

Group III: 11 subjects were dosed in one station [Group-III: Subject no. [redacted], [redacted] and [redacted] to [redacted] were dosed in station I [redacted] on 04-Jun-2020].

Period III:

Group I: 34 subjects were dosed in two stations [Subject no. [redacted] were dosed in station I at [redacted] and subjects no. [redacted] and [redacted] were dosed in station II at [redacted] on 01-Jun-2020].

Group II: 17 subjects were dosed in two stations [Subject no [redacted] and [redacted] were dosed in station I at [redacted] and subjects no. [redacted] and [redacted] were dosed in station II at [redacted] and [redacted] on 04-Jun-2020].

Group III: 11 subjects were dosed in one station [Group-III: Subject no. [redacted], [redacted] and [redacted] to [redacted]2 were dosed in station I at [redacted] on 09-Jun-2020].

Period IV:

Group I: 34 subjects were dosed in two stations [Subject no. [redacted] were dosed in station I at [redacted] and subjects no. [redacted] and [redacted] were dosed in station II at [redacted] on 06-Jun-2020].

Group II: 17 subjects were dosed in two stations [Subject no. [redacted] and [redacted] were dosed in station I [redacted] and subjects no. [redacted] were dosed in station II [redacted] on 09-Jun-2020].

Group III: 11 subjects were dosed in one station [Group-III: Subject no. [redacted] and [redacted] to 72 were dosed in station I [redacted] on 14-Jun-2020].

Note-: Dosing activity was done under sodium vapour lamp light conditions.

9.4.2 Identity of Investigational Products

All drug receipt, inventory, dispensing, dosing and reconciliation records were maintained in compliance with in-house SOPs. The study drug was dispensed by a qualified pharmacist under supervision of principal investigator, sponsor monitor and in presence of quality assurance auditor according to established procedures. Upon completion of the study, unused IPs were reconciled with remaining study drug. Investigational product receipt and accountability records are maintained in the pharmacy. IP verification, dispensing and retention of IP were done under sodium vapour lamp light. The details of the investigational products administered to the subjects during the study are provided in below Table 4.

Table 4: Identification of Test and Reference Products

Identifying Parameters	Test Product-T	Reference Product-R
Product Name	Glycopyrronium Bromide 2 mg Tablets	Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL
Manufactured	M.A Holder: Kinedexe UK Limited, Unit 15 Moorcroft, Harlington Road, Uxbridge. UB8 3HD, UK.	[redacted] Manufactured For: Merz North America, Inc
Description	White to off white round scored uncoated tablet engraved with "GP & "2" on either side of score line & plain on the other.	Clear colourless and viscous liquid
Lot No.	[redacted]	[redacted]
Manufacturing Date	[redacted]	[redacted]
Expiry Date	[redacted]	[redacted]

Note: Refer Appendix 16.1.6; Test product and Reference product COA along with accountability details.

The investigational test product was received on 18-Mar-2020 and reference product was received on 30-Mar-2020 by the pharmacist. The investigational products Test & Reference product verification was done on 16-Apr-2020 as per in-house SOP. The reference products were supplied in original market pack and both test and reference IP"s

were sent with their certificates of analysis (COA) and the details of the product (Product name, Strength, No. of dosage units, Manufacturer, Lot No. Manufacturing date, Expiry date etc.). During shipment of IPs no excursions were observed in temperature. Hence, the investigational products were considered safe for dose to human subjects. The Principal Investigator, Quality Assurance personnel, sponsor monitor and the pharmacist involved in dispensing of investigational products. Pharmacist and principal investigator were responsible for accountabilities of investigational products and ensured compliance to randomization schedule. Accountability for the investigational products was documented in the respective "Logbook for Investigational Product" for the test and reference products. The test and reference products received and stored according to the storage condition specified in investigational product storage unit. For test and reference product IPs are stored in investigational product storage unit maintained temperature between 15 to 25˚C and humidity 40-70% RH in controlled access pharmacy. Records of the receipt and dispensing of study products were made to provide complete accountability of the disposition of all Investigational products

Pharmacist performed the dispensing of investigational products for period-I on 22-May-2020 (group I), 25-May-2020 (group II), 30-May-2020 (group-III), for period-II on 27-May-2020 (group I), 30-May-2020 (group II), 04-Jun-2020 (group-III), for period III on 01-Jun-2020 (group I), 04-Jun-2020 (group II), 09-Jun-2020 (group-III), for period IV on 06-Jun-2020 (group I), 09-Jun-2020 (group II) and 14-Jun-2020 (group-III) in the presence of Quality Assurance personnel and Principal Investigator as per the randomization schedule. The dispensed drug products and reserve drug products were stored in investigational product storage unit. The dispensed investigational products were transferred to dosing area by the pharmacist. The balance investigational products, undoes IP"s which were not used in the study, were stored along with reserve investigational products. The investigational product accountability details are summarized in Table 5.

Note: IPs verification and dispensing were done under sodium vapour lamp light conditions.

Table 5: Accountability of Investigational Products

Product	Total No. of units in stock	No of units dispensed For			Purpose	Balance	No. Unused dispensed units		
		Subjects	Stand by	Total			Stand by	Subjects	Total
Test (T) - Glycopyrronium Bromide 2 mg Tablets	179 + 01*	18	02	20	934-19-P-I Group-I	159	02	00	02
	159	12	01	13	934-19-P-I Group-II	146	01	00	01
	146	17	02	19	934-19-P-II Group-I	127	02	00	02
	127	06	01	07	934-19-P-I Group-III	120	01	00	01
	120	10	01	11	934-19-P-II Group-II	109	01	00	01
	109	17	02	19	934-19-P-III Group-I	90	02	00	02
	90	10	01	11	934-19-P-III Group-II	79	01	00	01
	79	05	01	06	934-19-P-II Group-III	73	01	00	01
	73	17	02	19	934-19-P-IV Group-I	54	02	00	02
	54	07	01	08	934-19-P-IV Group-II	46	01	00	01
	46	06	01	07	934-19-P-III Group-III	39	01	00	01
	39	05	01	06	934-19-P-IV Group-III	33	01	00	01
	Dispensed: 146		**Undosed Dispensed: 16**			**Undispensed: 33**	**Total No. of units remained after completion of the study including the units taken for physical characteristic verification) = (01* + 16 + 33) = 50**		

* Indicate one unit taken for physical characteristic verification.

Product	Total No. of units in stock	No of units dispensed for			Purpose	Balance	No. Unused dispensed units		
		Subjects	Stand by	Total			Stand by	Subjects	Total
Reference (R) - Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL	471 ml +13bottle + 2 ml*	18	02	20	934-19-P-I Group-I	13 Bottles + Approx.271 ml	02	00	02
	13 Bottles + Approx.271 ml	12	01	13	934-19-P-I Group-II	13 Bottles + Approx.141 ml	01	00	01
	13 Bottles + Approx.141 ml	17	02	19	934-19-P-II Group-I	12 Bottles + Approx.424 ml	02	00	02
	12 Bottles + Approx.424 ml	06	01	07	934-19-P-I Group-III	12 Bottles + Approx.354 ml	01	00	01
	12 Bottles + Approx.354 ml	11	01	12	934-19-P-II Group-II	12 Bottles + Approx.234 ml	01	00	01
	12 Bottles + Approx.234 ml	17	02	19	934-19-P-III Group-I	12 Bottles + Approx.44 ml	02	00	02
	12 Bottles + Approx.44 ml	07	01	08	934-19-P-III Group-II	11 Bottles + Approx.437 ml	01	00	01
	11 Bottles + Approx.437 ml	06	01	07	934-19-P-II Group-III	11 Bottles + Approx.367 ml	01	00	01
	11 Bottles + Approx.367 ml	17	02	19	934-19-P-IV Group-I	11 Bottles + Approx.177 ml	02	00	02
	11 Bottles + Approx.177 ml	10	01	11	934-19-P-IV Group-II	11 Bottles + Approx.67 ml	01	00	01
	11 Bottles + Approx.67 ml	05	01	06	934-19-P-III Group-III	11 Bottles + Approx.07 ml	01	00	01
	11 Bottles + Approx.07 ml	06	01	07	934-19-P-IV Group-III	10 Bottles + Approx.410 ml	01	00	01
	10 ml of solution dispensed per syringe for subjects + stand by								
	Dispensed: 1480 ml	**Undosed Dispensed: 160 ml**				**Undispensed: 10 Bottles + Approx.410 ml**	**Total No. of units remained after completion of the study including the units taken for physical characteristic verification = (02 ml* + 160 ml + 10 Bottles + Approx.410 ml) = 10 Bottles + Approx. 572 ml**		

* indicate 02 mL taken for physical characteristic verification.

9.4.3 Method of Assigning Subjects to Treatment Groups

The eligible subjects, who fulfilled the inclusion and exclusion criteria for the study, were enrolled and randomly assigned to one of the possible sequences of test product (T) and reference product (R) (either T or R) in consecutive order using SAS® (SAS Institute Inc., USA) Version 9.3. Generated randomization schedule is appended in Appendix 16.1.7. The randomization was balanced and kept under controlled access. The study personnel involved in the sample analysis were kept blinded from the randomization till the completion of the bioanalytical phase of the study.

9.4.4 Selection of Dose in the Study

The Reference product strength of Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL [redacted] Manufactured For Merz North America, Inc., Inc is considered as relatively safe dose to administer in healthy, adult, human subjects and the selected dose was chosen to achieve sufficient plasma levels to characterize the pharmacokinetic profile.

9.4.5 Selection and Timing of Dose for each Subject

In each study period after an overnight fasting of 10.00 hours, as per the randomization schedule one tablet of Test product - Glycopyrronium Bromide 2 mg Tablets or 10 mL oral solution of Reference product (R) - Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL (10 mL containing 2 mg of Glycopyrronium Bromide) was administered at ambient temperature to each subject in sitting position by trained personnel.

Refer below details for timing of dose for each subject.

Period I:

Group I: 36 subjects were dosed in two stations [Subject no. [redacted] were dosed in station I [redacted] and subjects no. [redacted] were dosed in station II [redacted] on 22-May-2020].

Group II: 24 subjects were dosed in two stations [Subject no. [redacted] were dosed in station I at [redacted] and subjects no. [redacted] were dosed in station II [redacted] on 25-May-2020].

Group III: 12 subjects were dosed in one station [Subject no. [redacted] were dosed in station I [redacted] on 30-May-2020].

Period II:

Group I: 34 subjects were dosed in two stations [Subject no. [redacted] were dosed in station I [redacted] hours and subjects no. [redacted] and [redacted] were dosed in station II [redacted] on 27-May-2020].

Group II: 21 subjects were dosed in two stations [Subject no. [redacted] and [redacted] were dosed in station I [redacted] and subject no. [redacted] and 54 to 60 were dosed in station II [redacted] on 30-May-2020].

Group III: 11 subjects were dosed in one station [Group-III: Subject no. [redacted], [redacted] and [redacted] were dosed in station I [redacted] on 04-Jun-2020].

Period III:

Group I: 34 subjects were dosed in two stations [Subject no. [redacted] were dosed in station I [redacted] and subjects no. [redacted] and [redacted] were dosed in station II [redacted] on 01-Jun-2020].

Group II: 17 subjects were dosed in two stations [Subject no [redacted], [redacted] were dosed in station I [redacted] and subjects no. [redacted] were dosed in station II [redacted] on 04-Jun-2020].

Group III: 11 subjects were dosed in one station [Group-III: Subject no. [redacted] were dosed in station I [redacted] on 09-Jun-2020].

Period IV:

Group I: 34 subjects were dosed in two stations [Subject no. [redacted] were dosed in station I [redacted] and subjects no. [redacted] were dosed in station II [redacted] and [redacted] on 06-Jun-2020].

Group II: 17 subjects ere dosed in two stations [Subject no. [redacted] and [redacted] were dosed in station I [redacted] and subjects no. [redacted], [redacted] and [redacted] were dosed in station II [redacted] on 09-Jun-2020].

Group III: 11 subjects were dosed in one station [Group-III: Subject no. [redacted], [redacted] to [redacted] were dosed in station I [redacted] on 14-Jun-2020].

The Randomization order, Date & Time of Dosing and dosing status of subjects is given in Table 6.

Table 6: Randomization order, Date & Time of Dosing and dosing status of Subjects

Subject No.	Randomization Order				Group-I / Station-I / Dosing Time				Dosing Status			
	Period I	Period II	Period III	Period IV	Period-I (22-May-2020)	Period-II (27-May-2020)	Period-III (01-Jun-2020)	Period-IV (06-Jun-2020)	Period-I	Period-II	Period-III	Period-IV
[redacted]	T	R	T	R	[redacted]				Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed

Subject No.	Randomization Order				Group-I Station-II Dosing Time				Dosing Status			
	Period I	Period II	Period III	Period IV	Period-I (22-May-2020)	Period-II (27-May-2020)	Period-III (01-Jun-2020)	Period-IV (06-Jun-2020)	Period-I	Period-II	Period-III	Period-IV
[redacted]	R	T	R	T	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Dosed	Dosed	Dosed
[redacted]	T	R	T	R	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Dosed	Dosed	Dosed
[redacted]	R	T	R	T	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Dosed	Dosed	Dosed
[redacted]	T	R	T	R	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Not Dosed	Not Dosed	Not Dosed
[redacted]	R	T	R	T	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Not Dosed	Not Dosed	Not Dosed
[redacted]	T	R	T	R	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Dosed	Dosed	Dosed
[redacted]	R	T	R	T	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Dosed	Dosed	Dosed
[redacted]	T	R	T	R	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Dosed	Dosed	Dosed
[redacted]	T	R	T	R	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Dosed	Dosed	Dosed
[redacted]	R	T	R	T	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Dosed	Dosed	Dosed
[redacted]	T	R	T	R	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Dosed	Dosed	Dosed
[redacted]	R	T	R	T	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Dosed	Dosed	Dosed
[redacted]	T	R	T	R	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Dosed	Dosed	Dosed
[redacted]	R	T	R	T	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Dosed	Dosed	Dosed
[redacted]	T	R	T	R	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Dosed	Dosed	Dosed
[redacted]	R	T	R	T	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Dosed	Dosed	Dosed
[redacted]	T	R	T	R	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Dosed	Dosed	Dosed
[redacted]	R	T	R	T	[redacted]	[redacted]	[redacted]	[redacted]	Dosed	Dosed	Dosed	Dosed

Subject No.	Randomization Order				Group-II				Dosing Status			
					Station-I							
					Dosing Time							
	Period I	Period II	Period III	Period IV	Period-I (25-May-2020)	Period-II (30-May-2020)	Period-III (04-Jun-2020)	Period-IV (09-Jun-2020)	Period-I	Period-II	Period-III	Period-IV
[redacted]	R	T	R	T	[redacted]				Dosed	Dosed	Not Dosed	Not Dosed
	T	R	T	R					Dosed	Dosed	Not Dosed	Not Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Not Dosed	Not Dosed	Not Dosed
	R	T	R	T					Dosed	Not Dosed	Not Dosed	Not Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Not Dosed	Not Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed

Subject No.	Randomization Order				Group-II Station-II Dosing Time				Dosing Status			
	Period I	Period II	Period III	Period IV	Period-I (25-May-2020)	Period-II (30-May-2020)	Period-III (04-Jun-2020)	Period-IV (09-Jun-2020)	Period-I	Period-II	Period-III	Period-IV
[redacted]	R	T	R	T	[redacted]				Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Not Dosed	Not Dosed	Not Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Not Dosed	Not Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed

Subject No.	Randomization Order				Group-III Station-I Dosing Time				Dosing Status			
	Period I	Period II	Period III	Period IV	Period-I (30-May-2020)	Period-II (04-Jun-2020)	Period-III (09-Jun-2020	Period-IV (14-Jun-2020)	Period-I	Period-II	Period-III	Period-IV
[redacted]	T	R	T	R	[redacted]				Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Not Dosed	Not Dosed	Not Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed
	T	R	T	R					Dosed	Dosed	Dosed	Dosed
	R	T	R	T					Dosed	Dosed	Dosed	Dosed

Test Product(T): Glycopyrronium Bromide 2 mg Tablets M.A Holder: Kinedexe UK Limited, Unit 15 Moorcroft, Harlington Road, Uxbridge. UB8 3HD, UK.

Reference Product (R): Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL [redacted] Manufactured For: Merz North America, Inc.

9.4.6 Blinding

The study was an open-label in terms of the drug and dose, but the allocation of the test and reference products were not freely available, and the randomization schedules as well as the dispensing records were kept under controlled access in pharmacy. Study personnel involved in the sample analysis were kept blinded from the randomization schedule until the completion of the bio analytical phase of the study.

9.4.7 Prior and Concomitant Therapy

Subjects were selected on the basis of abstinence from any prescription medications within 14 days prior to study check in and throughout the study. They were instructed not to take prescription medications throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications throughout the study and they were selected on the basis of abstinence from over the counter medicinal products, herbal medications 07 days prior to study. No concomitant therapy was given to the subjects.

9.4.8 Treatment Compliance, Restriction and Posture Compliance

Treatment Compliance:

Subjects were provided subject ID card with photograph during check-in. Subjects were verified using a biometric device during check-in and ID cards were generated. Trained study personnel confirmed subject identity with subject ID cards before dosing. A thorough check of the oral cavity of the subject was carried out immediately after dosing with the help of a torch and a tongue depressor. The duplicate label of the dosing container was stuck on the dosing record of the respective subject CRF and this ensured the correct allocation of the investigational product as per the randomization schedule.

Restriction:

Subjects were instructed to abstain from consuming caffeine and /or xanthine products (*i.e.* coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.), cigarettes and tobacco containing products for at least 24 hours prior to check-in and throughout the study, alcohol and its products, grapefruit and its juice for at least 48 hours prior to

check-in and throughout the study. Subjects did not take an unusual diet, for whatever reason (*e.g.* low salt) for four weeks prior to check-in and throughout the study. Compliance assessments to these restrictions were performed prior to check-in of each period.

Urine scan for drugs of abuse (Marijuana-THC, Amphetamine-AMP, Barbiturates-BAR, Cocaine-COC, Benzodiazepines-BZO and Opiates (OPI)-Morphine (MOR)) and alcohol breath test was performed on the day of check-in of each period.

Subjects were instructed not to take any prescription medications within 14 days prior to check-in and throughout the study. Subjects were instructed not to take any OTC products, herbal medications, etc. within 07 days prior to check-in and throughout the study.

Subjects were received standard dinner on the day of check-in after which they were fasted for 10 hours prior to dosing. Being a fasting study, subjects not served breakfast on dosing day. The subjects were received standard meals at 04.00 (lunch), 08.00 (snacks) and 12.00 (dinner) hours after dosing in each period.

Water was restricted 01 hour prior to dosing until 01 hour post-dose (Except for 240 mL of drinking water was given during dosing). At other times, drinking water was provided *ad libitum*.

Posture Compliance:

Administration of investigational products were carried out while the subjects were in sitting posture and they were instructed to remain supine for first four hours after dosing in each period except when clinically indicated to change the posture or in case of natural exigency. Postural changes were also allowed while recording vitals and sample collection. Thereafter the subjects were allowed to engage in normal activities while avoiding physical exertion.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

The study was designed to evaluate the bioequivalence of single oral dose of Test product (T)- Glycopyrronium Bromide 2 mg Tablets M.A Holder Kinedexe UK Limited, Unit 15 Moorcroft, Harlington Road, Uxbridge. UB8 3HD, UK with Reference product (R)- Cuvposa® (Glycopyrrolate) Oral Solution 1mg/5mL of Glycopyrrolate as 1 mg/5mL of Glycopyrronium Bromide (10 mL containing 2 mg of Glycopyrronium Bromide) [redacted] Manufactured For Merz North America, Inc in healthy, adult, human subjects under fasting conditions. Therefore, efficacy was not measured, instead pharmacokinetic profile (in terms of primary and secondary pharmacokinetic parameters) of both test and reference products were evaluated based on measured concentration of Glycopyrronium in the human plasma sample collected in clinical phase.

Safety assessments were done based on clinical observations, that included laboratory data at the time of screening and at the end of the study.

Screening assessment comprised of detailed medical history and demographic data followed by physical examination, general medical examination and laboratory investigations (hematology, biochemistry, urine analysis (Routine & Microscopy) and serology) and ECG.

Clinical Examination was carried out at the time of screening, before Check-in in each period and before check-out in each period.

Vitals (Supine blood pressure, radial pulse rate, body temperature* and respiratory rate**) and well-being were performed at the time of screening, before check-in of each period (supine and standing blood pressure) [**Note:** Supine and standing blood pressure checked with a gap of 3 to 5 minutes. Supine v/s Standing blood pressure difference not more than 20 mmHg for Systolic and 10 mm Hg for Diastolic], before administration of investigational products (within -02.00 to 00.00 hours) and at 02.00, 06.00, 11.00 hours

after dosing in each period (within ± 60 minutes of the scheduled time) and before check-out in each period.

*Measurement of body temperature was performed at the time of screening, check-in of each period, before drug administration of each period and check-out of each period.

**Measurement of respiratory rate was performed at the time of screening.

Breath test for alcohol consumption was performed prior to check-in of each period and Urine screen for drug of abuse was performed prior to check-in of each period. Subject well-being was questioned at regular intervals during the course of the study. About 06 mL of blood was collected from each subject for safety evaluation [for specified hematology and biochemistry investigations] at the end of the study. Incidence of AE was recorded including the intensity and causal relationship to the investigational products as per in-house SOPs.

The schedule of assessments is summarized in Table 7.

Table 7: The schedule of assessments

Screening	Period-I (Group I)				Washout Period	Period-II (Group I)			Washout Period	Period-III (Group I)			Washout Period	Period-IV (Group I)		
Day	**D-21 to D-0**	**D-0**	**D1**	**D2**		**D-0**	**D1**	**D2**		**D-0**	**D1**	**D2**		**D-0**	**D1**	**D2**
General screening informed consent	✓	-	-	-		-	-	-		-	-	-		-	-	-
Study specific Informed consent	-	✓	-	-		-	-	-		-	-	-		-	-	-
Check-In	-	✓	-	-		✓	-	-		✓	-	-		✓	-	-
PK sampling (pre dose)	-	-	✓	-		-	✓	-		-	✓	-		-	✓	-
Dosing	-	-	✓	-		-	✓	-		-	✓	-		-	✓	-
PK sampling (post dose)	-	-	✓	✓	**5 days**	-	✓	✓	**5 days**	-	✓	✓	**5 days**	-	✓	✓
Check-out	-	-	–	✓		-	–	✓		-	–	✓		-	–	✓
Post study safety sample	-	-	-	-		-	-	-		-	-	-		-	-	✓
Safety Monitoring	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Screening	Period-I (Group II)				Washout Period	Period-II (Group II)			Washout Period	Period-III (Group II)			Washout Period	Period-IV (Group II)		
Day	**D-21 to D-0**	**D-0**	**D1**	**D2**		**D-0**	**D1**	**D2**		**D-0**	**D1**	**D2**		**D-0**	**D1**	**D2**
General screening informed consent	✓	-	-	-		-	-	-		-	-	-		-	-	-
Study specific Informed consent	-	✓	-	-		-	-	-		-	-	-		-	-	-
Check-In	-	✓	-	-		✓	-	-		✓	-	-		✓	-	-
PK sampling (pre dose)	-	-	✓	-		-	✓	-		-	✓	-		-	✓	-
Dosing	-	-	✓	-		-	✓	-		-	✓	-		-	✓	-
PK sampling (post dose)	-	-	✓	✓	**5 days**	-	✓	✓	**5 days**	-	✓	✓	**5 days**	-	✓	✓
Check-out	-	-	–	✓		-	–	✓		-	–	✓		-	–	✓
Post study safety sample	-	-	-	-		-	-	-		-	-	-		-	-	✓
Safety Monitoring	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Screening	Period-I (Group III)				Washout Period	Period-II (Group III)			Washout Period	Period-III (Group III)			Washout Period	Period-IV (Group III)		
Day	**D-21 to D-0**	**D-0**	**D1**	**D2**		**D-0**	**D1**	**D2**		**D-0**	**D1**	**D2**		**D-0**	**D1**	**D2**
General screening informed consent	✓	-	-	-		-	-	-		-	-	-		-	-	-
Study specific Informed consent	-	✓	-	-		-	-	-		-	-	-		-	-	-
Check-In	-	✓	-	-		✓	-	-		✓	-	-		✓	-	-
PK sampling (pre dose)	-	-	✓	-		-	✓	-		-	✓	-		-	✓	-
Dosing	-	-	✓	-	**5 days**	-	✓	-	**5 days**	-	✓	-	**5 days**	-	✓	-
PK sampling (post dose)	-	-	✓	✓		-	✓	✓		-	✓	✓		-	✓	✓
Check-out	-	-	–	✓		-	–	✓		-	–	✓		-	–	✓
Post study safety sample	-	-	-	-		-	-	-		-	-	-		-	-	✓
Safety Monitoring	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

✓ - Activity done on this day.

9.5.2 Appropriateness of Measurements

The selection and timing of blood samples for pharmacokinetic analysis were judged appropriately for characterizing the pharmacokinetic profiles for given treatment and dose administered. The pharmacokinetic parameters used / derived in this study are widely used and accepted in the assessment of the pharmacokinetic equivalence of two treatments. The safety assessments conducted in this study were judged appropriately by the principal investigator / clinical investigator and were documented in the raw data sheets and CRFs which served as source documents.

9.5.3 Primary Efficacy Variable(s)

The primary pharmacokinetic parameters calculated in the study were C_{max} and AUC_{0-t} for Glycopyrronium. The bioequivalence criteria were based on the 90% Confidence Intervals (CI) of the above parameters.

9.5.4 Drug Concentration Measurements

According to the guidelines, the determination of bioavailability is dependent on the reliable, precise and accurate measurement of the concentration levels of the active ingredient of the drug product in blood, plasma, serum or other biological matrices.

In this study, in each period, a total of 24 blood samples were collected from each subject in K_2EDTA vacutainers (containing K_2EDTA as an anticoagulant). Pre dose sample 08 mL (-02.00 to 00.00 hours) was withdrawn before dosing, (in the morning on the day of dosing) and the post dose samples of 04 mL were collected at 00.33, 00.67, 01.00, 01.33, 01.67, 02.00, 02.25, 02.50, 02.75, 03.00, 03.25, 03.50, 03.75, 04.00, 04.33, 04.67, 05.00, 06.00, 08.00, 10.00, 12.00, 16.00 and 24.00 hours after dosing in each period. All samples were collected as in-house samples.

Subjects were received standard dinner on the day of check-in after which they were fasted for at least 10 hours prior to dosing. Being a fasting study, subjects were not served breakfast on dosing day. The subjects received standard meals at 04.00 (lunch), 08.00 (snacks) and 12.00 (dinner) hours after dosing in each period.

Note: Post dose meals were provided with a window period of ± 30 minutes to the scheduled time except post dose lunch on dosing day. For lunch, on dosing day +30 minutes of window period was allowed.

In-house post-dose blood samples were collected on scheduled time with allowed deviation of +02 minutes. Any deviations greater than +02 minutes were recorded as protocol deviation and appropriate time corrections, for the actual time of sample collection were incorporated at the time of pharmacokinetic analysis.

All the deviation in the timing of blood sample collections was noted in the respective CRF as given in protocol deviation section Refer Appendix 16.2.2.

All blood samples were collected in pre-labelled K_2EDTA vacutainers via an indwelling intravenous cannula placed in the one of the forearm vein of the subject. The vacutainers prelabelled with Study no., Sub. No., Period No., Sampling time point and Serial No. The vacutainers were immediately inverted manually to ensure proper mixing of blood with anticoagulant and placed upright in a rack kept in wet ice bath until centrifugation and during separation.

Heparin-lock technique (about 0.5 mL of 05 IU/ mL heparin in normal saline solution was injected into the cannula after each sample collection) was used to prevent clotting of the blood in the indwelling cannula. When blood samples were collected from intravenous cannula in which heparinized saline was injected previously, initial 0.5 mL of blood drawn was discarded. Then the required volume of blood was collected. In case of difficulty in blood withdrawal due to partial cannula blockage, alternatively blood samples were drawn by a fresh venipuncture.

Indwelling intravenous cannula kept in place up to 16.00 hours after dosing. Cannula was removed after 16.00 hours blood sample collection and the cannulations site was evaluated. The blood samples at 24.00 hours were collected via a direct venipuncture.

For post study safety assessment sample of 06 mL of blood was collected for Hematology and Biochemistry test as safety sample from each subject.

Blood samples were centrifuged in a refrigerated centrifuge machine set at 4000 rpm for 10 minutes at 5 ± 2°C within 45 minutes of sample collection. The plasma sample stored within 60 minutes from the blood sample collection. Both activities were carried out with respect to last sample collection of that time sequence. Samples were kept in wet ice bath during separation until storage.

The separated plasma samples were transferred to pre-labelled polypropylene tubes labelled with Study no., Sub. No., Period No., Sampling time point, Aliquot No. and Serial No. in two aliquots.

For pre dose sample 02 mL of plasma was transferred in aliquot I and the remaining in aliquot II using a Pasteur pipette.

For post dose samples 1.2 mL of plasma was transferred in aliquot I and the remaining in aliquot II using a Pasteur pipette.

The aliquots were stored upright in a clinical site deep freezer set at -30 ± 10ºC. Samples were transferred to the bioanalytical department of VerGo Clinicals under controlled temperature conditions at the end of the clinical phase of the study. Samples in the bioanalytical department stored at -70 ± 15ºC deep freezer till analysis. After completion of bioanalysis samples were stored at -20 ± 05ºC.

The total volume of blood withdrawn from each subject during the study was 452 mL combining all the periods. (During screening 08 mL blood sample was withdrawn for routine blood test of hematology biochemistry and serology test).

Note: IP dosing, blood sample collection, sample processing, segregation of samples and bioanalysis were done under sodium vapour lamp light conditions.

9.5.5 Analytical Methodology

Glycopyrronium in Human plasma was quantified using validated LC-MS/MS method. The method was validated over the CC Range: 5.106 pg/mL to 1999.538 pg/mL as per Method STP No. "BA-STP-188-00 " and the study was conducted over a CC range of 5.107 pg/mL to 1998.297 pg/mL as per the method STP No. BA-STP-188-01 at

Bioanalytical laboratory of VerGo Pharma Research Pvt. Ltd (Division - VerGo Clinicals) [redacted]

Extraction procedure steps:

Refer 16-5-ba-report.pdf. Bioanalytical Study Report.

Summary of Bioanalytical Method Validation:

Refer 16-6-ba-validation-report.pdf. Method Validation Report.

9.6 Data Quality Assurance

The study underwent quality assurance audits at various stages (study initiation phase, study in-process phase and retrospective phase) for conformance to the study protocol and all the governing in-house SOPs. QA auditors at the end of the study reviewed all completed CRFs. A statement that the relevant Standard Operating Procedures as well as the pertinent requirements of the ICH GCP E6 (R2) „Guidance on Good Clinical Practice" (GCP) for quality assurance duly signed by the Quality Assurance person is attached in Appendix 16.1.8.

9.7 Statistical Methods Planned In the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

Statistical analysis was performed by using SAS® statistical software version 9.3. Statistical analysis was performed on the data obtained from subjects who completed two periods (with one test and one reference or two reference treatment) of the study.

The following summary statistics for the primary pharmacokinetic parameters (C_{max} and AUC_{0-t}) and the secondary pharmacokinetic parameters (AUC_{0-inf}, T_{max}, $T_{1/2}$, K_{el}, and $AUC_{\_\%Extrap}$) were calculated for both the Test (T) and Reference (R) products Number of Subjects, Arithmetic Mean, SD, CV%, Minimum, Maximum, Median and Geometric mean.

Output of WinNonlin is annexed in Appendix 16.1.9 for Glycopyrronium Statistical analysis of pharmacokinetic parameters were performed using SAS® Version 9.3, Output of SAS is annexed in Appendix 16.1.9

The natural log transformed (*i.e.* Ln-transformed) values for the pharmacokinetic parameters C_{max} and AUC_{0-t} were analyzed for statistical difference between test and reference formulations with ANOVA by using a Generalized Linear Model (GLM) ANOVA using SAS® software with the main effects of treatment, period, sequence and subject (sequence) as fixed effect. Level of significance was considered at 5% for Treatment, Period, Subject and Subject (Sequence) effects in the ANOVA.

As the study was conducted in groups, according to the Statistical Analysis plan, the Ln-transformed values for the pharmacokinetic parameters C_{max} and AUC_{0-t} were analyzed for statistical differences between test and reference formulations with ANOVA by using a Generalized Linear Model (GLM) ANOVA using SAS® software with the main effects of Treatment, Period, Sequence, Group, Treatment*Group and Subjects (Sequence*Group) as fixed effects. All the effects i.e. Treatment, Period, Sequence, Group, Treatment*Group and Subjects (Sequence*Group) were tested at 5% level of significance.

After statistically analysis, for Glycopyrronium, it was observed that the Treatment*Group effects for C_{max} (p-values= 0.0710) was statistically insignificant and Treatment*Group effects for AUC_{0-t} (p-values= 0.0412) was statistically significant.

Therefore, According the statistical analysis plan (SAP) as the Treatment*Group effect was statistically insignificant, the Conventional model was used i.e. for C_{max} i.e. the main effects of Treatment, Period, Sequence and Subject (Sequence) as fixed effects for Glycopyrronium. The level of significance was considered at 5 % for Treatment, Period, Sequence and Subject (Sequence) effect.

Where for AUC_{0-t} Treatment*Group effect was statistically significant therefore we used the following model. *i.e.* the main effects of Treatment, Period, Sequence, Group, Treatment*Group and Subjects (Sequence*Group) as fixed effects. All the effects i.e. Treatment, Period, Sequence, Group, Treatment*Group and Subjects (Sequence*Group) were tested at 5% level of significance.

The intra-subject variability of test and reference formulations was computed and reported for Log-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for Glycopyrronium.

Outliers in a data set was defined as observations that appear to be inconsistent in Test/Reference ratios with remaining data. They identified as the values that completely distort descriptive statistics. Subjects who exhibit extremely high or low Test/Reference values was detected using statistical method namely Studentized residual test (using

statistical package SAS® 9.3 or higher version). The outlier test was performed by using the Lund"s method for detection of outlier for pk parameter C_{max} and $AUC_{0-t.}$

Outlier test was performed during statistical analysis and it was observed that there is no outlier in the Glycopyrronium data set. Decision was taken on the basis of studentized residual values greater than the range of ± 3.

Ratio of geometric least square means of test and reference formulations was calculated and reported in percentage for Log-transformed C_{max} and AUC_{0-t} for Glycopyrronium

The power of study to detect 20% difference between test and reference formulation was reported.

The 90% confidence intervals for the difference of means between drug formulations were calculated for C_{max} and AUC_{0-t} using log-transformed data.

9.7.2 Determination of Sample Size

As per reference literature, the maximum intra-subject variability for pharmacokinetic parameter Cmax was found to be 32.30 %.

Hence, considering the CV of 32.30 % the following estimates were considered for the computation of sample size:

T/R ratio ≈ 92 %

Intra-Subject C.V (%) = 32.30 %

Significance Level = 5%

Power >= 80%

Bioequivalence Limits = 80.00% – 125.00%

Based on the above estimate, a sample size of 72 subjects was considered to be sufficient to establish bioequivalence between the formulations considering possible dropouts.

Reference Literature:- MHRA Public Assessment Report, Glycopyrronium Bromide 1mg/5mL Oral solution (Glycopyrronium Bromide), UK Licence No: PL 41344/0010, ProcedureNo.:UK/H/5892/001/DC, Colonis Pharma Limited.

https://mhraproductsprod.blob.core.windows.n et/docs
20200224/ca763f7b522d8b8e83ca59a9cd658e1309b83e9

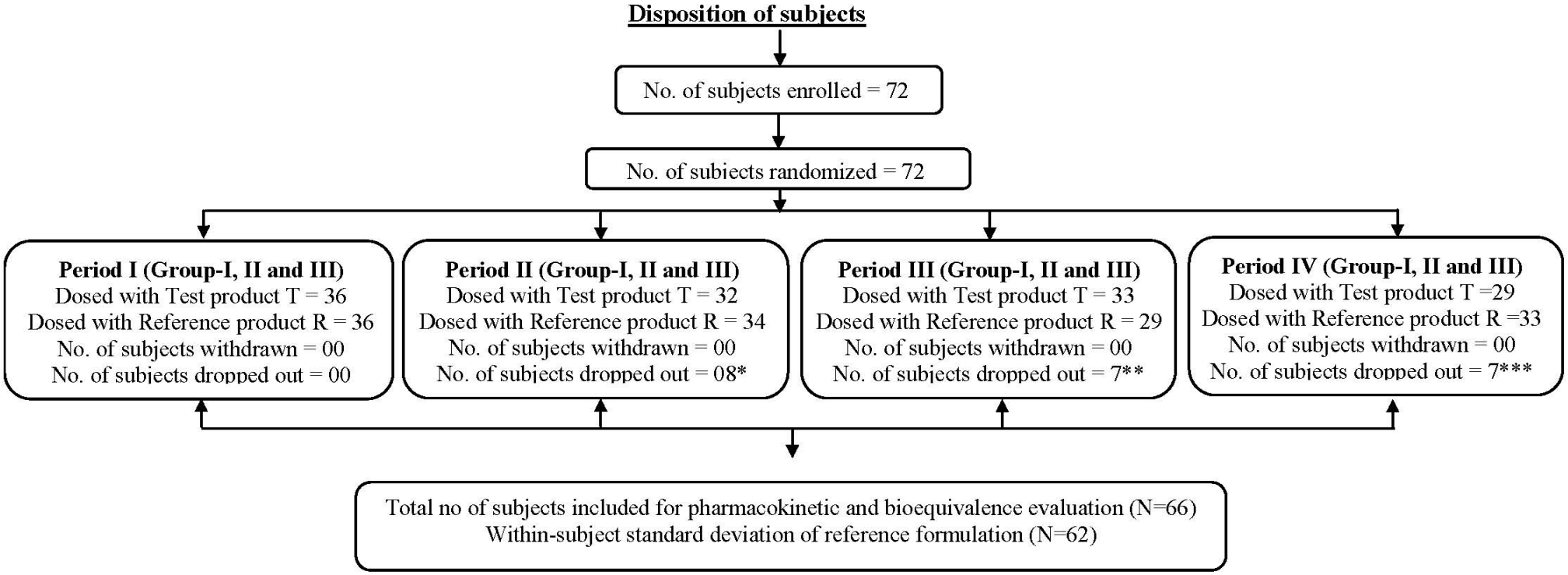
9.8 Changes in the Conduct of the Study or Planned Analyses

The entire study was conducted as described in the protocol and protocol amendments.

10.0 STUDY SUBJECTS

10.1 Disposition of Subjects

A total of 72 healthy, adult, human subjects who met the inclusion and exclusion criteria as described in the protocol were enrolled into the study. Total 72 subjects were dosed in period I, 66 subjects were dosed in II, 62 subjects were dosed in period III and IV. Total 62 subjects completed all four periods of the study.



* Subject no. [redacted] were considered as dropout for the study, as they did not report for period II, check-in. Subject no. [redacted] they were withdrawn their consent after check out of period II due to their personal reasons (they were leaving to their native place). Hence, considered as dropout. Subject No. [redacted] was withdrawn [redacted] consent on own accord on the day of check-in of period II due to his personal reason. Hence, considered as dropout for period II

** Subject no. [redacted] they did not report for period III, check-in. Hence, considered as dropout for period III. Subject no [redacted] was withdrawn [redacted] consent on own accord before dosing of period III due to [redacted] personal reasons. Hence, considered as dropout for period.

*** Subject no. [redacted] they did not report for period III, check-in. Hence, considered as dropout for period IV. Refer Appendix 16.2.1.

10.2 Protocol Deviations

Blood Sample Time Point Deviation:

As per protocol 934-19, section 5.0, 19.0, In-house post-dose blood samples will be collected on scheduled time with allowed deviation of + 02 minutes. Any deviation greater than + 02 minutes would be recorded as protocol deviation.

However deviation was occurred during blood sample collection for subject no. [redacted], [redacted] [redacted] and [redacted] in period-I, subject no. [redacted] [redacted], [redacted] and [redacted] in period II, subject no. [redacted] in period III and subject no. [redacted] [redacted] and [redacted] in period-IV.

This deviation occurred due to difficulty in finding vein, poor blood flow and cannula blocked. However, this deviation in blood sampling collection did not have any impact on study result. As the actual blood sample collection time was incorporated for pharmacokinetic and statistical analysis.

Refer below table for details in protocol deviations and refer Appendix 16.2.2.

Table 8: Blood Sample Time Point Deviation

Sr. No.	Subject No.	Date	Time Point (Hours)	Scheduled Time (Hours)	Actual Time (Hours)	Deviation (Minutes)	Reason for Deviation
Period-I (Group-I)							
01	[redacted]	23-May-2020	24.00	[redacted]	[redacted]	05	Difficulty in finding vein
02	[redacted]	22-May-2020	10.00	[redacted]	[redacted]	03	Poor blood flow
Period-I (Group-II)							
01	[redacted]	25-May-2020	00.33	[redacted]	[redacted]	04	Poor blood flow
02	[redacted]		12.00	[redacted]	[redacted]	03	
Period-II (Group-I)							
01	[redacted]	27-May-2020	01.00	[redacted]	[redacted]	03	Poor blood flow
Period-II (Group-II)							
01	[redacted]	30-May-2020	01.00	[redacted]	[redacted]	03	Poor blood flow
02			02.00	[redacted]	[redacted]	04	
03			04.33	[redacted]	[redacted]	05	
04	[redacted]		10.00	[redacted]	[redacted]	03	

Sr. No.	Subject No.	Date	Time Point (Hours)	Scheduled Time (Hours)	Actual Time (Hours)	Deviation (Minutes)	Reason for Deviation
05	[redacted]		06.00	[redacted]	[redacted]	05	
Period-III (Group-II)							
01	[redacted]	04-Jun-2020	00.67	[redacted]	[redacted]	05	Poor blood flow
02			03.50	12:32	[redacted]	04	
Period-IV (Group-II)							
01	[redacted]	09-Jun-2020	00.33	[redacted]	[redacted]	08	Poor blood flow
02	[redacted]	10-Jun-2020	16.00	[redacted]	[redacted]	03	Poor blood flow
03	[redacted]	09-Jun-2020	10.00	[redacted]	[redacted]	03	cannula blocked

11.0 EFFICACY EVALUATION

11.1 Data Sets Analyzed

A total of 72 healthy, adult, human subjects who met the inclusion and exclusion criteria as described in the protocol were enrolled into the study. Total 72 subjects were dosed in period I, 66 subjects were dosed in II, 62 subjects were dosed in period III and IV. Total 62 subjects completed all four periods of the study. Samples of 72 subjects were used in bio analytical analysis. Data from 66 subjects were used in the pharmacokinetic analysis (these subjects were completed two periods *i.e.* one test treatment and one reference treatment or two reference treatment), The data of 62 subjects were used in within subject standard deviation of reference formulation (these subjects were completed two reference treatment) and the data of 62 subjects were used for bioequivalence evaluation (these subjects received one test treatment and one reference treatment), according to the protocol. Bioequivalence was determined by statistical analysis of log-transformed data of C_{max} and AUC_{0-t} of Glycopyrronium for the test and reference products.

11.2 Demographic and Other Baseline Characteristics

A total number of 72 healthy, adult, human subjects were dosed in the study. Their mean age, height, weight and BMI was 26.9 years, 166.41 cms, 66.442 kg and 23.967 kg/m^2 respectively.

A total 62 subjects completed all four periods of the study and their mean age, height, weight and BMI were 26.9 years, 166.80 cms, 66.918 kg and 24.031 kg/m^2 respectively.

No. of subjects included in pharmacokinetic analysis 66 (Except the subject no. [redacted] and [redacted] they were not completed two periods of the study) their mean age, height, weight and BMI were 26.9 years, 166.75 cm, 66.737 kg and 23.983 kg/m^2 respectively.

No. of subject included in within-subject standard deviation of reference product 62 (Except subject no. [redacted] and [redacted] they were not completed two period of reference formulation) their mean age, height, weight and BMI were 26.9 years, 166.80 cms, 66.918 kg and 24.031 kg/m^2 respectively.

No. of subjects included in bioequivalence evaluation 66 (Except subject no. [redacted] and [redacted] they were not completed one test and one reference formulation) their mean age, height, weight and BMI were 26.9 years, 166.75 cm, 66.737 kg and 23.983 kg/m^2 respectively.

All subjects of Asian race were included for the study. Refer Table 9.

Table 9: Summarized Demographic Profile of Subjects

Demographic details of subjects who were dosed in the study (N= 72)					
Parameter	**Mean**	**SD**	**CV%**	**Min**	**Max**
Age (years)	26.9	5.55	20.65%	18	45
Height (cm)	166.41	5.772	3.47%	153.4	183.2
Weight (Kg)	66.442	10.5001	15.80%	50.73	96.86
BMI (Kg/m^2)	23.967	3.3244	13.87%	18.81	29.68
Demographic details of subjects who were completed all four periods of the study (N = 62)					
Parameter	**Mean**	**SD**	**CV%**	**Min**	**Max**
Age (years)	26.9	5.71	21.18%	18	45
Height (cm)	166.80	5.557	3.33%	153.4	183.2
Weight (Kg)	66.918	10.6308	15.89%	50.73	96.86
BMI (Kg/m^2)	24.031	3.3948	14.13%	18.81	29.68
Demographic details of subjects who were included in pharmacokinetic analysis (N= 66)					
Parameter	**Mean**	**SD**	**CV%**	**Min**	**Max**
Age (years)	26.9	5.54	20.63%	18	45
Height (cm)	166.75	5.718	3.43%	153.4	183.2
Weight (Kg)	66.737	10.4657	15.68%	50.73	96.86
BMI (Kg/m^2)	23.983	3.3598	14.01%	18.81	29.68
Demographic details of subjects who were included in within-subject standard deviation of reference product (N = 62)					
Parameter	**Mean**	**SD**	**CV%**	**Min**	**Max**
Age (years)	26.9	5.71	21.18%	18	45
Height (cm)	166.80	5.557	3.33%	153.4	183.2
Weight (Kg)	66.918	10.6308	15.89%	50.73	96.86
BMI (Kg/m^2)	24.031	3.3948	14.13%	18.81	29.68
Demographic details of subjects who were included in bioequivalence evaluation: (N = 66)					
Parameter	**Mean**	**SD**	**CV%**	**Min**	**Max**
Age (years)	26.9	5.54	20.63%	18	45
Height (cm)	166.75	5.718	3.43%	153.4	183.2
Weight (Kg)	66.737	10.4657	15.68%	50.73	96.86
BMI (Kg/m^2)	23.983	3.3598	14.01%	18.81	29.68

11.3 Measurements of Treatment Compliance

Subjects were provided subject Photograph ID card during check-in. Subjects were verified using a biometric device during check-in and an ID cards were generated. Trained study personnel confirmed subject identity, subject No. with Subject ID cards and dispensing container before dosing. Subject‟s oral cavity (mouth) was checked out immediately after dosing with the help of a torch and a tongue depressor. The duplicate label of the dosing container was stuck on the dosing record section of the respective subject case report form and this ensured the correct allocation of the investigational product as per the randomization schedule.

11.4 Efficacy Results and Tabulation of Individual Subject Data

11.4.1 Analyses of Efficacy

Non-compartmental Analysis was applied for the estimation of PK parameters C_{max}, AUC_{0-t}, AUC_{0-inf}, T_{max}, $T_{1/2}$, K_{el} and $AUC_{\_\%Extrap}$ from plasma concentration time profile of Glycopyrronium using Phoenix WinNonlin® software version 6.3. Output of WinNonlin is annexed in Appendix 16.1.9 for Glycopyrronium.

The area under the curve from 0 to the last time point with measurable plasma concentrations was computed using linear trapezoidal rule.

Individual Drug Concentration Data in pg/mL for Glycopyrronium is attached as Appendix 16.2.5.

The untransformed mean pharmacokinetic parameters C_{max}, AUC_{0-t}, AUC_{0-inf}, T_{max}, $T_{1/2}$, K_{el} and $AUC_{\_\%Extrap}$ from plasma concentration time profile of Glycopyrronium for test and reference formulation are tabulated in Table 10.

Table 10: Mean and Standard Deviation of Pharmacokinetic Parameters for Glycopyrronium (Test N = 128 and Reference = 128).

PK Parameters (Units)	Glycopyrronium (Mean ± SD)	
	Test (T)	Reference (R)
C_{max} (pg/mL)	642.9620 ± 433.33620	581.0435 ± 316.38537
AUC_{0-t} (hr*pg/mL)	3221.2630 ± 1872.20509	3065.6417 ± 1650.85661
AUC_{0-inf} (hr*pg/mL)	3349.5189 ± 1936.31928	3202.5926 ± 1698.57406
$AUC_{\_\%Extrap}$	3.871 ± 1.9097	4.550 ± 2.3007
T_{max} (hr)	3.641 ± 1.1221	3.840 ± 1.0461
$T_{1/2}$ (hr)	6.583 ± 2.1412	6.840 ± 2.2831
K_{el} (1/hr)	0.12004 ± 0.051305	0.11799 ± 0.055562
Glycopyrronium (Median (Min - Max))		
T_{max} (hr)	4.330 (1.00 - 4.67)	4.330 (1.33 - 8.00)
$T_{1/2}$ (hr)	6.642 (2.36 - 15.45)	7.027 (2.18 - 11.83)

The Least Square Mean, Geometric Least Square Mean, Ratio, 90% Confidence Interval, Intra subject Variability and Power for log transformed pharmacokinetic parameters C_{max} and AUC_{0-t} from plasma concentration time profile of Glycopyrronium for Test (T) and Reference(R) formulations are tabulated in Table 12.

Table 11: Within-subject standard deviation of the log-transformed value of C_{max} of the Reference Formulation for Glycopyrronium (N=62)

PK Parameter	DF	S^2_{WR}	S_{WR}	CV_{WR}	Lower_Limit	Upper_Limit
Ln (C_{max}) (pg/mL)	60	0.097586	0.31239	32.02	78.8664	126.797

Table 12: Least Square means, Geometric Least Square Means, Ratio, 90% confidence intervals, Power and Intra-subject Variability for the Log transformed C_{max} and AUC_{0-t} for Glycopyrronium (N = 66)

Parameters (units)	Least Square Means		Geometric Least Square Means		Ratio (%) (T Vs R)	90% Confidence Intervals (%)	Intra Subject CV (%)	Power (T Vs R) (%)
	T	R	T	R				
Ln (C_{max}) (pg/mL)	6.2971	6.2351	542.982	510.332	106.40	98.52 - 114.91	38.52	99.90
Ln (AUC_{0-t}) (hr *pg/mL)	7.8807	7.8340	2645.737	2524.977	104.78	97.37 -112.76	32.77	99.960

11.4.2 Statistical /Analytical Issues

The statistical analysis planned as in section 9.7 was carried out using the SAS® v 9.3, documentation of the same is attached as Appendix 16.1.9. Output of SAS is annexed in Appendix 16.1.9 for Glycopyrronium.

ANOVA Result for Glycopyrronium of Treatment *Group interaction

The study was conducted in three groups, the treatment, sequence, period, Group, Treatment x Group and subject (sequence x Group) as effect find in below table

Source	p-Value	
	C_{max}	AUC_{0-t}
Treatment	0.2072	0.2937
Sequence	0.0060	0.1824
Period	0.7786	0.5219
Group	<.0001	<.0001
Treatment*Group	0.0710	0.0412
Subject (Sequence*Group)	<.0001	<.0001

Discussion on ANOVA results of Treatment *Group Interaction.

C_{max}

The Treatment, Period and Treatment*Group effects were found to be statistically insignificant except the Sequence, Group and Subject (Sequence *Group) effects In the ANOVA Model.

AUC_{0-t}

The Treatment, Sequence and Period effects were found to be statistically insignificant except the, Group, Treatment*Group and Subject (Sequence*Group) effects in the ANOVA Model

Since Treatment x Group effect was statistically significant, the conventional model i.e. the main effects of Treatment, Period, Sequence and Subject (Sequence) as fixed effects was used for calculating 90% CI for Glycopyrronium.

Here Treatment x Group effect was statistically insignificant for C_{max} therefore we used the main effect of Treatment, period, Sequence and Subject (Sequence) as a fixed effect was used for calculating 90 % CI for Glycopyrronium.

Here Treatment x Group effect was statistically significant for AUC_{0-t} therefore we used the main effect of Treatment, period, Sequence, Group, Treatment x Group and Subject (Sequence *Group) as a fixed effect was used for calculating 90 % CI for Glycopyrronium.

Table 13: P-Value for Pharmacokinetic Parameters

Source	p-Value	
	C_{max}	AUC_{0-t}
Treatment	0.1844	0.2937
Sequence	0.0033	0.1824
Period	0.7665	0.5219
Subject (Sequence)	0.2161	0.5893*

* Subject (Sequence*Group)

Discussion on ANOVA Result:

C_{max}

The Treatment, Period and Subject (Sequence) effect were found to be statistically insignificant except the Sequence effect in the ANOVA model.

AUC_{0-t}

The Treatment, Sequence, Period and Subject (Sequence) effect were found to be statistically insignificant in the ANOVA model.

Justification of Significant Sequence effect in the ANOVA Model.

Significant sequence difference might be unequal carryover, but it also might be treatment by period interaction for the crossover design and such effect are confounded and cannot be separated. When a significant difference is present, the cause may not be found with certainty and such effects are considered to be negligible and may not have significant changes in the study result and some of finding for the clinical phase of the study were as mention below:

1. If it is a single dose study
2. The study involve only healthy volunteers
3. The drug is not an endogenous substance
4. An adequate washout period was established, and the pre-dose samples do not show any detectable levels (> 5% of Cmax) of the drugs in all the volunteers.
5. Design was balanced, randomized, cross-over
6. The study satisfies all the scientific and statistical criteria (for example protocol, validation, concentration data, statistical analysis, confidence interval).

Hence, significant sequence effect was ignored, it does not have any impact on the study outcome.

Justification of Significant effect related group in the ANOVA Model.

Group effect may be significant due to an unbalanced subject size between\ three groups. Group I containing dosed 36 subjects, group II containing dosed 24 subjects and group III containing dosed 12 subjects since, we analyzed the number of subjects in the (Group I - 34 subjects), (Group-II-21 subjects) and (Group-III -11 subjects)

However, the study was conducted in a scientifically controlled environment as per below:

All the subjects were given similar diet in all groups.

All the subjects went through the same environmental conditions.

All the subjects were recruited from the same enrollment pool.

All the enrolled subject were randomly assigned to the treatment groups of the study

Nevertheless, Group effects are not expected to influence the comparison of formulations and bioequivalence which is demonstrated. The decision of bioequivalence is based on the Schuirmann test and the 90% confidence interval is within the equivalence limit i.e. 78.86% -126.79%. Bioequivalence for the pharmacokinetic parameters C_{max} (Based on the ISCV of reference formulation) $AUC0_{-t}$ were within the acceptance range of 80.00-125.00%.

Hence Group Effect which is just statistically significant, it does not have any impact on the study outcome.

11.4.2.1 Adjustments for Covariates

Not applicable.

11.4.2.2 Handling of Dropouts or Missing Data

Total 72 subjects were dosed in period-I, 66 subjects were dosed in period II, 62 subjects were dosed in period III and IV. Total 62 subjects completed all four periods of the study. Samples of 72 subjects were used in bio analytical analysis. Data from 66 subjects were used in the pharmacokinetic analysis (these subjects were completed two periods *i.e.* one test treatment and one reference treatment or two reference treatment), The data of 62 subjects were used in within subject standard deviation of reference formulation (these

subjects were completed two reference treatment) and the data of 62 subjects were used for bioequivalence evaluation (these subjects received one test treatment and one reference treatment), according to the protocol. Bioequivalence was determined by statistical analysis of log-transformed data of C_{max} and AUC_{0-t} of Glycopyrronium for the test and reference products.

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

Missing Data: The missing sample details during the course of study are as below:

Period No.	Subject No.	Missing Sample Time points (Hrs)	No. of Missing Samples	Reason For Missing
II	Sub[redacted]	PD to 24.00	24	Subject did not report for period II check-in hence considered as dropout
II	Sub[redacted]	PD to 24.00	24	Subject did not report for period II check-in hence considered as dropout
II	Sub[redacted]	PD to 24.00	24	Subject did not report for period II check-in hence considered as dropout
II	Sub[redacted]	PD to 24.00	24	Subject did not report for period II check-in hence considered as dropout
II	Sub[redacted]	PD to 24.00	24	Subject did not report for period II check-in hence considered as dropout
II	Sub[redacted]	PD to 24.00	24	Subject withdrew his consent on own accord due to personal reasons hence considered as dropout
III	Sub[redacted]	PD to 24.00	24	Subject did not report for period III check-in hence considered as dropout
III	Sub[redacted]	PD to 24.00	24	Subject did not report for period III check-in hence considered as dropout
III	Sub[redacted]	PD to 24.00	24	Subject withdrew his consent after check-out of period II due to personal reasons hence considered as dropout
III	Sub[redacted]	PD to 24.00	24	Subject withdrew his consent after check-out of period II due to personal reasons hence considered as dropout
III	Sub[redacted]	PD to 24.00	24	Subject did not report for period III check-in hence considered as dropout
III	Sub[redacted]	PD to 24.00	24	Subject did not report for period III check-in hence considered as dropout
III	Sub[redacted]	PD to 24.00	24	Subject withdrew his consent on own accord due to personal reasons hence considered as dropout
III	Sub[redacted]	PD to 24.00	24	Subject did not report for period III check-in hence considered as dropout
III	Sub[redacted]	PD to 24.00	24	Subject did not report for period III check-in hence considered as dropout

Period No.	Subject No.	Missing Sample Time points (Hrs)	No. of Missing Samples	Reason For Missing
III	Sub[redacted]	PD to 24.00	24	Subject withdrew his consent on own accord due to personal reasons during period II hence considered as dropout
IV	Sub[redacted]	PD to 24.00	24	Subject did not report for period IV check-in hence considered as dropout
IV	Sub[redacted]	PD to 24.00	24	Subject did not report for period IV check-in hence considered as dropout
IV	Sub[redacted]	PD to 24.00	24	Subject withdrew his consent after check-out of period II due to personal reasons hence considered as dropout
IV	Sub[redacted]	PD to 24.00	24	Subject withdrew his consent after check-out of period II due to personal reasons hence considered as dropout
IV	Sub[redacted]	PD to 24.00	24	Subject did not report for period IV check-in hence considered as dropout
IV	Sub[redacted]	PD to 24.00	24	Subject did not report for period IV check-in hence considered as dropout
IV	Sub[redacted]	PD to 24.00	24	Subject did not report for period IV check-in hence considered as dropout
IV	Sub[redacted]	PD to 24.00	24	Subject did not report for period IV check-in hence considered as dropout
IV	Sub[redacted]	PD to 24.00	24	Subject did not report for period IV check-in hence considered as dropout
IV	Sub[redacted]	PD to 24.00	24	Subject withdrew his consent on own accord due to personal reasons during period II hence considered as dropout
Total Missing Samples= 624				

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 Patients

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 Appendix 16.2.6.

11.4.4 Drug Dose, Drug Concentration and Relationships to Response

A single dose of Glycopyrronium Bromide 2 mg Tablet (2 mg x 1 Tablet) was administered to the subjects in fasting condition.

For drug concentration data refer Appendix 16.2.5.1 and Appendix 16.2.5.2.

11.4.5 Drug-Drug and Drug-Disease Interactions

This section is not applicable.

11.4.6 By-subject Displays

For test and reference individual concentration profile for all 72 subjects are given in Appendix 16.2.6.

11.4.7 Efficacy Conclusions

The 90% confidence intervals for the test/reference ratios of the geometric least squares means between test and reference formulations calculated for primary pharmacokinetic parameter C_{max} and AUC_{0-t} were within the bioequivalence range of 78.86% – 126.79 and 80.00% – 125.00% respectively, for Glycopyrronium.

Based on the results obtained, it is concluded that Glycopyrronium Bromide 2mg Tablets manufactured for Kinedexe UK Limited, UK, is bioequivalent Cuvposa® oral solution 1 mg/5mL of Glycopyrrolate as 1 mg/5mL of Glycopyrronium Bromide (dose of 10 mL equivalent to 2 mg of Glycopyrronium Bromide) manufactured for Merz Pharmaceuticals, LLC in Healthy, Adult, Human Subjects Under Fasting Conditions.

12.0 SAFETY EVALUATION

12.1 Extent of Drug Exposure

The subjects were administered a single dose of test Product (T) – Glycopyrronium Bromide 2 mg Tablets or the reference product (R) - Cuvposa® oral solution 1 mg/5mL of Glycopyrrolate as 1 mg/5mL of Glycopyrronium Bromide (dose of 10 mL equivalent to 2 mg of Glycopyrronium Bromide) in this study.

A total number of 72 healthy, adult, human subjects were enrolled in the study. A total 72 subjects were dosed in period I, 66 subjects were dosed in II, 62 subjects were dosed in period III and IV. Total 62 subjects completed all four periods of the study.

12.2 Adverse Events

12.2.1 Brief summary of Adverse Events

During study from period I check-in (Group-I, II and III) till last PK sample in period IV (Group-I, II and III)) total 22 adverse events were occurred.

Subject No. [redacted]

In period I, subject was reported an adverse event of dry mouth [redacted] on 22-May-2020 after receiving test formulation (T) [redacted] on 22-May-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing assessed, which was found to be normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 22-May-2020.

Subject No. [redacted]

In period I, subject was reported an adverse event of dry mouth [redacted] on 22-May-2020 after receiving reference formulation (R) [redacted] on 22-May-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told

[redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing assessed which was found to be normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 22-May-2020.

Subject No. [redacted]

In period I, subject was reported an adverse event of dry mouth [redacted] on 22-May-2020 after receiving reference formulation (R) [redacted] on 22-May-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing assessed which was found to be normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 22-May-2020.

Subject No. [redacted]

In period I, subject was reported an adverse event of dry mouth [redacted] on 22-May-2020 after receiving test formulation (T) [redacted] on 22-May-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing assessed which was found to be normal. Hence, adverse event considered as resolved [redacted] on 22-May-2020.

Subject No. [redacted]

In period I, subject was reported an adverse event of dry mouth [redacted] on 22-May-2020 after receiving reference formulation (R) [redacted] on 22-May-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing

assessed, which was found to be normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 22-May-2020.

Subject No.[redacted]

In period I, subject was reported an adverse event of dry mouth [redacted] on 22-May-2020 after receiving reference formulation (R) [redacted] on 22-May-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing assessed which was found to be normal. [redacted] had no complains. Hence, adverse event considered as resolved at [redacted]

Subject No.[redacted]

In period I, subject was reported an adverse event of dry mouth [redacted] on 25-May-2020 after receiving reference formulation (R) [redacted] on 25-May-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing assessed, which was found to be normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 25-May-2020.

Subject No.[redacted]

In period I, subject was reported an adverse event of dry mouth [redacted] on 25-May-2020 after receiving test formulation (T) [redacted] on 25-May-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing

assessed which was found to be normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 25-May-2020.

Subject No. [redacted]

In period I, subject was reported an adverse event of dry mouth at [redacted] on 30-May-2020 after receiving test formulation (T) [redacted] on 30-May-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing assessed which was found to be normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 30-May-2020.

Subject No. [redacted]

In period II, subject was reported an adverse event of dry mouth [redacted] on 27-May-2020 after receiving reference formulation (R) [redacted] on 27-May-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing assessed which was found to be within normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 27-May-2020.

Subject No. 03

In period II, subject was reported an adverse event of dry mouth at [redacted] 27-May-2020 after receiving test formulation (T) [redacted] on 27-May-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing

assessed which was found to be within normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 27-May-2020.

Subject No. [redacted]

In period II, subject was reported an adverse event of dry mouth [redacted] on 27-May-2020 after receiving test formulation (T) [redacted] on 27-May-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing assessed which was found to be within normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 27-May-2020.

Subject No. [redacted]

In period II, subject was reported an adverse event of dry mouth [redacted] on 27-May-2020 after receiving reference formulation (R) [redacted] on 27-May-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing assessed which was found to be within normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted]s on 27-May-2020.

Subject No. [redacted]

In period II, subject was reported an adverse event of dry mouth [redacted] on 30-May-2020 after receiving reference formulation (R) [redacted] on 30-May-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing

assessed which was found to be within normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 30-May-2020.

Subject No. [redacted]

In period III, subject was reported an adverse event of dry mouth [redacted] on 01-Jun-2020 after receiving test formulation (T) [redacted] on 01-Jun-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing assessed which was found to be within normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 01-Jun-2020.

Subject No. [redacted]

In period III, subject was reported an adverse event of dry mouth [redacted] on 01-Jun-2020 after receiving reference formulation (R) [redacted] on 01-Jun-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing assessed which was found to be within normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 01-Jun-2020.

Subject No. [redacted]

In period III, subject was reported an adverse event of dry mouth [redacted] on 04-Jun-2020 after receiving test formulation (T) [redacted] on 04-Jun-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing

assessed which was found to be within normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 04-Jun-2020.

Subject No. [redacted]

In period III, subject was reported an adverse event of dry mouth [redacted] on 04-Jun-2020 after receiving test formulation (T) [redacted] on 04-Jun-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing assessed which was found to be within normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 04-Jun-2020.

Subject No. [redacted]

In period IV, subject was reported an adverse event of dry mouth a [redacted] on 06-Jun-2020 after receiving test formulation (T) [redacted] on 06-Jun-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing assessed which was found to be within normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] 06-Jun-2020.

Subject No. [redacted]

In period IV, subject was reported an adverse event of dry mouth [redacted] on 06-Jun-2020 after receiving reference formulation (R) [redacted] on 06-Jun-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing

assessed which was found to be within normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 06-Jun-2020.

Subject No. [redacted]

In period IV, subject was reported an adverse event of dry mouth [redacted] on 09-Jun-2020 after receiving test formulation (T) [redacted] on 09-Jun-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & nonserious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing assessed which was found to be within normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 09-Jun-2020.

Subject No. [redacted]

In period IV, subject was reported an adverse event of dry mouth [redacted] on 09-Jun-2020 after receiving reference formulation (R) [redacted] on 09-Jun-2020. The adverse event was mild in severity, definitely related to the investigational product and adverse event was expected & non-serious. Subject was assured about [redacted] condition and kept under observation. Subject was advised to take sip of water for mouth wetting and told [redacted] to inform principal or clinical investigator if any complain arises. Subject wellbeing assessed which was found to be within normal. [redacted] had no complains. Hence, adverse event considered as resolved [redacted] on 09-Jun-2020.

Total of 10 adverse events were observed at the time of post study safety assessment.

Subject No. [redacted]

During post study safety assessment, subject Eosinophils count had increased *i.e.* 11.9 % on 07-Jun-2020 after receiving test product (T) [redacted] on 06-Jun-2020. The adverse event was mild in severity and unlikely related to the investigational product. The adverse adverse event was unexpected & non-serious. Subject was advised to have a well balance diet with fruits and vegetables. Subject was advised to avoid consumption of cold beverages, avoid exposure to cold and avoid consumption alcoholic beverages. The

subject was told to come to the facility for follow-up visit after 15 days. Subject was reported to the facility for follow-up visit on 28-Jun-2020. Subject blood sample was repeated for Eosinophils count. After repeat Eosinophils count was found to be within acceptable limits *i.e.* 08 %. Hence, adverse event considered as resolved on 28-Jun-2020.

Subject No. [redacted]

During post study safety assessment, subject Eosinophils count had increased *i.e.* 13.1 % on 07-Jun-2020 after receiving reference product (R) [redacted] on 06-Jun-2020. The adverse event was mild in severity and unlikely related to the investigational product. The adverse adverse event was unexpected & non-serious. Subject was advised to have a well balance diet with fruits and vegetables. Subject was advised to avoid consumption of cold beverages, avoid exposure to cold and avoid consumption alcoholic beverages. The subject was told to come to the facility for follow-up visit after 15 days. Subject was reported to the facility for follow-up visit on 28-Jun-2020. Subject blood sample was repeated for Eosinophils count. After repeat subject Eosinophils count was found to be within acceptable limits *i.e.* 07 %. Hence, adverse event considered as resolved on 28-Jun-2020.

Subject No. [redacted]

During post-study safety assessment, subject Eosinophils count had increased i.e. 9.9 % on 07-Jun-2020 after receiving test product (T) [redacted] on 06-Jun-2020. The adverse event was mild in severity and unlikely related to the investigational product. The adverse adverse event was unexpected & non-serious. The subject was advised to have a well-balanced diet with fruits and vegetables. The subject was advised to avoid consumption of cold beverages, avoid exposure to cold, and avoid consumption alcoholic beverages. The subject was told to come to the facility for a follow-up visit after 15 days. The subject was reported to the facility for a follow-up visit on 15-Jun-2020. The subject was told to come to the facility after 15 days but he came early for follow up sample. The subject blood sample was repeated for Eosinophils count. After repeat Eosinophils count was found to be within normal limits i.e. 06 %. Hence, the adverse event considered as resolved on 15-Jun-2020.

Subject No. [redacted]

During post-study safety assessment, subject Eosinophils count had increased *i.e.* 13.4 % on 07-Jun-2020 after receiving reference product (R) [redacted] on 06-Jun-2020. The adverse event was mild in severity and unlikely related to the investigational product. The adverse adverse event was unexpected & non-serious. The subject was advised to have a well-balanced diet with fruits and vegetables. The subject was advised to avoid consumption of cold beverages, avoid exposure to cold, and avoid consumption alcoholic beverages. The subject was told to come to the facility for follow-up visit after 15 days. The subject was reported to the facility for a follow-up visit on 28-Jun-2020. The subject blood sample was repeated for Eosinophils count. After repeat Eosinophils count was found to be within acceptable limits i.e. 09 %. Hence, the adverse event considered resolved on 28-Jun-2020.

Subject No. [redacted]

During post-study safety assessment, subject Eosinophils count had increased *i.e.* 10.0 % on 10-Jul-2020 after receiving reference product (R) [redacted] on 25-May-2020. The adverse event was mild in severity and unlikely related to the investigational product. The adverse adverse event was unexpected & non-serious. The subject was advised to have a well-balanced diet with fruits and vegetables. The subject was advised to avoid exposure to cold and cold beverages. Subject was advised to avoid alcoholic beverages. Subject was told to come to the facility for follow-up visit after 7 days. Subject was called after 7 days for remind about their pending follow-up for post study safety assessment and requested to visit the facility. However, Subjects told that [redacted] will not able to come for follow-up. Hence, the adverse event considered lost to follow-up.

Subject No. [redacted]

During post-study safety assessment, subject Eosinophils count had increased *i.e.* 10.2 % on 10-Jun-2020 after receiving reference product (R) [redacted] on 09-Jun-2020. The adverse event was mild in severity, unexpected, non-serious and unlikely related to the investigational product. The subject was advised to have a well-balanced diet with fruits and vegetables. The subject was advised to avoid exposure to cold and consumption

alcoholic beverages. the subject was told to inform principal or clinical investigator if any complain arise and come to the facility for follow-up visit after 15 days. Subject was called after 15 days for remind about their pending follow-up for post study safety assessment and requested to visit the facility. However, Subjects told that [redacted] will not able to come for follow-up. Hence, the adverse event considered lost to follow-up.

Subject No. [redacted]

During post-study safety assessment, subject Eosinophils count had increased *i.e.* 10.8 % on 10-Jun-2020 after receiving test product (T) [redacted] on 09-Jun-2020. The adverse event was mild in severity, unexpected, non-serious and unlikely related to the investigational product. The subject was advised to have a well-balanced diet with fruits and vegetables. The subject was advised to avoid exposure to cold, and consuming alcoholic beverages. the subject was told to inform principal or clinical investigator if any complain arise and come to the facility for follow-up visit after 15 days. The subject was reported to the facility for a follow-up visit on 16-Jul-2020. The subject blood sample was repeated for Eosinophils count. After repeat Eosinophils count was found to be within normal limits *i.e.* 06 %. Hence, the adverse event considered resolved on 16-Jul-2020.

Subject No. [redacted]

During post-study safety assessment, subject ALT level had increased *i.e.* 168 U/L on 10-Jun-2020 after receiving reference product (R) [redacted] on 09-Jun-2020. The adverse event was mild in severity and unlikely related to the investigational product. The adverse adverse event was unexpected & non-serious. The subject was advised to have a well-balanced diet and avoid consumption of fatty food, oily food and alcoholic beverages. The subject was told come to the facility for a follow-up visit after 15 days. The subject was reported to the facility for a follow-up visit on 30-Jun-2020. The subject blood sample was repeated for ALT level. After repeat ALT level was found to be within acceptable limits *i.e.* 72 U/L. Hence, the adverse event considered resolved on 30-Jun-2020.

Subject No. [redacted]

During post-study safety assessment, subject ALT level had increased *i.e.* 190 U/L on 29-Jun-2020 after receiving test product (T) [redacted] on 30-May-2020. The adverse event was mild in severity and unlikely related to the investigational product. The adverse adverse event was unexpected & non-serious. The subject was advised to have a well-balanced diet with fruits and vegetables. Subject was advised to avoid consumption of fatty food and oily food and avoid consumption of alcoholic beverages. The subject was told come to the facility for a follow-up visit after 15 days. The subject was reported to the facility for a follow-up visit on 22-Jul-2020. The subject blood sample was repeated for ALT level. After repeat ALT level was found to be within normal limits *i.e.* 57 U/L. Hence, the adverse event considered resolved on 22-Jul-2020.

Subject No. [redacted]

During post-study safety assessment, subject Eosinophils count had increased *i.e.* 14.1 % on 15-Jun-2020 after receiving reference product (R) [redacted] on 14-Jun-2020. The adverse event was mild in severity, unexpected, non-serious and unlikely related to the investigational product. The subject was advised to have a well-balanced diet with fruits and vegetables. The subject was advised to avoid exposure to cold and consumption of alcoholic beverages. The subject was told to come to the facility for a follow-up visit after 15 days. Subject was called after 15 days for remind about their pending follow-up for post study safety assessment and requested to visit the facility. However, Subjects told that [redacted] will not able to come for follow-up. Hence, the adverse event considered lost to follow-up.

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

12.2.2 Display of Adverse Events

The details of the AEs including the subject number, adverse event term, treatment, period, time and date of last dosing, time and date of onset of event, time and date of

resolution, duration, severity, relationship to the drug, action taken to manage the adverse event and outcome are presented in Appendix 16.2.7.

The table below summarizes the intensity and the causality of the adverse events reported by treatment group receiving Test product (T) during the course of the study.

Table 14: Intensity and the causality of the adverse events for test product (T)

Body System / Adverse Event	Mild		Moderate		Severe		Total
	N = 130						
	Related[1]	NR[2]	Related[1]	NR[2]	Related[1]	NR[2]	
	n(%)		n(%)		n(%)		
Investigations	-						
Dry Mouth	11 (8.46 %)	-	-	-	-	-	11 (8.46 %)
Increased Eosinophils count	-	3 (2.31%)	-	-	-	-	3 (2.31%)
Increased ALT Level	-	1 (0.77 %)	-	-	-	-	1 (0.77 %)
Total	**11 (8.46 %)**	**4 (3.08)**	-	-	-	-	**15 (11.54 %)**

N = Total number of subjects dosed with test product T.

n (%)= Number (percentage) of subjects dosed with test product T who had the specific adverse event.

1=Related = possibly related/Definite related/probably.

2 = NR= Not related/ unlikely related/unrelated.

The table below summarizes the intensity and the causality of the adverse events reported by treatment group receiving reference product (R) during the course of the study.

Table 15: Intensity and the causality of the adverse events for reference product (R)

Body System / Adverse Event	Mild		Moderate		Severe		Total
	N = 132						
	Related[1]	NR[2]	Related[1]	NR[2]	Related[1]	NR[2]	
	n(%)		n(%)		n(%)		
Investigations	-						
Dry Mouth	11 (8.33 %)	-	-	-	-	-	11 (8.33 %)
Increased Eosinophils count	-	5 (3.79 %)	-	-	-	-	5 (3.79 %)
Increased ALT Level	-	1 (0.76 %)	-	-	-	-	1 (0.76 %)
Total	**11 (8.33 %)**	**6 (4.55 %)**	-	-	-	-	**17 (12.88%)**

N = Total number of subjects dosed with reference product R.

n (%)= Number (percentage) of subjects dosed with reference product R who had the specific adverse event.

1=Related = possibly related/Definite related/probably.

2 = NR= Not related/ unlikely related/unrelated

12.2.3 Analysis of Adverse Events:

Total of 32 adverse events were reported in this study. Out of 32 AEs, 22 AEs were reported during study from period I check-in (Group-I, II and III) till last PK sample in period IV (Group-I, II and III)) and 10 AEs were reported at the time of post study safety assessment. Out of 32 AEs, 15 AEs were reported with test product and 17 AEs reported with reference product.

Incidence of AEs reported for each treatment group is provided below:

Table 16: Analysis of AEs

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Test (N = 130)	Reference (N = 132)
Digestive system		
Dry Mouth	11 (8.46 %)	11 (8.33 %)
Post Study Safety Investigations		
Increased Eosinophils count	3 (2.31%)	5 (3.79 %)
Increased ALT Level	1 (0.77 %)	1 (0.76 %)
Total	**15 (11.54 %)**	**17 (12.88%)**

12.2.4 Listing of Adverse Events by Subjects

The details of the AEs including the subject number, adverse event term, treatment, period, time and date of last dosing, time and date of onset of event, time and date of resolution, duration, severity, relationship to the drug, action taken to manage the adverse event and outcome are presented in Appendix 16.2.7.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no deaths, SAE or significant adverse events noted in this study.

12.3.1 Listing of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1.1 Deaths

No deaths were reported during the study.

12.3.1.2 Other Serious Adverse Events

No serious adverse events were reported during any of the study.

12.3.1.3 Other Significant Adverse Events

No significant adverse events were reported during any of the study.

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

Not Applicable.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Not Applicable.

12.4 Clinical Laboratory Assessment

12.4.1 Listing of Individual Laboratory Measurements by Subject

The individual laboratory measurements of each subject are given in Appendix 16.2.8.

12.4.2 Evaluation of Laboratory Parameter

12.4.2.1 Laboratory Values over Time

Safety laboratory examination was carried out at the time of screening and at the completion of clinical phase of the study (post study laboratory assessment). All laboratory parameters were evaluated. Any value beyond the laboratory reference range was subjected to clinical correlation to declare whether it is significant or insignificant.

There were no clinically significant abnormal findings in laboratory test of subjects at the end of the study except subject number [redacted] and [redacted] Refer to Appendix 16.2.7 for the abnormal laboratory values found during the post-study assessments that were clinically significant.

Subject no. [redacted] had adverse event of increased Eosinophils count.
Subject no. [redacted] had adverse event of increased Eosinophils count.
Subject no. [redacted] had adverse event of increased Eosinophils count.
Subject no. [redacted] had adverse event of increased Eosinophils count.
Subject no. [redacted] had adverse event of increased Eosinophils count
Subject no. [redacted] had adverse event of increased Eosinophils count.
Subject no [redacted] had adverse event of increased Eosinophils count.

Subject no. [redacted] had adverse event of increased ALT level.

Subject no. [redacted] had adverse event of increased ALT level.

Subject no. [redacted] had adverse event of increased Eosinophils count.

12.4.2.2 Individual Subject Change

Not applicable

12.4.2.3 Individual Clinically Significant Abnormalities

Not applicable

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Vitals (Supine blood pressure, radial pulse rate, body temperature* and respiratory rate**) and well-being were performed at the time of screening, before check-in of each period (supine and standing blood pressure) [**Note:** Supine and standing blood pressure checked with a gap of 3 to 5 minutes. Supine v/s Standing blood pressure difference not more than 20 mmHg for Systolic and 10 mm Hg for Diastolic], before administration of investigational products (within -02.00 to 00.00 hours) and at 02.00, 06.00, 11.00 hours after dosing in each period (within ± 60 minutes of the scheduled time) and before check-out each period.

*Measurement of body temperature was performed at the time of screening, check-in of each period, before drug administration of each period and check-out of each period.

**Measurement of respiratory rate was performed at the time of screening.

ECG was performed at time of screening

Clinical Examination was carried out at the time of screening, before Check-in in each period and before check-out in each period.

Breath test for alcohol consumption was performed prior to check-in of each period and Urine screen for drug of abuse was performed prior to check-in of each period.

Subject well-being was questioned at regular intervals during the course of the study.

Clinical laboratory tests (hematology, biochemistry, urine (Routine & Microscopy) and serology) were performed at the time of screening and Clinical laboratory tests

(hematology and biochemistry) were performed at the time of post study safety assessment.

12.6 Safety Conclusions

A total of 72 healthy, adult, human subjects were enrolled and included in safety assessment. Safety assessment was carried out at the time of screening, during the course of the study and at the end of study by conducting medical examination, recording of vital signs and enquiring about the well-being, laboratory assessments and ECG (screening only).

Total of 32 adverse events were reported in this study. Out of 32 AEs, 22 AEs were reported during study from period I check-in (Group-I, II and III) till last PK sample in period IV (Group-I, II and III)) and 10 AEs were reported at the time of post study safety assessment. Out of 32 AEs, 15 AEs were reported with test product and 17 AEs reported with reference product.

During the study period there were clinically significant changes observed in post laboratory data and same were noted in Appendix 16.2.8.

During post study safety assessment, values of the laboratory parameters tested were found to be within acceptable limit and clinically insignificant for all subjects, except subject number [redacted] and [redacted]

Subject no. [redacted] had adverse event of increased Eosinophils count.
Subject no. [redacted] had adverse event of increased Eosinophils count.
Subject no. [redacted] had adverse event of increased Eosinophils count.
Subject no. [redacted] had adverse event of increased Eosinophils count.
Subject no. [redacted] had adverse event of increased Eosinophils count
Subject no [redacted] had adverse event of increased Eosinophils count.
Subject no [redacted] had adverse event of increased Eosinophils count.
Subject no. [redacted] had adverse event of increased ALT level.
Subject no. [redacted] had adverse event of increased ALT level.
Subject no [redacted] had adverse event of increased Eosinophils count.

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

There were no clinically significant values observed during vital signs examination, and no clinically significant deviations observed from the baseline values.

All reported adverse events were resolved completely without any sequelae except subject no. [redacted], [redacted] and [redacted](subject did not report to the facility for post study safety assessment follow-up. Hence, considered to be lost to follow-up); details are given in Appendix 16.2.7. There were no deaths reported during the course of study. Hence the test product was 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

Discussion:

The Primary objective of this study was to compare the rate and extent of absorption of single dose of Glycopyrronium Bromide 2mg Tablets manufactured for Kinedexe UK Limited, UK with Cuvposa® oral solution 1 mg/5mL of Glycopyrrolate as 1 mg/5mL of Glycopyrronium Bromide (dose of 10 mL equivalent to 2 mg of Glycopyrronium Bromide) manufactured for Merz Pharmaceuticals, LLC administered under fasting conditions in healthy, adult, human subjects in a randomized cross over study.

The secondary objective of this study was to evaluate the safety and tolerability of a single dose of Glycopyrronium Bromide 2mg Tablets when administered orally in healthy, adult, human subjects under fasting conditions.

A total number of 72 healthy, adult, human subjects were enrolled in the study and total 62 subjects completed all four periods of the study.

The design of the study was adequate to determine the pharmacokinetic parameters of the test and the reference formulations. Blood sampling was done up to 24 hours post dose such that the plasma concentrations could be measured for adequately profiling the pharmacokinetics of the investigational products [test products (T) and reference products (R)].

A. Efficacy Assessment:

Rate of Absorption:

C_{max}:

For C_{max}, the ratio of geometric least squares means of Test Product and Reference Product for Log-transformed pharmacokinetic parameter C_{max} is 106.40%. The 90 % confidence interval for the ratio of geometric least squares means is 98.52 – 114.91%. This interval is within the acceptance limits of 78.86 –126.79 % required for the conclusion of bioequivalence as per the criteria for evaluation.

T_{max}:

For T_{max}, the median (min – max) T_{max} for Test Product and Reference Product were 4.330 (1.00 - 4.67) hours and 4.330 (1.33 - 8.00) hours respectively.

Extent of Absorption:

AUC_{0-t}:

For AUC_{0-t}, the ratio of geometric least squares means of Test Product and Reference Product for Log-transformed pharmacokinetic parameter AUC_{0-t} was 104.78%. The 90 % confidence interval for the ratio of geometric least squares means was 97.37% - 112.76%. This interval is within the acceptance limits of 80.00 –125.00 % required for the conclusion of bioequivalence as per the criteria for evaluation.

B. Safety Assessment:

There were no clinically significant values observed during vital signs examination.

During the study period there were clinically significant changes observed in post laboratory data and same were noted in Appendix 16.2.8.

All the subjects found fit to the study and there were no reports of death, serious or unexpected adverse events reported during the course of study. Test product was found to be safe and well tolerated upon single dose administration in healthy adult human subjects under fasting conditions.

Conclusion:

The 90% confidence intervals for the test/reference ratios of the geometric least squares means between test and reference formulations calculated for primary pharmacokinetic parameter C_{max} and AUC_{0-t} were within the bioequivalence range of 78.86% – 126.79 and 80.00% – 125.00% respectively, for Glycopyrronium.

Based on the results obtained, it is concluded that Glycopyrronium Bromide 2mg Tablets manufactured for Kinedexe UK Limited, UK, is bioequivalent Cuvposa® oral solution 1 mg/5mL of Glycopyrrolate as 1 mg/5mL of Glycopyrronium Bromide (dose of 10 mL equivalent to 2 mg of Glycopyrronium Bromide) manufactured for Merz Pharmaceuticals, LLC in Healthy, Adult, Human Subjects Under Fasting Conditions

14.0 TABLES AND FIGURES REFFERED IN TEXT

14.1 Demographic Data Summary Tables

Subject demographic data is provided in Appendix 16.2.4.

14.2 Efficacy Data

Refer Appendix 16.2.6 for this report for efficacy data.

14.3 Safety Data

14.3.1 Display of Adverse Events

Refer Appendix 16.2.7.

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Not Applicable.

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Not Applicable.

14.3.4 Abnormal Laboratory Value Listing (Each Subject)

Refer Appendix 16.2.8.

15.0 REFERENCES

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16.0 APPENDICES

16.1 Study Information

16.1.1 Protocol and protocol amendment

16.1.2 Sample Case Report Form

16.1.3 IEC Documents and Sample Informed Consent Form

16.1.4 List and Description of Investigators 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 subject receiving test drug(s)/investigational product(s)

16.1.7 Randomization Schedule

16.1.8 Audit certificates

16.1.9 Documentation of Statistical Methods

16.1.10 Documentation of Inter-laboratory Standardization Methods and Quality Assurance Procedures if used

16.1.11 Publications Based on the Study

16.1.12 Important Publications Referred in the report

16.2 Subject Data Listings

16.2.1 Discontinued Subjects

16.2.2 Protocol deviations

16.2.3 Subjects Excluded from the Pharmacokinetic Analysis

16.2.4 Demographic Data

16.2.5 Individual Drug Concentration Data

16.2.5.1 Individual plasma concentrations Vs Time curves for Test formulation

16.2.5.2 Individual plasma concentrations Vs Time curves for Reference formulation

16.2.6 Individual Efficacy Response Data

16.2.7 Adverse event listings

16.2.8 Listing of individual laboratory measurements by subject, when required by regulatory authorities

16.3 Case Report Forms (CRFs)

16.3.1 CRFs for Deaths, other serious adverse events and withdrawals for AE

16.3.2 Other CRFs Submitted

16.4 Individual Subject Data Listings

16.5 Bioanalytical Study Report

16.5.1 20 % Chromatograms of subject sample analysis

16.5.2 Certificate of analysis for working standard

16.5.3 Bioanalytical SOPs

16.5.4 Assay of investigational product in human plasma

16.6 Method validation report