CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-714

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-714	**SERIAL NO.:** 008
NAME: Nicotrol Inhaler	
SPONSOR: Pharmacia & Upjohn Company, 7000 Portage Road, Kalamazoo, MI	
TYPE OF SUBMISSION: Study Report	**SUBMISSION DATE:** March 7, 1997
REVIEWER: Suresh Doddapaneni, Ph.D.	**REVIEW DATE:** April 18, 1997

INTRODUCTION

Pharmacia & Upjohn currently has NDA 20-714 (Nicotrol Inhaler) under review with the Division. This submission pertains to a final report of a study conducted to assess the risk associated with the improper use of the inhaler in children, i.e., putting the porous plug impregnated with nicotine in the mouth and sucking on it. Since, such a study is risky to conduct in children, the sponsor in consultation with the Agency, conducted the study in adults.

STUDY DESIGN

This was a one-way, single dose study in seven (7) healthy subjects (regular users of snuff). Immediately prior to the plug placement in the mouth, 1 mL of saline was administered orally. The plug was left in the mouth for 1 minute. Serial blood samples were drawn at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, and 30 minutes. Dose of nicotine released, C_{max} and t_{max} were evaluated. Statistical analysis was not required for this study.

RESULTS AND DISCUSSION

The scope of this study is modest and it was conducted mainly to investigate if and when children accidentally put the porous plug in the mouth sufficiently high nicotine amounts are released resulting in high systemic levels and asociated acute toxicity. However, since such a safety study could not be conducted in children, it was conducted in adults and an attempt was made to extrapolate the results to children to assess the degree of safety hazard of such a scenario. The potential acute toxicity was evaluated in terms of the resulting plasma nicotine concentrations and safety parameters (pulse, systolic and diastolic blood pressure etc.). Assessment of the safety parameters will be deferred to the reviewing medical officer.

A total of 300 unused plugs were analyzed for nicotine content to determine the starting nicotine dose. A mean of 10.28 mg was found to be contained in the 300 plugs with a maximum of 11.62 mg in one of the plugs. The mean dose that was released (calculated from the difference of mean nicotine amount contained in the unused plug and used plug from this study) was 1.21 mg (range mg). To estimate the worst case scenario, the mean dose released was also calculated using the maximum amount of nicotine contained in any single plug among the 300 plugs analyzed (11.62 mg) as the starting dose. The mean dose released under this worst case scenario was 2.55 mg (1.9-3.5).

After placing the plug in the mouth, nicotine was rapidly released and absorbed. Mean C_{max} (baseline uncorrected) of 6.5 ng/mL (range ; occurred at 5 minutes.

A similar study *in vitro* conducted to determine the amount of nicotine extracted after immersion of an unused plug in 1 mL of water at 37° C showed that approximately 1.4 mg (range , was released over 1 minute. The amount extracted over 10

minutes was 4.2 mg. Since the oral bioavailability via sublingual absorption is about 50%, *in vitro* data suggests that if the plug is kept in the mouth for 10 minutes, roughly 2.1 mg of nicotine will be systemically absorbed. If an used plug is mishandled in a similar manner, the dose that will be absorbed systemically would be relatively low compared to mishandling an unused plug based on the starting low nicotine content in the used plug.

The above discussion pertains to the plug kept in the mouth. However, if the plug is swallowed, same situation also probably applies with the lower oral bioavailability of 30-40% from the GIT overcome by the possible prolonged residence time of the plug.

The sponsor attempted to extrapolate the *in vivo* data collected in adults to children using the 'surface area' rule. Using this rule, the dose to a child weighing 10 kg would be one-fourth of the adults dose. Although, the present study was performed in adults, the dose released from the plug over 1 minute (mean of 1.2 mg) would be the same as that in a child. Using the surface rule, this would correspond to four fold plasma levels over those seen in the adults i.e., peak levels of approximately 20 ng/mL (range ng/mL). To a nicotine naive subject, this concentration would induce nausea, vomiting and other symptoms. Children with the highest plasma concentration are likely to develop severe toxicity. It is important to recognize the fact that this kind of an extrapolation from adult data to children to predict the consequences of a hypothetical situation without really knowing the manner in which this would occur should be treated with caution.

CONCLUSION

Based on the data presented in this study, accidental ingestion of the plug is not likely to result in fatalities in children.

RECOMMENDATION

Language in the package insert should be strengthened regarding the handling and proper disposal instructions for the inhaler with respect to children.

D Suresh 4/18/97

Suresh Doddapaneni, Ph.D.
Pharmacokineticist
DPE II/OCPB

RD initialed by Dale Conner, Pharm.D.
FT initialed by Dale Conner, Pharm.D.: DPC 4/18/97
CC:
NDA 20-714 (Original), HFD-170 (Division files, McNeal), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Conner), HFD-340 (Viswanathan).

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

McNeal

NDA: 20-714	**CODE:** 3S	**BRAND NAME:** Nicotrol® Inhaler
GENERIC NAME: Nicotine		**NOMINAL DOSE:** 10 mg/unit
SPONSOR: Pharmacia Upjohn Company, 7000 Portage Road, Kalamazoo, MI		
TYPE OF SUBMISSION: Original NDA		**SUBMISSION DATE:** 2 May, 1996
REVIEWER: Suresh Doddapaneni, Ph.D.		**REVIEW DATE:** 25 October, 1996

SYNOPSIS

Pharmacia Upjohn Company has developed a new dosage form for nicotine, Nicotrol® Inhaler for use as an aid to smoking cessation. A total of nine (9) studies were conducted in 144 smokers to investigate the pharmacokinetics of nicotine after the use of the inhaler. The pharmacokinetics of the inhaler seemed identical irrespective of the way the inhaler is used- deep inhalation or shallow sucking. An average dose of approximately 4 mg of nicotine is released upon intense use of the inhaler for 20 minutes. Individual data indicated that in total up to 6 mg nicotine may be released from one single inhaler unit. The absolute bioavailability of the nicotine released from the inhaler was approximately 50%. Peak plasma concentrations were reached approximately 15 minutes after the end of the inhalation. The mean plasma levels following intense use (employed in pharmacokinetic studies) reached about 26 ng/mL, i.e, levels seen after the use of 4 mg Nicorette® gum. However, after *ad lib* use, about 6-8 ng/mL were seen. After *ad lib* use of the inhaler, the resulting plasma concentrations replace about 30% of nicotine levels resulting from *ad lib* cigarette smoking. In contrast to the high and rapid arterial nicotine plasma concentrations achieved after cigarette smoking, the arterial nicotine concentrations rise slowly to much lower levels after the use of the inhaler indicating minimal pulmonary absorption with the inhaler. Nicotine release from the inhaler is dependent on environmental temperature. However, nicotine plasma levels obtained with the inhaler at the highest environmental temperature studied (104°F) were still within the range of levels found among smokers.

RECOMMENDATION

Section 6 of the New Drug Application 20-714 is acceptable from the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics.

D Suresh 11/14/96

Suresh Doddapaneni, Ph.D.
Pharmacokineticist
DPE II/OCPB

R/D initialed by Dale Conner on 10/23/96
F/T initialed by Dale Conner 11/14/96
CC:
NDA 20-714 (Original), HFD-170 (Division files, McNeal), HFD-850 (Lesko), HFD-870 (Doddapaneni, Lockwood, Mei-Ling Chen, Conner, Chron, Drug, Reviewer)

TABLE OF CONTENTS

Notes:

(1) The inhaler was interchangeably referred to as vaporizer and vapour inhaler throughout the study reports. However, all three terms refer to the same final inhaler product.

(2) Most of the pharmacokinetic studies conducted in this NDA were multiple dose studies as single dose would yield too low nicotine concentrations to properly characterize the pharmacokinetics. Therefore the C_{max} and AUC values calaculated correspond to the last dosing interval.

1.0. INTRODUCTION:

Nicotrol® inhaler is the third nicotine product, Pharmacia Upjohn Company has developed as an aid to smoking cessation. The other two products, Nicotrol® patch (NDA 20-150) and Nicotrol® NS nasal spray (NDA 20-385) were approved in April 1992 and March 1996 respectively. In addition, there are other nicotine products that are currently marketed by other pharmaceutical companies such as the Nicoderm® patch (Alza), Prostep® patch (Elan), Habitrol® patch (Ciba), and Nicorette® gum (SmithKline Beecham).

The Nicotrol® Inhaler is not a traditional inhaler in the sense that the drug is not in a powder form and is not meant for pulmonary absorption. It consists of a 10 mg nicotine loaded porous plug (flavored with 1 mg menthol) made of polyethylene inserted into a plastic cartridge which is then sealed with an aluminum foil on both sides. During use, the cartridge is inserted into a mouth piece (which can be separated into two pieces for insertion of the plug and then re-assembled) at which time the seal is automatically broken. For nicotine administration, the patient draws air through the device, which releases gaseous nicotine from the porous plug to the air stream and into the mouth, where a majority of it is absorbed buccally. Best effect is achieved by the patient by frequent continuous puffing (20 minutes). For effective control of nicotine withdrawal symptoms, patients are advised to use between 6-12 cartridges per day. All the batches used in the human pharmacokinetic and bioavailability studies were manufactured with the formulation intended for the marketing of nicotine inhaler. Nicotine loss caused by absorption to the mouth-piece is negligible.

Currently, the Nicotrol® inhaler is approved for use in Denmark, Italy, Sweden, and Netherlands with applications pending in ten other countries. A total of nine (9) pharmacokinetic studies were conducted in 144 smokers to investigate the pharmacokinetics of Nicotrol inhaler in this NDA.

2.0. OVERVIEW OF THE PHARMACOKINETICS OF NICOTINE:

Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring. It is a weak base with a pKa of 8.0 and is soluble both in lipid and in water. At physiological pH, about 31% of nicotine is unionized and readily crosses cell membranes.

Nicotine from tobacco smoke is rapidly absorbed from the small airways and alveoli of the lung. Orally, bioavailability of 30-44% is reported in the literature. Absorption from the oral mucosa is the principal site of absorption from chewing tobacco and nicotine gum and is highly pH dependent. The volume of distribution following iv administration of nicotine is approximately 2 to 3 liter/kg. Plasma protein binding of nicotine is <5%. Therefore, changes in nicotine binding from use of concomitant drugs or alterations of plasma proteins by disease states would not be expected to have significant effects on nicotine kinetics. Nicotine is rapidly and extensively metabolized, primarily in the liver. Nicotine has a terminal half-life of approximately 2 hours after iv administration. Cotinine is the major plasma metabolite of nicotine and persists for a considerably longer time in plasma with a half-life of approximately 15-20 hours and concentrations that exceed nicotine by -fold. Cotinine is very weakly active (> 1000 times weaker than nicotine in its affinity for the nicotine receptor). More than 20 metabolites of nicotine have been identified. The primary urinary metabolites are cotinine (15% of the dose) and trans-3-hydroxycotinine (45% of the dose). Usually about 10% of nicotine is excreted unchanged in the urine. As much as 30% nicotine may be excreted unchanged in the urine with high urine flow rates and acidification below pH 5.

Nicotine pharmacokinetics in renal and hepatic disorders have not been studied. Since a minor fraction of unchanged nicotine is excreted in the urine, steady-state concentrations of nicotine may not be influenced to a large extent by impaired renal function. However, since nicotine is eliminated primarily by hepatic metabolism, hepatic dysfunction should influence pharmacokinetics of nicotine. The pharmacokinetics of nicotine in hepatic and renal failure patients is being investigated as a phase 4 commitment for Nicotrol® NS nasal spray (NDA 20-385) product and concrete data on these issues should be available to the agency once these study reports are submitted.

3.0. SUMMARY OF BIOAVAILABILITY STUDIES

Two studies were conducted to determine the dose and bioavailability of nicotine from the inhaler. Each inhaler has 10 mg nicotine impregnated in the polyethylene plug and it is important to know, how much of the nicotine is sytemically available. The inhaler can be used in two different ways- deep inhalation or shallow sucking. Study 92NNIN005 investigated the effect of these two different modes of inhalation on the bicoavaialbility of nicotine from the inhaler.

3.1. Dose And Absolute Bioavailability Of Nicotine From The Nicotine Vaporizer When Used In Two Standardized Ways:

Fifteen (15) otherwise healthy male and female smokers (smoking at least 10 cigarettes per day) participated in this open label, three-way cross-over, multiple dose (12 inhalers) study (study 92NNIN005). The objective of the study was to determine the dose and bioavailability of nicotine from the inhaler when used in two different inhalation modes-pulmonary (deep inhalation) and buccal (shallow sucking).

The mean amounts of nicotine released were 3.87 mg and 4.00 mg for the buccal and pulmonary modes respectively (Table 1). Individual data indicates that in total up to 6 mg nicotine may be released from one single inhaler unit. The mean absolute bioavailability (F) of nicotine based on the dose released from the inhaler following the buccal mode of administration was 0.51 compared to 0.56 for the pulmonary mode with the difference being not statistically significant. The mean C_{max} of the last dosing interval after the buccal and pulmonary modes of administration were 32 ng/mL and 34.2 ng/mL respectively and were not statistically significant. Thus, the pharmacokinetics of nicotine from the inhaler seem to be the same irrespective of the mode of inhalation.

Table 1. C_{max}, t_{max}, Dose, AUC_{inf} (iv infusion), AUC_{11-12} (AUC of the last dosing interval 11-12 hours for the inhaler), and absolute bioavailability of nicotine from the inhaler (mean (CV)).

Pharmacokinetic Parameter	Buccal Mode	Pulmonary Mode	Intravenous Infusion
C_{max}, ng/mL	32.0 (27)	34.2 (26)	
t_{max}*, hours	0.33	0.50	
Dose, mg	4.00 (15)	3.87 (19)	2.09 (2)
AUC_{11-12}, ng. hour/mL	29.5 (26)	30.9 (28)	29.9* (23)
Absolute Bioavailability, F#	0.51, 0.40 - 0.65	0.56, 0.47 - 0.67	

* Median, * AUC_{inf}, # For bioavailability, values are mean and 95% confidence intervals

3.2. Amount of Nicotine Available to the Systemic Circulation from the Nicotine Vaporizer 10 mg/unit:

This was an open, non-randomized, multiple dose (11 inhalers), cross-over study conducted in 12 adult healthy smoking volunteers (study T91NI07). The inhaler part of the data was derived from study T91I06 (effect of environmental temperature on the bioavailability of nicotine from the inhaler). A supplementary intravenous infusion of 2 mg nicotine was given to a subset of volunteers from this study and data for the inhaler determined at room temperature for this subset of volunteers was used for determining the bioavailability.

The dose that was available to the systemic circulation from the inhaler was estimated to be 1.35 mg. This value is lower than that obtained in the previous study (1.9 - 2.0 mg) and the sponsor attributed this to volunteers having more experience in using the inhaler than in the previous study (study 92NNIN005). There was a large inter-individual variation (40% CV) in the ability to release nicotine from the vaporizer, which, may in part be due to performance of the subject participating in the study. Although, the inhalation frequency, inhalation technique, and number of inhalations are standardized, differences in the puff volume can result in the differences seen.

4.0. COMPARATIVE STUDIES WITH CIGARETTES AND NICORETTE® GUM:

Inhalation of nicotine from cigarette smoke introduces drug rapidly into the arterial circulation and then into the brain. Absorption of nicotine from the lungs is facilitated by a huge alveolar surface area, thin alveolar epithelial and endothelial layers, and an extensive capillary bed. Also, since pulmonary blood flow is very high, with passage of the entire blood volume through the lung every minute, nicotine absorbed from the lungs is carried quickly to various parts of the body and to target organs.

It is believed that nicotine from cigarettes with its bolus like input stimulates nicotine receptors in the brain and activates the dopaminergic reward system resulting in pleasurable effects and positive reinforcement. Withdrawal effects will occur when nicotine's effect on the brain disappears due to elimination of the drug (within a few hours after the last cigarette). Therefore, the aim of nicotine replacement products is to avoid the arterial spike (to prevent euphoria) and to alleviate the withdrawal effects by providing a constant source of nicotine at low levels.

Therefore, nicotine plasma concentrations delivered by the inhaler should be in the range of those produced from smoking cigarettes yet at the same time avoid the arterial spike characteristic of cigarettes.

Four studies were conducted to investigate if the inhaler delivers similar plasma levels as cigarettes but without the arterial spike and also to find out if the plasma levels are similar to those delivered by the 2 mg Nicorette® gum which is an established nicotine replacement product.

4.1. A Comparative Study of the Concentrations of Nicotine and Cotinine After Inhaling Nicotine Vapour From a Nicotine Inhaler Device and After Normal Smoking of Cigarettes:

This was a pilot, open label, randomized, two-way cross-over, multiple dose study (8 inhalers) conducted in eighteen (18) adult male and female smokers to compare the plasma levels after 8 hour use of the inhaler and smoking (Study T88NI02). The results of this study were used to find out if the inhaler delivered nicotine levels are a good substitution for the cigarette delivered nicotine levels.

The subjects smoked a mean of about 10 cigarettes (range; cigarettes) during the *ad lib* smoking arm. The corresponding mean plasma nicotine concentration after 8 hours of

smoking, C_{8smoke} was about 23 ng/mL (range; ng/mL). For the inhaler, the subjects used a mean of about 7 inhalers (range;). After 8 hours use of inhaler, the mean $C_{8inhaler}$ was about 8.4 ng/mL (range; ng/mL). The mean degree of substitution, $C_{8inhaler}/C_{8smoke}$ was 35% (range; %). Therefore, after 8 hours use of the inhaler, the mean plasma concentrations delivered replace about 35% of that delivered by 8 hours of *ad lib* smoking.

4.2. Plasma Nicotine Levels Achieved After *ad libitum* Use of the Nicotine Vaporizer During a Five-day Smoking Free Period:

This study was conducted in forty (40) adult smokers in an open, multiple dose (6-12 inhalers) setting to investigate the nicotine plasma levels achieved after *ad lib* use of the inhaler in real life situation (Study 95NNIN011). The subjects during a baseline period smoked cigarettes *ad lib*, followed by a period where they replaced as many cigarettes as possible with inhalers, and in the third period the subjects used only the inhalers (they were advised to use between 6-12 inhalers per day). Each period lasted five days and blood samples were collected once a day during the last four days of the baseline cigarette period and the inhaler period.

The mean nicotine plasma concentrations during the baseline period of smoking cigarettes alone ranged from ng/mL on the four consecutive days. On each of the four days both the mean nicotine plasma concentrations as well as the range of the minimum to maximum concentrations on each day were similar. The corresponding mean number of cigarettes smoked ranged from with the minimum to maximum number of cigarettes smoked ranging from cigarettes on the four consecutive days.

For the inhaler, the mean plasma nicotine concentrations ranged from 5.4 to 6.1 ng/mL. The mean number of inhalers used ranged from 4.1 to 6.2 with the minimum to maximum ranging from 1 to 17. On each of the four days both the mean nicotine plasma concentrations as well as the range of the minimum to maximum concentrations on each day were similar.

Overall, this study indicates that under real life conditions, an average nicotine substitution of approximately 30% of normal smoking levels is produced by an average number of 5-6 inhalers used *ad lib*.

4.3. Arterial and Venous Plasma Concentrations of Nicotine After Use of The Nicotine Vapour Inhaler:

This was an open, two-way, exploratory single-dose, cross-over study conducted in eight (8) subjects conducted to investigate if nicotine released from the inhaler is absorbed via the pulmonary route (Study 94NNIN010) .

Nicotine delivered from cigarettes because of the pulmonary absorption has a different arterial plasma concentration-time profile with a relatively high C_{max} and a short t_{max} compared to nicotine absorbed buccally.

After use of the cigarette, arterial (brachial artery) nicotine concentrations rose quickly with a mean C_{max} of about 55 ng/mL achieved at a median t_{max} of 5 minutes (Figure 1a). The plasma concentrations then rapidly declined as nicotine distributed into peripheral tissues. On the other hand, the arterial nicotine concentrations rose relatively slowly with the inhaler with a mean C_{max} of about 5 ng/mL fold higher for the cigarette over the inhaler) achieved at a median t_{max} of 10 minutes. Figures 1b and 1c show the plasma concentration-time profiles of nicotine (arterial and venous) for the inhaler and cigarette respectively. In the case of the inhaler, the venous concentrations are very much higher than the arterial concentrations. Since the jugular vein drains the buccal site, this confirms the buccal absorption of nicotine from the inhaler. On the other hand, for the cigarette, the arterial concentrations are much higher than the venous concentrations. Since

the brachial artery drains the pulmonary area, this indicates pulmonary absorption of nicotine from the cigarette. The arterial blood levels then declined relatively slowly. Viewed together, these results indicate the absence of pulmonary absorption of nicotine from the inhaler. Thus from a pharmacokinetic standpoint, the abuse liability potential of the inhaler should be no greater than that of the 4 mg gum (NDA 18-612) which is also absorbed buccally and produces similar nicotine plasma levels.

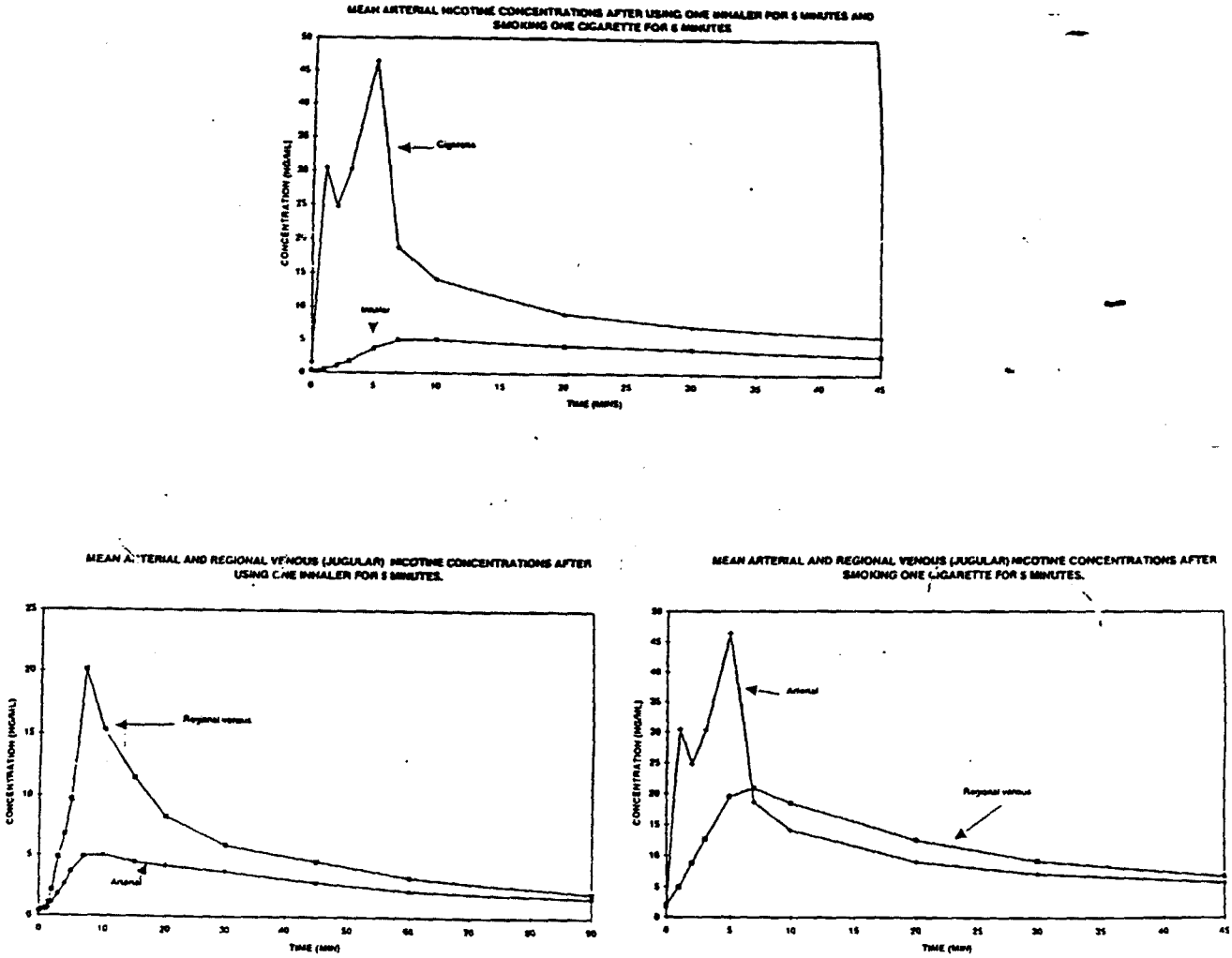

Figure 1. Mean plasma concentrations after the use of a single inhaler and cigarette. (a) Arterial concentrations for both the inhaler and cigarette (b) Arterial and venous concentrations after the use of inhaler (c) Arterial and venous concentrations after smoking the cigarette.

4.4. Nicotine Deposition and Body Distribution from a Nicotine Vaporizer and a Cigarette - a Pharmacokinetic Study with Positron Emission Tomography:

Six subjects participated in an open, two-way cross-over study on the deposition of ^{11}C-nicotine in the respiratory tract from nicotine inhaler. The deposition of ^{11}C-nicotine was visualized by means of positron emission tomography. Two inhalation techniques were studied, shallow frequent inhalations (buccal) and deep inhalations (pulmonary).

Table 2. Radioactivity deposition in different organs and at different times, in percent of radioactivity released from the inhaler (mean (CV)).

Treatment	Oral cavity	Soft tissue	Trachea	Oesophagus	Bronchi	Lungs	Oral cavity	Soft tissue
Time (minute)	6.5	6.5	10	10 + 15*	15	15	50	50
Pulmonary	40.1 (22)	15.2 (64)	1.6 (25)	10.6 (42)	2.3 (74)	6.2 (65)	7.0 (73)	64.3 (42)
Buccal	49.4 (20)	12.1 (179)	0.7 (43)	9.2 (32)	1.0 (120)	4.5 (69)	8.4 (62)	55.7 (42)
Total	44.8 (23)	13.7 (118)	1.1 (55)	9.9 (36)	1.7 (94)	5.4 (65)	7.7 (64)	60 (41)

*Radioactivity calculated from upper 10 cm segment measured at 10 minutes + radioactivity in lower 10 cm segment measured at 15 minutes.

During five minutes of inhalation about 15% of the total radioactivity was released from the inhaler. Approximately 45% of the dose released from the inhaler was found in the oral cavity (Table 2). A significant amount of radioactivity was observed in the oesophagus, suggesting a transfer of a major fraction of the dose to the stomach. Lungs and bronchi had relatively lower amounts of radioactivity. There was no major difference in the depostion pattern in the various organs between the two modes of inhalation. However, this experiment did not focus on the intial deposition of nicotine in the lungs (first few minutes of inhalation). For example, the radioactivity measured in the lungs at 10 minutes after end of administration might not reflect how much was deposited via the airways during the inhalation. At that timepoint distribution of buccally absorbed nicotine should contribute to a large extent to the radioactivity measured in the lungs. Therefore, an additional investigation in one subject was conducted with the addition of a cigarette arm focussing on the initial deposition in the lung. About 14% of the total radioactivity contained in the inhaler was released. A marked buccal deposition pattern was observed with most of the released radioactivity, 36%, appearing in the oral cavity. Another 36% of the dose was recorded in the oesophagus and the stomach. A minor fraction was recovered in the large bronchi, and only a minimal fraction, 4%, was found in the lungs. With the cigarette on the other hand, a marked pulmonary deposition was observed, 14%, with only minimal amounts of radioactivity appearing in the oral cavity, oesophagus, and stomach. The total radioactivity recorded in the lung was only 14% of total released radioactivity, although about 90% of the radioactivity contained in the cigarettes was released from the cigarettes. This low fraction is probably explained by the rapid passage of nicotine from the lung parenchyma to the systemic circulation and also by a major fraction that was never inhaled i.e, literally went up in the smoke.

Therefore results from these PET scans indicate similar absorption pattern for both buccal

and pulmonary modes of inhalation and also a buccal absorption site for the inhaler as opposed to absorption in the lungs for the cigarettes.

4.5. A Comparison of Nicotine Plasma Levels After Repeated Dosing With a Nicotine Vaporizer and a 2 mg Nicotine Polacrilex Chewing Gum:

This was a open label, randomized, two-way cross-over study conducted in eighteen (18) healthy smokers to compare plasma levels of nicotine after repeated dosing (12 inhalers or pieces of gum) with nicotine vaporizer and 2 mg Nicorette® gum (study T91NI05).

Both C_{max} and AUC_{10-11} values were significantly higher for the inhaler over the 2 mg gum (Table 3). C_{max} and AUC_{10-11} were about 2.3 and 2.4 fold higher for the inhaler. The mean trough plasma levels (determined at 9, 10, and 11 hours) were approximately 2.5 times as high for the inhaler over the gum. However, the t_{max} values were not statistically significant between the two. Overall, these results show that inhaler delivers nicotine levels about 2-2.5 fold higher when compared to the gum. Similar t_{max} values may indicate similar absorption site for the inhaler as for the gum ((buccal). Although not included in this study, comparison of the nicotine plasma levels delivered by the inhaler with those delivered by the 4 mg Nicorette® gum would have been more appropriate. Nicotine C_{max} values after chewing several pieces of gum are approximately 30 ng/mL and as such would compare well with the inhaler.

Table 3. Pharmacokinetic parameters after the administration of multiple doses of the inhaler and the gum (mean (CV)).

Pharmacokinetic Parameter	Inhaler	Gum
C_{max}, ng/mL	25.8 (36)	11.2 (17)
t_{max}, minute	28 (46)	33 (40)
AUC_{10-11}, hour ng/mL	23.7 (36)	9.9 (16)
AUC_{inh}/AUC_{gum}	2.42 (47)	

5.0. OTHER RELEVANT STUDIES

5.1. Effects of Elevated Environmental Temperature on the Relative Bioavailability of Nicotine from a Nicotine Vaporizer:

This study was conducted in 18 healthy smokers in a randomized, three way cross-over, multiple dose (11 inhalers) setting to investigate if the relative bioavailability of nicotine from the inhaler increases at elevated environmental temperatures of 86°F and 104°F when compared to ambient temperature of 68°F (Study T91NI06). *In vitro* tests revealed an approximate doubling of nicotine release rate for every 10°C rise in temperature and a similar occurrence *in vivo* could result in elevated nicotine levels causing adverse effects.

Both C_{max} and AUC_{10-11} increased significantly as the environmental temperature was raised from 68°F to 104°F. Compared to the C_{max} value at room temperature, there was a 41% increase in C_{max} at 86°F, and a 70% increase in C_{max} at 104°F (Table 4). Similarly for AUC_{10-11}, compared to the room temperature value, there was a 39% and 66% increase in AUC_{10-11} at 86°F and 104°F respectively. The plasma concentrations achieved at the higher temperatures 86°F and 104°F are within the normal concentrations achieved by smokers at room temperature and do not pose any undue adverse effect. Also, approximate steady state concentrations achieved with 4 mg gum are

about 30 ng/mL. As such the plasma concentrations achieved at the higher temperatures do not pose additional safety concern any more than that seen with 4 mg gum.

Table 4. Pharmacokinetic parameters of nicotine determined at the three different environmental temperatures of 68°F, 86°F, and 104°F respectively (mean (CV)).

Pharmacokinetic Parameter	68°F	86°F	104°F
C_{max}, ng/mL	22.49 (34)	29.74 (28)	34.03 (20)
t_{max}, hour	10.49 (2)	10.47 (2)	10.40 (2)
AUC_{10-11}, ng/mL hour	20.53 (35)	26.51 (27)	30.26 (20)

5.2. The Effect of a Nicotine Vaporizer, on the Relief of Nicotine Abstinence Symptoms During a Two-day Smoke Free Period:

Fifteen subjects participated in a placebo-controlled, four-way cross-over study on the effect of nicotine inhaler on craving (urge to smoke, missing cigarettes) and other withdrawal symptoms (urges to smoke, missing cigarettes, impatience, irritability, difficulty concentrating, and dizziness) during a two-day smoke-free period (study 92NNIN004). Two inhalation techniques were studied, one with shallow, frequent puffing (buccal technique) and one with deep inhalations (pulmonary technique). Craving and other withdrawal symptoms were rated nine times over a two-day period on 10-point scales. Plasma nicotine concentrations were determined in the afternoon of each study day.

Results showed that active inhaler treatment significantly decreased the craving and withdrawal symptom scores over the placebo inhalers with no difference between the two inhalation techniques. The average number of nicotine inhaler units used during the two-day smoke-free periods were 13 (buccal) and 12 (pulmonary technique). Average afternoon nicotine plasma levels in subjects using the pulmonary technique varied between 6.8.± 4.0 ng/mL (day 1) and 6.9 ± 5.0 ng/mL (day 2) and 6.8±4.0 ng/ml (day 1) and 6.9±5.0 ng/mL using the buccal technique. A strong correlation was found between afternoon nicotine plasma levels and total craving score. However, no such correlation was found between nicotine plasma levels and total withdrawal score. This might be due to the shorter duration of nicotine abstinence. Feelings of impatience, irritation, dizziness etc. would probably be more pronounced after a longer period of smoking abstinence.

6.0. CONCLUSIONS

(1) An average dose of approximately 4 mg of nicotine is released upon intense use of the inhaler for 20 minutes. Individual data indicates that in total up to approximately 6 mg nicotine may be released from one single inhaler unit. The absolute bioavailability of the nicotine from the inhaler is approximately 50%. *Ad lib* use of the inhaler yielded lower nicotine concentrations than those are seen in the bioavailability studies from which the dose and bioavailability is calculated indicating that these values may be an overestimation under real life conditions (see conclusion 2).

(2) The nicotine levels delivered by the inhaler appear to fall into two ranges. Intensive inhalation as was used in most of the pharmacokinetic studies yielded relatively large concentrations of

about 30 ng/mL, similar to those obtained after the use of 4 mg Nicorette® gum. On the other hand *ad lib* use of the inhaler yielded relatively low concentrations of about ng/mL corresponding to once hourly chewing of 2 mg Nicorette® gum. Typically peak plasma concentrations are reached within approximately 15 minutes after the end of the inhalation. After *ad lib* use of the inhaler, the resulting plasma concentrations replace about % of nicotine levels resulting from *ad lib* smoking

(3) The pharmacokinetics of the inhaler seem identical irrespective of the way the inhaler is used-deep inhalation or shallow sucking.

(4) There is a large inter-individual variability in the dose released, and thus in the dose available to the systemic circulation, mainly due to the variability in the volume of the inhaled air.

(5) In contrast to the high and rapid arterial nicotine plasma concentrations achieved after cigarette smoking, the arterial nicotine concentrations rise slowly to much lower levels after the use of the inhaler indicating absence of pulmonary absorption with the inhaler.

(6) Major fraction of the dose is deposited in the oral cavity, throat and upper respiratory tract and only a minor fraction is found in the lungs.

(7) Nicotine release is dependent on environmental temperature. However, nicotine plasma levels obtained with the inhaler at the highest environmental temperature studied (104°F) are still within the range of levels found among smokers.

7.0. PROPOSED PACKAGE INSERT.

All the marketed nicotine transdermal patches are labeled in terms of the delivered dose of nicotine rather than the nominal dose contained in the patch. The Nicotrol inhaler falls under the same category in that it contains a total of 10 mg while approximately 2 mg is delivered systemically. This issue was brought to the attention of the reviewing medical officer and is under consideration at this time by the Clinical Division.

Regarding the pharmacokinetics section of the proposed package insert, relevant changes were made by this reviewer to make the information more comprehensive and to accurately reflect the data and is presented below.

STUDY I

STUDY TYPE: Basic pharmacokinetics
STUDY TITLE: Dose and absolute bioavailability of nicotine from the nicotine vaporizer when used in two standardized ways.
NDA: 20-714 **SUBMISSION DATE:** May 2, 1996 **VOLUME:** 1.10 **STUDY:** 92NNIN005

STUDY DESIGN:

CLINICAL INVESTIGATOR:	**ANALYTICAL INVESTIGATOR:**

MULTIPLE DOSE: Yes **CROSS-OVER:** Three-way **OTHER DESIGN:** Open, randomized **FASTED:** No **WASH-OUT PERIOD**: *One week.*
SMOKING: No smoking prior to 12 hours before the dose and during blood sampling

SUBJECT BREAKDOWN

Normal Yes **Young** Yes **Number**= 14 **Male**= 6 **Female**= 8

Male				Female			
Weight; Mean 73	**Range**	kg		**Weight; Mean** 58	**Range**	kg	
Age; Mean 36	**Range**	yrs		**Age; Mean** 38	**Range**	yrs	

FORMULATION

Treatment Groups	Dose	Dosage Form	Strength	Lot	Lot Size
1) Buccal Mode 2) Pulmonary Mode	Nicotine vaporizer 120 mg	vaporizer	10 mg/unit	RF333	
3) Intravenous Infusion	2 mg	sterile solution	0.75 mg/mL	900307-01-001	6 mL

PLASMA SAMPLING TIMES: 5 mL venous blood samples at pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11 hours after the first dose administration and 10, 20, 30, 40, 50, and 60 minutes after the start of the last dose administration for the inhaler.
Pre-dose, 5, 10, 20, 30, 45, 60 minutes, 1.5, 2, 3, 4, 6, and 8 hours after start of the infusion for the intravenous administration.
ASSAY METHOD:

ASSAY SENSITIVITY: The limit of quantitation was ng/mL.
ASSAY ACCURACY: The precision and accuracy for nicotine were 9% at 12.5 ng/mL and 9.3% at 15.5 ng/mL respectively.
LABELLING CLAIMS: Inhalation releases on the average were 4 mg of the nicotine content of each cartridge.

OBJECTIVES

1) Primary objective is to assess the absolute bioavailability of nicotine from the vaporizer when two standardized inhalation techniques were used.

2) Secondary objective is to determine, if there is a relationship between released amount of nicotine and steady-state nicotine plasma levels.

STUDY DESIGN

15 otherwise healthy male and female smokers (smoking at least 10 cigarettes per day) participated in this open label, three-way cross-over, multiple dose study. The sequence between the two modes of inhalation was randomized while the intravenous dose was given at the start of the study. The subjects refrained from smoking for at least 12 hours before the start of drug administration and during the entire experimental session. A fresh inhaler was used for 20 minutes every hour for 11 hours (12 inhalers). For the pulmonary inhalation mode, one deep inhalation (5 seconds) every 15 seconds for 20 minutes (80 inhalations per unit) was used. For the buccal mode, the subjects sucked at the vaporizer, with the mouth closed while breathing through the nose, every second for 10 seconds. The nicotine vapor is not inhaled into the lungs. After a break of 10 seconds, the sucking is repeated. This was repeated for 20 minutes per hour. For the intravenous administration, 2 mg was administered over 20 minutes. C_{max}, t_{max}, Vaporizer dose (mean amount of nicotine released from the 12 vaporizers used by each individual), AUC_{inf} (iv), AUC_{11-12} (vaporizer), $C_{ss,av}$ (AUC_{11-12}/hour), and F were the pharmacokinetic parameters that were evaluated in comparing the treatments. C_{max}, AUC_{11-12}, and AUC_{inf} were adjusted for baseline nicotine.

RESULTS AND DISCUSSION

The actual amount of nicotine released from the inhaler was estimated from the difference in weight of it before and after use. However, this will also include menthol and ethanol that are released along with the nicotine. *In vitro* experiments gave the following linear relationship between the weight reduction of the inhaler and the amount of nicotine released.

$$N = 0.834\ W - 0.094\ (r=0.994)$$

where, 'N' is amount of nicotine and
'W' is the weight reduction of the vaporizer

The mean amounts of nicotine released were 3.87 mg and 4.00 mg for the buccal and pulmonary modes respectively. The mean absolute bioavailability (F) of nicotine from the inhaler following the buccal mode of administration was 0.51 compared to 0.56 for the pulmonary mode with the difference being not statistically significant. Individual data indicates that in total up to approximately 6 mg nicotine may be released from one single inhaler unit. The mean C_{max} of the last dosing interval after the buccal and pulmonary modes of administration were 32 ng/mL and 34.2 ng/mL respectively and were not statistically significant. These nicotine levels are similar to those seen in heavy smokers and also once hourly chewing of 4 mg Nicorette® gum.

CONCLUSIONS

(1) Approximately 4 mg of nicotine was released from the inhaler of which 2 mg was available systemically.

(2) Between the two modes of inhaling, pulmonary and buccal there is no statistically significant differences in terms of the systemically available nicotine from the inhaler.
(3) The steady state plasma nicotine levels averaged about 30 ng/mL which are similar to those seen in moderate to heavy smokers.

Table 1. C_{max}, t_{max}, Dose, AUC_{inf} (iv infusion), AUC_{11-12} (AUC of the last dosing interval 11-12 hours for the inhaler), and absolute bioavailability of nicotine from the inhaler (mean (CV)).

Pharmacokinetic Parameter	**Buccal Mode**	**Pulmonary Mode**	**Intravenous Infusion**
C_{max}, ng/mL	32.0 (27)	34.2 (26)	
t_{max}★, hours	0.33	0.50	
Dose, mg	4.00 (15)	3.87 (19)	2.09 (2)
AUC_{11-12}, ng. hour/mL	29.5 (26)	30.9 (28)	29.9* (23)
AUC/Dose	7.35 (24)	7.94 (20)	14.27 (23)
Absolute Bioavailability, F# (based on estimated dose delivered)	0.51, 0.40 - 0.65	0.56, 0.47 - 0.67	

★ Median
* AUC_{inf} for intravenous infusion
# For bioavailability, values are mean and 95% confidence interval

STUDY II

STUDY TYPE: Absolute bioavailability
STUDY TITLE: Amount of nicotine available to the systemic circulation from the nicotine vaporizer 10 mg/unit.
NDA: 20-714 **SUBMISSION DATE:** May 2, 1996 **VOLUME:** 1.09 **STUDY:**T91NI07

STUDY DESIGN:
CLINICAL INVESTIGATOR: **ANALYTICAL INVESTIGATOR:**

MULTIPLEDOSE: Yes **CROSS-OVER:**Two-way **OTHER DESIGN:**Open,non-randomized
SMOKING: No smoking prior to 12 hours before the dose and during blood sampling

SUBJECT BREAKDOWN:
Normal Yes **Young** Yes **Subject Type**: Male **Group** Normal **N=** 12 **M=** 6 **F=** 6

Male				Female			
Weight; Mean 76	**Range**	kg		**Weight; Mean** 61	**Range**	kg	
Age; Mean 37	**Range**	yrs		**Age; Mean** 37	**Range**	yrs	

FORMULATION:

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
A	Nicotine 120 mg	vaporizer	10 mg/unit	RF333	
B	Nicotine 2mg	IV Infusion (20 minutes)	0.1 mg/mL	900307-01-001	-

PLASMA SAMPLING TIMES: 5 mL venous blood samples for the inhaler were collected at 5, 6, 7, 8, 9, and 10 hours after the first dose and 10, 20, 30, 40, 50, and 60 minutes after the start of the last dose. For the intravenous infusion, samples were collected at before (0), 5, 10, 20, 30, 45, 60 minutes, 1.5, 2, 3, 4, 5, 6, 8, and 10 hours after start of the infusion.
ASSAY METHOD:

ASSAY SENSITIVITY: The limit of determination was set at 1.0 ng/mL.
ASSAY ACCURACY: The precision and accuracy of the method at 10.0 ng/mL were 3.9% and 95.3% respectively.
LABELLING CLAIMS FROM STUDY:
The mean amount available to the systemic circulation was estimated to be 1.35 ± 0.57 mg.

OBJECTIVES
To determine the amount of nicotine available to the systemic circulation from the nicotine

vaporizer 10 mg/unit.

STUDY DESIGN

This was an open, non-randomized, multiple dose, cross-over study conducted in 12 adult healthy smoking volunteers. The inhaler part of the data was derived from study T91I06 (effect of environmental temperature on the bioavailability of nicotine from the inhaler). A supplementary intravenous infusion of 2 mg nicotine was given to a subset of volunteers from this study and data for the inhaler determined at room temperature for this subset of volunteers was used for determining the bioavailability.

RESULTS AND DISCUSSION

The dose that was available to the systemic circulation from the inhaler was estimated to be 1.35 mg (Table 1). There is a large inter-individual variation in the ability to release nicotine from the vaporizer, in part, may be due to performance of the subject participating in the study. Although, the inhalation frequency, inhalation technique, and number of inhalations are standardized, still, differences in the puff volume can result in the differences that are seen.

Table 1. Pharmacokinetic parameters of nicotine (mean (CV)).

Pharmacokinetic Parameter	**Inhaler**	**IV Infusion**
C_{max}, ng/mL	22.1 (42)	
t_{max}, hour	0.50 (40)	
AUC_{10-11}#, hour ng/mL	19.5 (44)	
$AUC_{inf,iv}$#, hour ng/mL		30.8 (20)
Dose available from vaporizer	1.35 (42)	

AUC's are baseline corrected

STUDY III

STUDY TYPE: Basic pharmacokinetics
STUDY TITLE: A comparative study of the concentrations of nicotine and cotinine after inhaling nicotine vapour from a nicotine inhaler device and after normal smoking of cigarettes.
NDA: 20-714 **SUBMISSION DATE:** May 2, 1996 **VOLUME:** 1.10 **STUDY:** T88NI02

STUDY DESIGN:
CLINICAL INVESTIGATOR:
ANALYTICAL INVESTIGATOR:

MULTIPLE DOSE: Yes **CROSS-OVER:** Two-way **OTHER DESIGN:** Open, randomized
SMOKING: No smoking prior to 10 hours before the dose and during blood sampling

SUBJECT BREAKDOWN:
Normal Yes **Young** Yes **Number=** 19 **Male=** 5 **Female=** 14

FORMULATION:

Treatment Groups	Dose	Dosage Form	Strength	Lot	Lot Size
1) Inhaler	*ad lib*	vaporizer	10	881007-02	
2) Cigarette	*ad lib*	cigarette	mg/unit	own brand	

PLASMA SAMPLING TIMES: Pre-dose, 20, 30, 60 minutes, and at 2, 4, 6 and 8 hours for the inhaler arm and at 8 hours for the smoking arm.
ASSAY METHOD:

ASSAY SENSITIVITY: The limit of quantitation was 1.2 ng/mL.
ASSAY ACCURACY: The precision and accuracy for nicotine at 9.6 ng/mL were 4.8% and 101% respectively.
LABELLING CLAIMS: Pilot study - No labelling claims
OBJECTIVES
1) To study the plasma levels of nicotine after inhaling nicotine vapor from a nicotine inhaler device.
2) To compare the plasma levels after 8 hours use of the inhaler and smoking.
STUDY DESIGN

Nineteen (19) otherwise healthy male and female smokers (smoking at least 10 cigarettes per day) participated in this pilot, open label, randomized, two-way cross-over, multiple dose study. The inhaler was used by means of deep inhalations (5 seconds) every 15 seconds for 20 minutes (80 inhalations per unit). After the first inhaler, *ad libitum* dosing was used for at least 6 hours. Cigarette smoking was allowed *ad libitum* through out for the cigarette arm of the study period. C_{max}, t_{max}, $C_{8inhaler}$ (concentration of nicotine after 8 hours use of inhaler), C_{8smoke} (concentration of nicotine after 8 hours of smoking) $C_{8inhaler}/C_{8smoke}$ (degree

of substitution) were the pharmacokinetic parameters that were evaluated in comparing the treatments.

RESULTS AND DISCUSSION

The subjects smoked a mean of about 10 cigarettes (range; cigarettes) during the *ad lib* smoking arm. The corresponding mean plasma nicotine concentration after 8 hours of smoking, C_{8smoke}, was about 23 ng/mL (range; ng/mL). For the inhaler, the subjects used a mean of about 7 inhalers (range;). After 8 hours use of inhaler, the mean $C_{8inhaler}$ was about 8.4 ng/mL (range; ng/mL). The mean degree of substitution, $C_{8inhaler}/C_{8smoke}$ was 35% (range; %).

CONCLUSIONS

After 8 hours use of the inhaler, the mean plasma concentrations delivered replaced about 35% of that delivered by 8 hours of *ad lib* smoking.

STUDY IV

STUDY TYPE: Basic pharmacokinetics
STUDY TITLE: Plasma nicotine levels achieved after *ad libitum* use of the nicotine vaporizer during a five-day smoking free period.
NDA: 20-714 **SUBMISSION DATE:** May 2, 1996 **VOLUME:** 1.12 **STUDY:** 95NNIN011

STUDY DESIGN:
CLINICAL INVESTIGATOR:
ANALYTICAL INVESTIGATOR:

MULTIPLE DOSE: Yes **CROSS-OVER:** Yes **OTHER DESIGN:** Open, randomized

SUBJECT BREAKDOWN:
Normal Yes **Young** Yes **Number=** 40 **Male=** 13 **Female=** 27

Male			Female		
Weight; Mean 74.5	**Range**	kg	**Weight; Mean** 66	**Range**	kg
Age; Mean 33	**Range**	yrs	**Age; Mean** 32	**Range**	yrs

FORMULATION:

Treatment Groups	Dose	Dosage Form	Strength	Lot	Lot Size
1) Inhaler 2) Cigarette	*ad lib* *ad lib*	vaporizer cigarette	10 mg/unit ≈ 1 mg/cigarette	UI571B subjects preferred brand	

PLASMA SAMPLING TIMES: 5 mL venous blood samples were collected every afternoon between 16.30 and 19.00 for four consecutive days for both the baseline period and for the study period.
URINE SAMPLING: 10-15 mL urine samples were collected every afternoon between 16.30 and 19.00 for four consecutive days for both the baseline period and for the study period.
ASSAY METHOD:

ASSAY SENSITIVITY: The limits of quantitation were 1.0 and 5.8 ng/mL for nicotine and cotinine respectively.
ASSAY ACCURACY: The precision and accuracy of the method for nicotine were 5.4% at 10 ng/mL and 101% at 9.6 ng/mL respectively. For cotinine, the precision and accuracy were 5.5% at 400 ng/mL and 88-101% at 200 ng/mL respectively.
LABELLING CLAIMS: *Ad Libitum* use of the Nicotrol inhaler typically produces nicotine plasma levels of 6-8 ng/mL, corresponding to about 1/3 of those achieved with cigarette smoking.
OBJECTIVES
(1) Primary objective was to determine the nicotine plasma levels after *ad libitum* use of the vaporizer in a real use situation.

(2) Secondary objective was to determine the relationship between the number of inhalers/cigarettes used over a 24 hour period and the plasma nicotine levels.

STUDY DESIGN

There were three periods (5 consecutive days each) in this study. The subjects who participated in this study were intending to stop smoking. In period A (baseline), the subjects smoked cigarettes of their preferred brand and recorded the number. In period B (pre-study), the subjects replaced as many cigarettes as possible by the inhaler and tried to get used to the inhaler. In period C (main study), the subjects used only the inhaler (not less than 6 and not more than 12 inhalers per day). In periods A and C, blood and urine samples were collected once in the afternoons in the last four days of each period for determination of nicotine concentrations.

RESULTS AND DISCUSSION

The mean nicotine plasma concentrations during the baseline period of smoking cigarettes alone ranged from ng/mL in the afternoons of the four consecutive days. The range of minimum to the maximum plasma concentrations in these four days were ng/mL. On each of the four days both the mean nicotine plasma concentration as well as the range of the minimum to maximum concentrations were similar. The corresponding mean number of cigarettes smoked were ranged from with the minimum to maximum number of cigarettes smoked ranging from cigarettes in the four consecutive days.

For the inhaler, the mean plasma nicotine concentrations ranged from ng/mL with the minimum to maximum nicotine plasma concentrations achieved being ng/mL. The mean number of inhalers used ranged from with the minimum to maximum ranging from

The mean cotinine urine concentrations on the four days of urine sampling during *ad lib* cigarette smoking ranged from ng/mL. During *ad lib* inhaler use, the corresponding urine concentrations were ng/mL.

Regression analysis was performed for the relationship between number of cigarettes and nicotine plasma concentrations and also between number of cigarettes and nicotine plasma concentrations. In both cases the slope was significant except for day 2 for cigarettes. It is not certain what conclusions one can draw from this analysis. A regression analysis between number of inhalers used and number of cigarettes smoked would have given a better picture regarding the utility of inhalers as a replacement for cigarettes as a nicotine source.

CONCLUSIONS

Ad libitum use of the inhaler resulted in average of 5-6 inhalers being used per day producing an average nicotine substitution of approximately 30% of normal smoking levels. This is the lower end of the range recommended in the labelling: 6-12 inhalers per day.

COMMENTS

1. Blood should have been sampled at additional time points (instead of one sample per day) so as to obtain a mean concentration on that day rather than relying on a single time point.

STUDY V

STUDY TYPE: Basic pharmacokinetics
STUDY TITLE: Arterial and venous plasma concentrations of nicotine after use of the nicotine vapour inhaler.
NDA: 20-714 **SUBMISSION DATE:**May 2, 1996 **VOLUME:**1.12 **STUDY:**94NNIN010

STUDY DESIGN
CLINICAL INVESTIGATOR: **ANALYTICAL INVESTIGATOR:**

SINGLE DOSE: Yes **CROSS-OVER:** Two-way **OTHER DESIGN:**Open, randomized
SMOKING: No smoking prior to 24 hours before the dose and during blood sampling

SUBJECT BREAKDOWN
Normal Yes Young Yes Number= 8 Male= 5 Female= 3

Male				Female			
Weight; Mean 77	Range	kg		Weight; Mean 73	Range	kg	
Age; Mean 31	Range	yrs		Age; Mean 27	Range	yrs	

FORMULATION

Treatment Groups	Dose	Dosage Form	Strength	Lot	Lot Size
1) Inhaler	Nicotine 10 mg	Inhaler	10 mg/unit	TC510	
2) Cigarette	0.9 mg	Cigarette	0.9 mg/cigarette		

PLASMA SAMPLING TIMES: 5 mL arterial (from brachial artery) and venous blood (from antecubital vein) samples were collected at pre-dose, 30 sec, 60 sec, 1.5, 2, 3, 4, 5, 7, 10, 15, 20, 30, 45, 60, and 90 minutes for the inhaler. Pre-smoke (90 minute time point for the inhaler), 1, 2, 3, 5, 7, 10, 20, 30, and 45 minutes were the blood sampling time points for the cigarette. Blood samples were also collected from a regional vein (jugular vein) draining the blood from the oral cavity to measure buccally absorbed nicotine.
ASSAY METHOD:

ASSAY SENSITIVITY: The limit of quantitation was 0.6 ng/mL.
ASSAY ACCURACY: The precision and accuracy of the assay for nicotine at 4.9 ng/mL were 7.0% and 93% respectively.
LABELLING CLAIMS: After use of a single inhaler, the arterial nicotine concentrations rise slowly to an average of 5 ng/mL in contrast to those of a cigarette, which increase rapidly and reach an average peak of approximately 55 ng/mL within 5 minutes.

OBJECTIVES
To determine if any nicotine released from the vapor inhaler is absorbed via the

pulmonary route.

An important factor in determining the abuse liability potential of the inhaler is the delivery of nicotine in a manner similar to that of the cigarettes i.e., arterial spike. Absence of such an arterial spike would decrease the chances of the inhaler being abused.

STUDY DESIGN

This was an open, two-way, exploratory single-dose, cross-over study conducted in eight (8) subjects. The subjects used the inhaler first followed by smoking 90 minutes later. The inhaler was used for 5 minutes (one deep inhalation for 5 seconds with 4 inhalations/minute for a total of 5 minutes). The subjects smoked one cigarette for 5 minutes with equally spaced puffs. The subjects refrained from smoking for 24 hours prior to the start of the study.

RESULTS AND DISCUSSION

Nicotine from cigarettes is carried into the lungs by the smoke particles where it is absorbed into the systemic circulation. Absorption of nicotine from the lungs is facilitated by a huge alveolar surface area, thin alveolar epithelial and endothelial layers, an extensive capillary bed, an a high pulmonary capillary blood flow. Therefore, nicotine delivered from cigarettes has a different arterial plasma concentration-time profile with a relatively high C_{max} and a short t_{max} compared to nicotine absorbed buccally. .

After use of the cigarette, arterial (brachial artery) nicotine concentrations rose quickly with a mean C_{max} of about 55 ng/mL achieved at a median t_{max} of 5 minutes (Figure 1). The plasma concentrations then rapidly declined as nicotine distributed into peripheral tissues. On the other hand, the arterial nicotine concentrations rose relatively slowly with the inhaler with a mean C_{max} of about 5 ng/mL (11 fold higher for the cigarette over the inhaler) achieved at a median t_{max} of 10 minutes. Figures 2-3 show the plasma concentration-time profiles of nicotine (arterial and venous) for the inhaler and cigarette respectively. In the case of the inhaler, the venous concentrations are very much higher than the arterial concentrations. Since the jugular vein drains the buccal site, this confirms the buccal absorption of nicotine from the inhaler. On the other hand, for the cigarette, the arterial concentrations are much higher than the venous concentrations. Since the brachial artery drains the pulmonary area, this indicates pulmonary absorption of nicotine from the cigarette. The arterial blood levels then declined relatively slowly. Viewed together, these results indicate the absence of pulmonary absorption of nicotine from the inhaler.

It is believed that nicotine from cigarettes with its bolus like input stimulates nicotine receptors in the brain and activates the dopaminergic reward system resulting in pleasurable effects and positive reinforcement. Withdrawal effects will occur when nicotine's effect on the brain disappears due to elimination of the drug (within a few hours after the last cigarette). The nicotine inhaler much like other nicotine replacement products such as the patch, gum, and nasal spray reduces withdrawal symptoms, but with much less pleasure than is provided by smoke inhalation. Thus the smoker, may get what is needed to avoid nicotine withdrawal with Nicotrol inhaler but not necessarily what is wanted with respect to pleasure and euphoria. Thus from a pharmacokinetic standpoint the abuse liability potential of the inhaler should be no greater than that of the 4 mg gum which is also absorbed buccally and produces similar nicotine plasma levels..

CONCLUSIONS

Nicotine from the inhaler is absorbed buccally and there is no pulmonary absorption unlike with cigarettes. After use of a single inhaler, the arterial nicotine concentrations rise

slowly to an average of 5 ng/mL in contrast to those of a cigarette, which increase rapidly and reach an average peak of approximately 55 ng/mL within 5 minutes.

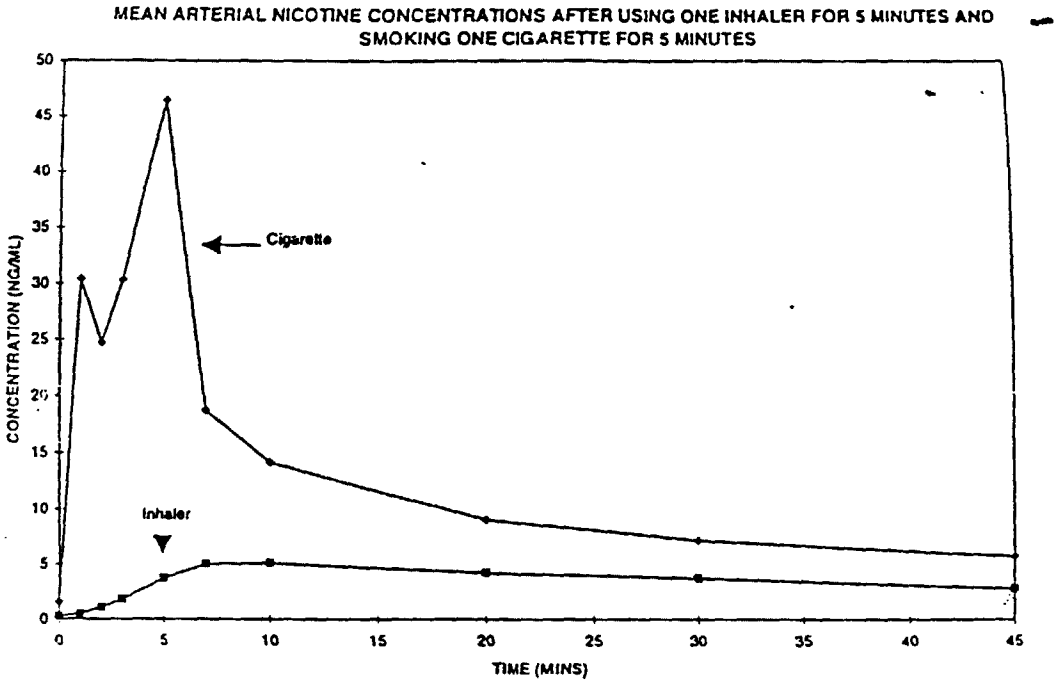

Figure 1. Mean nicotine arterial plasma concentrations after smoking a single cigarette and using a single inhaler.

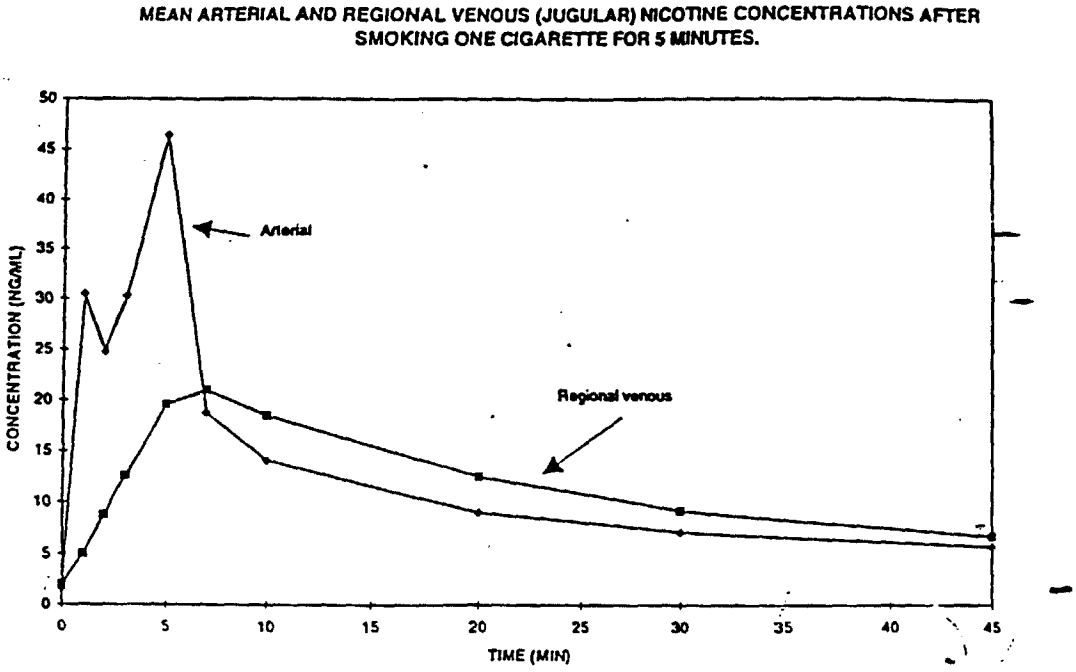

Figure 2. Mean nicotine arterial and venous plasma concentrations after smoking a single cigarette.

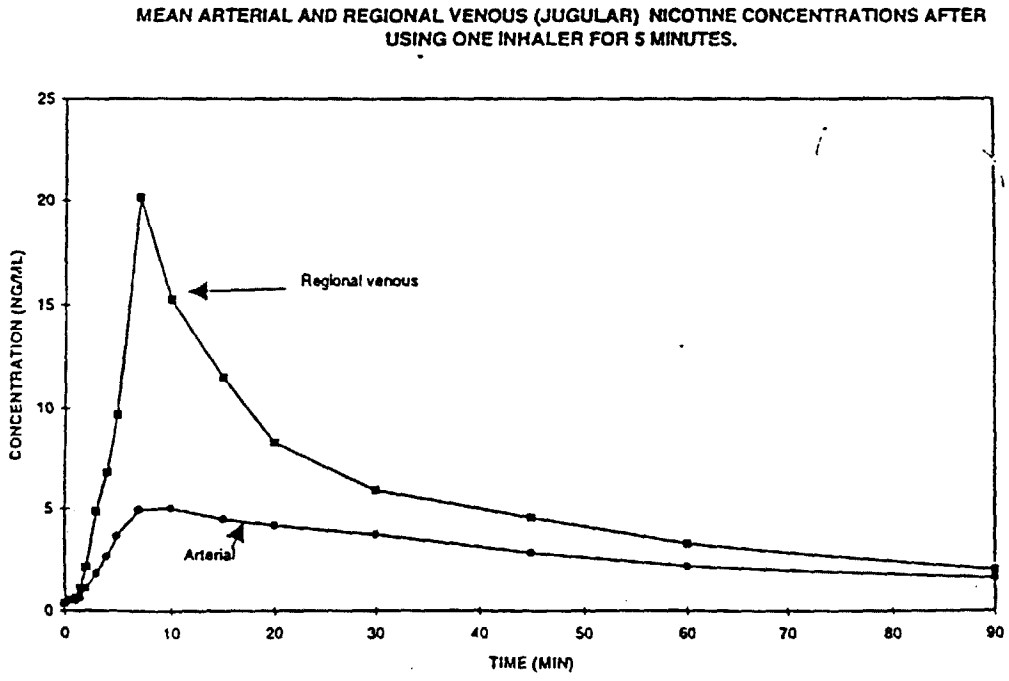

Figure 3. Mean nicotine arterial and venous plasma concentrations after a single inhaler.

STUDY VI

STUDY TYPE: Basic pharmacokinetics
STUDY TITLE: Nicotine deposition and body distribution from a nicotine vaporizer and a cigarette - A pharmacokinetic study with Positron Emission Tomography.
NDA: 20-714 **SUBMISSION DATE:** May 2, 1996 **VOLUME:**1.11-1.12 **STUDY:** 93NNIN007
STUDY DESIGN:
CLINICAL
INVESTIGATOR:

SINGLE DOSE: yes **CROSS-OVER:**Two-way **OTHER DESIGN:**Open
SMOKING: No smoking prior to 12 hours before the dose and during blood sampling

SUBJECT BREAKDOWN:
Normal Yes **Young** Yes **Number**= 6 **Male**= 6 **Female**= 0
Weight; 76 kg (range; **Age;** 39 yrs (range,

FORMULATION:

Treatment Groups	Dose	Dosage Form	Strength	Lot	Lot Size
1)Inhaler	Nicotine 10 mg	vaporizer	10 mg/unit	0103TA	
2)Cigarette	Nicotine 1-1.5 mg	Cigarette	1-1.5 mg/cigarette		

PLASMA SAMPLING TIMES: 14 blood samples, each 3 mL, were taken from a venous catheter in the foot and an arterial catheter in the forearm.
ASSAY METHOD:

OBJECTIVES
1) The primary objective was to assess the effect of two different inhalation techniques on the site of deposition of nicotine from the vaporizer.
2) Secondary objective was to compare arterial plasma levels of nicotine.
STUDY DESIGN
The six subjects inhaled using two modes of inhalation, buccal and pulmonary, each mode in a separate session separated by 3 hours. The pulmonary mode implies one deep inhalation for five seconds with 4 inhalations/minute for a total of 5 minutes (20 inhalations). The buccal mode is more like the use of a pipe. The subject sucks at the vaporizer, with his mouth closed while breathing through the nose, every second for 10 seconds. The nicotine vapor must not be inhaled into the lungs. This continues for 5 minutes.
Additional investigation;
One healthy male smoker (smoking about 20 cigarettes per day) was subjected to three sequential PET sessions with 2 hours of separation between each session. In the first session, the volunteer inhaled ^{11}C-nicotine from the vaporizer during 5 minutes using a deep inhalation mode of administration (one deep inhalation for 5 seconds every 15 seconds, i.e., four inhalations

per minute). In the following two sessions, the volunteer smoked a filterless cigarette for 3.5 minutes (top one third of the cigarette contained ^{11}C-nicotine). The inhaler and cigarette were analyzed for residual ^{11}C-nicotine for mass balance purposes.

RESULTS AND DISCUSSION

During five minutes of inhalation about 15% of the total radioactivity was released from the inhaler. Approximately 45% of the dose released from the inhaler was found in the oral cavity (Table 1). A significant amount of radioactivity was observed in the oesophagus, suggesting a transfer of a major fraction of the dose to the stomach. Lungs and bronchi had relatively lower amounts of radioactivity. There was no major difference in the depostion pattern in the various organs between the two modes of inhalation. However, this experiment did not focus on the intial deposition of nicotine in the lungs (first few minutes of inhalation). For example, the radioactivity measured in the lungs at 10 minutes after end of administration might not reflect how much was deposited via the airways during the inhalation. At that timepoint distribution of buccally absorbed nicotine should contribute to a large extent to the radioactivity measured in the lungs. Therefore, an additional investigation in one subject was conducted with the addition of a cigarette arm focussing on the initial deposition in the lung. About 14% of the total radioactivity contained in the inhaler was released. A marked buccal deposition pattern was observed with most of the released radioactivity, 36%, appearing in the oral cavity. Another 36% of the dose was recorded in the oesophagus and the stomach. A minor fraction was recovered in the large bronchi, and only a minimal fraction, 4%, was found in the lungs. With the cigarette on the other hand, a marked pulmonary deposition was observed, 14%, with only minimal amounts of radioactivity appearing in the oral cavity, oesophagus, and stomach. The total radioactivity recorded in the lung was only 14% of total released radioactivity, although about 90% of the radioactivity contained in the cigarettes was released from the cigarettes. This low fraction is probably explained by the rapid passage of nicotine from the lung parenchyma to the systemic circulation and also by a major fraction that was never inhaled i.e, literally went up in the smoke.

CONCLUSIONS

Therefore results from these PET scans indicate similar absorption pattern for both buccal and pulmonary modes of inhalation and also a buccal absorption site for the inhaler as opposed to absorption in the lungs for the cigarettes.

Table 1. Radioactivity deposition in different organs and at different times, in percent of radioactivity released from the inhaler (mean (CV)).

Treatment	Oral cavity	Soft tissue	Trachea	Oesophagus	Bronchi	Lungs	Oral cavity	Soft tissue
Time (minute)	5.5	5.5	10	10 + 15*	15	15	60	60
Pulmonary	40.1 (22)	15.2 (64)	1.6 (25)	10.6 (42)	2.3 (74)	6.2 (65)	7.0 (73)	64.3 (42)
Buccal	49.4 (20)	12.1 (179)	0.7 (43)	9.2 (32)	1.0 (120)	4.5 (69)	8.4 (62)	35.7 (42)
Total	44.8 (23)	13.7 (118)	1.1 (55)	9.9 (36)	1.7 (94)	5.4 (65)	7.7 (64)	50 (41)

*Radioactivity calculated from upper 10 cm segment measured at 10 minutes + radioactivity in lower 10 cm segment measured at 15 minutes.

STUDY VII

STUDY TYPE: basic pharmacokinetics
STUDY TITLE: A comparison of nicotine plasma levels after repeated dosing with a nicotine vaporizer and a 2 mg nicotine polacrilex chewing gum.
NDA: 20-714 **SUBMISSION DATE:** May 2, 1996 **VOLUME:** 1.11 **STUDY:** T91NI05

STUDY DESIGN

CLINICAL INVESTIGATOR:	**ANALYTICAL INVESTIGATOR:**

MULTIPLE DOSE: Yes **CROSS-OVER:** Two-way **OTHER DESIGN:** Open, randomized
SMOKING: No, smoking prior to 12 hours before the dose and during blood sampling

SUBJECT BREAKDOWN

Normal Yes **Young** Yes **Group** Normal **N=** 18 **M=** 8 **F=** 10

Male				Female			
Weight; Mean 73	**Range**	kg		**Weight; Mean** 60	**Range**	kg	
Age; Mean 32	**Range**	yrs		**Age; Mean** 35	**Range**	yrs	

FORMULATION

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
Inhaler	Nicotine vaporizer 120 mg	vaporizer	10 mg/unit	RF332	
Gum	Nicotine 24mg	gum	2 mg	RD 236	-

PLASMA SAMPLING TIMES: 5 mL venous blood samples were collected at pre-dose, 5, 6, 7, 8, 9, and 10 hours after the first dose and 10, 20, 30, 40, 50, and 60 minutes after the start of the last dose.
ASSAY METHOD:

ASSAY SENSITIVITY: The limit of determination was set at 1.2 ng/mL.
ASSAY ACCURACY AND PRECISION: The precision and accuracy of the method at 9.2 ng/mL were 7.9% and 101% respectively.
LABELLING CLAIMS FROM STUDY:
No labelling claims.

OBJECTIVES

To compare plasma levels of nicotine after repeated dosing with nicotine vaporizer and the 2 mg Nicorette gum.

Nicorette gum available in strengths of 2 and 4 mg is a well established product for nicotine replacement therapy. If the inhaler delivers nicotine plasma levels similar to those

delivered by the gum, then the inhaler would also be expected to be a successful product for nicotine replacement therapy.

STUDY DESIGN

One inhaler each was used for 20 minutes every hour for 11 hours at an inhalation frequency of one inhalation of 5 seconds every 15 seconds. One chewing gum was chewed every two seconds for 20 minutes each for 11 hours.

RESULTS AND DISCUSSION

Both C_{max} and AUC_{10-11} values were significantly higher for the inhaler over the 2 mg gum (Table 1). C_{max} and AUC_{10-11} were about 2.3 and 2.4 fold higher for the inhaler. The mean trough plasma levels (determined at 9, 10, and 11 hours) were approximately 2.5 times as high for the inhaler over the gum. However, the t_{max} values we not statistically significant between the two. Overall, these results show that inhaler delivers nicotine levels about 2-2.5 fold higher when compared to the gum. Similar t_{max} values may indicate similar absorption site for the inhaler as well as the gum (buccal).

Although not included in this study, comparison of the nicotine plasma levels delivered by the inhaler with those delivered by the 4 mg Nicorette gum would have been more appropriate. Nicotine C_{max} values after chewing several pieces of gum are approximately around 30 ng/mL and as such would compare well with the inhaler.

CONCLUSION

Compared to 2mg Nicorette gum, the inhaler delivers nicotine plasma levels >2 fold higher.

COMMENTS

1. 4 mg Nicorette gum would have been more appropriate comparator for the inhaler than the 2 mg strength.

Table 1. Pharmacokinetic parameters after the administration of multiple doses of the inhaler and the gum (mean (CV)).

Pharmacokinetic Parameter	Inhaler	Gum
C_{max}, ng/mL	25.8 (36)	11.2 (17)
t_{max}, minute	28 (46)	33 (40)
AUC_{10-11}, hour ng/mL	23.7 (36)	9.9 (16)
AUC_{inh}/AUC_{gum}	2.42 (47)	

STUDY VIII

STUDY TYPE: Basic pharmacokinetics
STUDY TITLE: Effect of Environmental Temperature on the relative bioavailability of nicotine from a nicotine vaporizer.
NDA: 20-714 **SUBMISSION DATE:** Mav 2, 1996 **VOLUME:** 1.10 **STUDY:** T91NI06
STUDY DESIGN:
CLINICAL **ANALYTICAL**
INVESTIGATOR: **INVESTIGATOR:**

MULTIPLE DOSE: Yes **CROSS-OVER:** Three-way **OTHER DESIGN:**Open, randomized **FASTED:** No **WASH-OUT PERIOD**: One week.
SMOKING: No smoking prior to 12 hours before the dose and during blood sampling

SUBJECT BREAKDOWN:
Normal Yes Young Yes Number= 18 Male= 9 Female= 9

Male				Female			
Weight; Mean 73	Range	kg		Weight; Mean 58	Range	kg	
Age; Mean 35	Range	yrs		Age; Mean 37	Range	yrs	

FORMULATION:

Treatment Groups	Dose	Dosage Form	Strength	Lot	Lot Size
1) 68°F 2) 86°F 3) 104°F	Nicotine vaporizer 120 mg	vaporizer	10 mg/unit	RF332	

PLASMA SAMPLING TIMES: Pre-dose, 5, 6, 7, 8, 9, and 10 hours after the first dose and 10, 20, 30, 40, 50, and 60 minutes after the start of the last dose.
ASSAY METHOD:

ASSAY SENSITIVITY: The limits of quantitation were 1.2 and 5.6 ng/mL for nicotine and cotinine respectively.
ASSAY ACCURACY: The precision and accuracy of the method for nicotine at 9.2 ng/mL were 6.6% and 101% respectively. For cotinine, the precision and accuracy were 3.6% and 95% at 28 ng/mL respectively.
LABELLING CLAIMS: The release of nicotine from the Nicotrol inhaler is temperature dependent. Average achievable steady state plasma levels after 20 minutes of forced inhalations each hour at ambient room temperature are on the order of 20 ng/mL. The corresponding nicotine plasma levels achievable at 86°F and 104°F, respectively, are on the order of 25 and 30 ng/mL.
OBJECTIVES

To determine the temperature dependency of the bioavailability of nicotine after inhaling nicotine vapor at three different environmental temperatures of 68°F, 86°F, 104°F.

In vitro experiments demonstrated an approximate doubling of the release rate with every 37.5 °F (10°C) rise in temperature. Since the nicotine dose released from the inhaler is dependent upon the volume as well as the temperature of the air passing through the plug, there is a possibility of elevated plasma nicotine levels resulting when the inhaler is used in elevated environmental temperatures.

STUDY DESIGN

Eighteen (18) otherwise healthy male and female smokers participated in this open label, randomized, three-way cross-over, multiple doses study. The inhaler was used by means of deep inhalations (5 seconds) every 15 seconds for 20 minutes. This was repeated with a new inhaler every hour for 10 hours. C_{max}, t_{max}, and AUC_{10-11} (last dosing interval) were the pharmacokinetic parameters that were evaluated in comparing the treatments.

RESULTS AND DISCUSSION

Both C_{max} and AUC_{10-11} increased significantly as the environmental temperature was raised from 68°F to 104°F (Table 1). Compared to the C_{max} value at room temperature, there was a 41% increase in C_{max} at 86°F, and a 70% increase in C_{max} at 104°F. Similarly for AUC_{10-11}, compared to the room temperature value, there was a 39% and 66% increase in AUC_{10-11} at 86°F and 104°F respectively. Interestingly, 2/18 subjects had lower C_{max}'s at 86°F compared to 68°F and 7/18 subjects had lower C_{max}'s at 104°F compared to 68°F. This could probably be due to a subconcious self-titration of the subjects of the puff volume to modulate the nicotine intake (inhalation number and frequency were controlled in this experiment). The plasma concentrations achieved at the higher temperatures 86°F and 104°F are within the normal concentrations achieved by smokers and do not pose any undue toxic effect. Approximate steady state concentrations achieved with the use of 4 mg gum are about 30 ng/mL. As such the plasma concentrations achieved at the higher temperatures do not pose additional safety concern over that of a 4 mg gum.

CONCLUSIONS

The plasma concentrations achieved at the three environmental temperatures of 68°F, 86°F, 104°F after one day of hourly puffing on the inhaler were within the normal nicotine plasma levels found in smokers. Therefore use of inhaler in a hot climate probably does not pose a safety concern.

Table 1. Pharmacokinetic parameters of nicotine determined at the three different environmental temperatures of 68°F, 86°F, and 104°F respectively (mean (CV) & minimum - maximum).

Pharmacokinetic Parameter	**68°F**	**86°F**	**104°F**
C_{max}, ng/mL	22.49 (34) 11.10 - 40.42	29.74 (28) 17.62 - 47.22	34.03 (20) 24.09 - 48.60
t_{max}, hour	10.49 (2) 10.00 - 11.00	10.47 (2) 10.00 - 11.00	10.40 (2) 10.00 - 10.83
AUC_{10-11}, ng/mL hour	20.53 (35) 10.47 - 38.17	26.51 (27) 16.35 - 44.02	30.26 (20) 22.75 - 44.08

STUDY IX

STUDY TYPE: basic pharmacokinetics
STUDY TITLE: The effect of a nicotine vaporizer, on the relief of nicotine abstinence symptoms during a two-day smoke-free period.
NDA: 20-714 **SUBMISSION DATE:** Mav 2, 1996 **VOLUME:**1.11 **STUDY:** 92NNIN004
STUDY DESIGN
CLINICAL INVESTIGATOR: **ANALYTICAL INVESTIGATOR:**

MULTIPLE DOSE: Yes **CROSS-OVER:**Four-way **OTHER DESIGN:**Open, randomized
SMOKING: No, smoking prior to 10 hours before the dose and during blood sampling

SUBJECT BREAKDOWN
Normal Yes **Young** Yes **Group** Normal **N=** 15 **M=** 9 **F=** 10

Male				**Female**			
Weight; Mean 73	**Range**	kg	**Weight;**	**Mean** 59	**Range**	kg
Age; Mean 32	**Range**	yrs	**Age;**	**Mean** 35	**Range**	yrs

FORMULATION

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
Inhaler	Nicotine vaporizer 120 mg	vaporizer	10 mg/unit	RF332	
Placebo	Nicotine 0 mg	inhaler	0 mg	QC 362	-

PLASMA SAMPLING TIMES: 5 mL venous blood samples were collected between 6 pm and 7pm each study day (at least 30 minutes separated blood sampling and smoking/inhaler).
ASSAY METHOD:

ASSAY SENSITIVITY: The limit of determination was set at 1.0 ng/mL.
ASSAY ACCURACY AND PRECISION: The precision and accuracy of the method at 11.0 ng/mL were 8% and 90% respectively.
LABELLING CLAIMS FROM STUDY:
No labelling claims.
OBJECTIVES
1) Primary objective was to assess the efficacy of the inhaler to decrease craving and other withdrawal symptoms during a two-day smoke-free period.
2) Secondary objectives were to evaluate the effect of different inhalation techniques (pulmonary

versus buccal) on craving and other withdrawal symptoms, to estimate the degree of plasma nicotine substitution and to establish a possible relationship between plasma nicotine levels and the craving/withdrawal symptoms and between the number of inhalers used per day and the craving/withdrawal symptom score.

STUDY DESIGN

All subjects received two treatments with active inhaler and two with placebo. Two different inhalation techniques (pulmonary and buccal) were used for both active and placebo treatments. Each treatment session lasted 2 consecutive working-days. The subjects were requested to use less than 5 and not more than 15 inhalers per study day (any time of the day of the subjects preference). The main efficacy parameter, total craving score, comprised (1) urges to smoke and (2) missing cigarettes to be rated by the subjects on a 10-point scale. Ratings were done at 8 am, 11 am, 3 pm, 6 pm, and 10 pm on the first study day and at 8 am, 11 am, 3 pm and 6 pm on day 2. Other withdrawal symptoms rated by the subjects on a 10-point scale at the same time points were irritability, impatience, difficulties in concentration, and dizziness.

RESULTS AND DISCUSSION

Number of inhalers used

The average number of active inhalers used were 13 and 12 (range) for the buccal and pulmonary techniques respectively. The average number of placebo inhalers were 11 (range) for both inhalation techniques. On both days 1 and 2, there was no difference between the number of inhalers (both active and placebo) used.

Craving and other withdrawal symptoms

Except for dizziness, which was the same, nicotine substitution decreased nicotine abstinence (urges to smoke, missing cigarettes, impatience, irritability, and difficulties in concentrating) by approximately 50%.

Nicotine plasma concentrations

After *ad lib* use of active inhalers, the afternoon nicotine plasma concentrations on day 1 and day 2 were ng/mL and ng/mL respectively with the buccal technique. For the pulmonary technique, the corresponding concentrations were ng/mL and ng/mL. The results thus indicate when the number of inhalers is equivalent, both the pulmonary and buccal techniques result in the same nicotine plasma levels. The mean afternoon nicotine plasma concentrations on two consecutive working-days of normal smoking were 21.6 ± 12.1 ng/mL on day 1 and 19.2 ± 9.0 ng/ml on day 2. The degree of nicotine substitution is on the order of 30%.

Plasma concentration-effect relationship

There was strong negative correlation (data combined for both buccal and pulmonary) between total craving score and afternoon plasma nicotine concentrations ($r=-0.53$, $p<0.001$) (Figure 1). However, such an inverse relationship found between high nicotine plasma concentrations and low scores of total craving was not seen for total withdrawal symtoms score. This might be due to the shorter duration of nicotine abstinence. Feelings of impatience, irritation, dizziness etc. would probably be more pronounced after a longer period of nicotine abstinence.

Subject preference

47% of the subjects considered the inhaler a good aid for smoking cessation. 80% preferred the buccal method of usage over pulmonary mode. 60% retrospectively considered buccal administration as the method that decreased their need to smoke most, while 27% found

pulmonary adminsitration more satisfactory.

CONCLUSIONS

(1) Craving and withdrawal symptoms are significantly reduced by use of the inhaler and to the same extent whether buccal or pulmonary techniques is used.

(2) The degree of plasma nicotine substitution was about 30% of normal smoking levels.

(3) There was strong corelation between afternoon plasma levels obtained and reduction of craving. The other withdrawal symptoms showed no such correlation

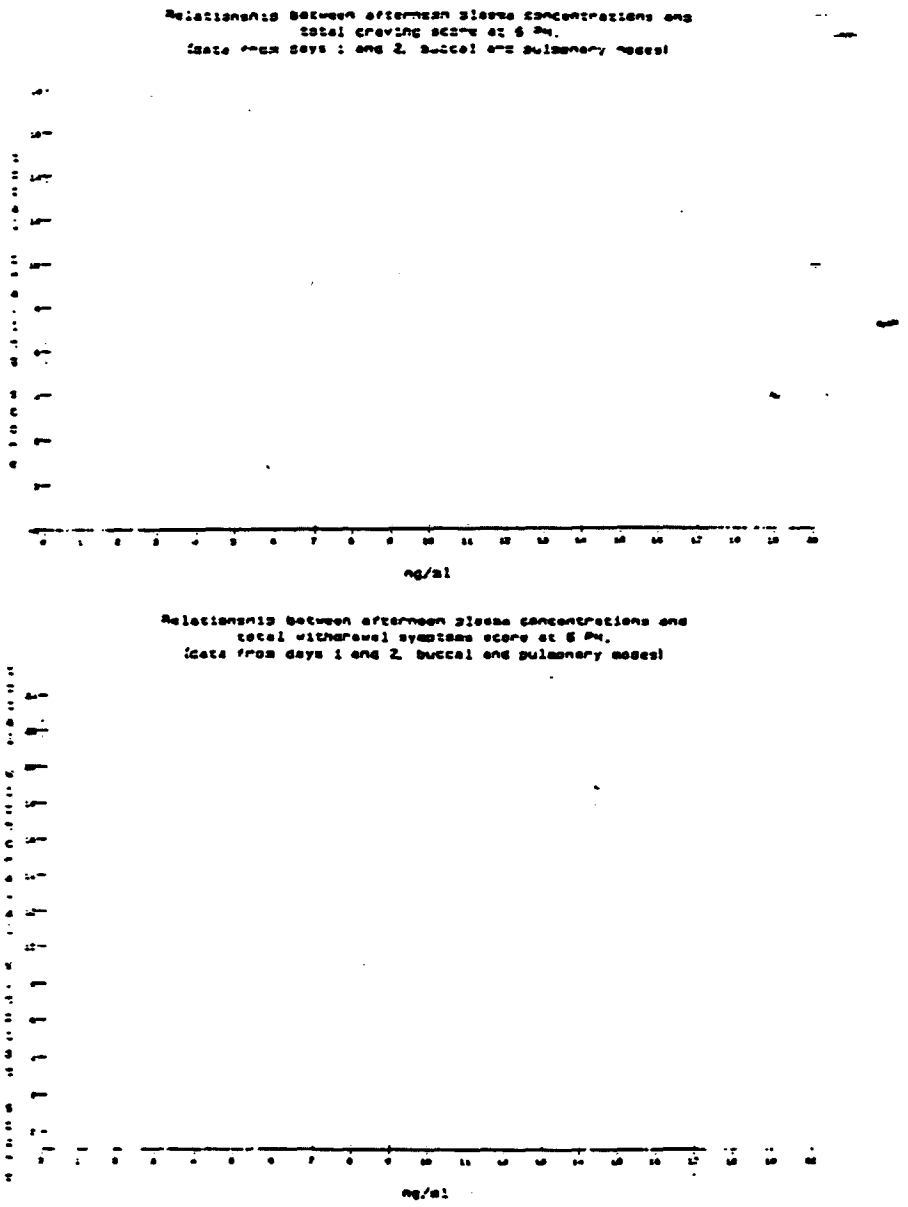

Figure 1. Total craving and withdrawal scores versus afternoon plasma nicotine level plotted for each individual (both buccal and pulmonary technique). Two clusters with break-point about 6 ng/mL are seen for craving score ($r=-0.533$), $p<0.001$) but not for withdrawal symptoms.