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A Bioequivalence Study of Two Nicotine 2 mg Lozenge Formulations in Healthy adult Indian human male smoker Subjects

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Introduction

- Nicotine 2 mg lozenges are used to help people stop smoking
- They can reduce the urge to smoke by replacing some of the nicotine provided by tobacco and help to resist cigarettes
- They do not have the health dangers of tobacco because they do not contain the tar or carbon monoxide of cigarette smoke
- This medicine contains nicotine resin which when sucked, slowly releases nicotine from the resin which is then absorbed through the lining of the mouth
- This nicotine relieves some of the cravings and unpleasant withdrawal symptoms, such as feeling ill or irritable, that smokers frequently feel when they try to give up

Instructions For Use

- Nicotine 2mg lozenges are for smokers who smoke their first cigarette more than 30 minutes after waking up. They can help them to stop smoking straight away
- Adults (aged 18 years and over)

Step 1 **Weeks 1 to 6**	**Step 2** **Weeks 7 to 9**	**Step 3** **Weeks 10 to 12**
Initial treatment period	Step down treatment period	Step down treatment period
1 lozenge every 1-2 hours	1 lozenge every 2-4 hours	1 lozenge every 4-8 hours

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Study Rationale And Objectives

- Sponsor had developed a new generic formulation of Nicotine 2 mg Lozenge having the same composition as the innovator brand NiQuitin® 2 mg Lozenge of GlaxoSmithKline Consumer Healthcare, UK
- Therefore, the aim of this study was to determine bioequivalence of a generic and innovator formulation of Nicotine 2 mg Lozenge for the purpose of marketing approval of the generic formulation
- To monitor the safety and tolerability of a single dose of Nicotine 2 mg when administered in 28 healthy adult human smoker subjects under fasting conditions

Study Design And Treatments

- This was an open label, randomized, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study in healthy adult human smoker subjects under fasting conditions
- 28 subjects randomized to receive two treatments with a washout period of 7 days

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Ethical Approval

- The study protocol and amendments were reviewed and approved by an Independent Ethics Committee
- The study was conducted in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and European Guidelines for the conduct of bioequivalence studies

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Screening And Eligibility Criteria

- Healthy volunteers screened within 21 days prior to the first dosing day. The screening included:
- Breath alcohol test, drugs of abuse test
- Clinical laboratory tests (which include haematology, biochemistry and urinalysis, HIV I and II, hepatitis A, B and C)
- Physical examination (including Vital signs examination, well being), ECG
- Eligible subjects: age 18 to 45 years, BMI 18.5 to 30 kg/m^2
- light smokers (who smoke ≤ 10 cigarettes per day regularly since last three months), and exhaled CO Level measurement (≥ 10 ppm) at screening and who agree to refrain from smoking during the housing period

Procedures On Check-in Day (Day 1)

- 33 healthy volunteers reported on check in day
- written informed consent was obtained from all willing volunteers
- First 28 volunteers were recruited into the study-
- exhaled carbon monoxide (≥ 10 ppm)
- Negative breath alcohol test and negative drugs of abuse test
- Normal vital signs examination and well-being before check in
- those volunteers who completed a training session conducted using commercially available confectionery lozenges before check-in
- Subject's belongings were thoroughly checked. They were instructed to remove all outer garments (which were confiscated until discharge), had shower and wore clothing provided by the CRO for the duration of confinement

Admission And Procedures

- Subjects were checked-in the clinical facility at least 36 hours before dosing to ensure abstinence from smoking and/or use of other nicotine containing products and remained in the clinical facility for at least 24 hours after dosing in each period

Procedures On Pre-study Day (Day 2)

- 6 readings of exhaled CO level measurement were taken as per randomization prior to dosing
- A downward trend in readings was observed
- Subjects ate standardized meal in the evening between 19:30 to 20:30. No foods were allowed after 21:00

Smokerlyzer

Smokerlyzer is a breath carbon monoxide (CO) monitor

It measures the amount of CO on a smoker's breath

Procedures On The Study Day (Day 3)

- Starting from 06:00, vital signs were checked and a cannula was placed
- Exhaled CO levels were measured within 30 minutes before dosing
- 5ml pre-dose blood sample was collected within 15 minutes prior to dosing
- A single oral dose of Nicotine 2 mg Lozenge of the test or the reference product was administered orally
- The lozenge was moved from side to side in subjects mouths every 4 seconds (prompted by metronome) until it is completely dissolved, for approximately 20-30 minutes. Every 30 seconds the subjects were instructed to swallow their saliva at a verbal command
- All subjects were dosed between 07:00 to 09:15 in both periods

Procedures On The Study Day (Day 3)

- Drug administration was followed by a mouth check to assess compliance
- After dosing, subjects were allowed to engage in non-strenuous activities such as watching television or reading newspaper but had to maintain a seating position for at least 2 hours
- Standardized meals were served 4 hours after dosing
- No water was permitted 1 hour before and 1 hour after dosing
- Subsequent blood samples of 5 ml each collected at 0.08, 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 2.00, 3.00, 4.00, 6.00, 9.00, 12.00 and 16.00 hours
- Blood samples were collected with time zero corresponding to the start time of dosing
- Total blood loss was approximately 197 ml

Handling Of Blood Samples

- Blood samples were collected into labelled tubes (free of nicotine contamination) containing sodium heparin anticoagulant
- Tubes were kept in an iced-water bath till they are centrifuged
- Plasma obtained by centrifugation at 8°C and at 3000 rpm for 10 minutes
- Each plasma sample was divided into two aliquots. The label on the vial did not have information related to the treatment and the time point, instead a specific code for each sample (aliquot 1 and 2 had same code) was assigned and the analyst did not have access to this code until the completion of the analysis
- All plasma samples were stored upright below –70 ± 10°C until analysis

Exhaled CO Level Measurements

- 4 post-dose readings of exhaled carbon monoxide (CO) levels were taken as per randomisation (Day 3)
- If CO level of subject were higher than previous reading and ≥ 10ppm, it assumed to indicate illicit smoking and the subject was to be discontinued
- At all time points where exhaled CO levels were measured; oral cavity examination was also done to detect any illicit use of tobacco products. Use of such tobacco products would result in subject being removed from the study

Safety Monitoring

- Vital signs were checked at 4hr, 8hr, 12hr, 24hr (± 1hr) post dose
- Subjects were asked questions at the time of vital signs examination regarding their overall well being and any feelings of discomfort
- A medical physician was present at all times throughout the study to monitor the subjects and provide treatment
- All adverse events reported by the subjects were recorded
- After 3 days from the dosing of period 2, all subjects had undergone post study safety examination and all subjects were found fit

Bioanalysis

- Nicotine plasma concentrations were determined using validated LC-MS/MS method
- The lower limit of quantification was 0.20 ng/ml for nicotine and calibration standards ranged from 0.20 to 25.00 ng/ml

Demographics

Subjects	Age (yrs) Mean ± SD	Weight (kg) Mean ± SD	Height (m) Mean ± SD	BMI (Kg/m^2) Mean ± SD
All 28 recruited	25 ± 6	65.6 ± 8.4	1.69 ± 0.06	23.0 ± 2.5
21 considered for final pharmacokinetic and statistical assessment	24 ± 5	65.8 ± 8.3	1.69 ± 0.06	23.0 ± 2.6

Results And Discussion

- 28 subjects were randomized and dosed for period 1
- 1 subject was discontinued due to AE in period 1
- 27 subjects were dosed for period 2
- 27 subjects completed the study and all 28 subjects were analyzed
- 21 subjects were considered for final Pharmacokinetic and Statistical Assessment
- 6 subjects were not considered as their pre-dose concentration were greater than 5 percent of the Cmax

Safety And Tolerability

- Study treatments were generally well tolerated
- No serious adverse events/deaths
- 11/28 (39.29%) subjects reported 21 adverse events
- 14 AEs after administration of test and 7 AEs after reference formulation
- 1 subject was discontinued due to AE who had nausea, vomiting, giddiness
- AEs reported were giddiness (25%), nausea (17.86%), headache (14.29%), abdominal pain (7.14%), vomiting (3.57%), neck pain (3.57%), pain at cannulation site (3.57%)

Pharmacokinetic Parameters

- The pharmacokinetic results for nicotine are presented below (Mean ± SD):

Pharmacokinetic Parameters	Mean ± SD	
	Test (T)	Reference (R)
N	21	21
C_{max} (ng/ml)	9.18 ± 2.87	8.52 ± 2.43
AUC_{0-t} (hr.ng /ml)	39.59 ± 19.78	37.54 ± 12.27
$AUC_{0-\infty}$ (hr.ng /ml)	45.14 ± 26.60	42.46 ± 14.93
***T_{max} (hr)**	0.50 (0.33-1.50)	0.50 (0.33-2.02)
K_{el} (1/hr)	0.179 ± 0.069	0.191 ± 0.060
$T_{1/2}$ (hr)	4.54 ± 2.05	3.97 ± 1.22

*median (range)

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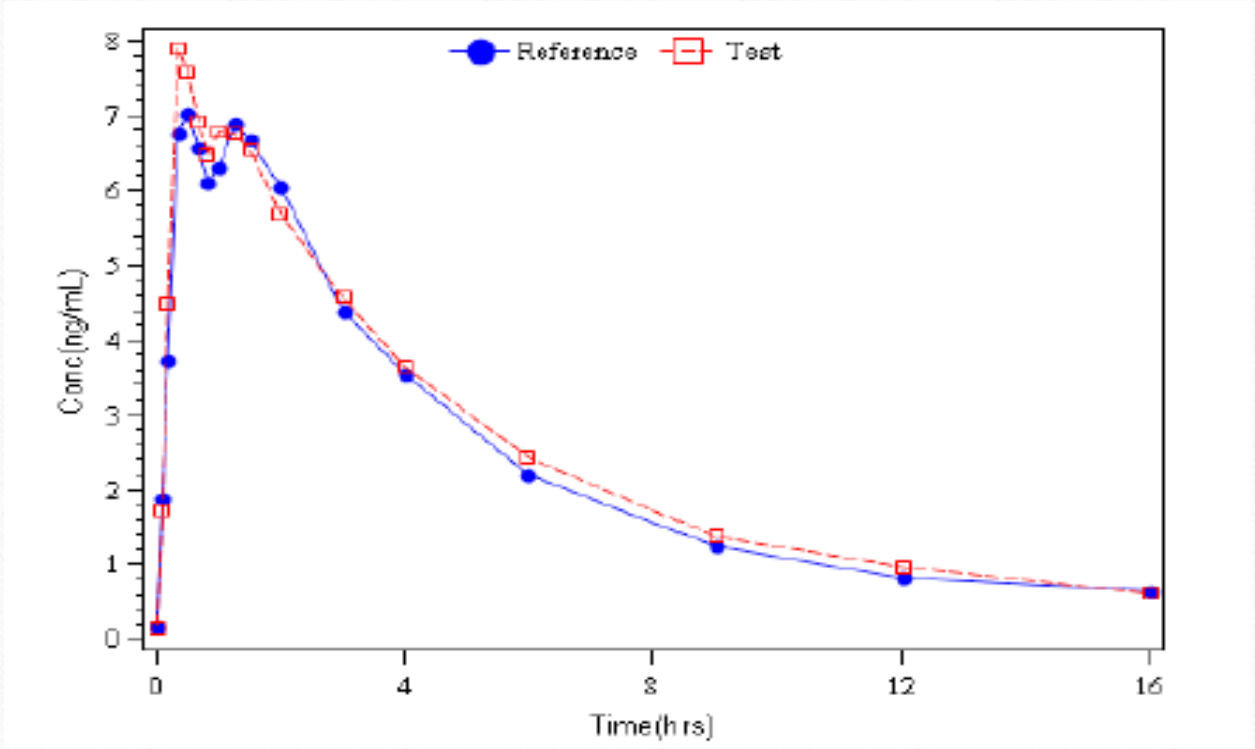
Mean Graph (Linear) For Plasma Concentration Vs Time Profile Of Nicotine



90% Confidence Intervals

- Geometric least square mean, %T/R and 90% confidence intervals of ln-transformed pharmacokinetic parameters of Test and Reference product of Nicotine without baseline adjusted are presented below:

Pharmacokinetic Parameters	TestGeoLSM	RefGeoLSM	*(%)T/R	90% Confidence Interval
N	21	21	-	-
C_{max} (ng/ml)	8.7850	8.2091	107.01	96.16-119.10
AUC_{0-t} (hr. ng/ml)	36.1669	35.6764	101.37	92.16-111.51

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Conclusion

- The 90% Confidence Intervals for C_{max} and AUC_{0-t} for Test and Reference products for nicotine 2mg lozenges were within predefined acceptance range of 80.00 to 125.00%
- Therefore, both the formulations of Nicotine 2 mg Lozenge were considered bioequivalent
- Both formulations were well tolerated in the population studied

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Thank you

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