2. SYNOPSIS

INVESTIGATOR: [redacted]

STUDY CENTER: [redacted]

PUBLICATIONS (REFERENCE): None

STUDY INITIATION AND COMPLETION DATES: 14 August 2017 to 09 January 2018

PHASE OF DEVELOPMENT: Phase 1

STUDY OBJECTIVES

The primary objective of this study was to demonstrate bioequivalence between Nicorette Extra Mint Gum 2 mg and Nicorette Mint Gum 2 mg, as well as between Nicorette Extra Mint Gum 4 mg and Nicorette Mint Gum 4 mg with respect to the single-dose pharmacokinetics of nicotine. The baseline-corrected maximum observed nicotine concentrations (cC_{max}) and the baseline-corrected areas under the concentration-vs.-time curves until the last measurable concentration and until infinity ($cAUC_t$ and $cAUC_{inf}$), were used to assess bioequivalence.

Secondary objectives were:

- to describe the nicotine pharmacokinetics of the investigational products with respect to the extrapolated parts of $cAUC_{inf}$ ($cAUC_{extra}$), the times at which the maximum concentration was observed (t_{max}), the terminal elimination rate constants (λ_z) and the terminal elimination nicotine half-lifes ($t_{1/2}$),
- to determine the amount of nicotine extracted from each gum, and
- to evaluate the tolerability of the treatments.

METHODOLOGY

STUDY DESIGN

This was a single-center, randomized, single-dose, fasting, open-label, cross-over study in 76 healthy male and female subjects (habitual smokers). Single doses of the investigational products (IP) (i.e. Nicorette Extra Mint Gum 2 and 4 mg, and Nicorette Mint Gum 2 and 4 mg) were administered as single doses at separate visits. Periods without NRT, lasting for at least 36 hours, separated treatment visits.

Following an at least12-hour long nicotine abstinence period at the study site, subjects received the IPs in the morning of treatment visit days.

Blood samples for pharmacokinetic analysis were drawn pre-dose (within 5 minutes prior to start of drug administration, i.e., start of chewing) and at 5, 10, 15, 20, 30, 45, and 60 minutes, as well as 1.5, 2, 4, 6, 7, 8, 9, and 10 hours after start of administration. Thus, 16 samples were collected per treatment visit.

The gums were collected after treatment administration (i.e. 30 minutes of chewing) and analyzed to determine residual amount of nicotine.

Subjects were monitored to capture any adverse events that may have occurred.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED)

Seventy-six (76) subjects, 71 males and 5 females, were randomized to treatment. In this study, all subjects had at least some valid pharmacokinetic (PK) data and were therefore included in the full analysis set. Seventy-one (71) subjects had evaluable cC_{max}, $cAUC_t$ and $cAUC_{inf}$ values for both 2 mg treatments and were therefore included in the bioequivalence assessment. The corresponding number for the 4 mg treatments were 68.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Healthy male subjects between the ages of 18 and 55 years, inclusive, and healthy female subjects between the ages of 18 and 45 years, inclusive, were enrolled. The subjects had to have a Body Mass Index (BMI) between 19 and 25 kg/m^2. Subjects were to be smokers of at least 10 tobacco cigarettes per day and were to have done so for at least one year preceding inclusion. Females of childbearing potential were to have a negative pregnancy test at the screening visit. Male or non-pregnant, non-lactating female agreed to the contraceptive requirements including male's and female's partner was to use of a highly effective methods of birth control for at least 3 months before the study, during the study and for 30 days after the last dose of the study drug

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Table S1 provides information about the investigational products.

Table S1: Identity of Investigational Products

	Treatment A	Treatment B	Treatment C	Treatment D
Compound Name	Nicotine	Nicotine	Nicotine	Nicotine
Product Name	Nicorette Extra Mint Gum	Nicorette Mint Gum	Nicorette Extra Mint Gum	Nicorette Mint Gum
Dosage Form	Chewing Gum	Chewing Gum	Chewing Gum	Chewing Gum
Unit Dose	2 mg	2 mg	4 mg	4 mg
Route of	Oral	Oral	Oral	Oral

	Treatment A	Treatment B	Treatment C	Treatment D
Compound Name	Nicotine	Nicotine	Nicotine	Nicotine
Administration				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subjects were instructed to place the gum on the tongue and chew it once every 2 seconds for 30 minutes; a metronome was used to time the chewing rate. They were also instructed to swallow saliva once every minute (±5 seconds). Talking was not allowed during the chewing period.

DURATION OF TREATMENT

Each of the four treatments was given on separate treatment days, separated by wash-out periods of at least 36 hours.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: N/A

CRITERIA FOR EVALUATION

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations

All randomized subjects with any valid pharmacokinetic parameter data from at least one of the investigational products were included in the full analysis set (FAS). However, in statistical treatment comparisons of the geometric means of cC_{max}, $cAUC_t$, and $cAUC_{inf}$, in each case only data from subjects with valid parameter values for both treatments were included in the statistical model-fitting process.

Safety Evaluations

All subjects that received any treatment were included in the safety analysis.

STATISTICAL METHODS

For all pharmacokinetic parameters, plasma nicotine concentrations and the amount of nicotine released from the gums, descriptive summary measures were presented by treatment and, were applicable, by measurement time. For continuous variables, they included mean values, standard deviations, medians and maximum as well as minimum values. In addition, geometric mean values and coefficients of variation were calculated for the primary

pharmacokinetic parameters, i.e. cC_{max}, $cAUC_t$ and $cAUC_{inf}$. For $t_{max,}$ the frequency distribution was additionally tabulated by treatment.

Statistical comparisons of treatments with respect to cC_{max}, $cAUC_t$ and $cAUC_{inf}$, were in each case be based on a linear model for log transformed (natural log) pharmacokinetic parameter data. The statistical models included treatment as a fixed effect, dichotomous variable and covariate adjustments for period, sequence, and subject, nested within sequence, as fixed effects. In addition, the model incorporated baseline plasma nicotine concentration (log transformed) as a covariate. Carryover effects were assumed ignorable.

Confidence intervals for parameter geometric mean ratios were derived using estimated means and residual variance estimates from the fitted model. In each case statistical estimates were based on data from subjects with non-missing, valid observations for both compared treatments.

For a given dose, bioequivalence between Nicotine Extra Mint Gum and Nicorette Mint Gum were concluded if

- the model-based 90% confidence interval for the treatment geometric mean ratio for cC_{max} was contained in the equivalence interval (0.8000, 1.2500), and
- the model-based 90% confidence interval for the treatment geometric mean ratio for $cAUC_t$, was contained in the equivalence interval (0.8000, 1.2500), and
- the model-based 90% confidence interval for the treatment geometric mean ratio for cAUCinf, was contained in the equivalence interval (0.8000, 1.2500).

All AEs reported during the AE reporting period were to be listed by subject ID and last treatment administered at or before the AE. Any SAE was listed separately. The number and percentage of subjects experiencing AEs were tabulated by treatment, system organ class, and preferred term. In addition, number and percentage of subjects' experienced AEs that were considered treatment-related, i.e. either possible, probable, or very likely relation the investigational product were separately tabulated by treatment, system organ class, preferred term, and worst recorded severity. Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 was used as AE classification system.

RESULTS

SUBJECT DISPOSITION AND DEMOGRAPHY

The numbers of subjects with valid PK data (per treatment) are displayed in Table S2.

Table S2: Subjects with Valid PK Data

Treatment	N
Nicorette Extra Mint Gum 2 mg	74
Nicorette Mint Gum 2 mg	72
Nicorette Extra Mint Gum 4 mg	71
Nicorette Mint Gum 4 mg	73

Seventy-one (71) subjects had evaluable cC_{max}, $cAUC_t$ and $cAUC_{inf}$ values for both 2 mg treatments and were therefore included in the bioequivalence assessment. The corresponding number for the 4 mg treatments were 68.

Seventy-six (76) subjects, 71 males and 5 females, were included in the study (Table 14.1.2). All were Asian. Their average age was 27.6 years (range 18-41 years) and their average BMI was 22.0 kg/m^2 (range 19.0-25.0 kg/m^2). The subjects were smokers consuming on average 17.4 cigarettes per day (range 10-40 cigarettes) and they had been smokers for 8.7 years on average (range 1-20 years). Thus, age, BMI and smoking habits were in accordance with the inclusion criteria.

All subjects were healthy adult volunteers. None of the subjects had conditions or a medical history that the principal investigator (PI) considered would affect the conduct of the study or to represent a potential risk to the subject during study participation.

All 76 subjects were analyzed with respect to safety information in this study.

PHARMACOKINETIC, PHARMACODYNAMIC, AND/OR OTHER RESULTS

Pharmacokinetic

Figure S1 displays the average plasma concentration profiles of nicotine for the study treatments, plotted over 10 hours after start of administration.

Observed means of PK parameter data are displayed in Table S3. Model-based estimates and corresponding 90% confidence intervals for the ratios of the population geometric means of the pharmacokinetic parameters between the Nicorette Extra Mint Gum 2 mg and Nicorette Mint Gum 2 mg, and Nicorette Extra Mint Gum 4 mg and Nicorette Mint Gum 4 mg, respectively, are presented in Table S4.

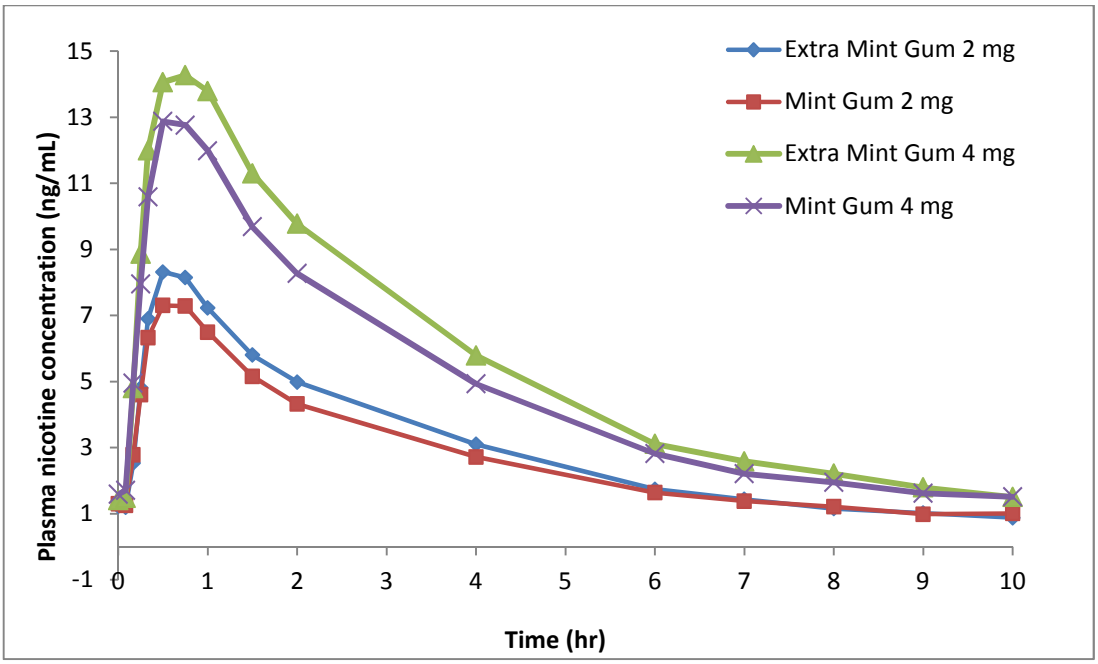

Figure S1: Mean Nicotine Plasma Concentration vs. Time Profiles over 10 hours after Start of Administration

Table S3: Pharmacokinetic Parameters Observed Means (SD) Subjects in Full Analysis Set

PK parameter	Nicorette Extra Mint Gum 2 mg (n=74)	Nicorette Mint Gum 2 mg (n=71-72)	Nicorette Extra Mint Gum 4 mg (n=70-71)	Nicorette Mint Gum 4 mg (n=72-73)
cC_{max} (ng/mL)	8.09 (2.50)	6.98 (2.20)	15.48 (4.08)	13.17 (4.15)
$cAUC_t$ (ng/mLxhr)	23.98 (6.42)	20.23 (6.04)	49.01 (15.43)	41.53 (14.12)
$cAUC_{inf}$ (ng/mLxhr)	27.19 (7.60)	23.31 (7.23)	54.56 (18.94)	47.03 (19.42)
$cAUC_{extrap}$ (%)	11.5 (4.8)	12.9 (5.3)	9.3 (4.5)	10.1 (5.6)
t_{max}* (hr)	0.63 (0.33-1.50)	0.75 (0.33-2.00)	0.75 (0.33-2.00)	0.75 (0.25-2.00)
λ_z (hr^{-1})	0.24 (0.06)	0.24 (0.05)	0.26 (0.05)	0.25 (0.06)
$t_{1/2}$ (hr)	3.01 (0.71)	3.03 (0.59)	2.74 (0.65)	2.92 (0.83)

* Median (Min–Max)

Table S4: Pharmacokinetic Parameters
Estimated Ratios of Geometric Means
Subjects in Full Analysis Set with Data from Both Treatments

PK Parameter	Nicorette Extra Mint Gum 2 mg vs. Nicorette Mint Gum 2 mg (n=71)		Nicorette Extra Mint Gum 4 mg vs. Nicorette Mint Gum 4 mg (n=68)	
	Ratio (%)	90% CI (%)	Ratio (%)	90% CI (%)
cC_{max}	116.69	111.36 – 122.27	121.87	114.21 – 130.04
$cAUC_t$	120.28	115.09 – 125.70	120.96	115.83 – 126.32
$cAUC_{inf}$	118.61	113.77 – 123.66	120.17	115.24 – 125.32

Table S5 provides across-subject averages and standard deviations for released amounts of nicotine from the used gums.

Table S5: Released Amount of Nicotine (mg)

	Nicorette Extra Mint Gum 2 mg (n=74)	Nicorette Mint Gum 2 mg (n=73)	Nicorette Extra Mint Gum 4 mg (n=71)	Nicorette Mint Gum 4 mg (n=73)
Mean	1.50	1.23	3.23	2.70
SD	0.21	0.21	0.47	0.53
Min – Max	0.9 – 1.8	0.6 – 1.5	1.5 – 3.8	0.9 – 3.4

SAFETY RESULTS

In total, 126 treatment-emergent AEs were reported. One-hundred and one (101) of these were considered to be "possibly", "probably" or "very likely" related to treatment Table S6. All of these were considered "mild" in severity.

No SAE was reported in this study. There were no deaths or other significant AEs.

Fourteen (14) subjects experienced at least one AE possibly, probably or very likely related to treatment with Nicorette Extra Mint Gum 2 mg and Nicorette Mint Gum 2 mg. The corresponding numbers with Nicorette Mint Gum 2 mg was 20. For Nicorette Extra Mint Gum 4 mg and Nicorette Mint Gum 4 mg the numbers were 19 and 27, respectively.

Respiratory, thoracic and mediastinal disorders represented the most commonly reported AEs, followed by Gastrointestinal disorders. In general, AEs were consistent with current understanding of the safety profile for nicotine gums.

Table S6: Number of Subjects with AEs Possibly, Probably or Very Likely Related to Treatment

System Organ Class	Adverse Event (Preferred Term)	Extra Mint Gum 2 mg (n=75)	Mint Gum 2 mg (n=75)	Extra Mint Gum 4 mg (n=74)	Mint Gum 4 mg (n=75)
Respiratory, thoracic and mediastinal disorders	Throat irritation	9	10	12	23
	Cough	-	2	-	-
	Hiccups	1	1	1	1
Gastrointestinal disorders	Nausea	1	5	4	1
	Salivary hypersecretion	1	3	3	-
	Eructation	1	1	2	2
	Dyspepsia	-	1	-	-
	Flatulence	-	1	-	-
	Vomiting	-	1	1	-
Nervous system disorders	Dizziness	1	1	1	2
	Dysgeusia	-	1	-	-
	Headache	1	-	-	-
	Vagus nerve disorder	-	-	-	1
Investigations	Alanine aminotransferase increased	1	-	1	-
	WBC increased	-	1	-	-
Skin and subcutaneous tissue disorders	Hyperhidrosis	-	1	-	1

CONCLUSIONS

- For the comparison of Nicorette Extra Mint Gum 2 mg and Nicorette Mint Gum 2 mg, the entire 90% confidence intervals of the ratios for cC_{max} as well as for $cAUC_{inf}$ were contained within the accepted interval. However, for $cAUC_t$ the upper limit of the confidence interval was slightly above 125%.
- Bioequivalence could not be demonstrated between Nicorette Extra Mint Gum 4 mg and Nicorette Mint Gum 4 mg, although the 90% confidence intervals of the ratios for $cAUC_t$ and $cAUC_{inf}$ were only slightly above 125%.
- On average, more nicotine was released from Nicorette Extra Mint Gums 2 and 4 mg than from Nicorette Mint Gums 2 and 4 mg, at corresponding strengths.
- Both Nicorette Mint Gum (2 and 4 mg) and Nicorette Extra Mint Gum (2 and 4 mg) were considered as well tolerated. All AEs were mild in severity.
- No new safety signals were identified in this study.

REPORT DATE: 19 September 2018