5.3.1.2 COMPARATIVE BIOAVAILABILITY (BA) AND BIOEQUIVALENCE (BE) STUDY REPORTS

INTEGRATED REPORT

PROJECT / PROTOCOL NO. 13-021

1. TITLE PAGE

A randomized, open-label, four-treatment, four-period, four sequence, single-dose, balanced, four-way crossover relative bioavailability study of Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution of NRIM Limited, U.K. and Glycopyrrolate 2mg tablets of NRIM Limited, U.K. with ROBINUL® FORTE 2mg Tablets of [redacted] and Glycopyrronium bromide oral solution 1mg /5mL (2 X 1mg /5mL) of [redacted] in healthy, adult, human subjects under fasting condition.

Protocol Version No.	:	01
Test Product (T1)	:	Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution
Test Product (T2)		Glycopyrrolate 2mg tablets
Reference Product (R1)	:	ROBINUL® FORTE 2mg Tablets
Reference Product (R2)	:	Glycopyrronium bromide oral solution 1mg/5mL (2 X 1mg /5mL)
Indication	:	To reduce chronic severe drooling and as adjunctive therapy in the treatment of peptic ulcer.
Sponsor	:	NRIM Limited, UK
Phase of Study	:	Relative Bioavailability
Clinical Study Dates		
Period 1 (Check-in date)	:	10/NOV/2013
Period 4 (Last sample collected date)	:	27/NOV/2013
Clinical study completion date	:	27/NOV/2013 (There was no AE in the study)
Principal Investigator Name	:	[redacted]
Date of Report	:	01/APR/2014

Study Centre [Clinical, Pharmacokinetic and Statistical (Randomization only) and Quality Assurance Services]	**Study Centre (Bioanalytical, Pharmacokinetic and Statistical and Quality Assurance Services)**	**Name and Address of Sponsor's Organization**
Department of Clinical Pharmacology Research and Development Centre, Cadila Pharmaceuticals Ltd.,	BA/BE Study Business Unit Jubilant Life Sciences Limited	NRIM Limited, Unit 15, Moorcroft Harlington Road, Hillingdon, Middlesex, UB8 3HD, UK. Phone No.: +20 3393 0200-05 Fax No.: +1895 238 656

This study was conducted in accordance with the Independent Ethics Committee (IEC) approved protocol complying all requirements regarding the obligations of sponsor and all other pertinent requirements of the Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 59th WMA General Assembly, 6th revision, Seoul, 2008), 21 CFR – Part 50 (Protection of Human Subjects), 21 CFR –Part 54 (Financial Disclosure by Clinical Investigator) and 21 CFR – Part 312 (Investigational New Drug), and are consistent with the ICH-GCP (E6-R1, Step 5) guidelines along with the local regulatory requirements of GCP for Clinical Research In India (2004, CDSCO), Schedule Y (Amendment version 2005, Drug and Cosmetics Rules, 2005), ICMR guidelines for Biomedical Research on Human Subjects (2006), Bioavailability and Bioequivalence studies for orally administered drug products – General Considerations (March 2003) and Committee for Medicinal Products for Human Use (CHMP) Guideline on the investigation of Bioequivalence, 20 January 2010.

1.1 Signature Page

Prepared by: This report is based on the raw data, which is accurate and credible to the best of my knowledge

[redacted]

[redacted]
(Sign and Date)

AUTHENTICATION: We, the undersigned declare that the study was conducted in accordance with the Independent Ethics Committee (IEC) approved protocol complying all requirements regarding the obligations of sponsor and all other pertinent requirements of the Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 59th WMA General Assembly, 6th revision, Seoul, 2008), 21 CFR – Part 50 (Protection of Human Subjects), 21 CFR –Part 54 (Financial Disclosure by Clinical Investigator) and 21 CFR – Part 312 (Investigational New Drug), and are consistent with the ICH-GCP (E6-R1, Step 5) guidelines along with the local regulatory requirements of GCP for Clinical Research In India (2004, CDSCO), Schedule Y (Amendment version 2005, Drug and Cosmetics Rules, 2005), ICMR guidelines for Biomedical Research on Human Subjects (2006), Bioavailability and Bioequivalence studies for orally administered drug products – General Considerations (March 2003) and Committee for Medicinal Products for Human Use (CHMP) Guideline on the investigation of Bioequivalence, 20 January 2010. We critically evaluated this report for internal consistency and this report reflects the raw data to the best of our knowledge.

Department of Clinical Pharmacology Research and Development Centre, Cadila Pharmaceuticals Limited

[redacted]

[redacted]
(Sign and Date)

BA/BE Study Business Unit Jubilant Life Sciences Limited

[redacted]

[redacted]

(Sign and Date)

[redacted]

[redacted]

(Sign and Date)

1.2 QA Audit Certificate

Project No. / Protocol No.: 13-021

The conduct of this project and related raw data were audited and verified for adherence to GCP regulations, IEC approved protocol and relevant SOPs by Quality Assurance department. The dates and the activity audited are presented below:

Version No.	QA Inspections dates	Activity Audited
N/A	10/NOV/2013 and 11/NOV/2013	In process audit of dispensing, dosing and conduct of study of Period 1
	15/NOV/2013 and 17/NOV/2013	In process audit of dispensing, dosing and conduct of study of Period 2
	21/NOV/2013 and 22/NOV/2013	In process audit of dispensing, dosing and conduct of study of Period 3
	26/NOV/2013 and 27/NOV/2013	In process audit of dispensing, dosing and conduct of study of Period 4
	17/DEC/2013 and 19/DEC/2013	Retrospective audit of clinical study documents
00	10/JAN/2014 & 13/JAN/2014	Retrospective audit of bioanalytical documents
		Retrospective audit of bioanalytical report
00	13/FEB/2014	Appendices of Clinical Study Report
00	18/FEB/2014	Retrospective audit of integrated pharmacokinetic report

This report accurately describes the methods and procedures followed in this study, which were as per IEC approved protocol and relevant SOPs. The reported data accurately reflects the raw data of the study.

Department of Clinical Pharmacology Research and Development Centre,
Cadila Pharmaceuticals Limited

Audited by:

[redacted]

[redacted]

(Sign and Date)

BA/BE Study Business Unit of Jubilant Life Sciences Limited

[redacted]

Audited by:

[redacted]

(Sign and Date)

[redacted]

Reviewed by:

[redacted]

(Sign and Date)

[redacted]

Authorized by:

[redacted]

(Sign and Date)

[redacted]

2. SYNOPSIS

Name of Sponsor	**Individual Study Table Referring to Part of the Dossier**	**(For National authority use only)**
NRIM Limited, UK	**Volume:**	
Name of Finished Products	**Page:**	
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

Title of Study
A randomized, open-label, four-treatment, four-period, four sequence, single-dose, balanced, four-way crossover relative bioavailability study of Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution of NRIM Limited, U.K. and Glycopyrrolate 2mg tablets of NRIM Limited, U.K. with ROBINUL® FORTE 2mg Tablets of [redacted] and Glycopyrronium bromide oral solution 1mg /5mL (2 X 1mg /5mL) of [redacted] in healthy, adult, human subjects under fasting condition.
Investigators
Department of Clinical Pharmacology Research and Development Centre, Cadila Pharmaceuticals Ltd.,
[redacted] Principal-Investigator
BA/BE Study Business Unit of Jubilant Life Sciences Limited
[redacted]

Name of Sponsor	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National authority use only)
NRIM Limited, UK		
Name of Finished Products		
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

Study Centre

Clinical, Pharmacokinetic and Statistical Services (randomization only) and Quality Assurance Services

Department of Clinical Pharmacology Research and Development Centre,

Cadila Pharmaceuticals Ltd.,

[redacted]

Bioanalytical and Quality Assurance Services

BA/BE Study Business Unit Jubilant Life Sciences Limited

[redacted]

Pharmacokinetic and Statistical Services

BA/BE Study Business Unit of Jubilant Life Sciences Limited

[redacted]

Publications (reference)

Not Applicable (No publications have been issued based on the results of the study)

Name of Sponsor	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National authority use only)
NRIM Limited, UK		
Name of Finished Products		
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

Study Period		
Check- in dates	Period 1: 10/NOV/2013	Period 2: 15/NOV/2013
	Period 3: 20/NOV/2013	Period 4: 25/NOV/2013
Dosing dates	Period 1: 11/NOV/2013	Period 2: 16/NOV/2013
	Period 3: 21/NOV/2013	Period 4: 26/NOV/2013
Clinical study completion date	27/NOV/2013 (There was no AE in the study)	
Sample Analysis (Start Date)	06/DEC/2013	
Sample Analysis (End Date)	28/DEC/2013	
Phase of development		
Relative Bioavailability		
Objectives		

Primary objective of the study was to compare the relative bioavailability of Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution of NRIM Limited, U.K. and Glycopyrrolate 2mg tablets of NRIM Limited, U.K. with ROBINUL® FORTE 2mg Tablets of [redacted] and Glycopyrronium bromide oral solution 1mg/5mL (2 X 1mg /5mL) of [redacted] in healthy, adult, human subjects under fasting condition.

Secondary objective was to evaluate safety parameters, including adverse events and clinical laboratory tests.

Name of Sponsor	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National authority use only)
NRIM Limited, UK		
Name of Finished Products		
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

Methodology

The study was designed as a randomized, open-label, four-treatment, four-period, four-sequence, single dose, balanced, four-way crossover relative bioavailability study. The allocation of treatment sequence for each subject in each study period was carried out as per the randomization schedule. In each study period, a single dose of drug product [either Test product (T1 / T2) or Reference Product (R1 / R2)], each tablet/oral solution was administered to the subjects after 10.00 hours overnight fasting. Serial blood sampling from pre-dose within 1 hour (prior to drug administration) and up to post-dose 24.00 hours (after drug administration) was done in each period.

Glycopyrrolate concentrations in plasma were quantified by using a validated bioanalytical method (LC–MS/MS) for Test (T) and Reference products (R). The following pharmacokinetic parameters C_{max}, AUC_{0-t}, dose-adjusted AUC_{0-inf}, T_{max}, $t_{1/2}$ and K_{el} were computed for the study drugs using pharmacokinetic software WinNonlin®. Statistical comparison of the pharmacokinetic parameter (dose-adjusted AUC_{0-inf}) to assess the relative bioavailability of Test product (T1 / T2) or Reference Product (R1 / R2) was performed using statistical software SAS® package (SAS Institute Inc., India, version 9.2).

Number of Subjects planned and analyzed

Planned: 20 subjects + 02 additional subjects (as stand by)

Enrolled: 20 subjects + 02 additional subjects (as stand by)

Dosed: 20 subjects

Withdrawn: 00

Dropped out: 01[A] subject

Completed: 19 subjects

Bio-sample analyzed:

Period 1: 20 subjects

Period 2: 19 Subjects

Period 3: 19 Subjects

Period 4: 19 Subjects

Name of Sponsor	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National authority use only)
NRIM Limited, UK		
Name of Finished Products		
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

Pharmacokinetic and statistical data analyzed: 19 subjects

A: Subject no [redacted] was considered as dropout from the study hours on 16/NOV/2013, as subject did not report to the clinical facility for Period-II check-in.

Main criteria for inclusion

The subjects who met all of the following criteria were included in the study:

- Healthy, adult, human subject aged from 18 to 45 years (inclusive of both).
- Subject's Body Mass Index (BMI) within normal limit of 18.5-24.9 kg/m^2 (inclusive of both).
- Willingness to sign statements of written informed consent form (for screening & study related procedures).
- No contraindications with the study medication with any previous medical or surgical history.
- Willingness to undergo pre- and post-study physical examinations and laboratory investigations.
- Normal general physical examination.
- Normal ECG finding and vital signs, or abnormalities, which the clinical investigator did not considered a disqualification for participation in the study.
- Availability of subject for the entire study period and willingness to adhere to protocol.
- Non-smokers.

Main Criteria for exclusion

The subjects had none of the following criteria were included in the study:

- The subject with known drug hypersensitivity or idiosyncratic reaction to Glycopyrrolate or any related drug.
- Subjects incapable of understanding the informed consent process / procedure.
- Evidence of psychiatric disorder, antagonistic personality, poor motivation, emotional or intellectual problems likely to limit the validity of consent to participate in the study, or limit the ability to comply with protocol requirements.

Name of Sponsor	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National authority use only)
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Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

- Resting heart rate of >100 beats/min or < 60 beats/min on the screening day.
- History of hypotensive episodes, or systolic blood pressure reading of < 100 mm of Hg or a diastolic reading of < 60 mm of Hg at time of general Physical examination.
- History of hypertension, or systolic blood pressure reading of > 139 mm of Hg or a diastolic reading > 89 mm of Hg at time of general Physical examination.
- The subject had any evidence of organ dysfunction or any clinically significant deviation from the normal, in physical or clinical determinations.
- Subject who had taken any enzymes modifying drugs within the past four weeks prior to start of clinical period.
- Subject who had taken any prescribed medications beginning two weeks prior to and OTC medications beginning one week prior to first dosing of study.
- The subject with known history of clinically significant psychiatric or medical diseases.
- History of or current alcohol abuse (>600 mL weekly) or history of exposure to other substance of abuse.
- Investigations with blood samples of the subject shown presence of disease marker of HIV 1 and 2, Hepatitis B & C viruses.
- Positive test for urinary screen testing of drugs of abuse (Amphetamines, Morphine, Benzodiazepines, Marijuana, Cocaine and Barbiturate).
- Subject found positive for alcohol breath test.
- Investigations with blood sample of the subject shown the presence of values which are clinically significantly different from normal reference range.
- Investigations with urine sample of the subject shown clinically abnormal chemical and microscopic examination of urine defined as presence of RBC, WBC (> 4/HPF), epithelial cells (>4/HPF), glucose (positive) and protein (positive) (unless the clinical investigator considers the deviation to be irrelevant for the purpose of the study).
- Subject who participated in any other clinical investigation using experimental drug or had bleed more than 300 mL in the past 3 months.
- Xanthine-containing food or beverages (tea, coffee, chocolates, soft drinks like cola etc.) within 24 hours prior to the dosing of each period or alcoholic products consumption

Name of Sponsor	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National authority use only)
NRIM Limited, UK		
Name of Finished Products		
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

within 48 hours prior to the dosing of each period.

- Subjects who had consumed "Grape fruit" or its juice within 72 hours prior to dosing of each period.
- Subject without adequate venous access in their left or right arm to allow collection of all samples via venous cannula in each period.
- X-ray chest finding suggesting of any abnormality/ies like cardiomegalia, pneumonia etc.
- Subject with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, hepatic and /or renal function, that could have interfered with the absorption, metabolism, and /or excretion of the study drugs. Subjects with a history of cholecystectomy were excluded.
- Females who were falling in menstruation period during study.
- Females who were found positive in Urinary Pregnancy Test.
- Females who were lactating their children.
- Females who were using any type of hormonal contraceptives

Products, dose and mode of administration, batch number:

	Test Product (T1)	**Test Product (T2)**
Product Name	Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution	Glycopyrrolate 2mg tablets
Brand Name	Not applicable	Not applicable
Dosage Form	Oral solution	Tablets
Manufactured by	[redacted]	[redacted]
Dose and mode of administration	A single oral dose of Test Product (T1) Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution was administered to the subjects in sitting posture with 240 mL of drinking water at room temperature on the day of dosing as per	A single oral dose of Test Product (T2) one Glycopyrrolate 2mg tablet was administered to the subjects in sitting posture with 240 mL of drinking water at room temperature on the day of dosing as per the randomization

Name of Sponsor	Individual Study Table Referring to Part of the Dossier	(For National authority use only)
NRIM Limited, UK	Volume:	
Name of Finished Products	Page:	
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

	the randomization schedule under fasting conditions.	schedule under fasting conditions.
Batch/ Lot Number	[redacted]	[redacted]
Batch Size	[redacted]	[redacted]
Manufacturing Date	[redacted]	[redacted]
Retest/ Expiry Date	[redacted]	[redacted]
	Reference Product (R1)	**Reference Product (R2)**
Product Name	Glycopyrrolate 2mg Tablets	Glycopyrronium bromide oral solution 1mg/5mL (2 X 1mg /5mL)
Brand Name	ROBINUL® FORTE	Not applicable
Dosage Form	Tablets	Oral solution
Manufactured by	[redacted]	[redacted]
Dose and mode of administration	A single oral dose of Reference Product (R1) one Glycopyrrolate 2mg tablet was administered to the subjects in sitting posture with 240 mL of drinking water at room temperature on the day of dosing as per the randomization schedule under fasting conditions.	A single oral dose of Reference Product (R2) Glycopyrronium bromide oral solution 1mg/5mL (2 X 1mg /5mL) was administered to the subjects in sitting posture with 240 mL of drinking water at room temperature on the day of dosing as per the randomization schedule under fasting conditions.
Batch/ Lot Number	[redacted]	[redacted]
Batch Size	[redacted]	[redacted]
Manufacturing Date	[redacted]	[redacted]
Retest/ Expiry Date	[redacted]	[redacted]

Name of Sponsor	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National authority use only)
NRIM Limited, UK		
Name of Finished Products		
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

Analytical Method	
Analyte(s)	Glycopyrrolate
Method	LC-MS/MS
Quantification Limit	5.042 pg/mL
Calibration Range	5.042 pg/mL to 1004.138 pg/mL

Duration of Treatment

Total duration of the study was 18 days from Period 1 check-in till the end of fourth period, including a washout period of 05 days between each dosing. The housing duration of the subjects in the clinical facility was 11 hours prior to dose administration until 24 hours post-dose in each study period.

Blood Sampling Points

Samples were collected at pre-dose (within one hour prior to the dosing) and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.25, 4.50, 4.75, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00 and 24.00 hours post-dose in each study period.

Pre-dose blood sample was collected within a period of 01.00 hr before dosing. Post-dose samples during housing were collected within ± 2 minutes from the scheduled time for all samples.

Criteria for evaluation

The 95% confidence intervals (CI) for the (T1/R1) and (T2/R2) ratio of geometric least square means of primary parameter (Dose adjusted $AUC_{0\text{-}inf}$) was calculated using natural log-transformed data. The 95% confidence interval and p-value for the mean relative bioavailability were presented for test formulations (T1, T2) and Reference formulations (R1, R2).

Statistical Methods

Descriptive Statistics were calculated and statistical analysis was performed by using ANOVA on untransformed and a natural log-transformed dose-adjusted $AUC_{0\text{-}inf}$ of Glycopyrrolate by using SAS® software version 9.2.

Name of Sponsor	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National authority use only)
NRIM Limited, UK		
Name of Finished Products		
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

Efficacy Results

The mean and standard deviation (SD) of pharmacokinetic parameter dose-adjusted $AUC_{0\text{-}inf}$ was estimated for Test Product (T1 and T2) and Reference Product (R1 and R2) were as follows:

Parameters (Units)	Un-transformed Data (N=19) Mean ± SD	
	Test Product (T1)	**Reference Product (R1)**
Dose-adjusted $AUC_{0\text{-}inf}$ (pg*hr/mL)	2199.2567 ± 714.68244	2338.5243 ± 877.22421
	Test Product (T2)	**Reference Product (R2)**
Dose-adjusted $AUC_{0\text{-}inf}$ (pg*hr/mL)	2851.6047 ± 1226.01010	2219.1614 ± 695.53374

Pharmacokinetic Results

The geometric least squares mean, ratio of Test Product (T1) and Reference Product (R1), (T1 / R1) % and 95% confidence intervals (CI) for the Ln-transformed pharmacokinetic parameters dose-adjusted $AUC_{0\text{-}inf}$ are summarized in Table 2-1.

The geometric least squares mean, ratio of Test Product (T2) and Reference Product (R2), (T2 / R2) % and 95% confidence intervals (CI) for the Ln-transformed pharmacokinetic parameters dose-adjusted $AUC_{0\text{-}inf}$ are summarized in Table 2-2.

The test/reference ratio of NRIM Limited's Glycopyrrolate 1mg/5mL (2 x 1mg/5mL) oral solution (Test product-1) and ROBINUL® FORTE 2mg Tablets (Reference product-1) of [redacted] was 95.49%, the 95% confidence interval was 84.61% - 107.78% and p-value was 0.0001following an overnight fasting.

The test/reference ratio of NRIM Limited's Glycopyrrolate 2mg Tablets (Test product-2) and Glycopyrronium bromide oral solution 1mg/5mL (2 x 1mg/5mL) (Reference product-2) of [redacted] was 123.14%, the 95% confidence interval was 102.74% - 147.59% and p-value was 0.0001 following an overnight fasting.

The detailed Studentised residuals (Lund's method) for Dose adjusted $AUC_{0\text{-}inf}$ are presented in Appendix-11 of pharmacokinetic and statistical report.

Name of Sponsor	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National authority use only)
NRIM Limited, UK		
Name of Finished Products		
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

Table 2-1 Summary Statistics of Pharmacokinetic Parameters T1 vs. R1(Glycopyrrolate)

SUMMARY RESULTS	Dose-Adjusted - $AUC_{0\text{-}inf}$ (pg*hr/mL)
Untransformed Data	
TEST (T1)	
Arithmetic Mean	2199.2567
SD	714.68244
CV (%)	32.50
N	19
REFERENCE (R1)	
Arithmetic Mean	2338.5243
SD	877.22421
CV (%)	37.51
N	19
Log Transformed Data	
LSM (T1)	7.6566
LSM (R1)	7.7027
Geometric Mean (T1)	2114.5289
Geometric Mean (R1)	2214.3510
T1/R1 Ratio (%)	95.49
95% CI (Calculated)	84.61 - 107.78
Power (%)	97.70
Intra-subject CV (%)	17.68
Inter-subject CV (%)	21.64
p-value	0.0001

Name of Sponsor	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National authority use only)
NRIM Limited, UK		
Name of Finished Products		
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

Table 2-2 Summary Statistics of Pharmacokinetic Parameters T2 vs. R2(Glycopyrrolate)

SUMMARY RESULTS	Dose-Adjusted - $AUC_{0\text{-}inf}$ (pg*hr/mL)
Untransformed Data	
TEST (T2)	
Arithmetic Mean	2851.6047
SD	1226.01010
CV (%)	42.99
N	19
REFERENCE (R2)	
Arithmetic Mean	2219.1614
SD	695.53374
CV (%)	31.34
N	19
Log Transformed Data	
LSM (T2)	7.8714
LSM (R2)	7.6633
Geometric Mean (T2)	2621.2538
Geometric Mean (R2)	2128.6813
T2/R2 Ratio (%)	123.14
95% CI (Calculated)	102.74 - 147.59
Power (%)	80.04
Intra-subject CV (%)	26.71
Inter-subject CV (%)	20.22
p-value	0.0001

Name of Sponsor	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National authority use only)
NRIM Limited, UK		
Name of Finished Products		
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

Table 2-3 Summary Statistics of Pharmacokinetic Parameters T1 vs. R2 (Glycopyrrolate)

SUMMARY RESULTS	Dose-Adjusted - $AUC_{0\text{-}inf}$ (pg*hr/mL)
Untransformed Data	
TEST (T1)	
Arithmetic Mean	2199.2567
SD	714.68244
CV (%)	32.50
N	19
Reference (R2)	
Arithmetic Mean	2219.1614
SD	695.53374
CV (%)	31.34
N	19
Log Transformed Data	
LSM (T1)	7.6566
LSM (R2)	7.6633
Geometric Mean (T1)	2114.5289
Geometric Mean (R2)	2128.6813
T1/R2 Ratio (%)	99.34
95% C.I. (Calculated)	84.60 - 116.91
Inter-subject C.V. (%)	16.72
Intra-subject C.V. (%)	23.60
Power (%)	87.33
p-value	<0.0001

Name of Sponsor	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National authority use only)
NRIM Limited, UK		
Name of Finished Products		
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

Table 2-4 Summary Statistics of Pharmacokinetic Parameters T2 vs. R1 (Glycopyrrolate)

SUMMARY RESULTS	Dose-Adjusted - $AUC_{0\text{-}inf}$ (pg*hr/mL)
Untransformed Data	
TEST (T2)	
Arithmetic Mean	2851.6047
SD	1226.01010
CV (%)	42.99
N	19
Reference (R1)	
Arithmetic Mean	2338.5243
SD	877.22421
CV (%)	37.51
N	19
Log Transformed Data	
LSM (T2)	7.8714
LSM (R1)	7.7027
Geometric Mean (T2)	2621.2538
Geometric Mean (R1)	2214.3510
T2/R1 Ratio (%)	118.38
95% C.I. (Calculated)	98.10 - 143.16
Inter-subject C.V.(%)	18.26
Intra-subject C.V. (%)	27.71
Power (%)	77.15
p-value	<0.0001

Name of Sponsor	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National authority use only)
NRIM Limited, UK		
Name of Finished Products		
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

Table 2-5 Summary Statistics of Pharmacokinetic Parameters T1 vs. T2 (Glycopyrrolate)

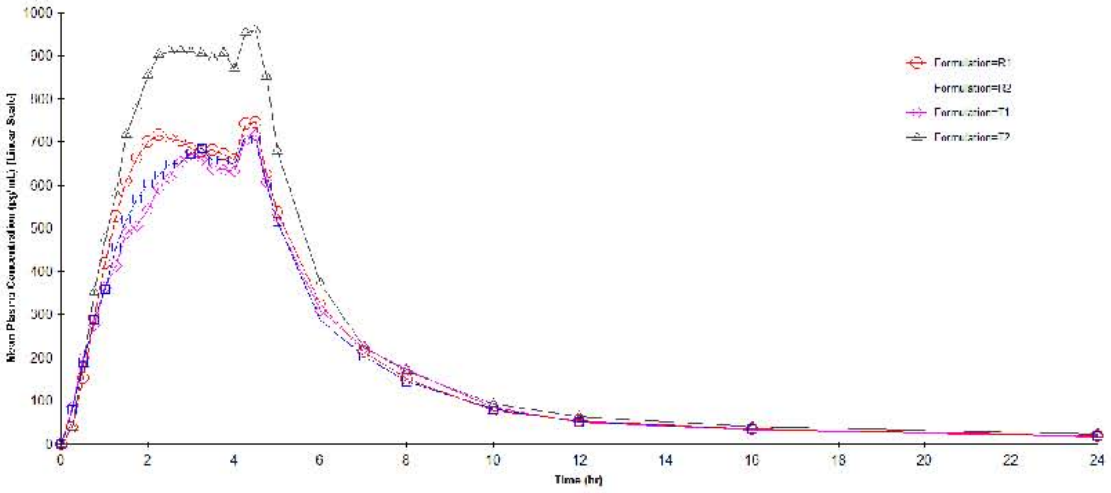
SUMMARY RESULTS	Dose-Adjusted - $AUC_{0\text{-}inf}$ (pg*hr/mL)
Untransformed Data	
TEST (T1)	
Arithmetic Mean	2199.2567
SD	714.68244
CV (%)	32.50
N	19
TEST (T2)	
Arithmetic Mean	2851.6047
SD	1226.01010
CV (%)	42.99
N	19
Log Transformed Data	
LSM (T1)	7.6566
LSM (T2)	7.8714
Geometric Mean (T1)	2114.5289
Geometric Mean (T2)	2621.2538
T1/T2 Ratio (%)	80.67
95% C.I. (Calculated)	67.42 - 96.66
Inter-subject C.V.(%)	16.49
Intra-subject C.V. (%)	26.36
Power (%)	80.57
p-value	<0.0001

Name of Sponsor	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National authority use only)
NRIM Limited, UK		
Name of Finished Products		
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

The linear time profile for mean Glycopyrrolate plasma concentration is presented in Figure 1.

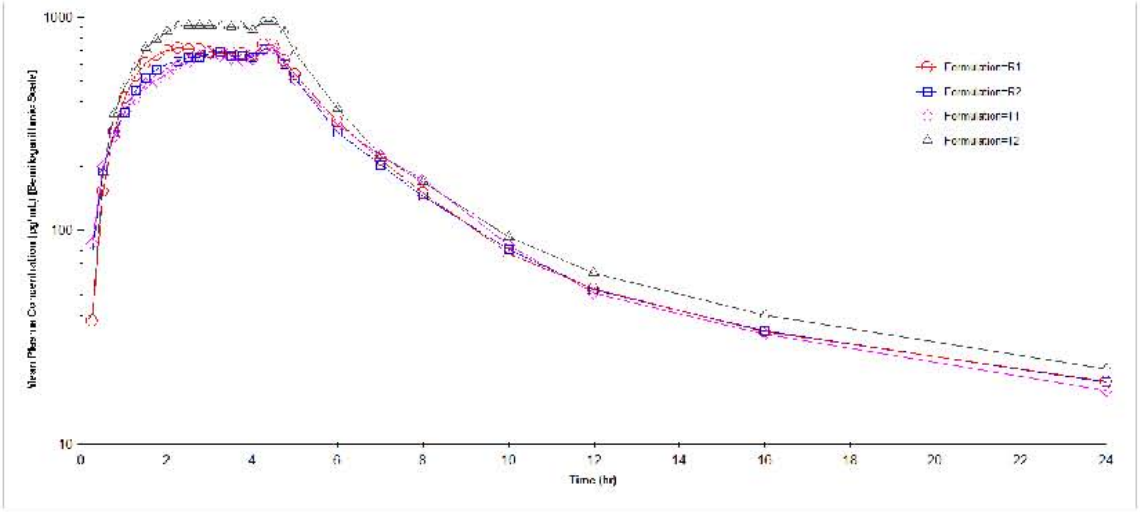
The semi-logarithmic time profile for mean Glycopyrrolate plasma concentration is presented in Figure 2.

Figure 1 Mean Glycopyrrolate Plasma Concentration – Linear Time Profile



Name of Sponsor	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National authority use only)
NRIM Limited, UK		
Name of Finished Products		
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

Figure 2 Mean Glycopyrrolate Plasma Concentration – Semi-Logarithmic Time Profile



Safety Results

There was no adverse event or serious adverse event recorded in the study.

Name of Sponsor	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National authority use only)
NRIM Limited, UK		
Name of Finished Products		
Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution & Glycopyrrolate 2mg tablets		
Name of Active Ingredient		
Glycopyrrolate		

Conclusion

The test/reference ratio of NRIM Limited's Glycopyrrolate 1mg/5mL (2 x 1mg/5mL) oral solution (Test product-1) and ROBINUL® FORTE 2mg Tablets (Reference product-1) of [redacted] was 95.49%, the 95% confidence interval was 84.61% - 107.78% and p-value was 0.0001following an overnight fasting.

The test/reference ratio of NRIM Limited's Glycopyrrolate 2mg Tablets (Test product-2) and Glycopyrronium bromide oral solution 1mg/5mL (2 x 1mg/5mL) (Reference product-2) of [redacted] was 123.14%, the 95% confidence interval was 102.74% - 147.59% and p-value was 0.0001 following an overnight fasting.

The detailed Studentised residuals (Lund's method) for Dose adjusted $AUC_{0\text{-}inf}$ are presented in Appendix-11 of pharmacokinetic and statistical report.

Safety conclusion

A single oral dose of Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution or Glycopyrrolate 2mg tablet of the investigational product (both Test and Reference) was well tolerated in each period of the study. There was no adverse event or serious adverse event recorded in the study.

No clinically significant vital sign changes were observed during the study (Refer to Appendix 16.2.9).

Date of the Report: 01/APR/2014

3. TABLE OF CONTENTS

In Text-Tables

In-Text Figures

4. LIST OF ABBREVIATIONS

AE	Adverse Events
ANOVA	Analysis of Variance
AUC0-t	Area under plasma concentration-time curve from time zero to the last measurable concentration
$AUC_{0\text{-}inf}$	Area under plasma concentration-time curve from time zero to time infinity
ALP	Alkaline Phosphatase
ALT/AST	Alanine-/ Aspartate – Aminotransferase
BLLOQ	Below lower limit of quantification
BP	Blood pressure
CI	Confidence Interval
cm	centimeter
CC	Calibration Curve
Cmax	Maximum plasma concentration
CPL	Cadila Pharmaceuticals Limited
CPPU	Clinical Pharmacology and Pharmacokinetic Unit
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
cu.mm	cubic millimeter
DBP	Diastolic Blood Pressure
DCPRDC	Department of Clinical Pharmacology Research and Development Centre
ECG	Electrocardiogram
Ext	Extension
g/dL	grams/deciliter
GCP	Good Clinical Practice

GI	Gastrointestinal
gm	gram
Hb	Hemoglobin
HBsAg	Hepatitis B surface Antigen
HCT	Hematocrit
HDL	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HPLC	High Performance Liquid Chromatography
HR	Heart Rate
hrs	Hours
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMR	Indian Council of Medical Research
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IV	Intravenous
ISCV	Intra subject coefficient of variance
ISR	Incurred Sample Reanalysis
K_2EDTA	Di-potassium Ethylene Diamine Tetraacetate
Kel	Apparent first order elimination
kg	Kilogram
LCMS	Liquid Chromatography Mass Spectrometry
LOQ	Limit of Quantification
LSM	Least Square Means
Max	Maximum

MCH	Mean corpuscles hemoglobin
MCHC	Mean corpuscles hemoglobin concentration
MCV	Mean corpuscles volume
MW	Molecular Weight
mEq/L	Milli equivalents per liter
Min	Minimum
mm	Millimeter
mL	Milliliter
MS	Missing samples
No. / no.	Number
PCV	Packed Cell Volume
pH	The negative logarithm of the hydrogen ion concentration
PI	Principal Investigator
RBC	Red blood cells
rpm	Rotations per minute
RQA	Research Quality Assurance
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGOT/AST	Serum glutamate oxaloacetate transaminase / Aspartate Aminotransferase
SGPT/ALT	Serum glutamate pyruvate transaminase /Alanine Aminotransferase
SOP	Standard Operating Procedure
$t_{1/2}$	Apparent half-life

T_{max}	Time to maximum plasma concentration
UPT	Urine pregnancy test
VLDL	Very-low-density lipoprotein
WBC	White blood cells
WHO	World Health Organization
WMA	World Medical Association

5. ETHICS

5.1 Independent Ethics Committee (IEC)

Following documents were submitted to IBIOME Independent Ethics Committee, Gujarat for review and approval on 16/OCT/2013. The submitted documents were reviewed and approved by IBIOME IEC in the meeting held on 19/OCT/2013.

- Study protocol, version 01, dated 08/OCT/2013.
- Informed Consent Form (English), version 01, dated 12/OCT/2013.
- Informed Consent Form (Gujarati), version 01, dated 12/OCT/2013.
- Back translated Informed Consent Form (English), version 01, dated 12/OCT/2013.
- Translation certificate English to Gujarati.
- Translation certificate Gujarati to English.
- Product monograph.
- Investigator's CV.
- Insurance policy

A list of IEC members is enclosed under Appendix 16.1.3.

5.2 Ethical Conduct of the Study

The study was conducted in accordance with the Independent Ethics Committee (IEC) approved protocol, relevant SOPs, Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 59th WMA General Assembly, 6th revision, Seoul, 2008), 21 CFR - Part 50 (Protection of Human Subjects), 21 CFR – Part 54 (Financial Disclosure by Clinical Investigator) and 21 CFR – Part 312 (Investigational New Drug), and are consistent with the ICH-GCP (E6-R1, Step 5) guidelines along with the local regulatory requirements of GCP for Clinical Research In India (2004, CDSCO), Schedule Y (Amendment version 2005, Drug and Cosmetics Rules, 2005), ICMR guidelines for Biomedical Research on Human Subjects (2006), Bioavailability and Bioequivalence studies for orally administered drug products – General Considerations (March 2003) and Committee for Medicinal Products for Human Use (CHMP) Guideline on the investigation of Bioequivalence, 20 January 2010.

The Principal Investigator/Co-Investigator/designee was responsible for submitting all study-related documents (which included but not limited to protocol, informed consent form) to the IEC for review and approval. IEC approval for protocol (and amendments, if any), and related documents was obtained prior to implementation.

5.3 Subject Information and Consent

An adequate number of volunteers were screened as per internal SOP for Screening of Volunteers (Cadila Pharmaceuticals Ltd) after obtaining a written informed consent. The screen pass volunteers were enrolled in the study after obtaining written informed consent for participation in the study. Each volunteer was given the informed consent form (ICF) in his vernacular language, before participating in screening procedures for the study. Sufficient time was provided to all the volunteers to read and understand the ICF before signing it off. An oral presentation of the ICF was also given by the designated trained study personnel, in the presence of a medical officer to resolve medical/general queries of the volunteers; if any and all the medical and general queries were resolved appropriately. Each subject also had a one-to-one discussion with the Principal Investigator/ Medical-Officer/designee during the informed consent process to address any individual concern/query (s). The volunteers, who gave their voluntary written consent, were allowed to participate in the study. A photocopy of the signed ICF was given to all subjects who provided written informed consent.

Study specific informed consent procedure was carried including distribution of study specific ICF to volunteers, oral presentation of ICF and one to one ICF discussion with the Principal Investigator/Medical-Officer/Designee and obtaining written informed consent from volunteers prior to the admission (only in Period I).

A sample copy of the ICF (all versions of English and Gujarati) for the study is presented in Appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study was conducted at Department of Clinical Pharmacology Research and Development Centre, Cadila Pharmaceuticals Limited [Clinical, Pharmacokinetic and Statistical (Randomization only) and Quality Assurance Services] and at BA/BE Study Business unit of Jubilant Life Sciences Limited (Bioanalytical, Pharmacokinetic and Statistical and Quality Assurance Services). The following personnel were responsible for protocol development, study coordination, clinical monitoring, bioanalytical procedures, pharmacokinetic and statistical analysis, reporting of data and audit of the study in compliance with the protocol and SOPs.

Principal Investigator	[redacted]
Project Manager	[redacted]
Project Leader	[redacted]

Director-BA/BE	[redacted]
Sponsor Monitor	[redacted]
Sponsor Representative	[redacted]
Medical Writer	[redacted]

Head-Quality Assurance	[redacted]

The list of investigators with their affiliations, their role in the study and their qualifications (curriculum vitae) are presented in Appendix 16.1.4.

STUDY ADMINISTRATIVE STRUCTURE

Clinical, Pharmacokinetic and Statistical Services (Randomization only) and Quality Assurance Services	Department of Clinical Pharmacology Research and Development Centre, Cadila Pharmaceuticals Ltd., [redacted]
Analytical Services	BA/BE Study Business Unit Jubilant Life Sciences Limited, [redacted]
Pharmacokinetic and Statistical Services	Biostatistics and Programming BA/BE Study Business Unit of Jubilant Life Sciences Limited (Refer NTF for Organizational Change) [redacted]
Clinical Pathology Laboratory	[redacted]
Radiology Services	[redacted]
Medical Emergency Hospital	[redacted]

Waste Management and Disposal	[redacted]

7. INTRODUCTION

The study was designed as a randomized, open label, four-treatment, four-sequence, single-dose, balanced, four-way, crossover, relative bioavailability study. Primary objective of the study was to compare the bioavailability of Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution of NRIM Limited, U.K. and Glycopyrrolate 2mg tablets of NRIM Limited, U.K. with ROBINUL® FORTE 2mg Tablets of [redacted] and Glycopyrronium bromide oral solution 1mg/5mL (2 X 1mg /5mL) of [redacted] in healthy, adult, human subjects under fasting condition. Secondary objective was to evaluate safety parameters, including adverse events and clinical laboratory tests.

Twenty (20) subjects + two (02) additional subjects (as stand by) were enrolled in the study as per IEC approved protocol. Stand by subjects were not replaced and discharged without dosing in Period I. Nineteen (19) subjects completed all periods of the study. One (01) subject dropped out of the study (Subject no. 04). Details are provided Appendix 16.2.1.

Bioanalytical report describes the application of a validated bioanalytical method "Estimation of Glycopyrrolate (CC Range: 5.041 pg/mL to 1005.198 pg/mL) in Human Plasma (K_2EDTA) using LC-MS/MS" for determining concentration of Glycopyrrolate in human plasma.

The analysis was performed on API 4000 Q TRAP Acquity™ LC-MS/MS (BE/LC/09, BE/MS/07) system using Glycopyrrolate D3 as an internal standard. The interface used was a turbo ion spray. Negative ions were measured in MRM mode. The analytes were extracted using a Solid Phase Extraction Method. The lower limit of quantification of Glycopyrrolate (LLOQ) was 5.042 pg/mL whereas; the upper limit of quantification (ULOQ) was 1004.138 pg/mL. The data was acquired and integrated on applied bio systems "Analyst" version 1.5.2 software. Bioanalytical report provides the results of study data generated throughout the study.

The primary pharmacokinetic parameter in the present study was dose-adjusted $AUC_{0\text{-}inf}$ and secondary pharmacokinetic parameters like C_{max}, $AUC_{0\text{-}t}$, T_{max}, $t_{1/2}$ and K_{el} were calculated on the plasma-concentration time data of Glycopyrrolate of all the subjects who complete all the periods of the study using non-compartmental model of WinNonlin Pro-software, Version 5.3 or higher, Pharsight Corporation, USA.

Indications

Glycopyrrolate is indicated to reduce chronic severe drooling in patients aged 3 to 16 years with neurologic conditions associated with problem drooling (e.g. cerebral palsy). Glycopyrrolate tablets use as adjunctive therapy in the treatment of peptic ulcer.

Mechanism of Action

Glycopyrrolate is a competitive inhibitor of acetylcholine receptors that are located on certain peripheral tissues, including salivary glands. Glycopyrrolate indirectly reduces the rate of salivation by preventing the stimulation of these receptors.

Basic Pharmacokinetic Properties

Absorption: In a parallel study of children (n=6 per group) aged 7-14 years undergoing intraocular surgery receiving either intravenous (IV) or oral glycopyrrolate as a premedication, the mean absolute bioavailability of glycopyrrolate tablets was low (approximately 3%) and highly variable among subjects (range 1.3 to 13.3%). A similar pattern of low and variable relative bioavailability is seen in adults.

Analysis of population pharmacokinetic data from normal adults and children with cerebral palsy associated chronic moderate to severe drooling failed to demonstrate linear pharmacokinetics across the dose range. In the same analysis, population estimates of the apparent oral clearance (scaled by weight in children and adults) ranged from 5.28 ~ 38.95 L/hr/kg for healthy adults and 8.07 ~ 25.65 L/hr/kg for patients with cerebral palsy, a reflection of the low and highly variable oral bioavailability of glycopyrrolate.

Absorption of Glycopyrrolate (fasting) was compared to that of a marketed glycopyrrolate oral tablet. The C_{max} after oral solution administration was 23% lower compared to tablet administration and the $AUC_{0-\infty}$ was 28% lower after oral solution administration. Mean C_{max} after oral solution administration in the fasting was 0.318 ng/mL, and mean AUC_{0-24} was 1.74 ng.hr/mL. Mean time to maximum plasma concentration for Glycopyrrolate was 3.1 hours, and mean plasma half-life was 3.0 hours.

In healthy adults, a high fat meal was shown to significantly affect the absorption of glycopyrrolate oral solution (10 mL, 1 mg/5 mL). The mean C_{max} under fed high fat meal conditions was approximately 74% lower than the C_{max} observed under fasting conditions. Similarly, mean AUC_{0-inf} was reduced by about 78% by the high fat meal compared with the fasting AUC_{0-inf}. A high fat meal markedly reduces the oral bioavailability of Glycopyrrolate. Therefore, Glycopyrrolate should be dosed one hour before or two hours after meals.

Distribution: After IV administration, glycopyrrolate has a mean volume of distribution in children aged 1 to 14 years of approximately 1.3 to 1.8 L/kg, with a range from 0.7 to 3.9 L/kg. In adults aged 60-75 years, the volume of distribution was lower (0.42 L/kg +/- 0.22).

Metabolism: In adult patients, who underwent surgery for cholelithiasis and were given a single IV dose of tritiated glycopyrrolate, approximately 85% of total radioactivity was excreted in urine and < 5% was present in T-tube drainage of bile. In both urine and

bile, > 80% of the radioactivity corresponded to unchanged drug. These data suggest a small proportion of IV glycopyrrolate is excreted as one or more metabolites.

Elimination: Approximately 65-80% of an IV glycopyrrolate dose was eliminated unchanged in urine in adults. In two studies, after IV administration to pediatric patients ages 1-14 years, mean clearance values ranged from 1.01- 1.41 L/kg/hr (range 0.32 – 2.22 L/kg/hr). In adults, IV clearance values were 0.54 ± 0.14 L/kg/hr.

8. STUDY OBJECTIVES

Primary objective of the study was to compare the relative bioavailability of Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution of NRIM Limited, U.K. and Glycopyrrolate 2mg tablets of NRIM Limited, U.K. with ROBINUL® FORTE 2mg Tablets of [redacted] and Glycopyrronium bromide oral solution 1mg/5mL (2 X 1mg /5mL) of [redacted] in healthy, adult, human subjects under fasting condition. Secondary objective was to evaluate safety parameters, including adverse events and clinical laboratory tests.

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan-Description

This was a randomized, open label, four-treatment, four-sequence, single-dose, balanced, four-way, crossover, relative bioavailability study in healthy adult, human subjects, under fasting conditions.

Briefly, an adequate number of volunteers were screened as per in-house SOP for Screening of Volunteers (Cadila Pharmaceuticals Ltd) after obtaining a written informed consent. The screen pass subjects were enrolled in the study after obtaining written informed consent for participation in the study, and pre-study clinical and lab evaluations. The subjects were remained in an overnight fasting for 10 hours prior to dosing till about 04 hours after dosing. Drinking water was not allowed for one hour before and one hour after dosing except while administration of the dose with 240 mL of drinking water and at all other times subjects had a free access to drinking water. All subjects were dosed at the scheduled time and advised to remain in sitting posture for the first 2 hours after dose administration in each period.

After an overnight fast of 10 hours, subjects received a single dose of either Test products (T1 or T2) or Reference products (R1 or R2) in sitting posture along with 240 ml of drinking water at room temperature in each period as per the randomization schedule. For oral solution, a single dose of 2 mg/10 mL of the investigational product was measured and administered using a syringe. The syringe was rinsed with water (from the 240 mL water allocated for that subject for drug administration), till no content were left in the syringe. The rinsate was administered to the subject after which, subject was asked to consume the remaining water. For tablet, the investigational product was administered with 240 ml of drinking water. The actual time of drug administration was the time when study personnel placed the investigational product in

the buccal cavity and it was documented in study source document. Compliance for dosing was assessed by conducting a thorough examination of the oral cavity using flashlight and spatula by trained study personnel after dosing in each period. All subjects were dosed at the schedule time and were required to remain in sitting position for the first 2 hours following drug administration. Subjects were allowed to be ambulatory and were advised to avoid severe physical exertion for remaining time of the each period. First 2 hours post dose samples were collected at bedside or at the respective dosing station and remaining blood samples were taken at sample collection area. The order of administration of the Tests (T1 or T2) product and References (R1 or R2) product to each subjects was determined according to the randomization scheduled prepared by Biostatistician.

Subjects were instructed during screening to refrain from smoking, chewing tobacco, pan or pan masala, gutkha, masala (containing betel nut and tobacco) and consuming alcohol for 48 hrs prior to dosing and "Grape-fruit" or its juice, for 72 hours prior to dosing and until after the last blood sample is collected in the study. Subjects were advised not to consume xanthine-containing beverages (tea, coffee, soft drinks like cola etc.), foods (chocolates) for 24-hours before dosing and until the last PK sample collection in each period.

The actual wash out period between the two dose administrations was 05 days as per IEC approved protocol.

A total of 28 blood samples were collected during each period. Pre-dose blood sample of 4.0mL was collected within one hour prior to the dosing. Post-dose blood samples of 4.0mL each was drawn at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.25, 4.50, 4.75, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00 and 24.00 hours following drug administration in each period. The total volume collected per subject in this study did not exceed 496.6 mL ± 10 mL (including 448 mL for pharmacokinetic analysis, up to 10 mL for screening, up to 5 mL for post study safety analysis and then 33.6 mL blood loss due to 0.3 mL discarded blood up to 24.00 hrs sampling time point in all periods).

Post-study safety assessment (Hematology and Biochemical parameters) were done at the end of study. A chart displaying the sequence of activities of the study is presented in Table 9-1.

Table 9-1 Summary Statistics of Pharmacokinetic Parameters (Glycopyrrolate)

Time points (hours)	ICF (Period - 1 only)	Check-in	Clinical Examination	Meal	Vital Record	ECG Recording	Blood sampling	Dosing	Post-study Assessment (End of the study)	Check-out	Ambulatory Visit
Before Check-in	X	-	X	-	X	X	-	-	-	-	-
At least -11 (Housing)	-	X	-	-	-	-	-	-	-	-	-
-10.00 Prior to dosing (Fasting)	-	-	-	Completion of Dinner	-	-	-	-	-	-	-
Pre-dose (within -60 min)	-	-	-	-	X	-	X	-	-	-	-
0.00	-	-	-	-	-	-	-	X	-	-	-
0.25	-	-	-	-	-	-	X	-	-	-	-
0.50	-	-	-	-	-	-	X	-	-	-	-
0.75	-	-	-	-	-	-	X	-	-	-	-
1.00	-	-	-	-	X	-	X	-	-	-	-
1.25	-	-	-	-	-	-	X	-	-	-	-
1.50	-	-	-	-	-	-	X	-	-	-	-
1.75	-	-	-	-	-	-	X	-	-	-	-
2.00	-	-	-	-	-	-	X	-	-	-	-
2.25	-	-	-	-	-	-	X	-	-	-	-
2.50	-	-	-	-	-	-	X	-	-	-	-
2.75	-	-	-	-	-	-	X	-	-	-	-
3.00	-	-	-	-	X	-	X	-	-	-	-
3.25	-	-	-	-	-	-	X	-	-	-	-
3.50	-	-	-	-	-	-	X	-	-	-	-
3.75	-	-	-	-	-	-	X	-	-	-	-
4.00	-	-	-	Lunch	-	-	X	-	-	-	-
4.25	-	-	-	-	-	-	X	-	-	-	-

Time points (hours)	ICF (Period - 1 only)	Check-in	Clinical Examination	Meal	Vital Record	ECG Recording	Blood sampling	Dosing	Post-study Assessment (End of the study)	Check-out	Ambulatory Visit
4.50	-	-	-	-	-	-	X	-	-	-	-
4.75	-	-	-	-	-	-	X	-	-	-	-
5.00	-	-	-	-	X	-	X	-	-	-	-
6.00	-	-	-	-	-	-	X	-	-	-	-
7.00	-	-	-	-	X	-	X	-	-	-	-
8.00	-	-	-	Snacks	-	-	X	-	-	-	-
10.00	-	-	-	-	-	-	X	-	-	-	-
12.00	-	-	-	Dinner	X	-	X	-	-	-	-
16.00	-	-	-	-	-	-	X	-	-	-	-
24.00	-	-	X	-	X	-	X	-	X (Period-IV)	X	-

Screening was carried out from -21 days to -1 days (screening period).

Urine screen for drugs of abuse was done at the time of admission in each period and alcohol breath test was done at the time of admission in each period. All activities after check-in of Period 1 were repeated for Period 2, 3 and 4 as well except informed consent process.

Blood sample was collected at the end of the study (after the last blood sample collection of Period 4) for post-study safety assessment.

A washout period of 05 days was maintained between two consecutive dosing days in the study as per IEC approved protocol.

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

This study used a randomized, open-label, four-treatment, four-period, four sequence single-dose, balanced, four-way crossover design that is standard in assessing relative bioavailability between Test product (T1 / T2) or Reference Product (R1 / R2). In this study, the pharmacokinetic profile of the Test Product (T) was characterized relative to that of the Reference Product (R) to assess relative bioavailability for Glycopyrrolate. Being a relative bioavailability study with a crossover design, each subject acted as his/her own control. Therefore, no control group was required for the study.

The time to reach peak plasma concentration (T_{max}) for Glycopyrrolate is approximately 3.1 hours. Based on half-life, a washout period of 05 days was considered adequate.

9.3 Selection of Study Population

Subjects were screened within twenty one (21) days prior to Period I dosing of the study. Screening involved obtaining demographic data, conducting clinical (physical & systemic) examination with vital signs (sitting blood pressure, oral temperature and radial pulse rate), complete medical history, conducting clinical laboratory tests (Haematology, Biochemistry, Serology and Urine analysis), ECG recordings and Chest X- ray (taken within 6 months prior to Period I dosing of the study).

Alcohol breathe test and urine screen for abuse drugs was performed for all subjects on the day of check-in of each period of the study. Subjects were selected based on following inclusion and exclusion criteria.

9.3.1 Inclusion Criteria

Subjects were fulfilling all of the following criteria were considered for inclusion into this study:

- Healthy, adult, human subject aged from 18 to 45 years (inclusive of both).
- Subject's Body Mass Index (BMI) within normal limit of 18.5-24.9 kg/m^2 (inclusive of both).
- Willingness to sign statements of written informed consent form (for screening & study related procedures).
- No contraindications with the study medication with any previous medical or surgical history.
- Willingness to undergo pre- and post-study physical examinations and laboratory investigations.
- Normal general physical examination.
- Normal ECG finding and vital signs, or abnormalities, which the clinical investigator did not considered a disqualification for participation in the study.

- Availability of subject for the entire study period and willingness to adhere to protocol.
- Non-smokers.

9.3.2 Exclusion Criteria

Subjects having none of the following criteria were included in the study:

- The subject with known drug hypersensitivity or idiosyncratic reaction to Glycopyrrolate or any related drug.
- Subjects incapable of understanding the informed consent process / procedure.
- Evidence of psychiatric disorder, antagonistic personality, poor motivation, emotional or intellectual problems likely to limit the validity of consent to participate in the study, or limit the ability to comply with protocol requirements.
- Resting heart rate of >100 beats/min or < 60 beats/min on the screening day.
- History of hypotensive episodes, or systolic blood pressure reading of < 100 mm of Hg or a diastolic reading of < 60 mm of Hg at time of general Physical examination.
- History of hypertension, or systolic blood pressure reading of > 139 mm of Hg or a diastolic reading > 89 mm of Hg at time of general Physical examination.
- The subject had any evidence of organ dysfunction or any clinically significant deviation from the normal, in physical or clinical determinations.
- Subject who had taken any enzymes modifying drugs within the past four weeks prior to start of clinical period.
- Subject who had taken any prescribed medications beginning two weeks prior to and OTC medications beginning one week prior to first dosing of study.
- The subject with known history of clinically significant psychiatric or medical diseases.
- History of or current alcohol abuse (>600 mL weekly) or history of exposure to other substance of abuse.
- Investigations with blood samples of the subject shown presence of disease marker of HIV 1 and 2, Hepatitis B & C viruses.
- Positive test for urinary screen testing of drugs of abuse (Amphetamines, Morphine, Benzodiazepines, Marijuana, Cocaine and Barbiturate).
- Subject found positive for alcohol breath test.
- Investigations with blood sample of the subject shown the presence of values which are clinically significantly different from normal reference range.
- Investigations with urine sample of the subject shown clinically abnormal chemical and microscopic examination of urine defined as presence of RBC, WBC (> 4/HPF), epithelial cells (>4/HPF), glucose (positive) and protein (positive) (unless

the clinical investigator considers the deviation to be irrelevant for the purpose of the study).

- Subject who participated in any other clinical investigation using experimental drug or had bleed more than 300 mL in the past 3 months.
- Xanthine-containing food or beverages (tea, coffee, chocolates, soft drinks like cola etc.) within 24 hours prior to the dosing of each period or alcoholic products consumption within 48 hours prior to the dosing of each period.
- Subjects who have consumed "Grape fruit" or its juice within 72 hours prior to dosing of each period.
- Subject without adequate venous access in their left or right arm to allow collection of all samples via venous cannula in each period.
- X-ray chest finding suggesting of any abnormality/ies like cardiomegalia, pneumonia etc.
- Subject with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, hepatic and /or renal function, that could have interfered with the absorption, metabolism, and /or excretion of the study drugs. Subjects with a history of cholecystectomy were excluded.
- Females who were falling in menstruation period during study.
- Females who were found positive in Urinary Pregnancy Test.
- Females who were lactating their children.
- Females who were using any type of hormonal contraceptives

9.3.3 Removal of subject from therapy or assessment

Principal Investigator was allowed to withdraw a subject from the study for any of the following:

- If subject suffered from significant inter-current illness or undergoes surgery during the course of study.
- If the subject was found to have entered the study in violation of this protocol.
- If subject required any concomitant medication, which could interfere with the pharmacokinetic property of study medication.
- If it was felt in the investigator's opinion that it was not in the subject's best interest to continue.
- Subject on his own wish to withdraw consent.
- If the subject experienced adverse event, then withdrawal was in the best interest of the subject.
- Emesis occurred at or before 2 times median T_{max}.

- If found positive in Urine Pregnancy Test before admission in study periods. (For Females).

Any subject withdrawal during study along with reason thereof was documented. Subjects, who were dropout/withdrawn from the study were not replaced.

9.4 Treatments

9.4.1 Treatments administered

Subjects were housed in the clinical facility of the CPPU from 11 hours before drug administration till up to 24 hours after drug administration in each period.

All subjects were required to fast (overnight) for 10 hours before their scheduled time for dosing. Subjects received a standard meal at about 04.00, 08.00 and 12.00 hours after dosing in each period. During housing, all meal plans were identical for all periods. In case, meal and blood sample collection times coincided, blood samples was given priority over meal. Drinking water was not allowed from one hour before dosing till one hour post-dose (except for 240 mL of drinking water given for dosing) until and unless clinically indicated. Before and after that, drinking water was allowed at all times.

A single dose of either Test products (T1 or T2) or Reference products (R1 or R2) was administered in sitting posture along with 240 ml of drinking water at room temperature in each period as per the randomization schedule.

Subjects were dosed at the scheduled time and were required to remain in sitting position for the first 02 hours following drug administration.

9.4.2 Identity of investigational products

The Test product (T1 / T2) or Reference Product (R1 / R2) information is provided in tables below. A list of subjects receiving investigational products from specified batches, and the Certificates of Analysis for Test product (T1 / T2) or Reference Product (R1 / R2) are provided in Appendix 16.1.6.

Test Product (T1)

Name and Strength	Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution
Formulation	Oral solution
Manufactured by	[redacted]
Batch No.	[redacted]
Manufacturing date	[redacted]
Expiry date	[redacted]
Storage Condition	Temperature: 25 ± 2° C, Relative Humidity: 60± 5%
Description	Clear Cherry Flavored Solution

Test Product (T2)

Name and Strength	Glycopyrrolate 2mg tablets
Formulation	Tablets
Manufactured by	[redacted]
Batch No.	[redacted]
Manufacturing date	[redacted]
Expiry date	[redacted]
Storage Condition	Temperature: 25 ± 2° C, Relative Humidity: 60± 5%
Description	White to off white round scored uncoated tablet engraved with 'GP' and '2' on either side of score line and plain on the other side.

Reference Product (R1)

Name and Strength	ROBINUL® FORTE 2mg Tablets
Formulation	Tablets
Manufacturer	[redacted]
Batch No.	[redacted]
Manufacturing date	[redacted]
Expiry date	[redacted]
Storage Condition	Temperature: 25 ± 2° C, Relative Humidity: 60± 5%
Description	White to off white round scored uncoated tablet engraved with 'GP' and '2' on either side of score line and plain on the other side.

Reference Product (R2)

Name and Strength	Glycopyrronium bromide oral solution 1mg/5mL (2 X 1mg /5mL)
Formulation	Oral solution
Manufacturer	[redacted]

Manufactured for	[redacted]
Batch No.	[redacted]
Manufacturing date	[redacted]
Expiry date	[redacted]
Storage Condition	Temperature: 25 ± 2° C, Relative Humidity: 60± 5%
Description	Clear Solution

9.4.3 Supply of Investigational Products

The drug products were received by the Principal Investigator (PI) or a suitable designate from [redacted] Reference products (R1 or R2) and Test products (T1 or T2) were supplied in the original manufacturer's packing, label had product name, strength, number of dosage units, manufacturer, lot number or batch number, expiry date in an appropriate package deemed to maintain the integrity of the products. At the clinical facility, the drug products were logged-in by the drug store in charge or a suitable designate and stored under prescribed storage conditions in a controlled access area. The investigator was accountable for the study drug products. Study drugs were dispensed according to the randomization schedule.

Drug store in-charge of DCPRDC, Cadila Pharmaceuticals Ltd. maintained the record of the total medication received, storage conditions, and quantity of drug used and retained.

9.4.3.1 Handling of Unused Samples

The dispensed but un-dosed (e.g. due to the subject being unwell or dropout or withdrawal from the study etc.) investigational products were returned to the pharmacy. The dispensed but un-dosed syringes were discarded after completion of dosing in each period.

9.4.3.2 Maintenance of Randomization Code and Dispensing Record

Randomization code and investigational product dispensing record was kept in pharmacy of [redacted] under controlled access. Personnel involved in dispensing of investigational products (dispensing pharmacist), Principal Investigator and Research Quality Assurance personnel was accountable for ensuring the compliance to randomization schedule. Analysts were blinded to the sequence of administration of Test (T1 or T2) and References (R1or R2) formulation

Test (T1 and T2) and Reference (R1 and R2) products were received at [redacted] on 02/NOV/2013, the received quantity details of investigational products are provided below;

Test Product (T1) = 300 mL

Test Product (T2) = 30 tablets

Reference Product (R1) = 30 tablets

Reference Product (R2) = 300 mL

Table 9-2 Drug Accountability Log

Note: For T1 and R2, 01 dispensing unit = 10 mL of oral solution containing 2 mg of Glycopyrrolate.

Product type	Period/date of dispensing	Opening balance (Units)	Quantity dispensed (units)		Total Closing balance (units)	
			For subjects	For standby	Un-dispensed [retained sample]	Returned + standby
Test (T1)	I (11/NOV/2013)	30	05	01	24	01^S
	II (16/NOV/2013)	24	05	01	18	01^S
	III (21/NOV/2013)	18	05	01	12	01^S+01^R
	IV (26/NOV/2013)	12	05	01	06	01^S
Total remaining investigational products (Test T1) in pharmacy after completion of conduct of the study					$06+04^S$=10 units (100 mL)	
Test (T2)	I (11/NOV/2013)	30	05	01	24	01^S
	II (16/NOV/2013)	24	05	01	18	01^S
	III (21/NOV/2013)	18	05	01	12	01^S
	IV (26/NOV/2013)	12	05	01	06	01^S+01^R
Total remaining investigational products (Test T2) in pharmacy after completion of conduct of the study					$06+04^S+01^R$=11 units (11 tablets)	

Product type	Period/date of dispensing	Opening balance (Units)	Quantity dispensed (units)		Total Closing balance (units)	
			For subjects	For standby	Un-dispensed [retained sample]	Returned + standby
Reference (R1)	I (11/NOV/2013)	30	05	01	24	01^{S}
	II (16/NOV/2013)	24	05	01	18	01^{S}
	III (21/NOV/2013)	18	05	01	12	01^{S}
	IV (26/NOV/2013)	12	05	01	06	01^{S}
Total remaining investigational products (Reference R1) in pharmacy after completion of conduct of the study					$06+04^{S}$=10 units (11 tablets)	
Reference (R2)	I (11/NOV/2013)	30	05	01	24	01^{S}
	II (16/NOV/2013)	24	05	01	18	$01^{S}+01^{R}$
	III (21/NOV/2013)	18	05	01	12	01^{S}
	IV (26/NOV/2013)	12	05	01	06	01^{S}
Total remaining investigational products (Reference R2) in pharmacy after completion of conduct of the study					$06+04^{S}$=10 units (100 mL)	

S: IP used as Stand by

R: Returned IP

Note: Returned IP unit (T1 and R2) were discarded after dosing.

Subject was considered as dropout from the study on 16/NOV/2013, as subject did not report to the clinical facility for period-II check-in.

Dose Preparation

Dispenser dispensed a quantity of Test (T1 or T2) and References (R1 or R2) formulations sufficient for dosing on the day of dosing in all the study periods as per

randomization schedule and the remaining Investigational Products were retained as per applicable regulatory requirements after completion of the project. The Test product (T1) and Reference product (R2) were dispensed in the syringes. The Test product (T2) and Reference product (R1) were dispensed in the container. The dispensing was done through pre-labeled dispensing syringes/containers and with information about For Clinical Research Use Only, Protocol No., Subject No., Period No., Randomization sequence (Test - T1 or Test - T2 or Reference - R1 or Reference - R2), Batch No. /Lot No., Number of Units and Storage condition and Sponsor name.

9.4.4 Storage

The investigational products were stored in the pharmacy under the manufacturer's recommended storage conditions. The drug accountability records were maintained in the pharmacy as per the relevant SOPs of Cadila Pharmaceuticals Limited.

9.4.5 Method of assigning subjects to treatment groups

The order of receiving Test products (T1 or T2) or Reference products (R1 or R2) for each subject during each period of the study was determined according to a randomization schedule, generated by using SAS® software (Version 9.2). Equal allocation of subjects to each sequence was ensured. The randomization was performed on 20 subjects

Study personnel involved in the sample analysis were kept blinded from the randomization sequence.

Personnel involved in dispensing study drug and in verifying the dispensing activity as well as administration of study drug were accountable for ensuring compliance with the randomization schedule.

9.4.6 Selection of doses in the study

Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution and Glycopyrrolate 2mg tablets were selected as it is normally accepted dose for relative bioavailability estimation for generic marketing, and this was within the recommended dose range.

A single dose of either Test products (T1 or T2) or Reference products (R1 or R2) was administered in sitting posture along with 240 ml of drinking water at room temperature in each period as per the randomization schedule.

Drinking water was not allowed from one hour before and one hour after dosing except 240 ml of drinking water given at the time of dosing.

Subjects were dosed at the scheduled time and were required to remain in sitting position for the first 02 hours following drug administration.

9.4.7 Selection and timing of dose for each subject

After an overnight fast of 10 hours, subjects received a single dose of either Test products (T1 or T2) or Reference products (R1 or R2) in sitting posture along with 240

ml of drinking water at room temperature in each period as per the randomization schedule. For oral solution, a single dose of 2 mg/10 mL of the investigational product was measured and administered using a syringe. The syringe was be rinsed with water (from the 240 mL water allocated for that subject for drug administration), till no content are left in the syringe. The rinsate was administered to the subject after which, subject was asked to consume the remaining water. For tablet, the investigational product was administered with 240 ml of drinking water. The actual time of drug administration was the time when study personnel placed the investigational product in the buccal cavity and it was documented in study source document. Compliance for dosing was assessed by conducting a thorough examination of the oral cavity using flashlight and spatula by trained study personnel after dosing in each period. All subjects were dosed at the schedule time and were remained in sitting position for the first 2 hours following drug administration. Subjects were allowed to be ambulatory and were advised to avoid severe physical exertion for remaining time of the each period. First 2 hours post dose samples was collected at bedside or at the respective dosing station and remaining blood samples were taken at sample collection area. The order of administration of the Tests (T1 or T2) product and References (R1 or R2) product to each subjects was determined according to the randomization scheduled prepared by Biostatistician.

A detailed description of time of reporting, admission, and discharge, and actual time of study drug administration is presented in Appendix 16.2.10.

The actual time of drug administration to the subjects in each study period is presented in Table 9-3.

Table 9-3 Drug Administration

Period I	
Dosing Time	[redacted]
Subject Number	

Period II	
Dosing Time	[redacted]
Subject Number	

*ND: Not Dosed

Period III	
Dosing Time	[redacted]
Subject Number	

*ND: Not Dosed

Period IV	
Dosing Time	[redacted]
Subject Number	

*ND: Not Dosed

9.4.8 Blinding

This study comprised of a randomized open-label, as it is needless to design double-blind study for relative bioavailability study. However analyst was blinded to the sequence of administration of Test (T1 or T2) and References (R1or R2) formulation.

9.4.9 Pre-Study Procedures

The screening for this study was carried out on 01/NOV/2013, 07/NOV/2013, 08/NOV/2013 and 09/NOV/2013.

Adequate numbers of volunteers were selected randomly from the volunteer data bank of clinical unit and underwent a standardized screening procedure as described in applicable Cadila Pharmaceuticals Limited SOP(s). Twenty (20) + 02 (stand by) healthy, adult, male subjects were enrolled in the study as per inclusion and exclusion criteria. Plasma samples of all subjects were analyzed.

The activities during screening included:

- Informed consent procedure for the screening including distribution of ICF to volunteers, oral presentation of ICF, one to one ICF discussion with the Principal Investigator/Medical-Officer/designee and obtaining written informed consent from volunteers.
- Demographic data: Initials, date of birth, age, gender, occupation, race and ethnicity height, weight and BMI

- Medical history: Present complaints, past medical history (including history of cardiovascular, respiratory (including tuberculosis, bronchial asthma), gastrointestinal and hepatic, Neurological (including seizure disorder), HEENT, psychiatric disorders, musculoskeletal, endocrine, dermatological, urogenital (including UTI), surgical (including trauma), bleeding disorders, and others (including sexually transmitted diseases, chronic illness), family medical history and history of any allergies, history of medication in last 30 days
- Life style and habits: consumption of alcohol, nicotine, consumption of food and xanthine-containing beverages (tea, coffee, cola drinks), chocolates and tobacco.
- Additional information concerning: last administration of any investigational drug, last participation in any clinical study, last donation of blood or plasma, any enzyme-modifying drugs within four weeks of screening or, administration/intake of any prescription or OTC drug including vitamins and natural supplements within four weeks of screening as well as specification of the drug name, dosage, start and end of treatment.
- Vital signs: recording of oral body temperature, measurement of radial pulse rate, blood pressure (BP) and respiration rate (RR).
- 12 lead electrocardiogram (ECG).
- Chest X-Ray (PA view), if not done in the last 6 months.
- Physical examination: general appearance (including pallor, icterus, cyanosis, clubbing, odema etc.) and systemic physical examination (Dermatological system, Cardiovascular system, Respiratory system, Musculo-skeletal system, Gastrointestinal system, Neurological system, Urogenital system, lymph nodes, extremities and hepatic system); head and neck, eyes, ears, nose and throat.
- Laboratory examination of blood (routine hematology and clinical chemistry including electrolytes).
- Serological tests for HIV 1 and 2, HBsAg and Anti-HCV
- Urinalysis: physical, chemical and routine microscopic examination
- Breath analyzer test for alcohol consumption

The laboratory examinations during screening, as applicable, are presented in Table 9-4.

Table 9-4 Laboratory Examinations at Screening

HEMATOLOGY	BIOCHEMISTRY
Hemoglobin, PCV, MCV, MCH, MCHC, RBC count, WBC count, Differential Leukocyte count, Absolute Leukocyte count and Platelet count.	ALT, AST, ALP, Total Bilirubin, Total Protein, Creatinine, Triglyceride, Urea, Cholesterol, Serum electrolytes (sodium, chloride and potassium), Random Blood-Glucose and Uric Acid.

URINE ANALYSIS	SEROLOGY
Color, Specific gravity, pH, Transparency, Protein, Ketones, Glucose, Bilirubin, Occult Blood, Urobilinogen and Microscopic examination.	Hepatitis B & C, HIV 1 and 2.

All laboratory tests were carried out in the [redacted] A by-subject list of individual laboratory data and reference range per laboratory reference range is presented in Appendix 16.2.8.3. A list of the normal ranges and units of measurement of the laboratory parameters was provided before the start of the study. An authorized copy of the original laboratory report was attached with source records. The investigator evaluated the laboratory results as per laboratory reference range (refer Appendix 16.2.8.3) for enrolling the subject into the study.

9.4.10 Study Procedures

The study was performed in four periods.

Day -1 (Admission Day): following procedures were carried out

- Informed consent procedure for the study including distribution of study specific ICF to volunteers, oral presentation of ICF and one to one ICF discussion with the Principal Investigator/ Medical-Officer/designee and obtaining written informed consent from volunteers prior to the admission (only in Period 1).
- Check of inclusion and exclusion criteria as per the approved protocol prior to the admission (only in Period 1).
- Volunteer identification by means of the volunteer registration card.
- Brief medical examination.
- Measurement of body temperature (oral), sitting blood pressure, radial pulse rate and respiratory rate.
- Drug of abuse test in urine for amphetamines, barbiturates, benzodiazepines, tetra hydro cannabinol, cocaine and morphine.
- Breathe test for alcohol consumption.
- Dispensing of study drug.
- Check of the luggage for not allowed items (foods, beverages, drugs, cigarettes).
- Allotment of subject number (only in Period 1).
- Admission of subjects in clinical ward.
- Check of study restrictions.
- Dinner was served between 21:00 to 21:20 hours in Period I, between 20:06 to 21:38 hours in Period II, between 21:30 to 21:59 hours in Period III and between 21:15 to 21:51 hours in Period IV.

- Establishing pre-dose fasting restriction of 10 hour.
- Regular monitoring for adverse/medical events.

Day 0 (Dosing Day): following procedures were carried out

- Measurement of pre-dose vital signs (sitting BP, radial pulse rate and oral body temperature).
- Checking health status before dosing.
- Insertion of the intravenous cannula.
- Blood sampling before dose (pre-dose pharmacokinetic sampling).
- Establishing water restriction (1 hour prior to dosing and 1 hours after dosing).
- The study drug was administered [Test product (T1 / T2) or Reference Product (R1 / R2)] as per the randomization schedule. Dosing started at 08:30 hours. To ensure the subject swallowed the drug, a "mouth check" was performed by trained study personnel using disposable spatula.
- Establishing fasting restriction of 4 hours post-dose.
- Establishing posture restriction for first 2 hours after dose administration. Post-dose pharmacokinetic blood sampling at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.25, 4.50, 4.75, 5.00, 6.00, 7.00, 8.00, 10.00,12.00 and 16.00 hours.
- Measurement of vitals (sitting BP and radial pulse rate) for safety concern at 1.00, 3.00, 5.00, 07.00, 12.00 hours (± 40 minutes) post-dose in each study period after dosing and checking of health status.
- Standard lunch at approximately 4 hours post-dose.
- Standard snacks at approximately 8 hours post-dose.
- Standard dinner at approximately 12 hours post-dose.
- Regular monitoring and recording for an adverse events.

Day 1 (Discharge Day): following procedures were carried out

- Blood sampling at 24.00 hour post-dose.
- A brief medical examination
- Measurement of oral body temperature, sitting blood pressure, radial pulse rate and respiratory rate.
- Discharge from the clinical facility.
- Regular monitoring of adverse events (till close out visit).

The procedures mentioned in day -1 to 1 were repeated in Period 2, 3 and 4 except informed consent process. Additionally, a blood sample for post study examination (hematology and biochemistry) was collected at the end of last sample of last period.

The actual washout period of 05 days was maintained between two consecutive dosing days as per IEC approved protocol.

9.4.11 Post-Study Procedures

A blood sample for post study laboratory assessment (hematology and biochemistry) was collected at the time of last PK sample collection in last period. Laboratory tests were carried out in the [redacted] during post-study safety assessment.

The investigator evaluated the laboratory results as per laboratory reference range (refer Appendix 16.2.8.3).

There was no adverse event in the study. The results of post-study laboratory examinations are presented in Section 12.4 "Clinical Laboratory Evaluation" of this report.

9.4.12 Flow Chart

An overview over the course of this study with the examinations that were performed at each of the visits scheduled for this study is given in the flow chart below Table 9-5.

Table 9-5 Study Event Flow Chart

The following schedule was observed for the study during Period- I, II, III and IV.

Study Events	Screening	Study Days in Period I, II, III & IV			
Activity	Within 21 days before dosing	Day -1 (Check-in)	Day 0 (Dosing)	Day 1 (Check-out)	Post Study Safety Analysis
Informed Consent for Screening	X	-	-	-	-
Demographic Data	X	-	-	-	-
Drug Allergy/Medication/ Medical Histories	X	X	-	X	-
General Physical Examination	X	X	-	X	-
Vital Signs[3]	X	X	X	X	-
ECG (12-lead)	X	-	-	-	-
X-ray chest[7]	X	-	-	-	-
Haematology	X	-	-	-	X
Serum biochemistry	X	-	-	-	X
Serology	X	-	-	-	-
Urine analysis	X	-	-	-	-
Informed Consent for Study[6]	-	X	-	-	-
Urine Drug Screen[4]	-	X	-	-	-
Alcohol breath test[4]	-	X	-	-	-
Record of Concomitant Medication	-	X	X	X	-
Check-in procedure	-	X	-	-	-
Housing [2]	-	X	X	-	-
Drug dosing	-	-	X	-	-
PK blood sampling [5]	-	-	X	X	-
Check-out procedures	-	-	-	X	-
Wash out period[1]	05 days				-

1. Each period was separated by a washout of 05 days.
2. Subject was housed in the Clinical Unit from 11 hrs prior dosing to 24 hrs post dose.
3. Measurements of vital signs (including Sitting Blood Pressure, Radial Pulse Rate and Oral temperature) were performed before check-in and check-out in each period. Vitals signs (including

Sitting Blood Pressure and Radial Pulse Rate) were also performed prior to administration of study drug in each period and at 1.00, 3.00, 5.00, 7.00 and 12.00hrs post-dose. Post-dose vital signs were measured and recorded within ± 40 minutes of scheduled time.

4. Urine drug screen test and alcohol breath test and were done during check- in time of each period.
5. Blood samples were taken prior to drug administration (0.0) followed by post-dose samples at different time points as per specified in protocol in each period.
6. Informed Consent for Study was taken only in period – I.
7. X-ray should have been taken within last 6 months (prior to 1st dosing of the study).

9.4.13 Diet

All subjects were fasted for 10 hours prior to dosing and four hours after dosing. A standardized meal was served to all the subjects at about 04.00, 08.00 and 12.00 hours respectively after dosing in each period. The meals were uniform in each the clinical periods. If time for giving meals coexists with blood sample collection time then blood sample collection was given preference. Information on the amount of meals consumed was recorded in the subjects "CRF". Drinking water was not be allowed from one hour before and one hour after dosing (except for 240 mL of drinking water given at the time of dosing) and until unless clinically indicated.

9.4.14 Prior and concomitant therapy

The subjects were advised not to take any medication (including OTC products), throughout the study period without consulting the investigator. If the medication(s) or pharmacological treatment other than the study drug were required for the monitoring the safety of the study subject(s) during the conduct of the study, it was to be recorded as a concomitant medication. The decision to continue or discontinue the subject in the study was made by Principal Investigator/Medical Officer based on whether the concomitant drug(s) has the potential to affect the pharmacokinetics of the study drug or compromised the safety of the subject. Each case was to be decided on an individual basis after consultation with the Sponsor as required. The subjects were instructed to inform the investigator about intake of any other drug(s) during the study duration. There was no subject reporting concomitant medication.

9.4.15 Treatment compliance

Dosing compliance was assessed by pasting duplicate label of dispensed container on the 'Dosing' section of individual Case Report Form (CRF) and by a thorough check of oral cavity using flashlight and spatula immediately after dosing.

All subjects were dosed at the schedule time and remained in sitting position for the first 2 hours following drug administration (except subject number 04 who dropped out of the study on 16/NOV/2013, as subject did not report to the clinical facility for period-II check-in). Subjects were allowed to be ambulatory and were advised to avoid severe physical exertion for remaining time of the each period. First 2 hours post dose samples

were collected at bedside or at the respective dosing station and remaining blood samples were taken at sample collection area. The order of administration of the Tests (T1 or T2) product and References (R1 or R2) product to each subjects was determined according to the randomization scheduled prepared by Biostatistician.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy (Pharmacokinetics) Variables

Being a bioavailability study, there was no clinical efficacy assessment. However, pharmacokinetic parameters of the Test (T1 or T2) and References (R1 or R2) formulations were assessed.

Pharmacokinetic primary parameters like Dose-adjusted $AUC_{0\text{-}inf}$ and secondary parameters like C_{max}, $AUC_{0\text{-}inf}$, T_{max}, $t_{1/2}$ and K_{el} were calculated using plasma concentration vs. time profile (Actual time of sample collection) data of both investigational products in individual subjects using WinNonlin Professional Software Version 5.3 or higher.

Pharmacokinetic parameters were calculated by non-compartmental analysis using WinNonlin pharmacokinetic software Version 5.3 or higher (Pharsight Corporation, USA). The peak level (C_{max}) and time to reach peak level (T_{max}) was estimated from the plasma concentration time profile data. The elimination rate constant (K_{el}) was estimated by linear regression of the terminal part of the log-concentration-time curve. The area under the plasma concentration-time curve ($AUC_{0\text{-}inf}$) was determined by the linear trapezoidal rule, and extrapolated to infinity ($AUC_{0\text{-}\infty}$) by dividing the last measurable concentration by the elimination rate constant (K_{el}). $T_{1/2}$ (elimination or terminal half-life) was calculated as $0.693/K_{el}$.

All concentration values below the Limit of Quantification (LOQ) were set to "zero" for all pharmacokinetic and statistical calculations. Any missing sample was reported as "MS" and was not included for pharmacokinetic and statistical analysis.

9.5.2 Safety Variables

9.5.2.1 Eligibility Assessments

The eligibility assessments were conducted before the entry of the subjects into the study as per selection and withdrawal criteria of the subjects.

9.5.2.2 Clinical Laboratory Test

Following clinical laboratory tests were conducted during screening-haematology, biochemistry, Urine-analysis & Serology. Post-study safety tests of haematology and biochemistry were done after completion of the study.

HEMATOLOGY	BIOCHEMISTRY
Hemoglobin, PCV, MCV, MCH, MCHC, RBC count, WBC count, Differential Leukocyte count and Platelet count.	ALT, AST, ALP, Total Bilirubin, Total Protein, Creatinine, Triglyceride, Urea, Cholesterol, Serum electrolytes (sodium, chloride and potassium), Random Blood-Glucose and Uric Acid.
URINE ANALYSIS	**SEROLOGY**
Color, Specific gravity, pH, Transparency, Protein, Ketones, Glucose, Bilirubin, Occult Blood, Urobilinogen and Microscopic examination.	Hepatitis B & C, HIV 1 and 2.

The normal acceptable ranges of laboratory test-values utilized are in Annexure-I (Protocol Number: 13-021 V01, Dated: 08/OCT/2013).

Urine Drugs Screen (for Amphetamines, Morphine, Benzodiazepines, Marijuana, Cocaine and Barbiturates) and Alcohol Breath Test: Both tests were done before check-in of each period of the study.

Hematology, Biochemistry, Urine-analysis and Serology tests were carried out at [redacted]

In the event of unexplained or unexpected laboratory test investigation values abnormalities during or post study, the tests were to be repeated and to be followed-up until the results returned to normal, however there was no such abnormality reported in the study. The investigator should indicate on the laboratory test page of the CRF all laboratory test values, which are potentially clinically significant.

9.5.2.3 Recording of Vital Signs and Clinical Examination

Vital signs (sitting blood pressure and radial pulse rate) were measured and recorded with the subject in sitting posture before dosing of investigational products (in the morning of the day of dosing) and at 1.00, 3.00, 5.00, 7.00 and 12.00 hours post-dose in each period. Post-dose vital signs were measured within ± 40 minutes of the scheduled time.

Clinical examination {vital signs (Sitting blood pressure, oral temperature and radial pulse rate), physical examination and systemic examination} were measured and recorded at the time of check- in and before check-out in each period. Clinical examination may also be done at any time during the conduct of study, if the clinical research physician feels it necessary. Subjects were questioned for well-being at the time of clinical examination and recording of vital signs. In case of abnormality during

pre-dose vital signs recording, medical opinion was taken whether to dose the subject or not. Physician was available on-site throughout the study period to provide medical monitoring to the subjects for adverse events, if any.

Normal limits for Vitals and Clinical examination

1. Systolic blood pressure between 100 mm of Hg to 139 mm of Hg

2. Diastolic blood pressure between 60 mm of Hg to 89 mm of Hg

3. Pulse rate between 60/minute to 100/minute

4. Oral temperature between 97.4 to 98.8^{0}F

Post-study safety assessment (Hematology and Biochemical parameters) were done at the end of study.

9.5.2.4 Handling and Reporting of Adverse Events

An adverse event (AE) can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guideline for Clinical Safety Data Management Definitions and Standards for Expedited Reporting).

The severity of the adverse events was graded on a three-point scale as follows:

Mild: Discomfort noticed but no disruption of normal daily activity

Moderate: Discomfort sufficient to reduce or affect normal daily activity

Severe: Inability to work or perform normal daily activity

The relationship of the adverse events encountered during the study was recorded in the adverse event form as per Cadila Pharmaceutical SOP.

The study physician was to do the emergency management of all ADR's. SAE requiring immediate transfer to a referral hospital was to be done with the help of the ambulance to the nearest specialty hospital [redacted]

9.5.2.5 Serious Adverse Events (SAEs)

All serious and unexpected adverse events that occurred during the study were to be reported by the investigator to the sponsor, regulatory authority (DCGI) and the ethics committee within 24 hours of their occurrence. The investigator was not to wait to receive additional information to fully document the event before notifying the sponsor, Ethics committee or the regulatory authority. A full written summary detailing relevant aspects of the SAE was to be followed in the initial report and was to be submitted to the sponsor, Ethics committee and the regulatory authority within 10 calendar days by the investigator. Where applicable, information from relevant hospital records and post mortem reports were to be obtained. A follow up SAE report was to be fully

documented and reported to the Sponsor, Ethics committee and the regulatory authority within 10 calendar days of receipt of additional information.

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. With respect to human clinical experience, this includes any experience which:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (as per reporter's opinion)
- Is a congenital anomaly/birth defect
- Other medically important condition

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than known therapeutic doses. It must be reported irrespective of outcome, even if toxic effects were not observed. A death occurring during the study or which comes to the attention of the investigator within 4 weeks after stopping the treatment, whether considered treatment-related or not, was must to be reported. Such preliminary reports were to be followed by detailed descriptions later, which included copies of hospital case reports, autopsy reports and other documents when applicable.

9.5.3 Appropriateness of measurements

Plasma concentration measurements were used for the estimation of pharmacokinetic parameters. The sampling time-points were planned based on the reported pharmacokinetics of the drug. The sampling time-points were chosen to assess Dose-adjusted $AUC_{0\text{-}inf}$, C_{max}, $AUC_{0\text{-}inf}$, T_{max}, $T_{1/2}$ and K_{el} appropriately. Based on these evaluations, comparison of the both products was performed. The safety monitoring of the subject was performed at regular intervals throughout the study.

9.5.4 Primary Efficacy Variable

This was a relative bioavailability study. The primary and secondary pharmacokinetic parameters were:

Pharmacokinetic Parameters	
Primary	**Secondary**
Dose-adjusted $AUC_{0\text{-}inf}$	C_{max}, $AUC_{0\text{-}t}$, T_{max}, $T_{1/2}$ and K_{el}

Primary pharmacokinetic parameters like Dose-adjusted $AUC_{0\text{-}inf}$ and secondary pharmacokinetic parameters like C_{max}, $AUC_{0\text{-}t}$, T_{max}, $T_{1/2}$, and K_{el} were calculated on the plasma-concentration time data of Glycopyrrolate of all the subjects who completed all

periods of the study. If the pre-dose concentration was ≤ 5 percent of C_{max} value in that subject, the subject's data without any adjustments was included in all pharmacokinetic measurements and calculations. If there was any subject for whom the pre-dose concentration was greater than 5 percent of the C_{max} value for the subject in that period, the statistical analysis was to be repeated with those subjects excluded. Results from both analyses were to be presented, but the analysis with the subjects excluded was to be considered as primary. Unbalanced sequences were to be considered for calculations when there were more dropouts/withdrawals from the same sequence.

The following pharmacokinetic parameters were estimated for Glycopyrrolate using WinNonlin® software Version 5.3 (Pharsight Inc, Cary NC, USA).

9.5.5 Drug concentration measurements

9.5.5.1 Collection of blood samples for pharmacokinetic measurements

Blood samples were withdrawn by an indwelling cannula placed in a forearm vein or fresh clean venipuncture using a disposable sterilized syringe and a needle in case of clotting of cannula.

The pre-dose blood sample was collected within a period of 01.00 hr before dosing and post-dose samples was collected within ± 2 minutes of the scheduled time till 24.00 hour blood sample. The time of collection of each blood sample was recorded in hh:mm format in CRF at the end of each blood collection procedure. The deviations greater than mentioned in this protocol from the scheduled sampling time were reported as protocol deviations. Actual time of sample collection was taken into consideration for pharmacokinetic calculation.

Intravenous indwelling cannula was kept in situ as long as possible by injecting, 0.3mL of 5IU/mL of heparin in normal saline solution to maintain the cannula patent. While sampling through cannula, blood samples were collected after discarding first 0.3mL of heparinized blood from cannula.

If insertion of cannula was not possible, alternatively blood samples was drawn by a fresh vein-puncture or in case of blockade in an existing cannula, extra heparinized saline was injected to stimulate the cannula and later blood samples were collected after discarding the heparinized blood.

The blood samples were collected in pre-labeled (label mentioning study number, subject number, period number and sampling time-point) vacutainer containing K_2EDTA as an anticoagulant.

In case meal and blood sample collection timings coincide, samples were collected before meals are provided.

After collection, blood samples were centrifuged at 3000 rpm for 10 minutes at 4^0C ± 2^0C as soon as possible. The plasma samples were divided into two aliquots and stored in two different pre-labeled (label mentioning study number, subject number, period

number and sampling time-point) RIA vials. Aliquot 1 contained approximately 1 mL plasma and aliquot 2 contained remaining amount of plasma.

All plasma samples were properly labeled and stored at –65±10°C until transfer to bioanalytical site.

A total of 28 blood samples were collected during each period. Pre-dose blood sample of 4.0mL was collected within one hour prior to the dosing. Post-dose blood samples of 4.0mL each was drawn at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.25, 4.50, 4.75, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00 and 24.00 hours following drug administration in each period. The total volume collected per subject in this study did not exceed 496.6 mL ± 10 mL (including 448 mL for pharmacokinetic analysis, up to 10 mL for screening, up to 5 mL for post study safety analysis and then 33.6 mL blood loss due to 0.3 mL discarded blood up to 24.00 hrs sampling time point in all periods).

9.5.5.2 Summary of Analytical Method

As per the study protocol (13-021; Version 01), 2240 (20 subjects x 28 time points x 4 Periods) clinical blood samples were to be collected from 20 subjects during four period of the study. However, a total of 2156 (20*28*4-84) samples for each aliquot were collected. Listed below are the samples that were not collected:

Subject Number	Period	Number of missing samples	Time Point (Hrs)	Dropout/ Withdrawn/Missing sample with Reason
04	II	28	All Time points	Drop Out
04	III	28	All Time points	Drop Out
04	IV	28	All Time points	Drop Out

The total number of samples analysed for the estimation of Glycopyrrolate were 2542 [2156 subject samples (20*28*4-84) + 170 Repeats (5 IP+ 3 IV + 162 VA) + 216 ISR samples].

9.6 Data quality assurance

9.6.1 Quality assurance

The raw data generated during the course of the study as well as reports undergone a random quality assurance process for conformance to this protocol and all the governing SOPs by auditors from Research Quality Assurance (RQA) department of Cadila Pharmaceuticals. After completion of the study, RQA auditors or BA/BE Study Business Unit of Jubilant Life Sciences Limited retrospectively checked bioanalytical report and final study report (including pharmacokinetic and statistical report) with compilation of raw data generated during the study. The final report contained a statement for quality assurance duly signed by the Head or designated person of RQA department. The audit certificate of QA audit is presented in Appendix 16.1.8.

The documentation of inter-laboratory standardization methods and quality assurance certificates are provided in Appendix 16.1.10.

9.7 Statistical methods planned in the protocol and determination of sample size

9.7.1 Statistical and Analytical Plans

In order to investigate the relative bioavailability of the test formulations (T1, T2) against the reference formulation (R1, R2), the intrasubject ratio (test/reference) of the geometric least square means of primary parameters (Dose adjusted $AUC_{0\text{-}inf}$).

The biostatistical evaluation was carried out by using the statistical software package SAS® for Windows, version 9.2 (Statistical Analysis System, SAS-Institute, Cary NC, USA).

The pharmacokinetic evaluation was carried out by using the pharmacokinetic software WinNonlin®, version 5.3 (Pharsight Inc, Cary NC, USA). Pharmacokinetic parameters were calculated for each formulation.

All pharmacokinetic primary and secondary parameters evaluations based on non-compartmental analysis details for the test and reference formulations are presented in Appendix-10 of pharmacokinetic and statistical report.

9.7.1.1 Analysis of variance

Ln-transformed pharmacokinetic parameters (Dose-adjusted $AUC_{0\text{-}inf}$) was analyzed using ANOVA model with the main effects of treatment, period and sequence as fixed effects and subjects nested within sequence as random effect.

The sequence effect was tested using the subjects nested within sequence mean square from the ANOVA as the error term. All other main effects were tested at the 5% level of significance against the residual error (mean square error/MSE) from the ANOVA as the error term. Each analysis of variance included calculation of least square mean (LSM). Two one-sided "t" test at 5% level of significance were used to compare the average values of pharmacokinetic parameters determined after administration of Test product (T1 / T2) or Reference Product (R1 / R2).

Each analysis of variance included calculation of least-square means, the difference between the adjusted formulation means and the standard error associated with the difference. The above analyses were done using procedure PROC GLM in SAS® 9.2."

9.7.1.2 Ratio analysis

The (T1/R1), (T1/R2), (T2/R1) and (T2/R2) ratios of geometric least square means of primary parameters (Dose adjusted $AUC_{0\text{-}inf}$) was calculated using natural log-transformed data where T1 = Test product 1; T2 = Test product 2; R1= Reference product 1; R2 = Reference product 2.

Additionally T1 versus T2 results are presented as additional information purpose only and not considered as final outcome.

9.7.1.3 Bioavailability criteria

Statistical evaluation methods were used for comparative bioavailability between two Test products (T1 & T2) and two Reference products (R1 & R2) as per given below:

95% Confidence Interval and p-value for the true mean relative bioavailability was presented for four formulations.

Formula to calculate relative bioavailability:

Relative bioavailability = (AUCtest / AUCreference) * (DOSEreference / DOSEtest)

9.7.1.4 Outliers

Subject who exhibited extremely high or low bioavailability relative to the reference formulation, were to be detected using statistical method namely Lund's method (using statistical package SAS® 9.2). A valid clinical or pharmacological or bioanalytical reason was to be explored for such outliers if found, and was to be reported if identified by the principal investigator of study. However to avoid the biasness in the result, both the pharmacokinetic and statistical analysis were to be performed on both the data sets i.e. including as well as excluding the outliers, if the outliers were justified clinically as well. The results with and without outlier were to be reported in the final study report. There was no outlier reported in the study.

9.7.2 Determination of sample size

Twenty (20) healthy, adult, male subjects between the age group of 18-45 years were enrolled in the study.

9.8 Changes in the conduct of the study or planned analyses

There were no changes in the conduct of the study or planned analysis.

10. STUDY SUBJECTS

10.1 Disposition of Subjects

Adequate number of volunteers was selected randomly from the volunteer data bank of clinical pharmacology unit of Cadila Pharmaceuticals and underwent a standardized screening procedure as described in applicable Cadila SOP(s). Twenty (20) subjects + two (02) additional subjects (as stand by) healthy adult, male subjects were enrolled in the study on the basis of inclusion and exclusion criteria. Plasma samples of all evaluable subjects completing all the periods of the study were analysed.

On the day of admission in Period I, twenty four (24) eligible (screening passed) volunteers reported for participation in the study. Twenty (20) subjects + two (02) additional subjects (as stand by) were enrolled in the study. Stand by subjects were not replaced and discharged without dosing in period I. Nineteen (19) subjects completed all periods of the study. One (01) subject dropped out of the study (Subject no. 04). A by-subject list of discontinued subjects is presented in Appendix 16.2.1. A by-subject list of subjects excluded from efficacy analysis is presented in Appendix 16.2.3.

The demographic data of all subjects admitted for the study are given in Section 14.1.

Table 10-1 Subject Disposition

	Number of Subjects
Reported on Day 1 of admission in Period I	24
Enrolled in the Study	20 + 02 Stand by
Completed the Study	19
Discontinued from the study	**01**
Due to Adverse Event(s)	-
Due to Predefined Discontinuation Criteria	-
Due to Lost to Follow-Up (Dropout)	01
Due to Administrative Reason(s)	-
Due to other Reason(s)	-

10.2 Protocol Deviations

Following protocol deviations were reported in the study. The protocol deviation details are provided in Appendix 16.2.2.

Table 10-2 - Protocol Deviations

Subject	Date	Period	Protocol Deviation	Impact Assessment
[redacted]	21/NOV/2013	III	As per protocol section 11.6 "sample collection procedure" post-dose in-house blood sample of subject number 06 in period-III was not collected within ± 02 minutes of the schedule time.	During statistical analysis actual time of blood sample collection were considered so there is no impact of these deviations on the outcome of study.

DETAILS OF SAMPLE COLLECTION

Subject No.	Date	Time-Point (Hours)	Schedule-time (HH:MM)	Actual-time (HH:MM)	Deviation	Deviation (Minutes)	Reason for deviation
[redacted]	21/NOV/2013	[redacted]	[redacted]	[redacted]	02	02	Cannula Blockage

11. EFFICACY EVALUATION

11.1 Data sets analyzed

Twenty (20) subjects + two (02) additional subjects (as stand by) were enrolled in the study. Stand by subjects were not replaced and discharged without dosing in Period I. Nineteen (19) subjects completed all periods of the study.

Table 11-1 Study Analysis Populations

	Number of Subjects
Dosed in Period I	20
Total Drop-outs/Withdrawals	01
Completed the Study	19
Post-Study Safety Population	20
Pharmacokinetics Population	19

11.2 Demographic and Other baseline characteristics

As per IEC approved protocol, twenty (20) subjects + two (02) additional subjects (as stand by) were enrolled in the study. Stand by subjects were not replaced and discharged without dosing in Period I. Nineteen (19) subjects completed all periods of the study. The demographic and baseline characteristics data is presented for (19) subjects who completed the study (Table 11-2). The age of subjects completing the study ranged from 21 – 44 years (29.0 ± 7.46 years). The weight of subjects ranged from 45.9 – 73.9 kg (59.05 ± 7.593 kg). The height of subjects ranged from 157.0 – 179.0 cm (168.05 ± 6.090 cm). The BMI of subjects ranged from 18.51 – 24.69 kg/m^2 (20.867 ± 2.0773 kg/m^2). All subjects were Asian. The data for demographics is presented in Section 14.1 and a by-subject listing of demographics is presented in Appendix 16.2.4.

Table 11-2 Demographics (Subjects Completing the Study)

		Treatment Group	
		Test Product N = 19	Reference Product N = 19
Age (years)	Mean ± SD	29.0 ± 7.46	29.0 ± 7.46
	Range	21 – 44	21 – 44
Age Groups N (%)	< 18 years	0 (0.00 %)	0 (0.00 %)
	18 – 40 years	16 (84.21 %)	16 (84.21 %)
	41 – 64 years	3 (15.79 %)	3 (15.79 %)
	65 – 75 years	0 (0.00 %)	0 (0.00 %)
	> 75 years	0 (0.00 %)	0 (0.00 %)
Sex N (%)	Male	19 (100.00 %)	19 (100.00 %)
	Female	0 (0.00 %)	0 (0.00 %)
Race N (%)	Asian	19 (100 %)	19 (100 %)
	White	-	-
	Black	-	-
	Caucasian	-	-
	Hispanic	-	-
	Other	-	-
Height (cm)	Mean ± SD	168.05 ± 6.090	168.05 ± 6.090
	Range	157.0 – 179.0	157.0 – 179.0
Weight (kg)	Mean ± SD	59.05 ± 7.593	59.05 ± 7.593
	Range	45.9 – 73.9	45.9 – 73.9
BMI (kg/m^2)	Mean ± SD	20.867 ± 2.0773	20.867 ± 2.0773
	Range	18.51 – 24.69	18.51 – 24.69
Other Factors		--	--

19 subjects completed the study.
BMI=Body Mass Index, SD=Standard Deviation

11.3 Measurements of Treatment Compliance

To ensure the subject swallowed the drug, a "mouth check" was performed by trained study personnel using disposable spatula and flashlight. The designated study personnel supervised the entire process of drug administration. The concentrations of Glycopyrrolate, measured in the present study confirmed the dosing compliance of subjects analyzed. Refer Appendix 16.2.5.

11.4 Efficacy Results and Tabulations of Individual Subject Data

11.4.1 Analyses of efficacy

Twenty (20) subjects + two (02) additional subjects (as stand by) were enrolled in the study. Stand by subjects were not replaced and discharged without dosing in Period I. Nineteen (19) subjects completed all periods of the study.

Data of 19 evaluable subjects completing the study was used for pharmacokinetic and statistical analysis and 20 subjects were considered for post study safety assessment.

None of the subject showed pre-dose concentrations > 5% of C_{max} values in any of the period of a particular subject. Hence, the subject's concentration data without any adjustment were used for the pharmacokinetic calculation in the study.

All the concentrations below the level of quantification (LLOQ) were set as zero (0) for pharmacokinetic calculations and statistical analysis.

The mean pharmacokinetic parameters of Glycopyrrolate for Reference Product (R1) and Test Product (T1) are summarized below in Table 11-3.

The mean pharmacokinetic parameters of Glycopyrrolate for Reference Product (R2) and Test Product (T2) are summarized below in Table 11-4.

Table 11-3 Summary Statistics of Pharmacokinetic Parameters T1 vs. R1 (Glycopyrrolate)

SUMMARY RESULTS	Dose-Adjusted - $AUC_{0\text{-}inf}$ (pg*hr/mL)
Untransformed Data	
TEST (T1)	
Arithmetic Mean	2199.2567
SD	714.68244
CV (%)	32.50
N	19
REFERENCE (R1)	
Arithmetic Mean	2338.5243
SD	877.22421
CV (%)	37.51
N	19
Log Transformed Data	
LSM (T1)	7.6566
LSM (R1)	7.7027
Geometric Mean (T1)	2114.5289
Geometric Mean (R1)	2214.3510
T1/R1 Ratio (%)	95.49
95% CI (Calculated)	84.61 - 107.78
Power (%)	97.70
Intra-subject CV (%)	17.68
Inter-subject CV (%)	21.64
p-value	0.0001

Table 11-4 Summary Statistics of Pharmacokinetic Parameters T2 vs. R2 (Glycopyrrolate)

SUMMARY RESULTS	Dose-Adjusted - $AUC_{0\text{-}inf}$ (pg*hr/mL)
Untransformed Data	
TEST (T2)	
Arithmetic Mean	2851.6047
SD	1226.01010
CV (%)	42.99
N	19
REFERENCE (R2)	
Arithmetic Mean	2219.1614
SD	695.53374
CV (%)	31.34
N	19
Log Transformed Data	
LSM (T2)	7.8714
LSM (R2)	7.6633
Geometric Mean (T2)	2621.2538
Geometric Mean (R2)	2128.6813
T2/R2 Ratio (%)	123.14
95% CI (Calculated)	102.74 - 147.59
Power (%)	80.04
Intra-subject CV (%)	26.71
Inter-subject CV (%)	20.22
p-value	0.0001

Table 11-5 Summary Statistics of Pharmacokinetic Parameters T1 vs. R2 (Glycopyrrolate)

SUMMARY RESULTS	Dose-Adjusted - AUC_{0-inf} (pg*hr/mL)
Untransformed Data	
TEST (T1)	
Arithmetic Mean	2199.2567
SD	714.68244
CV (%)	32.50
N	19
Reference (R2)	
Arithmetic Mean	2219.1614
SD	695.53374
CV (%)	31.34
N	19
Log Transformed Data	
LSM (T1)	7.6566
LSM (R2)	7.6633
Geometric Mean (T1)	2114.5289
Geometric Mean (R2)	2128.6813
T1/R2 Ratio (%)	99.34
95% C.I. (Calculated)	84.60 - 116.91
Inter-subject C.V. (%)	16.72
Intra-subject C.V. (%)	23.60
Power (%)	87.33
p-value	<0.0001

Table 11-6 Summary Statistics of Pharmacokinetic Parameters T2 vs. R1 (Glycopyrrolate)

SUMMARY RESULTS	Dose-Adjusted - AUC_{0-inf} (pg*hr/mL)
Untransformed Data	
TEST (T2)	
Arithmetic Mean	2851.6047
SD	1226.01010
CV (%)	42.99
N	19
Reference (R1)	
Arithmetic Mean	2338.5243
SD	877.22421
CV (%)	37.51
N	19
Log Transformed Data	
LSM (T2)	7.8714
LSM (R1)	7.7027
Geometric Mean (T2)	2621.2538
Geometric Mean (R1)	2214.3510
T2/R1 Ratio (%)	118.38
95% C.I. (Calculated)	98.10 - 143.16
Inter-subject C.V. (%)	18.26
Intra-subject C.V. (%)	27.71
Power (%)	77.15
p-value	<0.0001

Table 11-7 Summary Statistics of Pharmacokinetic Parameters T1 vs. T2 (Glycopyrrolate)

SUMMARY RESULTS	Dose-Adjusted - AUC_{0-inf} (pg*hr/mL)
Untransformed Data	
TEST (T1)	
Arithmetic Mean	2199.2567
SD	714.68244
CV (%)	32.50
N	19
TEST (T2)	
Arithmetic Mean	2851.6047
SD	1226.01010
CV (%)	42.99
N	19
Log Transformed Data	
LSM (T1)	7.6566
LSM (T2)	7.8714
Geometric Mean (T1)	2114.5289
Geometric Mean (T2)	2621.2538
T1/T2 Ratio (%)	80.67
95% C.I. (Calculated)	67.42 - 96.66
Inter-subject C.V.(%)	16.49
Intra-subject C.V. (%)	26.36
Power (%)	80.57
p-value	<0.0001

11.4.1.1 Pharmacokinetic parameters of Glycopyrrolate

The primary parameter in the present study was dose-adjusted AUC_{0-inf}. This parameter underwent descriptive and comparative statistical evaluation. Secondary parameters were T_{max}, AUC_{0-t}, K_{el}, $T_{1/2}$ and C_{max}.

The pharmacokinetic parameters that were estimated by using WinNonlin® software version 5.3 are presented in Table 11-8. The pharmacokinetic parameters are summarized in Table 11-9 and Table 11-10.

Table 11-8 Description of Pharmacokinetic Parameters

Parameter	Definition / Formula
C_{max}	Highest drug concentration.
T_{max}	Time at which the highest drug concentration occurs first time.
AUC_{0-t}	Area under the drug concentration-time curve from time zero to time (t), where t is the last time point with measurable concentration for individual formulation, by using linear trapezoidal rule. It can also be denoted as 'AUC_{last}'. $AUC_{0-t} = \Sigma((Ci + Ci\text{-}1) / 2) * (ti - ti\text{-}1)$ Where, i = 1,2,3…t Ci = Concentration at time ti ti = Time related to concentration Ci
Dose adjusted AUC_{0-inf}	Area under the drug concentration-time curve from time zero to time infinity after dose adjusted. It can also be denoted as 'AUCINF_D_obs'. Dose adjusted $AUC_{0-inf} = (AUC_{0-t} + C_t / K_{el})/dose$ Where, C_t = Last measurable concentration K_{el} = Terminal or elimination rate constant
$T_{1/2}$	Terminal half-life is the time taken by concentration to reduce by 50% during the elimination phase. It can also be denoted as HL_Lambda_z. $T_{1/2} = 0.693 / K_{el}$
K_{el}	Elimination rate or terminal rate constant is calculated as the negative slope of the log-linear terminal portion of the concentration–time curve by using linear regression. It can also be denoted as Lambda_z. $K_{el} = (\ln C_1 - \ln C_2) / (t_2 - t_1)$

All parameters listed above were determined in a model-independent way, considering sampling time deviation wherever applicable in the dataset as per Appendix-2 of Pharmacokinetic and Statistical Report. The highest concentration measured and the time at which first registered after each dose in subjects, were regarded as C_{max} and T_{max}, respectively. The $T_{1/2}$ was determined by means of a linear regression using the terminal elimination phase of the formulation according to the algorithm of program WinNonlin®. Parameters like K_{el}, $T_{1/2}$, and AUC_{0-t} were determined only for subjects in

which the log-linear terminal phase could clearly be defined. The summary of analysis of variance for Glycopyrrolate is provided in Table 11-11 and Table 11-12.

Table 11-9 Summary Statistics of Pharmacokinetic Parameters T1 vs. R1 (Glycopyrrolate)

Dose-Adjusted - AUC_{0-inf}	Mean peak concentration (Dose-Adjusted - AUC_{0-inf}) for the Test Product was 2199.2567 ± 714.68244 pg*hr/mL, as compared to 2338.5243 ± 877.22421 pg*hr/mL, for the Reference Product.

Table 11-10 Summary Statistics of Pharmacokinetic Parameters T2 vs. R2 (Glycopyrrolate)

Dose-Adjusted - AUC_{0-inf}	Mean peak concentration (Dose-Adjusted - AUC_{0-inf}) for the Test Product was 2851.6047 ± 1226.01010 pg*hr/mL, as compared to 2219.1614 ± 695.53374 pg*hr/mL, for the Reference Product.

Table 11-11 Summary of Analysis of Variance T1 vs. R1 (Glycopyrrolate)

PK Parameter	Source	DF	Type III SS	Mean Square	F Value	Pr > F	Interpretation
Dose Adjusted AUC_{0-inf}	SEQUENCE	2	1162254.142	581127.0708	3.23	0.0665	Non-Significant
	SUBJECT(SEQUENCE)	15	11335692.61	755712.8405	4.20	0.0035	Significant
	FORMULATION	1	147332.0047	147332.0047	0.82	0.3791	Non-Significant
	PERIOD	2	367873.6875	183936.8437	1.02	0.3824	Non-Significant
Dose Adjusted AUC_{0-inf}	SEQUENCE*	2	290563.5355	581127.0710	0.77	0.4809	Non-Significant
Dose Adjusted $LnAUC_{0-inf}$	SEQUENCE	2	0.14536054	0.07268027	2.36	0.1263	Non-Significant
	SUBJECT(SEQUENCE)	15	1.83501007	0.12233400	3.98	0.0047	Significant

PK Parameter	Source	DF	Type III SS	Mean Square	F Value	Pr > F	Interpretation
	FORMULATION	1	0.02009524	0.02009524	0.65	0.4309	Non-Significant
	PERIOD	2	0.05244458	0.02622229	0.85	0.4450	Non-Significant
Dose Adjusted $LnAUC_{0-inf}$	SEQUENCE*	2	0.03634014	0.07268027	0.59	0.5645	Non-Significant

Note: In the ANOVA the Sequence effects are compared with 10% level of significance and other factors are compared with 5% level of significance

* Tests of Hypotheses Using the Type III MS for SUBJECT(SEQUENCE) as an Error Term

Table 11-12 Summary of Analysis of Variance T2 vs. R2 (Glycopyrrolate)

PK Parameter	Source	DF	Type III SS	Mean Square	F Value	Pr > F	Interpretation
Dose Adjusted AUC_{0-inf}	SEQUENCE	2	5072912.005	2536456.003	4.87	0.0223	Significant
	SUBJECT(SEQUENCE)	15	17827163.50	1188477.567	2.28	0.0560	Non-Significant
	FORMULATION	1	3385895.912	3385895.912	6.50	0.0214	Significant
	PERIOD	2	2612428.772	1306214.386	2.51	0.1128	Non-Significant
Dose Adjusted AUC_{0-inf}	SEQUENCE*	2	1268228.001	2536456.003	2.13	0.1529	Non-Significant
Dose Adjusted $LnAUC_{0-inf}$	SEQUENCE	2	0.65951826	0.32975913	4.78	0.0235	Significant
	SUBJECT(SEQUENCE)	15	2.23589326	0.14905955	2.16	0.0685	Non-Significant
	FORMULATION	1	0.40919428	0.40919428	5.94	0.0269	Significant
	PERIOD	2	0.22651418	0.11325709	1.64	0.2244	Non-Significant
Dose Adjusted $LnAUC_{0-inf}$	SEQUENCE*	2	0.16487957	0.32975913	2.21	0.1439	Non-Significant

Note: In the ANOVA the Sequence effects are compared with 10% level of significance and other factors are compared with 5% level of significance

* Tests of Hypotheses Using the Type III MS for SUBJECT(SEQUENCE) as an Error Term

Interpretation of ANOVA Results:

The test/reference ratio of NRIM Limited's Glycopyrrolate 1mg/5mL (2 x 1mg/5mL) oral solution (Test product-1) and ROBINUL® FORTE 2mg Tablets (Reference

product-1) of [redacted] was 95.49%, the 95% confidence interval was 84.61% - 107.78% and p-value was 0.0001following an overnight fasting.

The test/reference ratio of NRIM Limited's Glycopyrrolate 2mg Tablets (Test product-2) and Glycopyrronium bromide oral solution 1mg/5mL (2 x 1mg/5mL) (Reference product-2) [redacted] was 123.14%, the 95% confidence interval was 102.74% - 147.59% and p-value was 0.0001 following an overnight fasting.

The detailed Studentised residuals (Lund's method) for Dose adjusted $AUC_{0\text{-}inf}$ are presented in Appendix-11 of pharmacokinetic and statistical report.

11.4.2 Statistical / Analytical issues

There were no statistical/ analytical issues in this study.

11.4.2.1 Adjustments for covariates

No adjustment for covariates was made, as this was a relative bioavailability study.

11.4.2.2 Handling of dropouts or missing data

Concentrations below the low level of quantification (LLOQ) at anywhere in the profile were set as zero (0) for pharmacokinetic calculations.

For Glycopyrrolate, LLOQ = 5.042 pg/mL.

The 'Missing' sample (marked as 'Missing') and the 'Not Reportable' sample (marked as NR'), if observed anywhere in the data, were not taken into account, when calculating the pharmacokinetic parameters. In such case, the previously available value had been automatically connected with the next available value, within the WinNonlin® software.

For Glycopyrrolate, a total of 2240 [(28 samples × 4 period × 19 subjects) – (0 NR + 0 Missing) = (2240 – 0) = 2240] drug concentration values from 19 evaluable subjects, who completed the study according to the approved protocol, were included in the pharmacokinetic calculation.

11.4.2.3 Interim analysis and data monitoring

As this is a relative bioavailability study, interim analysis and data monitoring were not carried out.

11.4.2.4 Multicenter studies

This section is not applicable.

11.4.2.5 Multiple comparisons/ Multiplicity

As this is a single dose relative bioavailability study, multiple comparisons were not carried out.

11.4.2.6 Use of an "Efficacy subset" of subjects

As this is a relative bioavailability, this section is not applicable.

11.4.2.7 Active-control studies intended to show equivalence

This section is not applicable.

11.4.2.8 Examination of subgroups

As this is a relative bioavailability study, this section is not applicable.

11.4.3 Tabulation of individual response data

Pharmacokinetic parameters of the Test product (T1 / T2) or Reference Product (R1 / R2) are presented in Appendix-4 of pharmacokinetics and statistical report.

11.4.4 Drug dose, drug concentration and relationships to response

As this is a relative bioavailability study, drug concentration-response relationship is not relevant as there was no measurement of pharmacodynamic or clinical effect.

11.4.5 Drug-drug and drug-disease interactions

As this is a relative bioavailability study, this section is not applicable.

11.4.6 By-subject displays

Drug concentration tables are presented in Appendix-3 of pharmacokinetic and statistical report. Tables for pharmacokinetic parameters are presented in Appendix- 4 of pharmacokinetic and statistical report.

Results from the comparative statistical evaluation of the relative bioavailability of the test formulation compared to the reference formulation are presented in Appendix-5 of pharmacokinetic and statistical report.

Graphical presentation of mean drug concentration profiles and formulation wise profiles for the test and reference formulations are found in Appendix-6 and Appendix-7 of pharmacokinetic and statistical report, respectively.

Graphical presentation of individual drug concentration profiles and K_{el} charts for the test and reference formulations are found in Appendix-8 and Appendix-9 of pharmacokinetic and statistical report, respectively.

All pharmacokinetic primary and secondary parameters evaluations based on non-compartmental analysis details for the test and reference formulations are presented in Appendix-10 of pharmacokinetic and statistical report and Geometric mean ratios are presented in Appendix-12 of pharmacokinetic and statistical report.

11.4.7 Efficacy conclusions

The test/reference ratio of NRIM Limited's Glycopyrrolate 1mg/5mL (2 x 1mg/5mL) oral solution (Test product-1) and ROBINUL® FORTE 2mg Tablets (Reference product-1) [redacted] was 95.49%, the 95% confidence interval was 84.61% - 107.78% and p-value was 0.0001following an overnight fasting.

The test/reference ratio of NRIM Limited's Glycopyrrolate 2mg Tablets (Test product-2) and Glycopyrronium bromide oral solution 1mg/5mL (2 x 1mg/5mL) (Reference product-2) of [redacted] was 123.14%, the 95% confidence interval was 102.74% - 147.59% and p-value was 0.0001 following an overnight fasting.

The detailed Studentised residuals (Lund's method) for Dose adjusted $AUC_{0\text{-}inf}$ are presented in Appendix-11 of pharmacokinetic and statistical report.

12. SAFETY EVALUATION

Twenty (20) subjects + two (02) additional subjects (as stand by) were enrolled in the study. Stand by subject were not replaced and discharged without dosing as there was no withdrawn or dropout in the study before dosing of Period I. All the twenty (20) subjects were included in the post-study safety evaluation.

12.1 Extent of Exposure

Twenty (20) subjects + two (02) additional subjects (as stand by) were enrolled in the study. Stand by subjects were not replaced and discharged without dosing in Period I. Nineteen (19) subjects completed all the periods of the study. A single dose of either Test products (T1 [Glycopyrrolate 2mg/10mL oral solution] or T2 [One Glycopyrrolate 2mg tablet]) or Reference products (R1 [One ROBINUL® FORTE 2mg Tablet] or R2 [Glycopyrronium bromide 2mg/10mL oral solution]) was administered in sitting posture along with 240 ml of drinking water at room temperature in each period as per the randomization schedule. Therefore, the total consumption of Glycopyrrolate oral solution for the subjects who completed this study was 4mg/20mL and the total consumption of Glycopyrrolate tablet was 4 mg. An actual wash out period of 05 days was maintained between two consecutive days as per IEC approved protocol.

12.2 Adverse Events (AEs)

12.2.1 Brief summary of adverse events

There were no adverse events reported in the study.

12.2.2 Display of adverse events

Not Applicable.

12.2.3 Analysis of adverse events

Not Applicable.

12.2.4 Listing of adverse events by subjects

Not Applicable.

12.3 Deaths, other serious adverse events and other significant adverse events

No deaths or other serious or significant adverse events were registered in the course of the study.

12.3.1 Listing of deaths, other serious adverse events and other significant adverse events

Not Applicable.

12.3.1.1 Deaths

12.3.1.2 Other serious adverse events

Not Applicable.

12.3.1.3 Other significant Adverse Events

Not Applicable.

12.3.2 Narratives of deaths, other serious adverse events or certain other significant adverse events

Not Applicable.

12.3.3 Analysis and discussion of deaths, other serious adverse events

Not Applicable.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of individual laboratory measurements of subject and each abnormal laboratory values

Screening Visit

All laboratory parameters were evaluated vs. laboratory reference range (Appendix 16.2.8.3). Any value beyond the laboratory reference range was subjected to clinical correlation to declare whether it is significant or non-significant.

Screening laboratory data is also listed by subject in data listings of Appendix 16.2.8.1.

Follow Up Visit

All laboratory parameters were evaluated vs. laboratory reference range (Appendix 16.2.8.3). Any value beyond the laboratory reference range was subjected to clinical correlation to declare whether it is significant or non-significant.

Follow-up laboratory data is also listed by subject in data listings of Appendix 16.2.8.2.

12.4.2 Evaluation of each laboratory parameter

A safety laboratory examination in blood was carried out during screening and after collection of last pharmacokinetic blood sample of last study period (post study laboratory evaluation). In general, the laboratory parameters were within the reference range of the clinical laboratory. All laboratory parameters were evaluated. Any value beyond the laboratory reference range was subjected to clinical correlation to declare whether it is significant or non-significant.

12.4.2.1 Laboratory values over time

As this is a relative bioavailability study, this section is not applicable.

12.4.2.2 Individual subject changes

As this is a relative bioavailability study, the changes in subject values were not analyzed.

12.4.2.3 Individual clinically significant abnormalities

None of the subjects had any significant abnormalities during the study.

Entry Laboratory Examination (Screening)

Refer to Appendix 16.2.8.1.

Final Laboratory Examination (Post study safety assessment)

Refer to Appendix 16.2.8.2.

12.5 Vital signs, physical findings and other observations related to safety

Safety Examinations during the Study

Please refer to Appendix 16.2.9.

Safety Examinations during in-house stay, Discharge from Clinical Facility

A complete clinical examination of the subject, including vital signs, was carried out at admission and at discharge in each study period.

Detailed vital signs data listings are presented in Appendix 16.2.9.

12.6 Safety conclusions

A single dose of oral solution containing Glycopyrrolate 2mg/mL or tablet containing Glycopyrrolate 2 mg (either of Test or Reference) was well tolerated in each study period. There was no adverse event or serious adverse event recorded in the study.

No clinically significant vital sign changes were observed during the study (Refer to Appendix 16.2.9).

13. DISCUSSION AND OVERALL CONCLUSIONS

13.1 DISCUSSION

Primary objective of the study was to evaluate the relative bioavailability of Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution of NRIM Limited, U.K. and Glycopyrrolate 2mg tablets of NRIM Limited, U.K. with ROBINUL® FORTE 2mg Tablets of [redacted] and Glycopyrronium bromide oral solution 1mg/5mL (2 X 1mg /5mL) of [redacted]. in healthy, adult, human subjects under fasting condition. Secondary objective was to evaluate safety parameters, including adverse events and clinical laboratory tests.

Twenty (20) subjects + two (02) additional subjects (as stand by) were enrolled in the study. Stand by subjects were not replaced and discharged without dosing in Period I. Nineteen (19) subjects completed all the periods of the study. One (01) subject dropped out of the study (Subject No. 04). Each subject who completed the study was administered two units of oral solution containing Glycopyrrolate 1mg/50mL or one table containing Glycopyrrolate 2 mg, either of Test product (T1 / T2) or Reference Product (R1 / R2) in each study period. Therefore, the total consumption of Glycopyrrolate oral solution was 4mg/20mL and total consumption of Glycopyrrolate tablet was 4 mg for the subjects who completed the study. An actual wash out period of 05 days was maintained between any two consecutive dosing days as per IEC approved protocol.

13.2 Efficacy

13.2.1 Extent of Absorption

Dose-adjusted $AUC_{0\text{-}inf}$

The ratio of geometric least squares mean of Test product (T1) and Reference product (R1) of ln-transformed pharmacokinetic parameter dose-adjusted $AUC_{0\text{-}inf}$ was 95.49 %.

The ratio of geometric least squares mean of Test product (T2) and Reference product (R2) of ln-transformed pharmacokinetic parameter dose-adjusted $AUC_{0\text{-}inf}$ was 123.14 %.

The ratio of geometric least squares mean of Test product (T2) and Reference product (R1) of ln-transformed pharmacokinetic parameter dose-adjusted $AUC_{0\text{-}inf}$ was 99.34 %.

The ratio of geometric least squares mean of Test product (T1) and Reference product (R2) of ln-transformed pharmacokinetic parameter dose-adjusted $AUC_{0\text{-}inf}$ was 118.38 %.

The ratio of geometric least squares mean of Test product (T1) and Test product (T2) of ln-transformed pharmacokinetic parameter dose-adjusted $AUC_{0\text{-}inf}$ was 80.67 %.

The two one-sided 95% confidence interval for the ratio of geometric least squares mean of Test product (T1) and Reference product (R1) was 84.61 - 107.78 % with a power of 97.70%.

The two one-sided 95% confidence interval for the ratio of geometric least squares mean of Test product (T2) and Reference product (R2) was 102.74 - 147.59 % with a power of 80.04%.

The two one-sided 95% confidence interval for the ratio of geometric least squares mean of Test product (T1) and Reference product (R2) was 84.60 - 116.91 % with a power of 87.33%.

The two one-sided 95% confidence interval for the ratio of geometric least squares mean of Test product (T2) and Reference product (R1) was 98.10 - 143.16 % with a power of 77.15%.

The two one-sided 95% confidence interval for the ratio of geometric least squares mean of Test product (T1) and Test product (T2) was 67.42 - 96.66 % with a power of 80.57%.

13.3 CONCLUSION

The test/reference ratio of NRIM Limited's Glycopyrrolate 1mg/5mL (2 x 1mg/5mL) oral solution (Test product-1) and ROBINUL® FORTE 2mg Tablets (Reference product-1) of [redacted] was 95.49%, the 95% confidence interval was 84.61% - 107.78% and p-value was 0.0001following an overnight fasting.

The test/reference ratio of NRIM Limited's Glycopyrrolate 2mg Tablets (Test product-2) and Glycopyrronium bromide oral solution 1mg/5mL (2 x 1mg/5mL) (Reference product-2) of [redacted] was 123.14%, the 95% confidence interval was 102.74% - 147.59% and p-value was 0.0001 following an overnight fasting.

The detailed Studentised residuals (Lund's method) for Dose adjusted $AUC_{0\text{-}inf}$ are presented in Appendix-11 of pharmacokinetic and statistical report.

Safety conclusion

A single oral dose of Glycopyrrolate 1mg /5mL (2 X 1mg /5mL) oral solution or Glycopyrrolate 2mg tablet of the investigational product (both Test and Reference) was well tolerated in each period of the study. There was no adverse event or serious adverse event recorded in the study.

No clinically significant vital sign changes were observed during the study (Refer to Appendix 16.2.9).

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

Subject No.	Initial of Subjects	Gender	Registration No.	Race	Ethnicity	Age (Years)	Height (cm)	Weight (Kg)	BMI (Kg/m^2)
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]

Subject No.	Initial of Subjects	Gender	Registration No.	Race	Ethnicity	Age (Years)	Height (cm)	Weight (Kg)	BMI (Kg/m^2)
[redacted]	[redacted]	Male	[redacted]	Asian	Not-Hispanic or Latino	[redacted]			
N						**20**	**20**	**20**	**20**
Mean						**28.8**	**168.13**	**59.39**	**20.966**
SD						**7.32**	**5.939**	**7.543**	**2.0699**
Minimum						**21**	**157.0**	**45.9**	**18.51**
Median						**26.5**	**168.0**	**59.7**	**21.09**
Maximum						**44**	**179.0**	**73.9**	**24.69**
CV%						**25.41**	**3.53**	**12.70**	**9.87**
Geom. Mean						**28.02**	**168.03**	**58.93**	**20.87**

14.1.1 Discontinued Subjects

Subject No.	Reason for Dropout or Withdrawn /Replacement	Period	Replaced?	Replaced With
[redacted]	Subject was considered as dropout from the study on 16/NOV/2013, as subject did not report to the clinical facility for period-II check-in.	II	NO	N/AP

14.2 Efficacy Data

Refer Section 11 of this report for efficacy data.

14.3 Safety Data

14.3.1 Display of adverse events

Not Applicable.

14.3.2 Listings of deaths, other serious adverse events

Not Applicable.

14.3.3 Narratives of Deaths, other serious adverse events

Not Applicable.

14.3.4 Clinically significant abnormal laboratory value listing (Each Subject)

Refer Appendix 16.2.8.1 for abnormal laboratory value listing.

15. REFERENCE LIST

15.1 References for Background Information

- Product Information: ROBINUL® FORTE 2mg Tablets, Shionogi Pharma, Inc., Atlanta, GA 30328
- Product Information: CUVPOSATM. Shionogi Pharma, Inc., Atlanta, GA 30328

15.2 References for Report Preparation

- ICH Topic E-3: Structure and Content of Clinical Study Reports. Step 4, Consensus Guideline from 30.11.1995. Note for Guideline on Structure and Content of Clinical Study Reports (CPMP/ICH/137/95). July 1996
- The European Agency for Evaluation of Medicinal Products, Human Medicines Evaluation Unit ICH Topic E2A Note for guidance on clinical safety data management: Definitions and standards for expedited reporting (CPMP/ICH/377/95). 1 6.1995

15.3 References for Statistical Evaluation

- ICH Guideline "Statistical Principles for Clinical Trial" Step 4, 1998
- Note for guidance on the investigation of Bioavailability and Bio-equivalence (CPMP/EWP/ QWP/1401/98) July 2001
- "Guideline on the investigation of bioequivalence" (CPMP/EWP/ QWP/1401/98 Rev. 1/Corr**), July 2010
- EMA/618604/2008 Rev. 4 of the EMA's Questions & Answers: positions on specific questions addressed to the pharmacokinetics working party; February, 2012.

16. APPENDICES

16.1 Study Information

16.1.1 Protocol and protocol amendments

16.1.2 Sample case report form

16.1.2.1 Sample screening source record form

16.1.2.2 Sample study source record form

16.1.3 List of IECs or of IRBs (plus name of the committee chair if required by the regulatory authority) – representative written information for volunteer and sample consent forms

16.1.4 List and description of investigators and others important in the study, including brief CVs or equivalent summaries of training and experience relevant to the performance of the clinical study and financial disclosure

16.1.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement

16.1.6 Listing of subjects receiving test drug(s)/ investigation products from specified batches, where more than one batch was used and certificate of analysis

16.1.7 Randomization scheme and codes (subject identification and treatment assignment) (SAS® system generated output)

16.1.8 Audit certificate (if available)/ QA certificate

16.1.9 Documentation of Pharmacokinetic and Statistical Methods (Pharmacokinetic and statistical report)

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 referenced in the Report

16.2 Subject data listings

16.2.1 Discontinued subjects

16.2.2 Protocol deviations

16.2.3 Subject's excluded from the efficacy analysis

16.2.4 Demographic data

16.2.5 Compliance and/or drug concentration data (if available)

16.2.6 Individual efficacy response data

16.2.7 Adverse events listing (each subject)

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

16.2.8.1 Subjects screening laboratory examination (Out of range values)

16.2.8.2 Subjects post study safety laboratory examination report (Out of range values)

16.2.8.3 Laboratory reference ranges

16.2.9 Vital Signs

16.2.9.1 Vital Signs at Screening

16.2.9.2 Vital signs during period I

16.2.9.3 Vital signs during period II

16.2.9.4 Vital signs during period III

16.2.9.5 Vital signs during period IV

16.2.10 Time of reporting, admission and discharge and actual time of study drug administration

16.2.11 Consumption of meal

16.3 Source record form

16.3.1 Source record form for deaths, other serious adverse events and withdrawals for AE

16.3.2 Other Source record form submitted