CLINICAL STUDY REPORT SYNOPSIS: PROTOCOL PROTOCOL A6431076

Protocol Title: Pharmacokinetics of Nicotine Film for Use in the Mouth. A Randomized, Crossover, Phase-I, Comparative Study 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: 17 January to 10 February 2005

Phase of Development: Phase 1

Study Objective(s):

The primary objective was:

- to investigate and to compare the pharmacokinetics of nicotine after administration of nicotine pullulan film at doses of 2 and 3 mg, respectively, of nicotine metolose film at a dose of 2 mg, and of Nicorette® gum 2 mg.

The secondary objectives were:

- to estimate the mean dose of the nicotine pullulan film that results in an AUC_{∞} equivalent to that of Nicorette® gum 2 mg,
- to assess irritation in mouth and throat associated with study treatments,
- to assess the general acceptance of study treatments,
- to assess urges to smoke at specified times during study treatments,
- 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 9-hour treatment visit consisted of a single morning dose of nicotine, an 8-hour nicotine free interval and a second single nicotine dose from the same type of product as given in the morning. The investigational products, given separately at 4 different visits in randomized order, included pullulan films containing 2 and 3 mg nicotine respectively, metolose film containing 2 mg nicotine, and Nicorette® gum 2 mg. After the first dose during each visit, blood was sampled for pharmacokinetic analyses, and treatment tolerability was assessed. The second dose was given to allow a preliminary evaluation

of treatment effects on craving in the study sample after witnessed nicotine abstinence and without potential disturbances by blood sampling procedures. Safety was assessed continuously throughout each visit. Subjects and trial personnel were aware of whether a film or a gum was given at a treatment visit. However, to improve interpretability of observed relationships treatment labels of the nicotine films were not revealed to subjects or trial personnel. Bioanalysts and pharmacokineticists were not aware of any of the treatment labels.

Twenty healthy smokers (>15 cigarettes per day) aged 18-50 with a BMI of 17.5-30 kg/m^2 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 AUC_∞, C_{max} and AUC_t. Secondary endpoints were t_{max}, $t_{1/2}$, $C_{max,\ 0\text{-}10min}$, AUC_{10min}, degree of irritation in mouth and throat, treatment acceptance, amount of nicotine extracted from Nicorette® gum, urges to smoke, and the occurrence of adverse events.

Diagnosis and Main Criteria for Inclusion: Twenty 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 and no intention to quit within three months from 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: All subjects received four treatments, each given on a separate day. Each treatment included two administrations, the first in the morning, and the second 8 hours later. Subjects remained at the investigator site until at least one hour after the second dose i.e. about 4 times 9 hours in total.

Only qualified personnel not using products containing nicotine dispensed the investigational products (Table S1).

Table S1. Investigational Products

Treatment	Drug	Lot Number	Route	Regimen
A	Nicotine pullulan film, 2 mg	FLN 1381	Oral	2 x 2 mg
B	Nicotine metolose film, 2 mg	FLN 1376	Oral	2 x 2 mg
C	Nicotine pullulan film, 3 mg	FLN 1375	Oral	2 x 3 mg
D	Nicorette® gum, 2 mg	FH030	Oral	2 x 2 mg

The study treatments were used according to the following instructions:

- Nicotine film: The subjects were instructed to place the film on the tongue, to let it melt in the mouth, and to not swallow it.
- Nicorette® gum: Each administration comprised 30 minutes of chewing, preceded by mouth rinsing with 100 ml tap water. 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 for storage until analysis.

A period of 36 hours or more without NRT passed between treatment visits.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and/or Other Evaluations: Blood samples for nicotine analysis were drawn before administration and at 2, 4, 6, 8, 10, 13, 16, 20, 30, 45 and 60 minutes as well as at 1.25, 1.5, 2, 4, 6 and 8 hours after administration.

For treatment D, used chewing gums were collected after 30 minutes' of chewing.

All treatment visits included repeated ratings of irritation in mouth and throat at 2.5, 5, 10, 20, 30 and 60 minutes. The degree of irritation was measured by means of a visual analogue scale with 0 mm corresponding to "Not at all" and 100 mm corresponding to "Worst imaginable".

All treatment visits included repeated ratings of urges to smoke at 1, 2, 3, 4, 5, 6, 7, and 8 hours, using a Likert scale with four ordered categories.

At all treatment visits, the following question was asked at 2 and 17 minutes: How acceptable is this product for you? Subjects were asked to rate the acceptability on a nine-grade scale.

Safety Evaluations: The investigator obtained and recorded on the CRF all observed and reported adverse events (AEs), the severity (mild, moderate, severe) of the events, and the investigator's opinion of the relationship to the study treatment. AEs included adverse drug reactions, illnesses with onset during the study, and exacerbation of previous illnesses. Additionally, the investigator was to record as an AE any clinically significant changes in physical examination findings and abnormal objective test findings (eg, ECG, laboratory results). The final protocol (Appendix A1) contains additional details concerning AE reporting.

For all AEs, the investigator pursued and obtained information adequate to determine both the outcome of the AE and whether it met the criteria for classification as a serious adverse event (SAE). If the AE or its sequelae persisted, follow-up was required until resolution or stabilization occurred at a level acceptable to the investigator and sponsor.

Statistical Methods: For all four treatments and all pharmacokinetic endpoints, means, standard deviations, medians as well as minimum and maximum values in the subject sample were calculated. For the means corresponding to the four treatments, 95% confidence intervals were calculated. 95% confidence intervals for the ratios of means of the primary pharmacokinetic endpoints were calculated.

Estimation of the mean interpolated dose of the nicotine pullulan film resulting in an AUC_{∞} equivalent with that of the Nicorette® gum 2 mg was performed on an individual basis. Descriptive statistics including a 95% confidence interval for the individual interpolated doses of the nicotine pullulan film were calculated.

Treatment differences in maximum irritation, time of maximum irritation, and area under irritation versus time curve from zero to 60 minutes were analyzed using the Mantel-Haenzel test. Descriptive statistics were tabulated.

Descriptive statistics were tabulated for product acceptance.

For urges to smoke assessments, the percentage of subjects in each of the four ordinal categories was tabulated for each time point.

RESULTS

Subject Disposition and Demography:

Table S2 shows the subject disposition and the number of subjects analyzed.

Table S2. Subject Disposition and Subjects Analyzed

Number of Subjects	Pullulan Film 2 mg	Metolose Film 2 mg	Pullulan Film 3 mg	Nicorette Gum 2 mg
Planned	20	20	20	20
Screened	25	25	25	25
Assigned to Treatment	19	19	19	19
Treated	19	19	19	19
Discontinued	0	0	0	0
Analyzed for PK/PD	17-18	15-19	18-19	18-19
Analyzed for Safety	19	19	19	19

Eleven female and eight male subjects were included in the study. All subjects were white. The subjects were smokers consuming an average of 18 cigarettes per day (range 15-23 cigarettes) and had been smokers for 13 years on average (range 6-31 years). Their average age was 29 years (range 23-45 years), and their average body mass index was 23 kg/m^2 (range 20-29 kg/m^2). Thus, smoking habits, age and BMI were in accordance with the inclusion criteria.

Pharmacokinetic, Pharmacodynamic, and/or Other Results:

Pharmacokinetic Variables

Figure S1 displays the average plasma concentration profiles for the four treatments over 8 hours. Table S3 shows descriptive statistics for the pharmacokinetic parameters. Table S4 shows parameter ratios and corresponding 95% confidence intervals for parameters representing the nicotine pharmacokinetics for the four treatments.

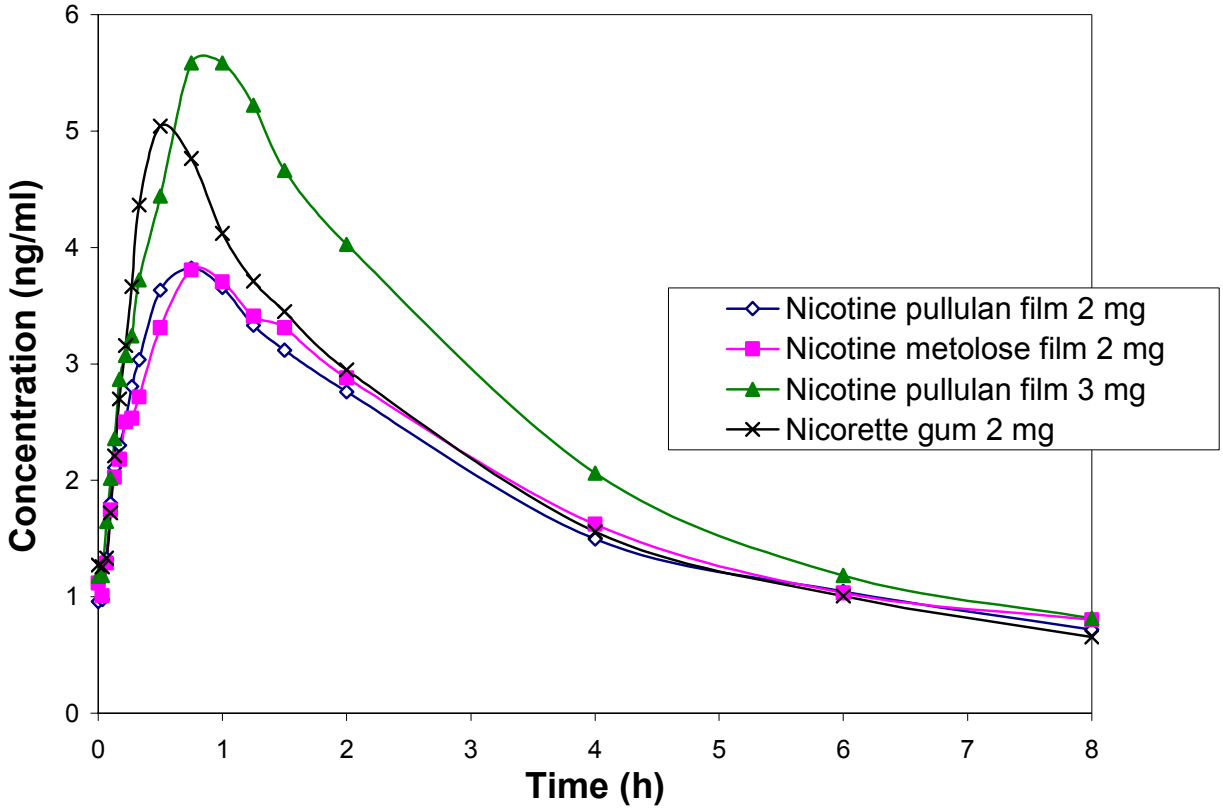

Figure S1. Mean Plasma Concentration versus Time Curves (n=18-19)

Table S3. Pharmacokinetic Parameters (Mean±SD) n=15-19

	$C_{max0-10min}$ (ng/mL)	AUC_{10min} (ng/mLxmin)	C_{max} (ng/mL)	T_{max} (h)	AUC_t (ng/mLxh)	AUC_∞ (ng/mLxh)
Pullulan Film 2 mg	1.5 ± 0.9	7.3 ± 5.1	3.6 ± 1.5	0.8	11.0 ± 4.8	14.3 ± 5.4
Metolose Film 2 mg	1.3 ± 0.6	5.5 ± 4.2	3.3 ± 1.9	0.8	10.4 ± 5.8	14.9 ± 6.8
Pullulan Film 3 mg	1.7 ± 0.9	7.8 ± 5.9	5.3 ± 2.7	0.8	15.5 ± 7.0	18.8 ± 7.8
Nicorette® gum	1.5 ± 0.8	5.6 ± 4.2	4.2 ± 1.0	0.5	10.7 ± 3.2	13.4 ± 3.8

Table S4. Pharmacokinetic Parameter Ratios Film/Gum (Geometric Mean (95% Confidence Interval) n=15-19)

Comparison vs. Gum	C_{max}	AUC_t	AUC_∞
Pullulan Film 2 mg	0.83 (0.69–1.01)	0.95 (0.78-1.15)	1.00 (0.85-1.17)
Metolose Film 2 mg	0.73 (0.58-0.91)	0.87 (0.67-1.12)	1.02 (0.87-1.19)
Pullulan Film 3 mg	1.17 (0.95-1.45)	1.35 (1.14-1.61)	1.34 (1.15-1.57)

Mouth and Throat Irritation

Table S5 provides across-subject averages and standard deviations for the degree of mouth and throat irritation.

Table S5. Mouth and Throat Irritation (Mean±SD, p-value for Comparison with Gum) n=19

Treatment	1:st administration			2:nd administration		
	Max (mm)	T_{max} (min)	AUC(mm·min)	Max (mm)	T_{max} (min)	AUC(mm·min)
Pullulan film 2 mg	34.0 ± 22.1 0.1712	2.9 ± 1.9 **0.0336**	383 ± 398 0.3146	32.2 ± 26.5 **0.0198**	2.6 ± 1.0 **0.0382**	306 ± 482 0.5322
Metolose film 2 mg	45.9 ± 28.8 **0.0075**	3.0 ± 1.3 0.1597	467 ± 464 0.7260	39.8 ± 22.4 **0.0029**	2.8 ± 1.1 0.0778	332 ± 305 0.6586
Pullulan film 3 mg	42.1 ± 28.4 **0.0095**	2.6 ± 1.0 **0.0190**	357 ± 381 0.1901	36.9 ± 20.2 **0.0022**	2.5 ± 0.8 **0.0329**	290 ± 254 0.7660
Nicorette® gum	26.9 ± 17.4	4.6 ± 3.3	465 ± 406	21.3 ± 14.6	4.3 ± 3.4	343 ± 312

Acceptance of the Product

Table S6 provides across-subject averages and standard deviations for the product acceptability.

Table S6. Product Acceptability (Mean±SD) n=19

Treatment	1:st administration		2:nd administration	
	2 min	17 min	2 min	17 min
Pullulan film 2 mg	5.8 ± 2.7	7.0 ± 1.8	5.9 ± 2.6	6.8 ± 1.9
Metolose film 2 mg	5.3 ± 2.6	6.5 ± 2.0	5.1 ± 2.3	6.4 ± 2.0
Pullulan film 3 mg	5.5 ± 2.3	6.8 ± 1.7	5.8 ± 2.2	6.8 ± 1.7
Nicorette® gum	6.4 ± 1.8	6.5 ± 1.8	6.4 ± 1.8	6.6 ± 1.6

Safety Results: There were no deaths, SAEs, or withdrawals due to AEs reported in this study. A total of 24 treatment-emergent adverse events were reported by 12 subjects. Eighteen of these adverse events were considered treatment-related. Nine treatment-related AEs were moderate in severity and 9 were mild in severity (Table S7).

Table S7. No. of Subjects Reporting Treatment-related AEs (n=19, mi=mild, mo=moderate)

System organ class/Preferred term	Pullulan Film 2 mg	Metolose Film 2 mg	Pullulan Film 3 mg	Nicorette® gum 2 mg
Gastrointestinal disorders				
Abdominal distension	-	-	-	1 mi
Abdominal pain upper	1 mi	-	-	-
Dry mouth	-	-	-	1 mi
Dry throat	-	-	-	1 mi
Hiccups	1 mo	2 mi	1 mo	-
Nausea	-	1 mi, 2 mo	-	-
Salivary hypersecretion	-	-	-	1 mo
Nervous system disorders				
Dizziness	-	1 mo	-	-
Headache NOS	1 mo	-	1 mo	1 mo
		-	-	-
Respiratory, thoracic and mediastinal disorders				
Hoarseness	1 mi	1 mi	-	-

Conclusion(s):

- The results suggest that C_{max} as indicator of rate of absorption of nicotine from the metolose film 2 mg was lower than that from Nicorette® gum 2 mg. The C_{max} of the pullulan film 2 mg tended to be lower than that of Nicorette® gum 2 mg although the difference was not significant. C_{max} of pullulan film 3 mg tended to be higher than that from Nicorette® gum 2 mg although the difference was not significant.

- The comparison of AUC_t and AUC_∞ as indicators of extent of absorption of nicotine from the 2 mg pullulan and metolose films and Nicorette® gum 2 mg suggest no significant difference. The AUC_t and AUC_∞ from pullulan film 3 mg, on the other hand, were significantly higher that that from Nicorette® gum 2 mg.

- The mean dose of the nicotine pullulan film that resulted in an AUC_{∞} equivalent to that of Nicorette® gum 2 mg was 2.03 mg.

- The maximum degree of mouth/throat irritation for the metolose film 2 mg and pullulan film 3 mg was higher than that for Nicorette® gum and it tended to occur earlier than for Nicorette gum. On the other hand, the comparison of overall mouth/throat irritation, measured as the area under the irritation vs. time curve, suggests no significant difference.

- The study was not designed to provide statistical support for quantitative differences in acceptability between treatments. However, there were no trends indicating that the acceptability of the nicotine films might differ from that of Nicorette® gum.
- The amount of nicotine extracted from Nicorette® gum was 1.4 mg. This figure corroborates well with what has previously been shown in studies using the same user's directions.
- The study was not designed to provide statistical support for quantitative differences in the likelihood of AEs between treatments. However, there were no incidents or trends indicating that the AE profile of the nicotine films might differ from that of other nicotine replacement products for use in the mouth.