NICOTINE

NICTDP0002

A PROOF OF CONCEPT WITH A NEW NICOTINE INHALER IN COMPARISON WITH NICOTINE INHALER 10 MG – AN EXPLORATORY STUDY IN ADULT HEALTHY SMOKERS

Indication Studied:	Tobacco dependence
Developmental Phase of Study:	NA
Study Initiation Date (First Subject Enrolled):	23 November 2011
Study Completion Date (Last Subject Completed):	14 December 2011
Status/Date:	FINAL 05 June 2012
Responsible Medical Officer:	Holger Kraiczi, MD, PhD +46 46 19 06 13 +46 46 14 29 17

2. SYNOPSIS

INVESTIGATORS: Holger Kraiczi.

STUDY CENTER(S): McNeil AB, Department of Clinical Pharmacology, Karl XII gatan 5, SE-222 20 Lund, Sweden.

PUBLICATIONS (REFERENCE): None.

STUDY INITIATION AND COMPLETION DATES: 23 November 2011 to 14 December 2011

PHASE OF DEVELOPMENT: Phase 1

STUDY OBJECTIVE(S):

Primary objective was:

- to compare the steady-state nicotine pharmacokinetics (as described by the maximum observed nicotine plasma concentration, C_{max}, the average nicotine plasma concentration, C_{av}, and the area under the nicotine plasma concentration-vs.-time curve during the last dosing interval, AUC_{τ}) of N1/3-I5 given every hour with that of Nicotine Inhaler 10 mg given every hour.

Secondary objectives were:

- to further describe the steady-state nicotine pharmacokinetics with respect to the time to C_{max} (t_{max}), the minimum observed nicotine plasma concentration (C_{min}), the peak-trough fluctuation (PTF), and the swing during the last dosing interval,
- to compare treatments with respect to baseline-corrected nicotine plasma concentrations immediately before user sessions (C_n),
- to compare treatments with respect to easiness of use,
- to compare treatments with respect to overall liking,
- to assess urges to smoke at specified time points during both treatments,
- to compare treatments with respect to the amounts of nicotine released from N1/3-I5 and Nicotine Inhaler 10 mg,
- to evaluate the tolerability of the treatments in terms of reported and observed adverse events (AE).

METHODOLOGY

STUDY DESIGN: The study was a multiple-dose, randomized, crossover study with 36 subjects. The investigational products, N1/3-I5 and Nicotine Inhaler 10 mg, were given as multiple doses (user sessions of 10 minutes every hour, during 12 hours) at separate visits. Periods without nicotine replacement products (NRT), lasting for at least 36 hours, separated treatment visits.

Subjects abstained from using nicotine-containing products (besides treatments specified in this protocol) and smoking from 12 hours before and throughout each treatment visit.

Used cartridges were collected for nicotine analysis.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED): Thirty-six (36) subjects were planned and included in the study. Thirty-six (36) subjects were analyzed for N1/3-I5 and 35 were analyzed for Nicotine Inhaler 10 mg.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy male and female subjects between the ages of 19 and 50 years, inclusive, smoking at least 10 cigarettes daily during at least one year preceding inclusion were enrolled. The subjects had to have a Body Mass Index (BMI) between 17.5 and 30.0 kg/m^2 and a total body weight ≥55.0 kg. Females had to be in a postmenopausal state or in a premenopausal/perimenopausal state with effective contraception (oral, injected or implanted hormonal contraceptives, intrauterine devices or status after operative sterilization).

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Table S1 provides information about the investigational products.

Table S1: Investigational Products and Identity

Investigational Product	Vendor Lot ID / Batch Number	Formula Number	Expiry Date
N1/3-I5	NFN1619	N/A	2012-07-11
Nicotine Inhaler 10 mg	NFN1618	N/A	2012-06-27

Subjects were instructed to puff on the inhaler in a manner they consider the most natural during 10 minutes, with a puff frequency of four puffs per minute (i.e. one puff every 15 seconds). A clock was used to control the pace of puffing.

A new cartridge was used for each inhalation session.

Talking was not allowed during the puffing period.

DURATION OF TREATMENT: For all 36 subjects there were no discrepancies between the randomization schedule and the actual dosing schedule.

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

Criteria for evaluation:

The full analysis set was defined as all subjects with any valid pharmacokinetic parameter values from at least one of the two treatments and without major protocol deviations. Carryover effects were assumed ignorable. No data imputation was performed. All subjects that received any treatment were included in the safety analysis.

EFFICACY EVALUATION: No evaluation of efficacy was made.

PHARMACOKINETIC, PHARMACODYNAMIC, AND/OR OTHER EVALUATIONS: During the treatments, blood for pharmacokinetic analyses was drawn prior to the first administration and immediately before administrations at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11. After the 11-hour administration samples were drawn at 5, 10, 15, 20, 25, 30, 45, and 60 minutes. Nicotine concentrations in plasma were measured using a validated capillary gas chromatography - chemical ionization mass spectrometry (GC-CIMS) method. Pharmacokinetic parameters were determined from concentration-time data using standard non-compartmental methods, using WinNonlin Professional (version 5.3, Pharsight Corporation, Mountain View, CA, USA). The pharmacokinetic parameters determined were C_{max}, t_{max}, C_{min}, C_{av}, C_n, AUC_τ, PTF and swing.

C_n was corrected for nicotine baseline plasma concentrations according to the following equation, where C_0 is the baseline nicotine plasma concentration and t_n is the time elapsed from the first administration: $cC_n = C_n - C_0 \cdot e^{-\lambda z\, tn}$

Residual amounts of nicotine in the cartridges after usage (pooled samples per subject and treatment) were analyzed using a validated HPLC-method.

Easiness of use was rated at 3, 6 and 9 hours using an 8-graded scale.

Overall liking was rated at 12 hours using an 8-graded scale.

Urges to Smoke was rated on a 4-grade scale immediately before and 15 minutes after the first administration, before and 15 minutes after the administration at 3, 6 and 9 hours, and at 12 hours.

Subjects were monitored to capture any adverse events that occurred.

SAFETY EVALUATIONS: At screening the following safety evaluations were performed: Laboratory safety tests and recording of blood pressure (mmHg), pulse rate (beats per minute) and ECG. In addition, female subjects of childbearing potential were tested for beta-human chorionic gonadotropin (β-hCG) before each treatment session.

Authorized study personnel obtained and recorded on the eCRF/CRF all observed or volunteered adverse events, the severity (mild, moderate, or severe) of the events, and the investigator's opinion of the relationship to the study medication. In addition, each study

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

STATISTICAL METHODS: Descriptive statistics (mean, standard deviation, median, minimum and maximum values) of the pharmacokinetic parameters were tabulated. For t_{max} the frequency distribution was tabulated for each treatment.In addition geometric mean values and coefficients of variation were calculated for the primary pharmacokinetic parameters as well as for the baseline-corrected nicotine plasma concentrations (cC_n) immediately before the user session at 1, 2, 3, …, 11 hours.

Statistical comparisons between N1/3-I5 and Nicotine Inhaler 10 mg with respect to primary pharmacokinetic endpoints, C_{max} and AUC_τ during the last dosing interval, respectively, were based on mixed linear models for log transformed (natural log) pharmacokinetic parameter data. Separate statistical comparisons between N1/3-I5 and Nicotine Inhaler 10 mg with respect to baseline-corrected nicotine plasma concentrations (cC_n) immediately before the user sessions at 1, 2, 3, …, 11 hours respectively, were based on mixed linear models for log transformed (natural log) baseline-corrected nicotine plasma concentrations.

Interval estimates of mean parameter treatment ratios with respect to secondary pharmacokinetic parameters (C_{min}, PTF and swing) were calculated by using normal approximation to subjects' corresponding individual parameter ratios. For the corresponding treatment comparison of t_{max}, i.e. time to C_{max}, point and interval estimates for the median subject treatment differences were calculated.

Statistical comparisons between N1/3-I5 and Nicotine Inhaler 10 mg with respect to the secondary pharmacodynamic endpoints assessments of easiness of use, overall liking and released amount of nicotine from inhalers, respectively, in each case used a Wilcoxon-Mann-Whitney test comparing corresponding period differences between the two sequence groups thus adjusting the evaluation for any period effects.

The number and percentage of subjects experiencing adverse events was tabulated by treatment, system organ class, and preferred term. In addition, number and percentage of subjects experiencing adverse events with a possible, probable, or very likely relation the investigational product was separately tabulated by treatment, system organ class, preferred term, and worst recorded severity. Medical Dictionary for Regulatory Activities (MedDRA, version 14.1) was employed as Adverse Event classification system.

RESULTS

SUBJECT DISPOSITION AND DEMOGRAPHY: All included subjects were analyzed for safety. Table S2 provides the subject disposition and the number of subjects analyzed for PK and PD.

Table S2: Subjects Included in the PK/PD Analyses

	Completed	Analyzed for PK/PD
N1/3-I5	36	36
Nicotine Inhaler 10 mg	36	35

Thirty-six (36) subjects, 24 males and 12 females, were included in the study. Thirty-five (35) of them were white and one was mixed (i.e. of mixed origin). The subjects were smokers consuming of, on average, 16.6 cigarettes per day (range 10-25 cigarettes) and had been smokers for 10.9 years on average (range 3-32 years). Their average age was 27.9 years (range 20-50 years), and their average BMI was 23.7 kg/m^2 (range 18.6-29.8 kg/m^2). Thus, smoking habits, age and BMI 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 investigator considered sufficient to affect the interpretability of study results or to represent a potential risk to the subject during study participation.

EFFICACY RESULTS: No efficacy evaluation was performed.

PHARMACOKINETIC, PHARMACODYNAMIC, AND/OR OTHER RESULTS:
Figure S1 displays the average plasma concentration profiles for the treatments over 12 hours after start of the first administration (user session). In Table S3 means and standard deviations of the pharmacokinetic steady-state parameters are presented.

Table S4 provides model-based, estimated ratios of geometric means and corresponding 95% confidence intervals between N1/3-I5 and Nicotine Inhaler 10 mg (with respect to C_{max} and AUC_{τ}/C_{av}).

Model-based, estimated ratios of geometric means of baseline-corrected nicotine plasma concentrations (measured immediately before user sessions) and corresponding 95% confidence intervals between N1/3-I5 and Nicotine Inhaler 10 mg are presented in Table S5.

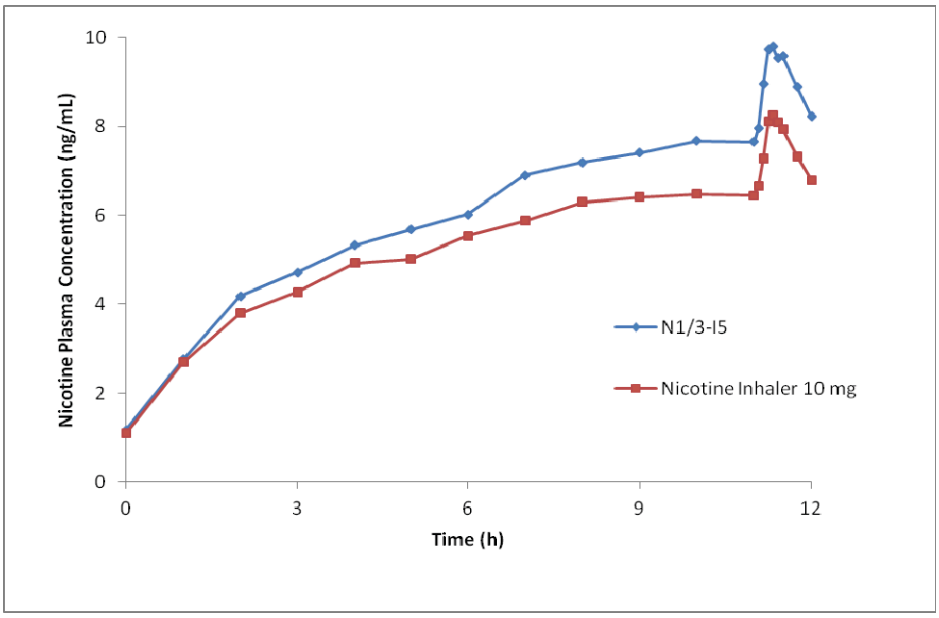

Figure S1: Mean Plasma Concentration versus Time Profiles over 12 hours after the First Administration.

Table S3: Pharmacokinetic Parameters

	Arithmetic Means (SD)		**Geometric Means (CV %) ***	
PK parameter	**N1/3-I5**	**Nicotine Inhaler 10 mg**	**N1/3-I5**	**Nicotine Inhaler 10 mg**
C_{max} (ng/mL)	10.25 (6.76)	8.63 (5.38)	8.20 (66.0)	7.29 (62.4)
AUC_{τ} (ng/mLxh) /C_{av} (ng/mL)	8.98 (6.08)	7.46 (4.64)	7.10 (67.7)	6.31 (62.2)
C_{min} (ng/mL)	7.37 (5.52)	6.21 (3.95)	-	-
PTF (%)	36.2 (16.0)	33.3 (13.9)	-	-
Swing (%)	49.9 (33.8)	42.1 (21.4)	-	-
t_{max} (minutes) **	20 (0, 30)	20 (15, 30)	-	-

* Only presented for parameters statistically analyzed on log-scale.
** Median (Min, Max).

Table S4: Estimated Geometric Mean Ratios of Pharmacokinetic Parameters between Treatments

	N1/3-I5 vs. Nicotine Inhaler 10 mg	
	Estimated Ratio	**95 % CI**
C_{max}	117 %	105-130 %
AUC_{τ}/C_{av}	117 %	106-129 %

Table S5: Estimated Geometric Mean Ratios of Baseline-Corrected Nicotine Plasma Concentrations immediately before User Sessions

User Session Starting at:	**N1/3-I5 vs. Nicotine Inhaler 10 mg**	
	Estimated Ratio	**95 % CI**
1 hour	99.6 %	83.3-119.1 %
2 hour	110.8 %	96.6-127.1 %
3 hour	111.5 %	98.1-126.8 %
4 hour	106.6 %	96.2-118.2 %
5 hour	110.5 %	98.9-123.4 %
6 hour	111.3 %	101.5-122.0 %
7 hour	112.9 %	99.7-127.7 %
8 hour	109.8 %	98.7-122.2 %
9 hour	107.6 %	94.6-122.4 %
10 hour	110.4 %	97.3-125.2 %
11 hour	112.6 %	101.5-124.9 %

The estimated average released amounts of nicotine from inhalers (pooled sample of the 12 used inhalers per treatment and subject) are presented in Table S6.

Table S6: Estimated amount of Nicotine Released from Inhalers (mg)*

	N1/3-I5	**Nicotine Inhaler 10 mg**
Mean (SD)	**1.00 (0.40)**	**0.75 (0.33)**
Median	**0.98**	**0.69**
Min-Max	**0.09-1.88**	**0.13-1.42**

* Test for H0: No differences in distributions ($p<0.001$).

The across-subject means and standard deviations for easiness of use (measured prior to administrations at 3, 6 and 9 hours) are presented in Table S7. On the scale used 1 corresponded to “extremely easy” and 8 to “extremely hard”.

Table S7: Easiness of Use (Mean (SD))

	N1/3-I5	Nicotine Inhaler 10 mg	p-value*
3 hours	**3.4 (1.3)**	**3.2 (1.1)**	**0.61**
6 hours	**3.6 (1.5)**	**3.2 (1.1)**	**0.16**
9 hours	**3.4 (1.6)**	**3.4 (1.5)**	**0.77**

* Test for H0: No differences in distributions.

The across-subject means and standard deviations for overall liking (measured at 12 hours) are presented in Table S8. On the scale used, 1 corresponded to “extremely good” and 8 to “extremely bad”.

Table S8: Overall liking (Mean (SD))

N1/3-I5	Nicotine Inhaler 10 mg	p-value*
4.3 (1.5)	**3.8 (1.3)**	**0.091**

* Test for H0: No differences in distributions.

Urges to smoke data are summarized in Table 14.2.6 and individual data are listed in Appendix 16.2.6.11.

SAFETY RESULTS: There was no SAE in this study.

A total of 48 treatment-emergent AEs were reported. Forty (40) were judged to be possibly, probably or very likely related to treatment. None of these treatment-related AEs were categorized as severe, 4 were moderate and 36 were of mild intensity

Among the 40 AEs considered possibly, probably or very likely related to treatment, 20 were reported (by 17subjects) for N1/3-I5 and 20 (by 15 subjects) for Nicotine Inhaler 10 mg. None of the AEs were categorized as severe, 4 were moderate and 36 were of mild intensity.

The numbers of subjects reporting AEs judged to be possibly, probably or very likely related to treatment are presented in Table S9.

Table S9: Overview of Number of Subjects Reporting Adverse Events Possibly, Probably or Very Likely Related to Treatment

Disorder (by body system)	N1/3-I5	Nicotine Inhaler 10 mg
Gastrointestinal		
Abdominal distension	1	-
Dyspepsia	6	2
Glossodynia	-	1
Nausea	-	2
Toothache	1	-
Nervous system		
Dizziness	1	-
Headache	-	1
Migraine	-	1
Respiratory, thoracic and mediastinal		
Cough	1	1
Dysphonia	-	1
Hiccups	1	3
Throat irritation	9	8

CONCLUSION(S):

- In this study, C_{max} C_{av} and AUC_{τ} were statistically significantly higher with N1/3-I5 than with Nicotine Inhaler 10 mg.
- Statistically significantly more nicotine was released from N1/3-I5 than from the Nicotine Inhaler 10 mg.
- Ratings of easiness of use and overall liking were similar for the investigational products.
- There were no indications that the types and frequencies of AE of the investigational products differ from those of other oral nicotine replacement products.

REPORT DATE: 05 June 2012