FINAL FULL CLINICAL STUDY REPORT: NICOTINE

Protocol Number: A6431081-P

Comparison of Single-dose Nicotine Pharmacokinetics of Three Variants of Nicotine Oral Drops 2 mg, and of Nicorette® Gum 2 mg in Healthy Smokers

Author(s):	Kraiczi H, Lomander A, Rasmussen T
Phase of Development:	Phase 1
Study Initiation and Completion Dates:	First Subject Visit: 08 June 2005 Last Subject Visit: 07 July 2005
Final Signoff Date:	Not Applicable
Sponsor's Signatories:	Björn Johansson, Holger Kraiczi, Andrea Lomander, Thomas Rasmussen, Edwin Schaart, Charlotte Verbaan, Åke Westin
Investigators:	See below.

Country	Center	Principal Investigator
Sweden	1001	Holger Kraiczi

This study was conducted according to local laws and regulations relevant to the use of new therapeutic agents in the country/countries of conduct.

CLINICAL STUDY REPORT SYNOPSIS: PROTOCOL A6431081

Protocol Title: Comparison of Single-dose Nicotine Pharmacokinetics of Three Variants of Nicotine Oral Drops 2 mg, and of Nicorette® Gum 2 mg in Healthy Smokers.

Investigators: Holger Kraiczi

Study Center(s): Pfizer Consumer Healthcare, Department of Clinical Pharmacology, Karl XI gatan 4, SE-222 20 Lund, Sweden

Publications Based on the Study: None

Study Initiation and Completion Dates: 08 June 2005 to 07 July 2005

Phase of Development: Phase 1

Study Objective(s):

The primary objective was:

To investigate and compare the rate and extent of absorption of nicotine after administration of nicotine oral drops 2 mg without buffer, nicotine oral drops 2 mg Tris-buffered, nicotine oral drops 2 mg carbonate-buffered and Nicorette® gum 2 mg.

The secondary objectives were:

To investigate and compare the pharmacokinetic profiles of nicotine after administration of nicotine oral drops 2 mg without buffer, nicotine oral drops 2 mg Tris-buffered, nicotine oral drops 2 mg carbonate-buffered and Nicorette® gum 2 mg.

To assess irritation in mouth and throat, as well as urges to smoke during treatments, and to evaluate the palatability of the nicotine oral drops.

To assess the amount of nicotine extracted from the Nicorette® gum during 30 minutes of chewing.

To assess tolerability and safety of study treatments.

METHODS

Study Design:

In the present four-way crossover study, each 8-hour treatment visit consisted of a single dose of nicotine. The investigational products, given separately at 4 different visits in randomized order, were 2 mg nicotine oral drops (100 µL) with or without a high or a low level of buffer, and Nicorette® gum 2 mg. Blood was sampled for pharmacokinetic analyses. Safety was assessed continuously throughout each visit. Eighteen subjects were randomized to one of 4 treatment sequences according to the following design:

1. A, B, C, D
2. B, D, A, C
3. C, A, D, B
4. D, C, B, A

A period without NRT, lasting for at least 36 hours, separated the treatment visits.

The primary study endpoints were nicotine AUC10min and Cmax, 0-10min. Secondary endpoints were Cmax, AUCt, AUC∞, tmax, degree of irritation in mouth and throat, palatability, amount of nicotine extracted from Nicorette® gum, urges to smoke, and the occurrence of adverse events.

Diagnosis and Main Criteria for Inclusion: Healthy male and female subjects between the ages of 18 and 50 years, inclusive, smoking at least 15 cigarettes daily during at least one year preceding inclusion. Subjects had to have a Body Mass Index (BMI) of 17.5 to 30.0 kg/m^2, and a total body weight ≥ 50.0 kg. Females had to be in a postmenopausal state with absence of menstrual discharge for at least two years and a serum FSH level >30 IU/L, or premenopausal/ perimenopausal state with effective contraception (oral or implanted hormonal contraceptives, intrauterine device or status after operative sterilization).

Study Treatment: Seventeen subjects (17) received four treatments and one subject (No. 13) received three treatments, each given on a separate occasion. Each treatment included one administration.

Table S1. Identity of Study Treatments

Investigational Product	Appearance	Lot Number	FID Number	Date of Reanalysis
Nicotine Oral Drops 2 mg/100 µL, unbuffered	Liquid	GDS1224	N/A	2005-10-27
Nicotine Oral Drops 2 mg/100 µL, Tris-buffered	Liquid	GDS1225	N/A	2005-10-27
Nicotine Oral Drops 2 mg/100 µL, carbonate- buffered	Liquid	GDS1226	N/A	2005-10-27
Nicorette® gum 2 mg	White squares	FM097	N/A	2005-10-27

The study treatments were used according to the following instructions:

Nicotine oral drops: About five minutes prior to administration, subjects rinsed their mouth with 100 mL of tap water. The bottle with the oral drops was shaken prior to administration to prevent formation of deposits. Using a micropipette with disposable pipette tips, study personnel administered 100 µL of the nicotine oral drops on the subjects' tongue. The subjects were

instructed to let the liquid spread in the mouth and to not swallow until one minute after administration.

Nicorette® gum: The administration comprised 30 minutes of chewing, preceded by mouth rinsing with 100 mL of tap water about five minutes prior to administration. The gum was chewed once every 2 seconds, using a metronome to control the chewing rate. Saliva was swallowed once every minute. Talking was not allowed during chewing periods. After 30 minutes of chewing, the gum was wrapped in a piece of aluminum foil, put in a labeled Minigrip® plastic bag, and frozen at -20°C for storage until analysis.

Pharmacokinetic and Pharmacodynamic Evaluations: Blood samples for nicotine analysis were drawn at specified times during each treatment visit (2, 4, 6, 8, 10, 13, 16, 20, 30, 45, 60 minutes as well as after 1.5, 2, 3, 4, 6, and 8 hours) after each administration.

After collection and centrifugation of samples, the plasma was removed, and analyzed for nicotine using a single-step liquid-liquid extraction followed by capillary gas chromatography with a nitrogen-sensitive detector.

To analyse the residual amounts of nicotine in medicated chewing gums after chewing, each gum was extracted in a two-phase system consisting of 50 mL n-heptane and 50 mL diluted sulphuric acid. After extraction, the aqueous phase, in which nicotine was dissolved, was diluted twice, pH-adjusted, filtered, and then injected into an HPLC-system for nicotine quantification.

The degree of perceived irritation in mouth and throat was rated and recorded by means of a visual analogue scale at 2.5, 5, 10, 20, 30 and 60 minutes after each treatment administration. On this scale, 0 mm corresponded to “No irritation at all” and 100 mm corresponded to “Worst imaginable”.

All treatment visits included repeated ratings of urges to smoke at 2, 5, 10, 15, 20, 25, 30, 45, and 60 minutes after administration. A Likert scale was used with the following 4-ordered categories: No/light urges, noticeable urges, disturbing urges, very strong/extreme urges.

For all treatments, the experienced palatability was recorded 2 and 30 minutes after the start of administration. The palatability was measured by means of a Visual Analogue Scale where 0 mm corresponded to “very unpleasant” and 100 mm corresponded to “most pleasant”

Safety Evaluations: Medical Dictionary for Regulatory Activities (MedDRA) was employed as adverse event classification system. The frequency of subjects experiencing a specific treatment-related adverse event was tabulated by treatment, preferred term, and severity. The number of each type was calculated. Adverse events that were considered treatment-related were listed separately by subject, preferred term, and severity.

RESULTS

Table S2. Subject Disposition and Subjects Analyzed

Planned	20
Screened	26
Assigned to Treatment	18
Treated	18
Completed	17
Discontinued	1
Evaluated for Pharmacokinetics	17
Analyzed for Safety	18
Adverse Events	33

Pharmacokinetic Results:

Table S3. PK Parameters of Nicotine without Buffer, with Tris Buffer, Carbonate Buffer, and the Nicorette® Gum (mean ± SD, median, min-max)

	$C_{max,0\text{-}10\ min}$ (ng/mL)	AUC_{10min} (ng/mLxmin)	C_{max} (ng/mL)	T_{max} (h)	AUC_{last} (ng/mLxmin)	AUC_{∞} (ng/mLxmin)
Oral Drops, no Buffer, pH 7-8	3.0±2.0 2.6 0.4-7.4	17.6±12.4 13.9 0.9-43.5	4.2±1.9 3.9 0.9-7.5	- 0.4 0.1-2.0	10.7±6.1 10.4 2.1-28.3	13.6±7.2 12.3 3.5-32.7
Oral Drops, Tris buffer, pH 8-9	3.7±1.8 3.8 1.1-7.8	21.9±12.0 21.6 2.8-49.5	4.4±1.7 4.0 2.1-7.8	- 0.2 0.1-1.0	10.4±4.5 9.8 3.0-19.9	13.1±5.8 12.1 4.1-26.4
Oral Drops, Carbonate Buffer, pH 9-10	4.3±2.1 3.9 1.5-9.5	26.0±13.3 24.9 7.4-53.8	5.0±1.7 4.6 2.9-9.7	- 0.2 0.1-1.0	11.5±5.2 11.0 4.1-21.4	14.2±6.1 14.1 5.9-24.6
Nicorette® Gum 2 mg	2.3±1.4 1.9 0.9-6.3	7.3±4.7 5.9 3.2-20.1	5.0±2.0 4.5 2.3-9.2	- 0.5 0.3-0.8	11.1±6.2 10.0 5.1-25.5	13.7±7.9 12.0 6.4-34.6

Pharmacodynamic results:

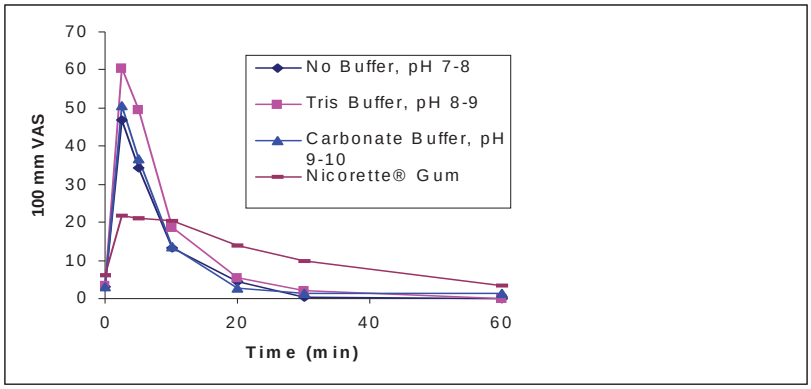

Figure S1. Degree of Mouth and Throat Irritation on 100 mm VAS.

Urges to Smoke:

For all treatments, the majority of subjects recorded a noticeable or disturbing Urges to Smoke prior to treatment, and no/light Urges to Smoke on every occasion Urges was recorded after administration.

Table S4. Palatability (mean ±SD, median, min-max)

Treatment	2 minutes	30 minutes
Oral Drops, No Buffer, pH 7-8	37.8 ± 14.8	54.7 ± 15.2
Oral Drops, Tris Buffered, pH 8-9	41.4 ± 18.1	51.8 ± 6.4
Oral Drops, Carbonate Buffered, pH 9-10	44.3 ± 21.7	55.5 ±10.7
Nicorette® Gum	43.3 ± 19.7	46.4 ± 17.9

Safety Results:

There were no deaths or SAEs reported in this study. One subject was withdrawn from the study prior to the last treatment due to a an AE (cold, considered not treatment related). A total of 33 AEs were reported by 13 subjects. Of these, 17 were mild, 15 moderate and one was severe. Nine AEs considered not related to treatment were reported by 8 subjects. There were no temporary discontinuations or dose reductions due to AEs.

Conclusion(s):

The highest baseline corrected C_{max} was found when subjects were treated with the carbonate buffered oral drops, and the Nicorette® gum (5 ng/mL for both). Tris buffered oral drops and oral drops with no buffer yielded a baseline corrected C_{max} of 4.4 and 4.2 ng/mL, respectively. The oral drops with buffer had both a T_{max} of about 12 minutes, the oral drops with no buffer had a T_{max} of 24 minutes and Nicorette® gum had a T_{max} of 30 minutes.

Maximum irritation score for all treatments was reported after 2.5 minutes. The highest irritation score was reported for the Tris buffered oral drops (60.5). The Nicorette® gum gave rise to the lowest score (21.9). Oral drops without buffer and with Carbonate buffer yielded irritation scores of 46.8 and 50.8, respectively.

All treatments yielded a higher palatability after 30 minutes than after 2 minutes. The oral drops resulted in palatability scores of 50-55, while Nicorette® gum yielded a palatability score of 46.4.

Subjects chewed out on an average 1.25 mg of nicotine from each Nicorette® gum.

For all treatments, the majority of subjects recorded a noticeable or disturbing Urges to Smoke prior to treatment, and no/light Urges to Smoke on every occasion Urges was recorded after administration.

Frequency and character of treatment-related AEs were in concordance with those observed with other types of oral NRT products.