CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-714

MEDICAL REVIEW(S)

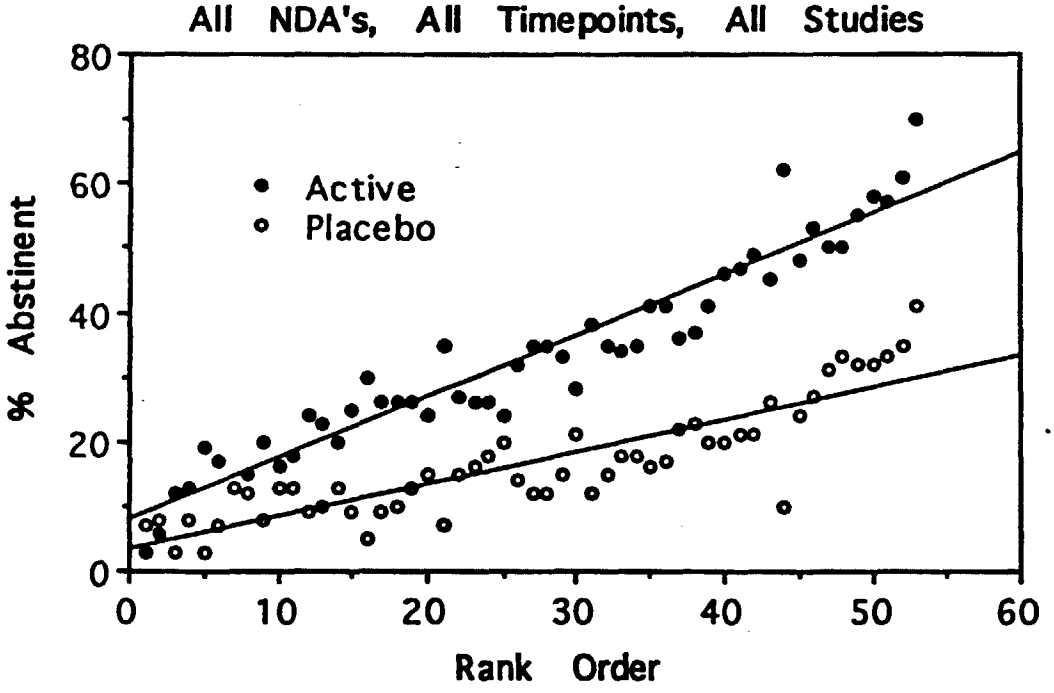
Medical Officer Overview
NDA 20-714 Nicotrol Inhaler

Sponsor	Pharmacia	NOV 15 1996
Drug	Nicotine Inhaler	
Received	May 3,1996	
Reviewer	AW Longmire	
Peer	ED Kramer	—

Cigarette smoking is a major public health problem in the United States with strong evidence linking smoking with lung cancer, heart disease, emphysema, and complications of pregnancy. This general knowledge, coupled with the increasing awareness of the dangers of sidestream smoke has resulted in a large market for products that assist in smoking cessation. One successful strategy for treating nicotine addiction has been to provide Nicotine Replacement Therapy, which is nicotine in a non-tobacco form.

There are 6 products marketed as Nicotine Replacement Therapy for smoking cessation. These include 4 patches, a nasal spray, and a gum. Minimal and maximal doses vary from 5 mg/day to 80 mg/day, but the approved products usually deliver 12-20 mg of nicotine a day and have steady state blood levels of 13 +/- 3 ng/ml, usual range ng/ml.

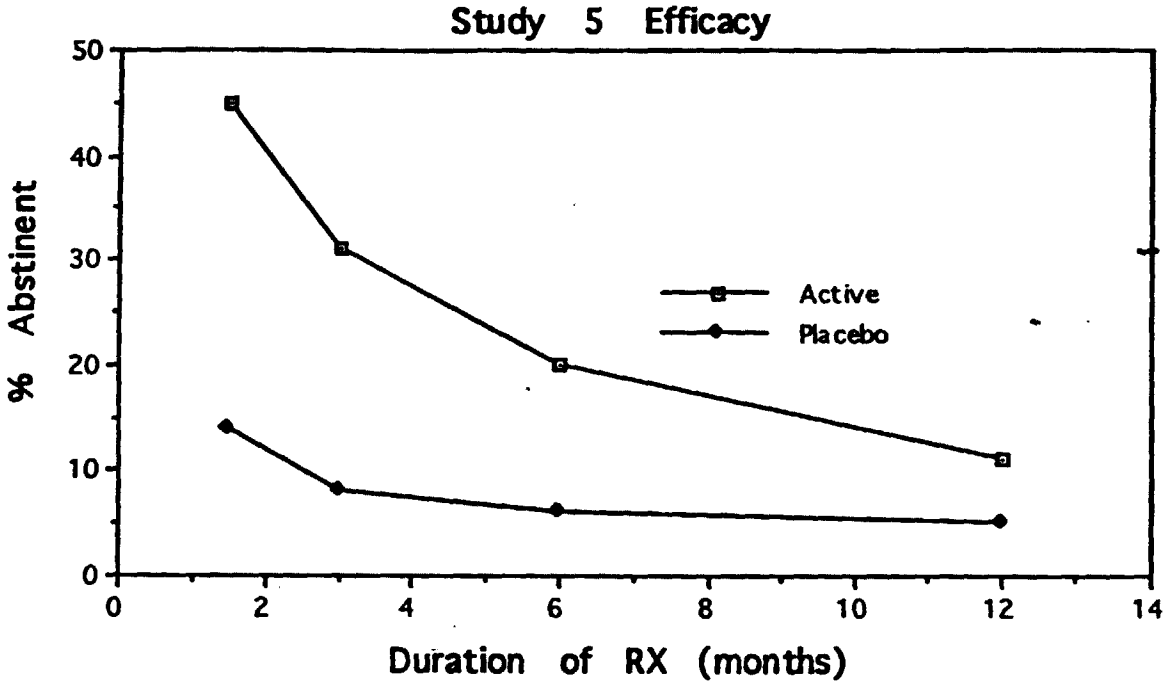
The efficacy of Nicotine Replacement Therapy is excellent. The following graph shows the results of the clinical trials done for smoking cessation for all current nicotine NDAs. The success rate varies with the product, the population and the trial, but patients on NRT consistently have about twice the quit rate of the placebo. Nearly all clinical trials show significant efficacy.



Pivotal Trials

There were two double-blind placebo controlled single center efficacy trials using the nicotine inhaler for smoking cessation that demonstrated substantial efficacy. The complete medical officer report of these studies is in Tab 8 . Both recruited healthy motivated subjects who self-titrated at doese between 4 to 20 inhalers per day for 3 months and the dose was then tapered from 3 to 6 months. Self-reported rates of complete abstinence from week 2 through 1 year were verified by CO levels < 10 ppm.

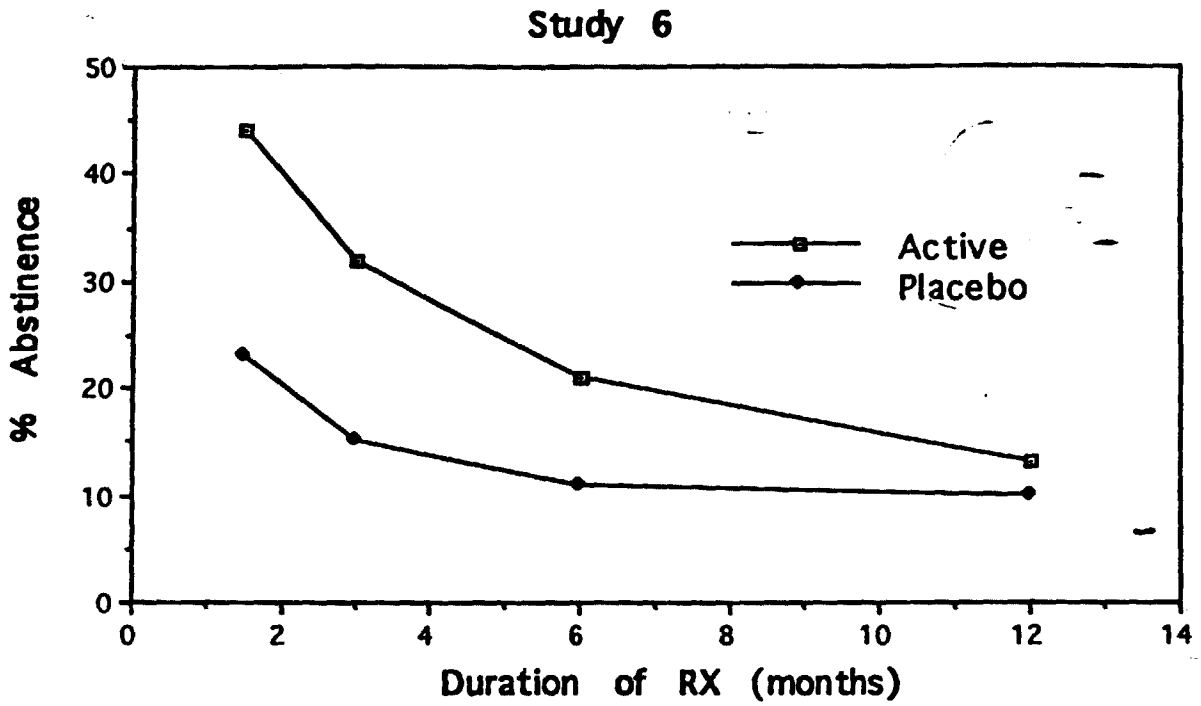
Primary Efficacy Analysis Study 5, CTN 92NNIN00



Duration of RX		6 weeks	3 months	6 months	12 months
Active N=111	# Quit Cigs	50	34	22	12
	% Quit Cigs	45%	31%	20%	11%
Placebo N =111	# Quit Cigs	15	9	7	6
	% Quit Cigs	14%	8%	6%	5%
	P value	<0.005	<0.005	<0.005	<0.22

Data display from sponsor's elettronic data sets. P values are by chi-square with continuity correction. All subjects were treated for 6 wleeks. Inhalations were recommended at 4 - 20 Inhalers a day until 3 months but then wcre required to begin tapering and no inhaler use was allowed after 6 months.

A similar efficacy result is seen in Study 6, CTN: 92NNIN003



Duration of RX		6 weeks	3 months	6 months	12 months
Active	# Quit Cigs	49	36	24	15
N=112	% Quit Cigs	44%	32%	21%	13%
Placebo	# Quit Cigs	26	17	12	11
N =111	% Quit Cigs	23%	15%	11%	10%
P Value		<0.005	0.002	0.049	0.547

The efficacy is in these studies is far better than the efficacy of the first studies of this product. The probable reason is the higher dose; subjects were instructed to use from 4 to 20 inhalers per day and were urged to use higher doses in the first days of treatment.

Adverse Events
There was one serious adverse event in trial 5 (non-cardiac chest pain) and multiple serious adverse events were reported in Trial 6, a study in a patient population with a high proportion of serious underlying medical conditions i.e. AIDS, life threatening surgery, cancer.

There were no serious adverse events credibly related to the study medication, (see stdy reports).

In both studies mouth and throat irritation and cough were more frequent on active drug in the first week of treatment. No unexpected adverse effects related to this therapy were identified.

Failed and Supportive Trials

Three clinical trials were done during 1990-92 with poor or marginal efficacy. These trials as well as a later trial with dosing similar to the pivotal trials are extensively reviewed in Tab 9 and in the ISS (Tab 10) and ISE (Tab 11).

Early studies, two failed and 1 supportive study.

These are the first 3 double-blind placebo controlled single center efficacy trials with the Nicotine Inhaler for smoking cessation .

Study: 1, CTN: T90NI01, 223 subjects David PL Sachs, MD Palo Alto, CA
Study: 2, CTN: T90NI02, 241 subjects ED. Glover, Ph.D.W Vir University
Study: 3, CTN: T90NI03, 283 subject P Tønnesen, M.D Copenhagen, Denmark

Methods

In all 3 studies the research subjects were smoking men and women motivated to stop smoking aged 20 and older, smoking 10 or more cigarettes per day and being a daily smoker for 3 years or longer. Doses of the inhaler were self-titrated between 2 to 10 inhalers per day and were used whenever the subjects felt an urge to smoke. No subject was allowed to use the inhaler after 6 months. Self-reported rates of complete abstinence from week 2 through 12-18 months were verified by CO levels < 10 ppm.

Results

The complete abstinence rates with Nicotine Inhaler treatment were not significantly different from placebo in study one and study two. Study three achieved similar smoking cessation rates in the treatment group, but the control group had much lower quit rates. For study 3 there was a significant higher complete abstinence rates as shown on the following table

Table 5. Abstinence % (N) From Week 2 through All Visits, No Slips Allowed

	Study One			Study Two			Study Three		
Months	Active % N=112	Control % N=111	P value	Active % N=129	Control % N=112	P value	Active % N=143	Control % N=140	P value
1.5	33 (37)	33 (37)	0.962	28 (36)	25 (28)	0.610	37 (53)	19 (26)	0.001
3	22 (25)	30 (30)	0.207	21 (27)	18 (20)	0.548	25 (36)	13 (18)	0.008
4	21 (23)	23 (26)	0.603						
5	15 (17)	21 (23)	0.281						
6	14 (16)	20 (22)	0.272	17 (22)	15 (17)	0.693	19 (27)	10 (14)	0.034
9				14 (18)	14 (16)	0.941			
12	12 (13)	18 (20)	0.178	13 (17)	14 (16)	0.803	17 (24)	7 (10)	0.013
18	7 (8)	17 (19)	0.022						

* Data are extracted from the sponsor's reports. P-values are based on Pearson's Chi-Square with continuity correction, but they are not corrected for multiple comparisons

Study three had considerably better results with the same study design. The inconsistency of results may be related to medication dose, patient education, and selection of study population as follows:

1) The minimum dose effective in the studies is 4 inhalers per dayand the % of subjects who took at least 4 inhalers / day or > is as follows: 10% (study one), 45% (study two), and 46% (study three).

2) There is well documented literature to support the use of self-help materials as a treatment component in smoking cessation programs. The placebo group in study three did not receive self-help manuals, and educational interventions were less intense than those in study one and two. This "minimum education intervention" approach may have enhanced the trial sensitivity. (The first two studies had such good behavioral treatment that all the quitters serious about quitting, quit on placebo).

3) Research subjects in study three smoked less than those in study one and two, measured by number of years smoked, average daily cigarettes consumption and low CO levels. In general lighter smokers respond better to smoking cessation therapy, especially with products that are delivering lower levels of nicotine.

Conclusions:

The two US studies failed to show that the inhaler is as effective in aiding smoking cessation, while the Denmark study has provided supportive evidence of efficacy of Nicotine Inhaler. The probable reason for the lack of efficacy in the early trials is inadequate dosing - all used at least 2 and not more than 10 cartridges/day. Efficacy was far better in the subsequent 3 trials with subjects using at least 4 cartridges/day.

Later Supportive Study 4, CTN: T91NI04

Investigator: A Hjalmarson, Ph.D, 247 subjects, Gothenburg Sweden

Design

This study was distinctively different from the previous 3 studies in that the subjects were instructed to use at least 4 inhalers per day on an ad libitum basis and encouraged to use the inhalers as frequently as possible. Except for dose, the study was very much like the previous studies.

Results

The Nicotine Inhaler treatment showed significant higher complete abstinence rate from 2 weeks through 12 months as compared to the control group: 46% vs. 33% at 6 weeks, 37% vs. 22% at 3 months, 35% vs. 19% at 6 months, and 29% vs. 18% at 12 months. However, the study provided only supportive evidence of efficacy of Nicotine Inhaler as an aid to smoking cessation because of an enrollment problem. Twenty-three quitters (or 40% quitters) in the active group and 14 quitters (or 34% quitters) in the placebo group had a baseline CO < 10 ppm. It is impossible to classify them as smoking cessation successes or failures based upon their exhaled CO levels at week 6. The differences in quit rates between the two groups were marginally insignificant (P=0.056) after adjusting the problem.

Integrated Summary of Safety

An extensive review of adverse events is presented in Tab 10.

The adverse event profile of the Nicotine Inhaler is similar to that of other currently marketed products of nicotine. The most frequent adverse events are coughing, throat irritation, stomatitis, headache, rhinitis and pharyngitis. A potential risk associated with the inhaler is the possibility of bronchospasm but the magnitude of this risk is unknown for only 9 patients with bronchospastic disease were included in the clinical trials.

Two deaths occurred in patients participating in the clinical studies are described on page 19 and 20 of the Integrated Summary of Safety. Neither of the reported deaths was attributable to study medication and both were related to diseases associated with smoking. One death was post cardiac surgery in a 43 year old patient with valvular heart disease and aneurysm and the other a CVA in a 67 year old. Neither was on active medication.

No unexpected or serious related adverse events were noted. The Reviewer concluded that the Nicotine Inhaler was of acceptable risk .

Integrated Summary of Efficacy

The Integrated Summary of efficacy is in Tab 11.

The following table summarizes the % quit rate in all 6 clinical trials.

All patients	active successes	placebo successes p-value
Sachs, US	37/112 (37%)	33/111 (33%) 1.0
Glover, U.S.	36/129 (28%)	28/112 (25%) 0.6
Tonnesen, Denmark	53/143 (37%)	26/140 (19%) <0.001
Hjalmarson, Sweden	57/123 (46%)	41/124 (33%) 0.03
Leischow, U.S.	50/111 (45%)	15/111 (14%) <0.001
Schneider, U.S.	49/112 (44%)	26/112 (23%) <0.001

Reviewer s table, after sponsor's Table 5, p. 10-2482.
P-values from chi-square test (reviewer's calculation).

The statistician evaluated the above with a Mantel-Haenszel test. The chi-square (1 d.f.) was 35, strong evidence of efficacy. Separate analyses of efficacy were carried out for men and women showing the drug to work similarly in each gender and for patients over 60. The inhaler was effective in both heavy (> 20 cig /day) and light (< 20 cig /day) smokers.

Pharmacology and Pharmacokinetics

The pharmacology of nicotine is well described and can be reviewed from the draft label (Tab 4). The product is currently undergoing human toxicology buccal studies. There are no known pharmacology or safety issues.

The pharmacokinetic studies of this product are particularly important because the unique delivery system has not been previously tested on this or any other medicinal product, and because pharmacokinetics are important determinants of abuse potential. A total of nine PK studies were conducted in 144 smokers and include the following:

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

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:

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

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

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

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

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

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

The pharmacokinetic review of these studies is in Tab 12. It was determined that:

1) 4 mg of nicotine is released upon intense use of the inhaler for 20 minutes.

2) The absolute bioavailability of the nicotine released from the inhaler was approximately 50%.

3) Peak plasma concentrations were reached approximately 15 minutes after the end of the inhalation.

3) Mean plasma levels following intense use (employed in pharmacokinetic studies) reached about 26 ng/mL,

4) Mean plasma levels following ad lib use reached about 6-8 ng/mL.

5) Arterial nicotine concentrations rise slowly indicating minimal pulmonary absorption

6) Nicotine release from the inhaler is dependent on environmental temperature.

The slow peak concentration (3) and low arterial concentrations (5) suggest that the abuse potential of this delivery system will be lower than that of a cigarette.

The pharacokinetic values were acceptable to the reviewer.

Abuse Liability

The Clinical Abuse Liability Review and Medical Officer's Review of the Nicotrol Inhaler "Abuse Liability Determination" study are in Tab 11.

Clinical Abuse Liability Summary

There is an extensive review of the pharmacokinetics of this product in this submission, but the kinetics of comparative abuse liability are probably best presented on the graph on page 2 of the Clinical Abuse Liability Review (Tab 11). In this figure the Inhaler looks most like the 4 mg gum. This is suggestive of a product with less addiction potential than nicotine nasal spray, and similar to smokeless tobacco, pipes or cigars. It is also reassuring that the arterial level is about 10 % of that achieved by cigarette (Tab 12 p 6) and that dose escalation was not apparent during the clinical trials.

However, there are multiple reasons to be cautious. The PK profile is affected by temperature and there are higher levels with temperature increase. Seven active and 6 placebo subject s in the 2 clinical trials (N=445) reported symptoms of possible drug dependence and a pattern of possible drug dependence symptoms emerged in active quitters when drug was tapered and again when drug was discontinued. Furthermore, the product looks, feels, and is used like a cigarette - how this will effect abuse potential is currently unknown.

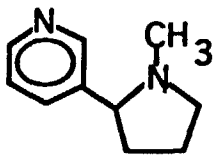
Nicotrol Inhaler "Abuse Liability Determination Study"

In this study, 12 volunteer cigarette smokers, had physiological and subjective effects measured after varying doses of placebo, cigarette or inhaler. All 4 cigarette doses significantly increased ratings of: *any drug effect, good effects*, and *liking*. The Vapor Inhaler significantly increased good effects (but not liking) and significantly increased drug effect and bad effects (throat burning, and coughing). This study indicates (in a single dose situation) that there are differences in the abuse liability of this product as compared to cigarettes, but does not address the question of abuse potential after chronic use or abuse liability in young people.

The abuse potential of this product is thought to be between that of the nicotine gum and the nicotine nasal spray. Prescription availability should be adequate control.

Chemistry

Nicotine is a tertiary amine obtained from the tobacco plant whose structure and weight is shown below.



Chemical Name: S-3-(1-methyl-2-pyrrolidinyl) pyridine
Molecular Formula: $C_{10}H_{14}N_2$
Molecular Weight: 162.23

A brief description of the manufacturing process is in Tab 14. The agency chemist is currently in communication with the sponsor and there are no major deficiencies known.

Devices Consult

A consult to devices and their reply is in Tab 14.

The device planned for marketing (3 piece device) is not the same as the device used in the clinical trials (2 piece device). The extra piece was a cover end piece and there was a different shape to the mouth piece. To evaluate if this might affect the performance of the product, a consult was sent to medical devices and I discussed the ongoing medical review and the consult with Dr Baseril of devices. They responded that the testing as submitted to us was somewhat less than optimal in that devices will often ask the sponsor to submit a flow pressure curve (the testing that they did was at 1 L /min only). They did feel that as a practical matter the devices were nearly functionally equivalent for delivery of nicotine.

SUMMARY

The Nicotine Inhaler treatment showed substantial efficacy as compared to placebo.

Subjects were required to use greater than 4 inhalers per day before efficacy was achieved.

There was a higher incidence of local effects (Irritation in Mouth and Throat and Cough) in the active group at the beginning of therapy. The severity was mild. No severe or unexpected adverse effects of this therapy were identified. Two deaths and multiple serious adverse events were reported in this submission; however, neither the investigator or the reviewer considered them to be related to the nicotine inhaler.

Pharmacokinetic study did not indicate a high abuse potential for this product, but there was evidence in the clinical trials of withdrawal symptoms at drug tapering and drug discontinuation. Prescription availability would adequately control the abuse liability of this product.

There were few patients with bronchospastic disease in the clinical trials (9) and the effect of nicotine inhalation on bronchospastic disease is unknown.

Regulatory Recommendations

I recommend approval with the marked up draft labeling. Scheduling under the CSA is not required.

AW Longmire MD
Medical Review Officer

11/15/96
CW Wright MD
Secondary Reviewer

CC: Original NDA
HFD-170 Division File
HFD-170 AW Longmire
HFD-170 CW Wright
CSO E McNeal

NDA 20-714

CC:
Orig. NDA 20-714
Division File
HFD-170/ Kramer/Chang Li/Ross/Doddapaneni/Geyer/Permutt/McNeal

Clinical Abuse Liability Review

NOV 14 1996

NDA #:	20714 (Supplement #000)
Drug:	Nicotine Inhaler
Sponsor:	Pharmacia Upjohn
Submitted:	May 1996
Reviewer:	E Douglas Kramer
Peer Reviewer:	A W Longmire
CSO:	B McNeal
Review Date:	November 13, 1996

Background

The nicotine inhaler is proposed for prescription use as an aid to smoking cessation. The inhaler consists of a disposable cartridge containing a porus plug impregnated with 10mg of nicotine. The nicotine is consumed by inserting the cartridge into a holder and inhaling air through the cartridge. It takes about 20 to 30 minutes of puffing on the inhaler to release about 4mg of the nicotine contained in the plug. About 2mg of this nicotine is systemically available.

Information on the abuse liability of the nicotine inhaler is drawn from several sources: a consideration of product design, pharmacokinetic studies, an assessment of adverse events possibly related to nicotine withdrawal an assessment of drug use patterns during the 2 pivotal trials, and single dose abuse liability testing in smokers.

Product design aspects of abuse liability

The existing nicotine replacement products fall into two categories: self-titrated dosage forms (gum and nasal spray) and dosage forms that deliver a fixed daily dosage (transdermal patches). In general, fixed dosage forms have a lower abuse liability than variable dosage forms. Among the self titrated dosage forms, the nasal spray appears to have a greater abuse liability than the gum. Possible contributing factors for this difference include relatively more rapid delivery of nicotine from nasal spray than the gum and a greater recommended frequency of use of the nasal spray.

In terms of the frequency of administration, the nicotine inhaler is a product that is intermediate between the gum on one hand and the nicotine nasal spray on the other. While the number of inhalers actually used daily is similar to the number of pieces of gum used, the method of administration of the inhaler involves taking several inhalations from each device. While such a design may

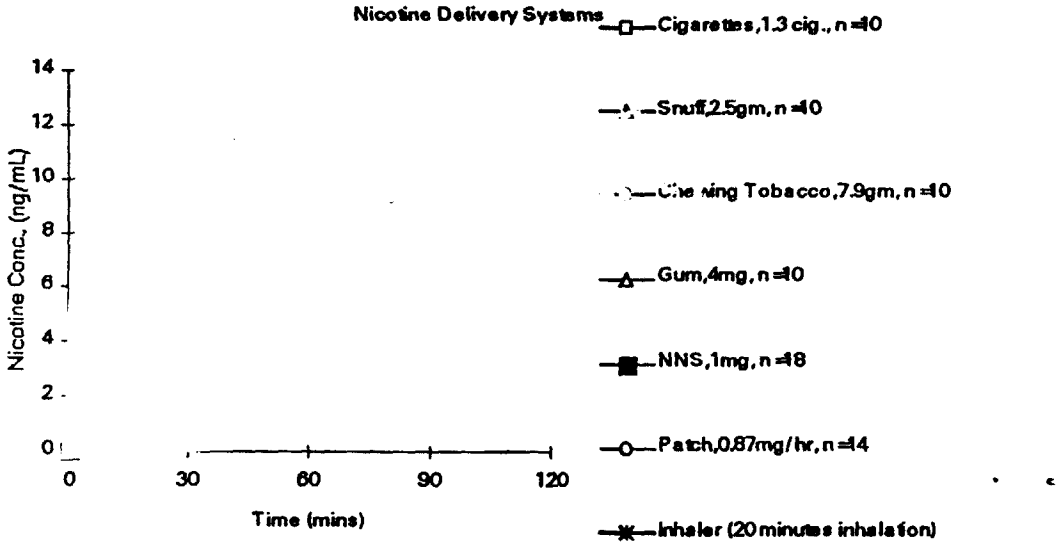
be helpful to smokers who find the behavioral aspects of smoking an obstacle to quitting, it may also tend to increase the abuse liability of this product relative to nicotine gum.

Pharmacokinetic aspects of abuse liability

A mean dose of 4mg nicotine is released over 20 minutes of intensive inhalation, of which 2mg is systemically absorbed. 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.

Delivery of nicotine from the inhaler does not cause the arterial nicotine spike seen with smoking.

Single dose pharmacokinetics of the nicotine inhaler are shown in the following figure. The curve for the inhaler represents use at room temperature, where the kinetics is most similar to the 4mg gum. At 104°F, the inhaler Cmax is about 70% higher and probably similar to chewing tobacco (data not shown).



Original figure made by Dr Ruth Stevens. Data for the nicotine inhaler added courtesy of Dr Suresh Doddapaneni.

Data is not yet available on the pharmacokinetics of buccal absorption of nicotine when the plug is removed from the cartridge (e.g. with a paper clip).

Adverse events possibly related to nicotine withdrawal

The numbers of patients who spontaneously reported adverse events possibly related to nicotine withdrawal (based on the reviewer's assessment) are listed in the following table.

Spontaneously reported symptoms of possible nicotine withdrawal

Adverse Event	Study 5 Active N=111	study 5 Placebo N=111	Study 6 Active N=112	Study 6 Placebo N=111
ANXIETY	12	8	11	7
DIZZINESS	12	8	12	17
MYALGIA	7	3	2	0
DEPRESSION	5	2	7	4
DRUG DEPENDENCE	5	2	2	4
FATIGUE	4	1	7	1
IRRITABILITY	4	0	2	7
SLEEP DISORDER	4	4	11	11
CONCENTRATION IMPAIRED	3	5	3	6
EMOTIONAL LABILITY	3	0	0	4
WITHDRAWAL SYNDROME	3	3	7	4
APPETITE INCREASED	2	0	2	5
SOMNOLENCE	2	1	3	1
AGITATION	1	2	2	4
APATHY	1	1	0	1
TREMOR	1	0	1	0
CONFUSION	0	3	1	0

Table made by the reviewer based on recoding of the sponsor's electronic data set.

The overall number of subjects reporting at least 1 possible withdrawal symptom is approximately the same between treatment groups, although the symptoms reported vary somewhat from study to study. This is consistent with the observation that the inhaler produced short-lived reductions in craving in study 5 and no change in craving in study 6. This could reflect either a subtle imbalance between treatment groups in their severity of dependence on nicotine at baseline (unlikely) or it could reflect the fact that more dependent smokers were able to quit on active drug (these subjects would be more likely to both experience withdrawal symptoms yet stay in the trial to report them).

A total of 13 subjects in these studies (7 in study 5 and 6 in study 6) (7 on active medication, 6 on placebo) reported symptoms of possible drug dependence. The experiences of these subjects are described below.

Subjects reporting possible drug dependence (study 5)

Subject	Event	Outcome	Last Drug Dispensed
placebo 57 yo M, FTQ=8, 35cig/day	ineffective and no satisfaction day 2	Failure	Study Start
placebo 53 yo F, FTQ=7, 20 cig/day	satisfaction level down and craving day 7	Failure	Day 7
active 52 yo F, FTQ=7, 20 cig/day	drug dependence day 180; malaise, fatigue day 14, 21	6 week Success	Day 90
active 66 yo F, FTQ=6, 18 cig/day	increased appetite, difficulty concentrating, headache, craving, drug dependence day 180. No other ae's reported during trial.	6 week Success	Day 90
active 48 yo M, FTQ=10, 60 cig/day	Drug dependence (inhaler) reported at 180 days. No other WD reported.	6 week Success	Day 90
active 40 yo M, FTQ=3, 13 cig/day	Drug dependence (inhaler) reported at day 180. Stress reported days 180, 365. No other WD.	Failure	Day 90
active 25 yo F, FTQ=9, 35 cig/day	Drug dependence (inhaler) reported day 180. Reported crying for no reason day 7	Failure	Day 90

Table made by the reviewer from the sponsor's electronic data set. Drug could be dispensed through the 90 day visit in these studies.

Subjects reporting possible drug dependence (study 6)

Subject	Report	Outcome	Last drug dispensed
placebo, 38,M 30cig/day FTQ=6	Felt addicted to inhaler (day 7)	6 week success 1 year failure	Day 42
placebo, 65 M 20cig/day FTQ=6	Not strong enough (day 2)	6 week success 1 year failure	Day 21
active 36 M 20cig/day FTQ=7	Drinking a lot of alcohol (day 180)	6 week success 1 year failure	Day 90
placebo 63 F 20cig/day FTQ=7	Inhaler not helping (day 2)	6 week failure 1 year failure	Day 21
active 50 M 30cig/day FTQ=9	inhaler too weak (day 2)	6 week success 1 year failure	Day 90
placebo 49 M 20cig/day	Necessary to use inhaler constantly (day 2)	6 week success 1 year success	Day 21

Table made by the reviewer from the sponsor's electronic data set. Drug could be dispensed through the 90 day visit in these studies.

Among subjects on placebo, reports possibly involving drug dependence occur early in the trial and (correctly) involve the subject's observation that there is no therapeutic benefit from the inhaler. Among subjects on active drug the situation is quite different. Reports of dependence refer to the inhaler itself and they emerge in many cases at the first visit after the last day the drug has been dispensed. In all cases, subjects reporting possible dependence on active drug in these studies used the inhaler for the maximum length of time allowed.

The difference in the timing of drug dependence suggested that some patients (2 to 4%) on active drug may have felt dependent on the treatment and may have experienced withdrawal symptoms at the time that tapering of the inhalers began. This is explored in the following tables:

Number of subjects reporting withdrawal symptoms by treatment group and 6 week outcome (study 5)

Rx	Outcome	Day of Study	2	7	14	21	42	90	180	365
Active N = 111	Failures N = 61	Reports Withdrawal	9	10	9	7	3	0	3	1
		Continuing Abstinent								
		Came to Visit	59	53	39	37	30	19	13	7
	Quitter N = 50	Reports Withdrawal	7	4	5	3	3	1	9	6
		Continuing Abstinent					50	34	22	12
		Came to Visit	50	50	50	50	50	46	39	30
Placebo N = 111	Failures N = 96	Reports Withdrawal	17	15	7	3	1	0	0	0
		Continuing Abstinent								
		Came to Visit	88	70	49	35	26	12	3	2
	Quitter N = 15	Reports Withdrawal	0	0	0	1	1	1	2	2
		Continuing Abstinent					15	9	7	6
		Came to Visit	15	15	15	15	15	14	12	9

Table made by the reviewer from the sponsor's electronic data set. All numbers in this table are numbers of patients. The population of patients referred to by each row is the same at all time points based on treatment and outcome at 6 weeks (e.g. 15 placebo quitters). The number of patients reporting withdrawal is based on the table of spontaneously reported symptoms of possible nicotine withdrawal above. The last day drug was available for dispensing in this trial was day 90.

Number of Patients reporting possible withdrawal symptoms by study day by 6 week outcome (Study 6)

Rx	Outcome	Day of Study	2	7	14	21	42	90	180	365
Active N=112	Failure N=63	Reports Withdrawal	16	6	4	2	4	2	0	0
		Continuing Abstinent								
		Came to Visit	54	32	26	26	20	12	8	3
	Quitter N=49	Reports Withdrawal	10	7	4	4	8	3	8	7
		Continuing Abstinent					49	36	24	15
		Came to Visit	49	49	49	49	49	46	39	25
Placebo N=111	Failure N=85	Reports Withdrawal	22	6	5	2	2	0	0	0
		Continuing Abstinent								
		Came to Visit	71	47	29	26	16	6	5	2
	Quitter N=26	Reports Withdrawal	7	5	3	4	3	1	0	0
		Continuing Abstinent					26	17	12	11
		Came to Visit	25	26	25	26	26	23	19	13

Table made by the reviewer from the sponsor's electronic data set. All numbers in this table are numbers of patients. The population of patients referred to by each row is the same at all time points based on treatment and outcome at 6 weeks (e.g. 26 placebo quitters). The number of patients reporting withdrawal is based on the table of spontaneously reported symptoms of possible nicotine withdrawal above. The last day drug was available for dispensing in this trial was day 90.

Close inspection of these tables reveals a possible re-emergence of withdrawal symptoms among active quitters following the day 90 visit, the last visit at which subjects would have been able to have additional drug dispensed to them under these protocols. In study 5, for example, 3 of 50 quitters reported withdrawal symptoms at 6 weeks (6%). By 6 months only 39 of these subjects remained in the trial, and 9 of them reported withdrawal (23%). This figure would increase to

40% if the 11 subjects who did not show up for the 6 month visit are assumed to have relapsed because of withdrawal symptoms. A similar pattern is apparent in study 6.

Extent of inhaler use in the clinical trials

The duration of nicotine inhaler use based on outcome at 6 weeks in clinical trials 5 and 6 is shown in the following figures.

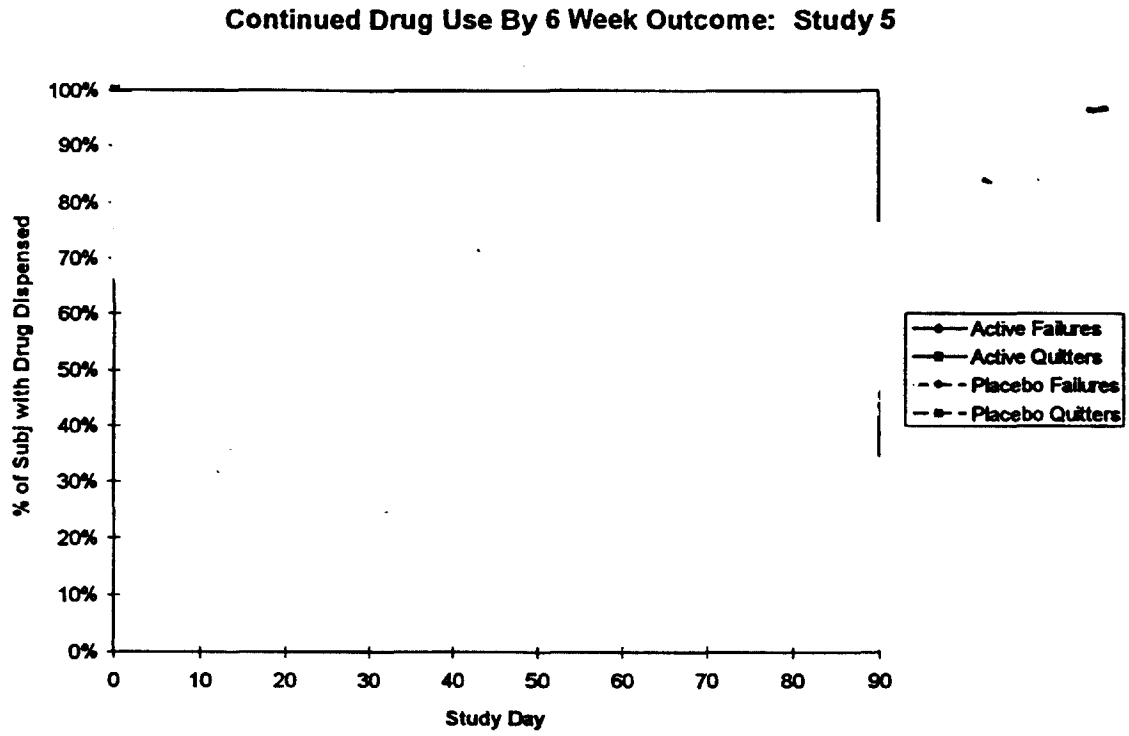


Figure made by the reviewer from the sponsor's electronic data set.

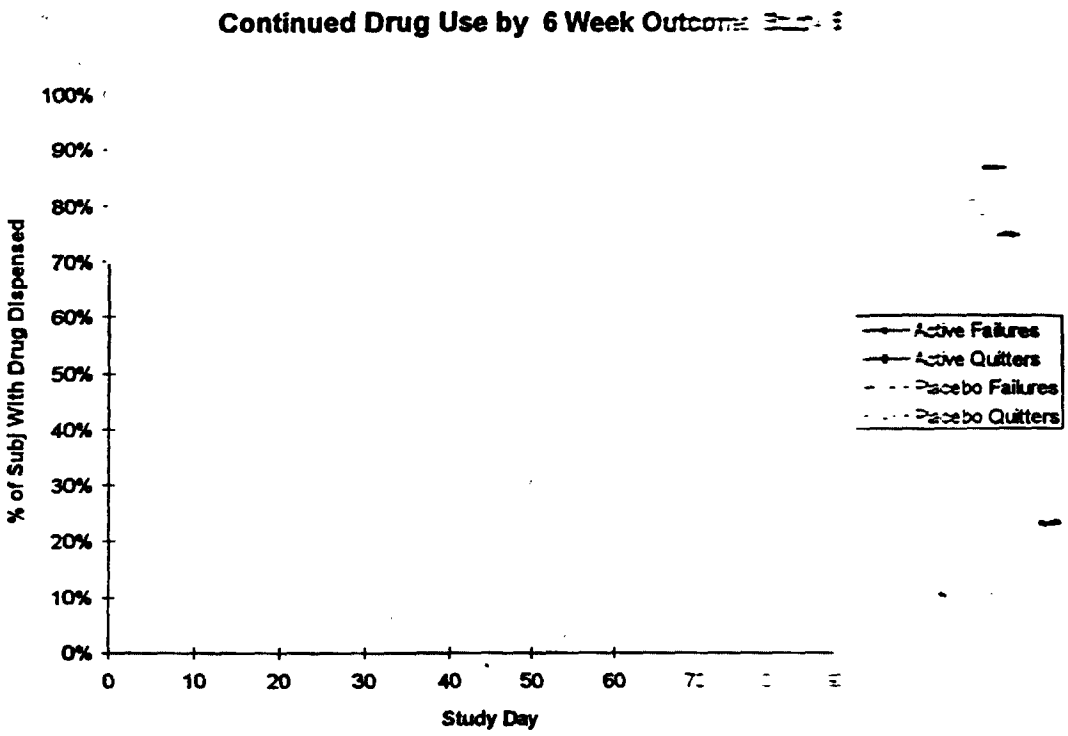
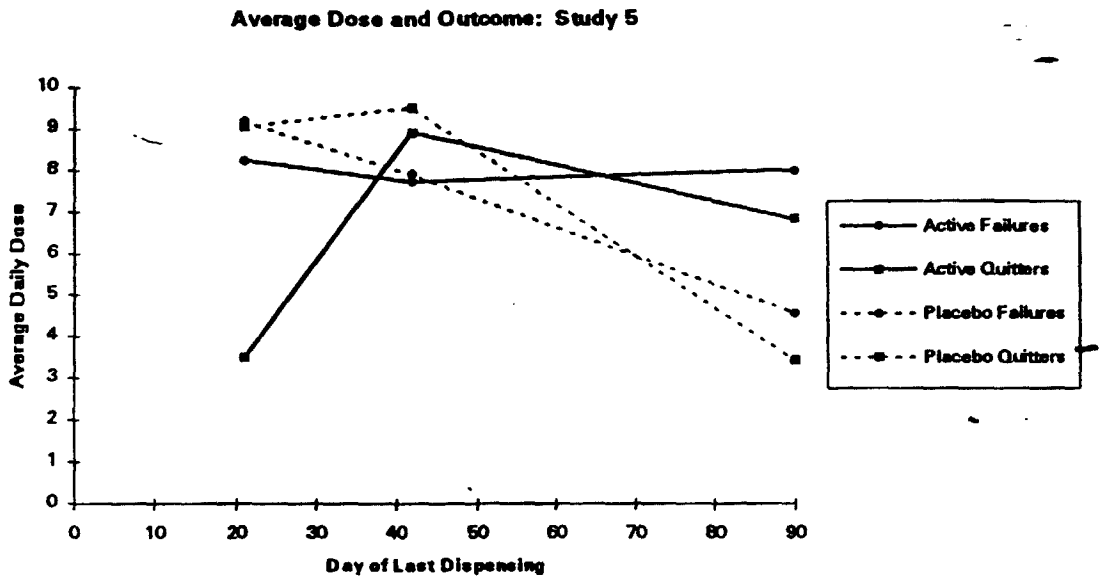


Figure made by the reviewer from the sponsor's electronic data set.

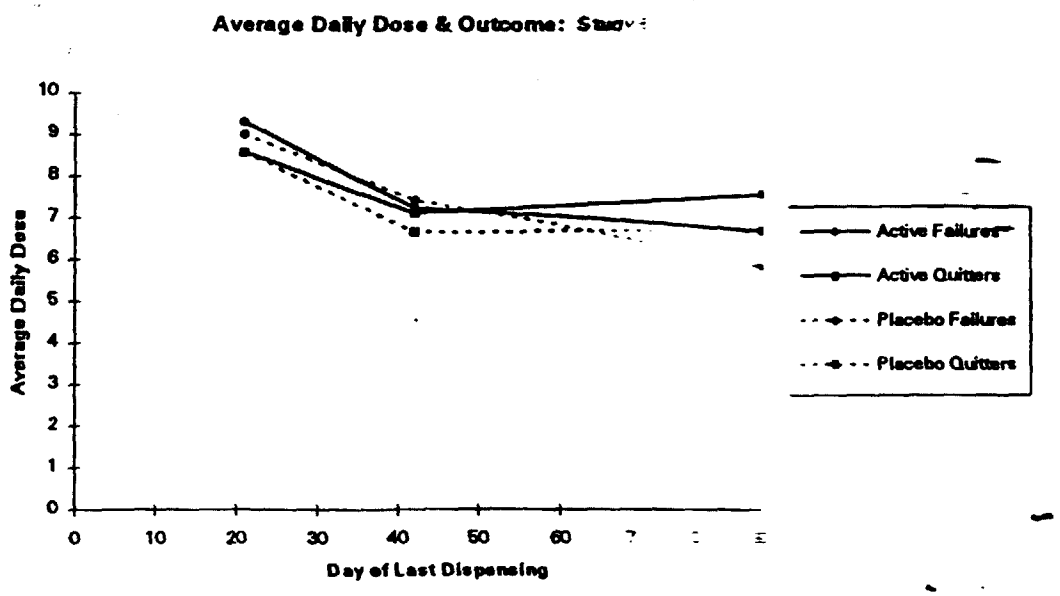
The duration of drug use in these trials is similar and suggests that a number of quitters may continue to use the inhaler after they have been successfully abstinent. There are also a number of successful quitters in placebo inhalers who continue to use the product. These data raise the question of whether the inhaler may encourage prolonged use by virtue of its design. Direct comparison with other nicotine replacement products is not available.

The average number of inhalers used daily through the last day of dispensing for those subjects who had drug dispensed for at least 3 weeks is shown in the following figures.



Rx	Outcome	Day Last Dispensing	21	42	90
Active N=111	Failures N=61	Average Daily Use Thru Day	8.2	7.7	8.0
		Number of Subjects	11	11	12
	Quitter N=50	Average Daily Use Thru Day	3.5	8.9	6.8
		Number of Subjects	1	13	35
Placebo N=111	Failures N=96	Average Daily Use Thru Day	9.2	7.9	4.6
		Number of Subjects	11	12	2
	Quitter N=15	Average Daily Use Thru Day	9.0	9.5	3.4
		Number of Subjects	2	7	5

Table made by the reviewer from the sponsor's electronic data set. Averages are based on the number of inhalers dispensed for the period up to the visit that the subject last received medication. Four to 20 inhalers per day were recommended for use during this trial.



Rx	Outcome	Day Last Dispensing	[illegible]	90
Active	Failure	Average Daily Use Thru Day	[illegible]	6.7
N=112	N=63	Number of Subjects	[illegible]	8
	Quitter	Average Daily Use Thru Day	[illegible]	7.5
	N=49	Number of Subjects	[illegible]	34
Placebo	Failure	Average Daily Use Thru Day	[illegible]	6.8
N=111	N=85	Number of Subjects	[illegible]	6
	Quitter	Average Daily Use Thru Day	[illegible]	7
	N=26	Number of Subjects	[illegible]	[illegible]

Table made by the reviewer from the sponsor's electronic data set. Average [illegible] number of inhalers dispensed for the period up to the visit that the subject last received medication. [illegible] were recommended for use during this trial.

These studies may differ somewhat in their [illegible] of drug use. Overall, the data suggest that subjects did not [illegible] maximum number of inhalers allowed on average. General [illegible] use of active medication appears more sustained than use of placebo. A trend to increasing drug use over time is not apparent.

Formal abuse liability testing

The subjective effects of various nicotine doses [illegible] nicotine inhaler or cigarettes were compared in 12 volunteer smokers [illegible] placebo controlled crossover design. Subjects were aged 21 to 45 and smoked at least 20 cigarettes per day. The inhaler was compared to [illegible] subjects' usual brand (or a Next cigarette). Doses tested were [illegible] mg nicotine by each route of administration.

All 4 cigarette doses tested (including Next) immediately increased scores for drug effects, good effects and liking in a dose-related manner. All doses increased nicotine and stimulant identification. Elevations in the placebo condition were not sustained through the 16 minute post dose observation period.

The 3 active doses of the inhaler immediately increased ratings of good effects, any drug effects, and bad effects (throat burning and coughing), but not liking. The active doses decreased placebo identification and increased nicotine and stimulant identification. These changes were not sustained through the 16 minute observation point.

In a single dose situation, the cigarette is more easily identified by smokers as a stimulant than the nicotine inhaler. Irritant effects were identified for the inhaler but not for cigarettes. These finds are not unexpected for 2 reasons. First, the inhaler has been shown not to cause the arterial nicotine spikes that are associated with pulmonary nicotine delivery via smoking. Second, smokers are accustomed to their usual brand of cigarettes, but not to inhaler use, which may make the inhaler relatively unpleasant in acute use.

Conclusions

The nicotine inhaler is a self titrated nicotine replacement dosage form for use in smoking cessation. Nicotine delivery from the inhaler is affected by ambient temperature. At room temperature, the product is most similar to 4mg nicotine gum. At higher temperatures, nicotine delivery from the inhaler is increased. Data on the pharmacokinetics of buccal absorption of nicotine from the porus plug are not yet available.

When used as an aid to smoking cessation in clinical trials reports of possible drug dependence may be seen in approximately 2 - 4% of subjects. In addition, there may be an emergence of withdrawal symptoms among quitters when the drug is tapered or discontinued.

Examination of patterns of drug use reveal that a substantial fraction of both active and placebo quitters used the drug for the maximum length of time allowed. The average dose does not exceed the amount recommended. A tendency to dose escalation is not observed. Direct comparison of prolonged use with other nicotine replacement products is not available.

The inhaler does not produce a rapid arterial nicotine spike as does smoking and has relatively slow absorption and low peak concentrations. Subjective effects following a single dose are less than cigarettes.

Overall, the data suggest that the abuse liability of the nicotine inhaler is substantially less than cigarettes and that it is likely to be similar to other products in this class. It is not known at present whether the abuse liability is more similar to 4mg nicotine gum or nicotine nasal spray as no direct comparison data is available.

Recommendation

Prescription status is recommended for this product.

E Douglas Kramer, MD
Medical Officer
11/14/96

AW Longmire, MD
Medical Officer

MEDICAL OFFICER'S REVIEW

The Nicotine Inhaler, NDA 20-714

NOV 13 1996

Sponsor	Pharmacia
Drug	Nicotine Inhaler
Received	May 3,1996
Reviewer	AW Longmire
Peer	ED Kramer
Study Location	John Hopkins University, Baltimore MD

ABSTRACT

The Drug Abuse and overdose Information section of the Nicotrol Inhaler NDA 20-714 contained a clinical study entitled, "Nicotine Nasal spray and Nicotine Vapor Inhaler: Abuse Liability Determination" This is a summary of the cigarette and inhaler (but not the nasal spray) results of that study.

PROCEDURE OVERVIEW

Using volunteer cigarette smokers, the study measured the physiological and subjective effects produced by the nicotine vapor inhaler (NVI) in an acute dosing paradigm to help ascertain their abuse liability. Several doses were tested, including placebos and the effects were compared to a regular cigarette

PROCEDURE

Twelve subjects (9 males), ages 21 -45, smoking at least 20 cigarettes/day were recruited by advertising. For active cigarettes, the subjects took puffs from their usual brand. Placebo puffs were from the "Next" brand of cigarettes which is a non-nicotine cigarette.

Subjects were overnight nicotine deprived. Doses were determined by the number of inhalations (0, 20, 60, or 120) or puffs (0, 4, 8, or 16 for the cigarettes). The doses were selected to approximate an equivalent range of nicotine, an average inhalation of the NVI contains 0.013 mg of nicotine, and an average puff of a Marlboro cigarette contains about 0.1 mg of nicotine. Thus, total nicotine doses were 0, 0.39, 0.79, and 1.56 mg for the NVI, and 0, 0.4, 0.8 and 1.6 mg for the cigarettes.

Each of the 8 doses was tested twice per subject for a total of 16 conditions. Subjective measures included the Profile of Mood States (POMS), visual analog scales, the Single Dose Questionnaire (SDQ), and the Addiction Research Center Inventory (ARCI) short form.

The POMS was presented once before and once after each drug administration.

The visual analog scales were presented once before and 3 times after (0, 8, and 16 minutes) each drug administration. Questions were as follows: Do you feel any drug

effects?. Do you feel and good effects?, Do you feel any bad drug effects?, How much do you like the medication?, How much are you craving a cigarette right now?, Are you experiencing nausea, dizziness, or lightheadedness, Are you experiencing hunger?, Are you experiencing throat burning or harshness, Are you experiencing nose burning or harshness?, Are you experiencing coughing?, Are you experiencing sneezing?, Are you experiencing watery eyes?, Are you experiencing runny nose?, Are you experiencing heart racing?, Are you experiencing sweating?, Are you experiencing headache?, and Are you experiencing a calming effect?

The Single Dose Questionnaire (SDQ) was presented once before and 3 times after each drug administration. The SDQ contains 4 scales: drug detection ("blank" or "active "), drug liking (0 to 4 scale of "not at all" to "awful lot"), identification (11 names of commonly used and abused drugs), and a symptomatic checklist.

The ARCI questionnaire included 49 true/false questions that are scored as 5 subscales: morphine-benzedrine group (MBG), an index of "euphoria," pentobarbital-chlorpromazine-alcohol group (PCAG), and index of "sedation," lysergic acid diethylamide (LSD), an index of "dysphoria," and the benzedrine group (BG) and amphetamine (A) scales, which are sensitive to amphetamine-like effects.

Performance measures were completed once before and once after each drug administration. Blood samples were also taken before and after each dose. The data were derived from 4 cigarette doses and 4 vapor inhaler doses. Each condition was tested twice. Data were analyzed using a 4 way ANOVA.

RESULTS

Cigarettes

Visual analog scales. Graphs of the visual analog scale results were provided by the sponsor and are included with this report.

Immediately after administration, all 4 cigarette doses significantly increased any drug effect, good effects, and liking. At the second time point, all 4 doses significantly increased liking, but only the 3 active doses increased any drug effect, and good effects. At the second time point, only the 8 puff condition significantly increase good effects. However, both the 8 and 16 puff conditions increased liking.

Single-Dose Questionnaire. All 4 cigarette conditions produced significant increases in nicotine and stimulant identifications. All 4 conditions also increased liking scores while the 3 active puff conditions significantly increased feel the medication. At the second time point, the only difference is that the 0 active puff condition no longer increased liking. At the last time point, all 3 active puff conditions significantly increased stimulant identification, only the 8 and 16 puff conditions continued to significantly increase liking.

ARCI. No significant results.

POMS. No significant differences.

Physiological Measures. The 3 active cigarette conditions produced significant increases in heart rate.

Vapor Inhaler

Visual analog scales. Graphs of the visual analog scale results were provided by the sponsor and are included with this report

Immediately the 3 active doses significantly increased good effects but not liking and significantly increased any drug effect and bad effects (throat burning, and coughing). At the second time point, the only significant effects were increased good effects, throat burning with the highest dose. There were no significant effects on the analog scales at the last time point.

Single-Dose Questionnaire. Immediately the 3 active inhalation conditions significantly decreased placebo identification while increasing nicotine and stimulant identification, and feel medication. At the second time point, the only significant results were an increase on nicotine and stimulant identification after the 39 active inhalation condition. There were no significant effects at the last time point.

ARCI. No significant results.

POMS. No significant differences.

Physiological Measures. No significant results.

Summary

The cigarette and inhaler exhibited changes in the Visual analog scales and the Single-Dose Questionnaire:

"Any drug effect" occurred at the first time point for all products
For the vapor inhaler, these effects appear to be mainly bad.
Cigarettes produced significant Good effects and subjective liking.

Conclusion

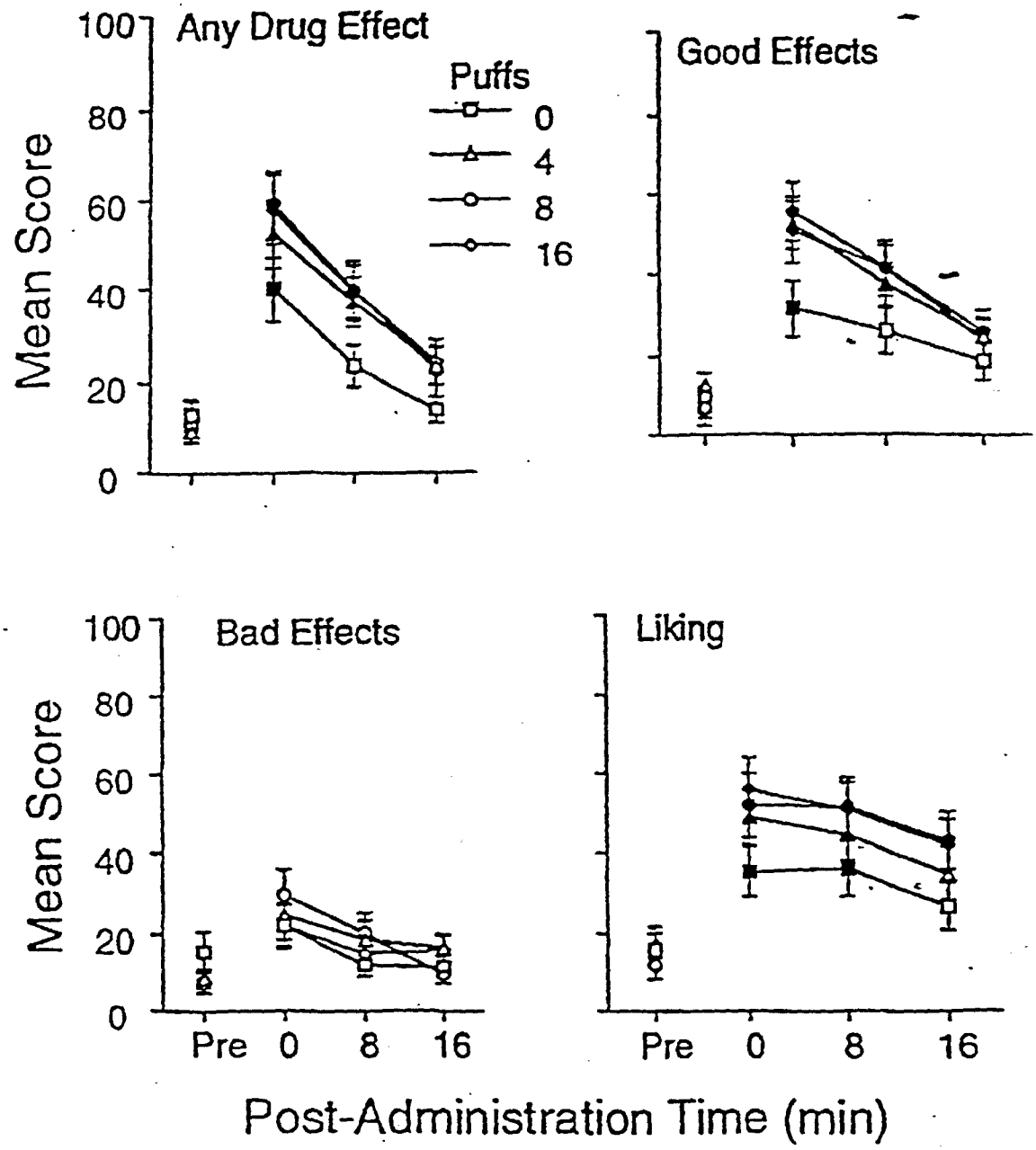
This study indicates (in a single dose situation) that there are differences in the abuse liability of this product as compared to cigarettes, This study does not address the question of abuse potential after chronic use or abuse liability in young people.

AW Longmire MD
Medical Review Officer

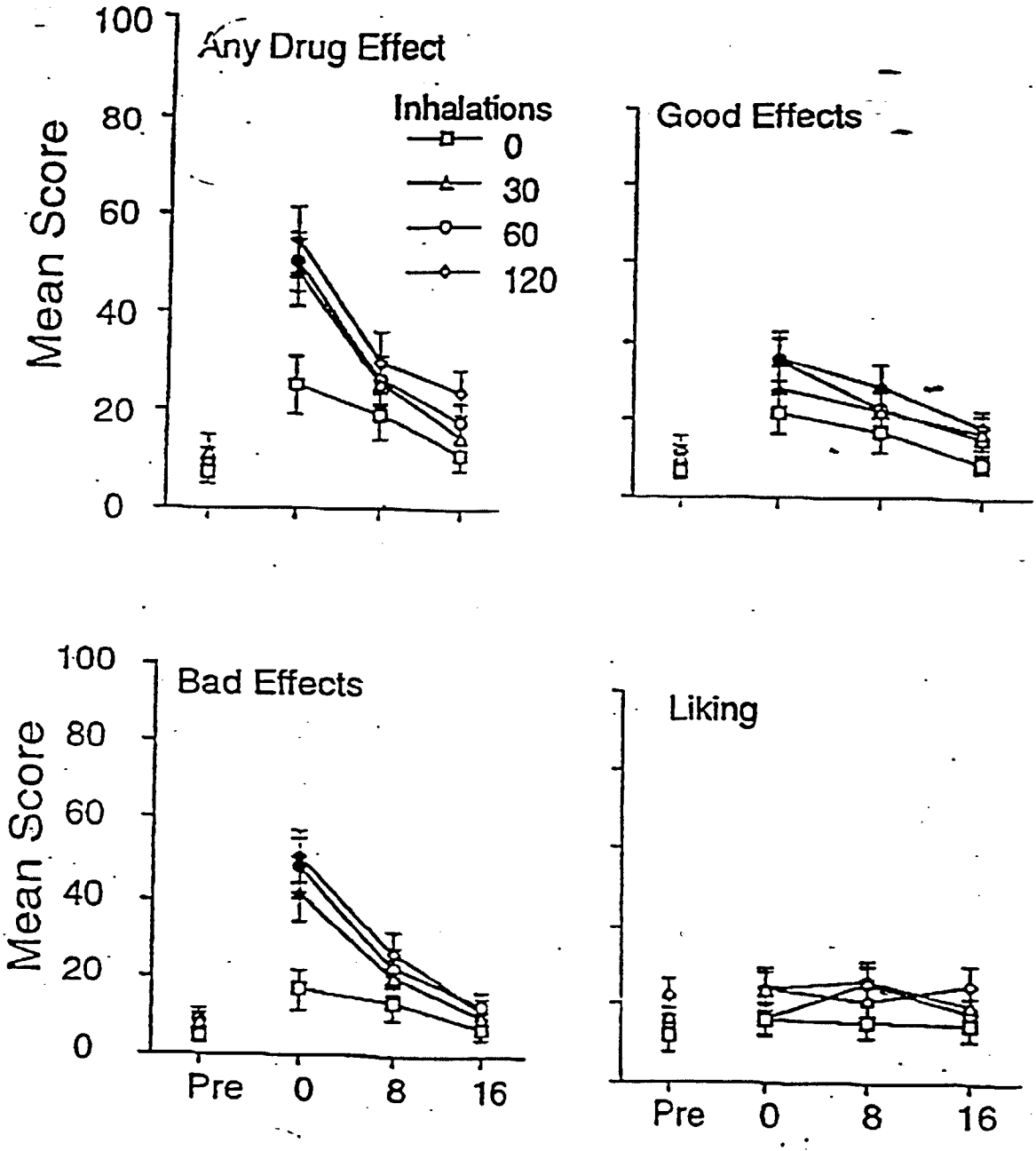
11/13/96

ED Kramer MD
Peer Review

Cigarettes


Any Drug Effect
Puffs
0
4
8
16
Good Effects
Bad Effects
Liking
Mean Score
100
80
60
40
20
0
Pre
0
8
16
Post-Administration Time (min)

Vapor Inhaler



NDA 20-714

CC:
Orig. NDA 20-714
Division File
HFD-170/ Kramer/Chang Li/Ross/Doddapaneni/Geyer/Permutt/McNeal

Medical Officer Review
The Nicotine Inhaler

NDA #: 20-714
Sponsor: Pharmacia
Compound: Nicotine Inhaler (Nicohaler)
Date of Submission: May 1996
Date of Review: 7/96
Medical Reviewer: Chang Qing Li, MD, DrPH, MSHA
Peer: E. Douglas Kramer, MD
Proposed Indications: Smoking Cessation

Study:	1, CTN: T90NI01
Investigator:	David PL Sachs, MD
Location:	Palo Alto Center for Pulmonary Disease Prevention 3000 El Camino Real, Palo Alto, California 94304-1509, USA
Study:	2, CTN: T90NI02
Investigator:	Elbert D. Glover, Ph.D.
Location:	Mary Babb Randolph Cancer Center Tobacco Research Center West Virginia University School of Medicine Morgantown, West Virginia, USA
Study:	3, CTN: T90NI03
Investigator:	Philip Tønnesen, M.D., Ph.D.
Location:	Medical Department P, Pulmonary Medicine Bispebjerg Hospital, Copenhagen, Denmark
Title:	Nicotine Inhaler (Nicohaler) versus Placebo in Smoking

Summary

The three studies were double-blind placebo controlled single center efficacy trials with the Nicotine Inhaler (NIH) in smoking cessation. The studies are reviewed concurrently because of the same inhaler treatment protocol. The main study objective was to determine if active NIH is more effective as treatment of tobacco dependence. The research subjects were smoking men and women motivated to stop smoking aged 20 and older, smoking 10 or more cigarettes per day and being a daily smoker for 3 years or longer. The study sizes were 223 subjects for study one, 241 for study two and 283 for study three. The Nicotine Inhaler used contained 10 mg of nicotine and 1 mg of menthol with about 4 mg of nicotine available for release. About half of the released nicotine is

absorbed. Doses of the inhaler were self-titrated between 2 to 10 inhalers per day and was used whenever the subject felt an urge to smoke. No subject was allowed to use the inhaler after 6 months. Self-reported rates of complete abstinence from week 2 through 12-18 months and verified by CO levels < 10 ppm were measured.

The complete abstinence rates with Nicotine Inhaler treatment were not significantly different when compared to placebo for both study one and study two. Study three achieved similar smoking cessation rates in the treatment group, but the control group had much lower quit rates than those found in study one and two. The Nicotine Inhaler treatment in study three, therefore, showed significant higher complete abstinence rate from 2 weeks through 12 months as compared to the control group: 37 % vs 19 % at 6 weeks, 25 % vs 13 % at 3 months, 19 % vs 10 % at 6 months and 17% vs 7 % at 12 months. Study three conduced in Denmark provided supportive evidence of efficacy of Nicotine Inhaler as an aid to smoking cessation. The two US studies, however, failed to show the efficacy.

The inhaler was associated with irritant side effects in the mouth, the throat and with coughing. No unusual risks emerged.

STUDY DESCRIPTIONS:

The three studies were designed in a similar fashion, and study methods were synthesized below.

Subjects: Men and women age ≥ 20, who had been smoking ≥10 cigarettes per day for ≥ 3 years and motivated to quit smoking. Subjects were recruited by newspaper and television notices. Members of the same household or close friends were allowed to participate in the study, then randomized to the same treatment. Persons with severe or symptomatic cardiovascular disease were excluded.

Treatment: Treatment consisted of two components: Nicotine Inhaler or Placebo Inhaler for a maximum period of 6 months, and educational interventions, including individual sessions, group sessions and follow-up visits.

Nicotine Inhaler or Placebo Inhaler were used at self-titrated doses. Subjects were instructed to use the inhaler on an ad libitum basis of 2 to 10 inhalers per day, whenever they felt an urge to smoke. The first week they were recommended to use the inhalers as frequently as possible in order to adjust to the use and sensation. After 3 months if then necessary, the number of inhalers were tapered for a maximum period of 3 months until 6 months. Follow-ups were scheduled for 18 months in study one and for 12 months in study two and three.

The dosage level was based on the following calculation. Forced inhalation (80 deep inhalation over 20 minutes) *releases* up to 40% (4 mg) from each 10 mg cartridge. About half of the released nicotine is absorbed. After use of the single inhaler the arterial nicotine cencentrations rise to an average of 5 ng/ml in contrast to those of a cigarette, which reach an average peak of approximately 55 ng/ml within 5 minutes. Ad libitum use

of the inhaler typically produces nicotine plasma levels of 6-8 ng/ml, corresponding to about 1/3 of those achieved with cigarette smoking.

The educational components are partially different in the studies (Table 1). Interventions in study three were less intensive than those in study two or three.

Table 1. The Educational Components by Study

	Study one	**Study two**	**Study three**
Educational materials	American Academy of Family physicians Stop Smoking Book	Consumers' Guide to smoking Cessation Participant Manual: Quit & Win	An article: Advice in connection to quitting smoking
Individual Sessions	9 sessions over 6 months	9 sessions over 12 months	6 sessions over 3 months
Group Sessions	None	5 sessions over the first 6 weeks	None
Individual Follow-up Visits	2 visits at 12 and 18 months	2 visits at 9 and 12 months	2 visits at 6 and 12 months

Study visits by Study (Table 2): Before the first scheduled visit, subjects who answered to the notices were screened over the phone for possible eligibility. Other visits were shown in Table 2.

Table 2. Study Visits by Study

	Study one	Study two	Study three
Eligibility	screened over the phone, Visit 1 and 2	screened over the phone and Visit 1	screened over the phone and Visit 1
Randomization and study medication	Visit 3	Visit 1	Visit 1
Follow-up at 1, 2, 3, 6, 12, 26 and 52 weeks	Yes	Yes	Yes
Additional Follow-up visits	at 20 and 78 weeks	at 36 weeks	None

* Each individual visit lasted about 1 hour in study one, about 20 minutes in study two and about 15-20 minutes in study three. The group sessions in study two lasted about 1 hour.

Primary outcome variable: Smoking cessation rate of Nicotine Inhaler vs placebo. For review purposes abstinence is defined as complete abstinence (no "slips" allowed) for at least 4 weeks from week 2 to week 6 and must be confirmed by exhaled CO < 10 ppm. Failure is assumed if subject drop out or report any use of cigarettes.

Secondary outcome variables: Assessments of subjective parameters as withdrawal symptoms, acceptability and self-perceived helpfulness.

Safety outcome variables: Findings of experiences from specific questions recorded in a diary through 6 weeks as well as open-ended questions about any problems experienced throughout the study period.

Usage assessment: Daily use of inhalers were recorded in a diary through 6 weeks (3 weeks for study three). They were also asked to estimate their remaining stock of unused inhalers at each follow-up visit through 6 months.

RESULTS:

Table 3 shows recruitment process by study and number of subjects who were eligible and willing to enter the trial, and received study medication.

Table 3. Research Subject Recruitment by Study

	Study One	Study Two	Study Three
Responsed to Ads	not reported	450	350
Called in for Interview and examination	254	334	300
Showed up for the Interview	254	286	287
Rejected due to exclusion criteria and non-compliance	31	44	4
Subjects recruited	223	242	283

Subject Demographics: The demographics of the subjects randomized to treatment are given in Table 4. The demographical characteristics were compatible within each study. Research subjects in study three, however, were younger, smoked less (both years smoked and daily cigarettes smoked), and had lower CO levels than study one and two.

Table 4. Subject Characteristics at Baseline - Demographics

	Study One		Study Two		Study Three	
	Active N=112	**Placebo N=111**	**Active N=129**	**Placebo N=112**	**Active N=143**	**Placebo N=140**
Age	44.9 (11.1)	45.7 (10.6)	41.5 (9.1)	42.8 (9.6)	39.3 (11.5)	39.5 (13.4)
% Female	55%	54%	58.9%	55.4%	58%	63.6%
Weight (kg)	73.1 (14.8)	74.7 (16.9)	76.5 (18.1)	73.3 (16.0)	67.6 (11.4)	68.9 (11.9)
Smoking Years	26.2 (10.5)	28.1 (10.9)	23.3 (8.8)	24.4 (9.4)	21.4 (10.3)	20.3 (11.0)
Cigarettes/ day	26.7 (12.3)	27.0 (10.4)	27.9 (11.2)	29.7 (12.3)	20.0 (5.9)	20.2 (6.5)
FTQ Score	6.9 (1.7)	6.9 (1.7)	6.9 (1.7)	6.9 (1.7)	7.4 (1.6)	7.3 (1.7)
CO (ppm)	28.4 (11.4)	28.9 (10.5)	29.3 (10.0)	30.6 (10.7)	23.2 (11.7)	22.5 (11.2)
Cotinine (ng/ml)	285.0 (107.7) *Plasma	288.3 (112.7) *plasma	416.3 (177.3) *saliva	423.7 (154.3) *saliva	407.3 (176.6) *saliva	379.9 (186.6) *saliva

Data are extracted from the sponsor's reports. Mean (SD)

Primary Efficacy Analysis

The graph and table 5 below show rates of complete abstinence from cigarettes since week 2 through follow-up visits. The primary efficacy assessment is the comparison of quit rate at 6 weeks (1.5 months).

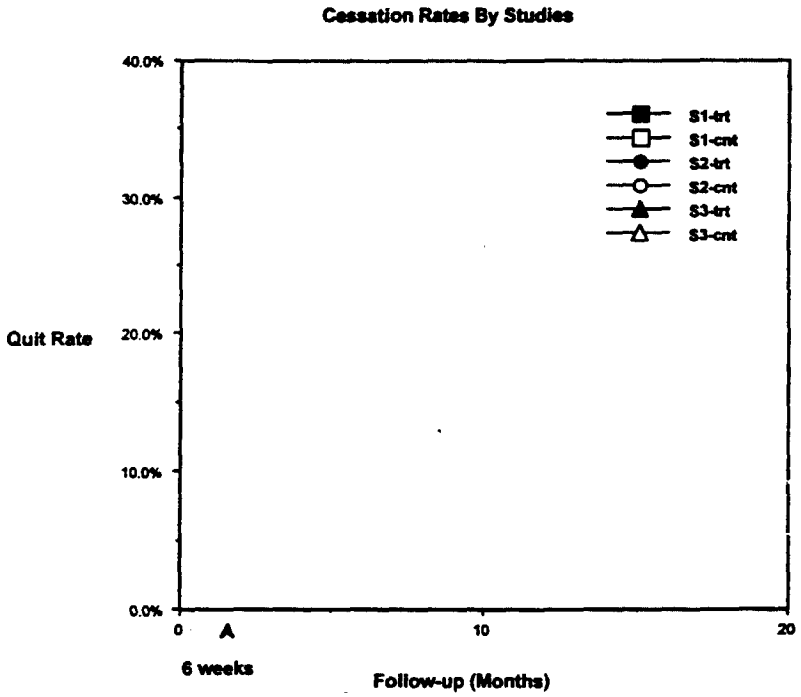


Table 5. Abstinence % (N) From Week 2 through All Visits, No Slips Allowed

Months	Study One Active % N=112	Study One Control % N=111	P value	Study Two Active % N=129	Study Two Control % N=112	P value	Study Three Active % N=143	Study Three Control % N=140	P value
1.5	33 (37)	33 (37)	0.962	28 (36)	25 (28)	0.610	37 (53)	19 (26)	0.001
3	22 (25)	30 (30)	0.207	21 (27)	18 (20)	0.548	25 (36)	13 (18)	0.008
4	21 (23)	23 (26)	0.603						
5	15 (17)	21 (23)	0.281						
6	14 (16)	20 (22)	0.272	17 (22)	15 (17)	0.693	19 (27)	10 (14)	0.034
9				14 (18)	14 (16)	0.941			
12	12 (13)	18 (20)	0.178	13 (17)	14 (16)	0.803	17 (24)	7 (10)	0.013
18	7 (8)	17 (19)	0.022						

* Data are extracted from the sponsor's reports. P-values are based on Pearson's Chi-Square with continuity correction, but they are not corrected for multiple comparisons.

The complete abstinence rates with Nicotine Inhaler treatment at 6 weeks were 33% in study one vs 28% in study two vs 37% in study three. By contrast, the cessation rates with placebo at 6 weeks were 33% vs 25 % vs 19% in study one to three, respectively. Note that while active treatment achieved similar cessation rates across studies, rates of abstinence from placebo in study three were low at all time points. As a result, study three showed that the Nicotine Inhaler treatment had significant higher complete abstinence rate from 2 weeks through 12 months as compared to the control group. Study one and two failed to show the active treatment was more effective than placebo. In this analysis, dropouts were assumed to return to smoking, as is traditional in smoking cessation studies.

Review of the electronic data supplied by the sponsor revealed that no subjects in active or placebo groups were incorrectly classified as failures. All subjects, regardless of treatment assignment, recorded as abstinent for longer than 6 week had biochemical verification after week 6.

Abstinent and Drug use

Quitters in the active groups had consistently reported a higher daily use (pooled mean=4.2) of inhalers than the quitters in the placebo groups (pooled mean=3.3) across the studies although the magnitude of the difference varied. The difference in mean of daily inhaler use was 1.3 (4.6 vs 3.3) between the active and the placebo group in study three, while such differences were only 0.2 (2.5 vs 2.3) and 0.7 (4.9 vs 4.2) in study one and two, respectively (data is not included in the table).

Table 6 presents data on continine concentration at entry and during use of active inhalers among quitters. The mean geometric cotinine substitution suggests the amount of nicotine that needs to be replaced for successful smoking cessation as compared to baseline smoking levels.

Table 6. Continine Concentrations (ng/ml) of Quitters in the Treatment Groups by Study

	Success 6 weeks Mean(SD) ng/ml			Success 6 weeks Substitution, geometric mean		
	N	Entry	At Visit	%	95% CI lower	95% CI upper
Study One		Plasma				
Week 3	32	279± 82	109±122	23	15	35
Week 6	24	299± 81	100± 99	21	12	35
Study two		Saliva				
Week 3	35	405±169	209±124	44	32	60
Week 6	33	408±171	200±141	41	29	57
Study three		Saliva				
Week 3	43	407±203	153±159	25	17	36
Week 6	38	437±207	144±138	21	13	32

* Data are extracted from the sponsor's reports.

The mean geometric cotinine substitution was 21-44% of the baseline smoking level in the studies, and the substitution may go up to 60%.

Safety Outcome Analysis

Table 7 presents data associated with adverse events, including withdrawn or permanently or temporarily discontinued their treatment due to an adverse event, and frequencies of irritant side effects in the mouth/throat in the first 3-6 weeks of treatment. More than 40% of patients reported the irritation in the first few weeks of the active treatment. Coughing occurred in similar frequencies. Paraesthesia, headache, stomatitis, dyspepsia, nausea and pharyngitis were increased in one or two studies.

Table 7. Safety Outcomes and Selected Adverse Events

	Study One		Study Two		Study Three	
	Active	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**
# withdrawn	4	2	2	3	0	0
# permanently discontinued treatment	9	7	19	12	2	1
# temporarily discontinued treatment	19	4	17	16	4	0
% Irritation 1 week	39% (N=40)	25% (24)	47% (58)	24% (26)	47% (55)	21% (19)
2 weeks	40% (40)	27% (24)	40% (48)	14% (14)	39% (39)	15% (10)
3 weeks	28% (24)	19% (15)	30% (34)	13% (12)	42% (33)	17% (9)
4 weeks	27% (22)	25% (17)	33% (33)	11% (8)		
5 weeks	26% (20)	12% (8)	29% (29)	9% (7)		
6 weeks	31% (15)	23% (9)	24% (22)	6% (4)		
Paraesthesia	79% (88)	76% (84)	85%(110)	58% (65)	83%(118)	47% (66)
# Serious Adverse Events	2	1	1	0	1	0

* Data are extracted from the sponsor's reports.

Serious Adverse Events: There were a total of five serious adverse events reported in the studies. The events were not considered to be related to the study drug by investigators or the medical reviewer.

Three (3) subjects experienced a serious adverse event in study one. Two (2) on active treatment, subject No. a cancer of the left lung and subject No. , a depression and one (1) on placebo treatment, subject No. , a depression.

One serious adverse event was reported (No. in study two. One male, 43 years of age (smoking 25 cigarettes per day for 20 years), with heart murmur, who after cardiology examination was found to have a defective heart valve and a 6.5 cm aneurysm. Upon decision for an open heart surgery the subject was removed from the study at his 3 months visit, May 10, 1991. On May 18, 1991, following complications during surgery, the subject died. The event was not considered be related to the study drug by investigator. The medical reviewer concurs.

One serious adverse event was reported (No.) in study three. One female, 43 years of age, reported an event at her 6 weeks visit. She had been admitted to the hospital for one week. She had experienced a paralysis of her left arm and leg. Her diagnosis was migraine and transient cerebral ischemia. She received treatment and recovered. She was not excluded from the study and her treatment code envelope was not broken. She did not use any inhalers while in hospital. She continued in the study remaining abstinent, used 2 inhalers per week at her 6 months visit when inhaler treatment stopped and was abstinent at her 12- months follow up visit. She was on active drug.

Comments

The submitted studies are intended to support a primary efficacy claim - improved quit or abstinence rates over placebo by using nicotine inhaler. The results from the three studies submitted are mixed. The two US. studies failed to shown that the inhaler is effective in aiding smoking cessation, while the Denmark study has provided some evidence of efficacy of Nicotine Inhaler. Many factors may contribute to the inconsistent results, but the three most important factors are medication dose, patient education and selection of study population. The minimum dose effective in the studies is 4 inhalers per day. A minimum dose of 2 inhalers per day, however, was recommended in the protocols. As a result, only 10% (study one), 45% (study two), and 46% (study three) of research subjects in the treatment groups reported the use of 4 or more inhalers per day in the first 3-6 weeks of treatment. The recommended dose in the studies, therefore, was probely too low to start with.

There is well documented literature to support the use of self-help materials as a treatment component in smoking cessation programs. There is also a strong dose-response relation between counseling intensity and cessation success. The placebo group in study three did not receive self-help manuals, and educational interventions were less intense than those in study one and two. This "minimum education intervention" approach may enhance the trial sensitivity, and may play an important role in study three.

Patient selection may also contribute the inconsistent efficacy results. Research subjects in study three smoked less than those in study one and two, measured by number of years smoked, average daily cigarettes consumption and low CO levels. The combination of relatively less tobacco dependence and minimum education intervention may make study three more sensitive to show efficacy.

Conclusions:

The results from the three studies submitted are mixed. The two US studies failed to show that the inhaler is as effective in aiding smoking cessation, while the Denmark study has provided supportive evidence of efficacy of Nicotine Inhaler due to the increased trial sensitivity.

The recommended minimum dose of 2 inhaler per day is less opitimal, and 4 inhalers per day is preferred. The amount of substituted nicotine may be up to 60% of baseline nicotine level.

The inhaler was associated with irritant side effects in the mouth, the throat and with coughing. More than 40% of patients reported such irritation in the first few weeks of treatment. No unusual risks emerged.

Chang Qing Li 11/6/96

Chang Qing Li, MD, DrPH, MSHA
Medical Officer

E Douglas Kramer 11-6-96

E Douglas Kramer, MD
Peer Medical Officer

NDA 20-714

cc:
Orig. NDA 20-714
Div. File
HFD-170/Kramer/Ross/Doddapaneni/Geyer/Permutt/McNeal
HFD-344

NOV 6 1996
McNeal

Medical Officer Review
The Nicotine Inhaler

NDA #: 20-714
Sponsor: Pharmacia
Compound: Nicotine Inhaler
Date of Submission: May 1996
Date of Review: 8/96
Medical Reviewer: Chang Qing Li, MD, DrPH, MSHA
Peer: E Douglas Kramer, MD
Proposed Indications: Smoking Cessation

Study:	4, CTN: T91NI04
Investigator:	Agneta Hjalmarson, Ph.D.
Location:	Smoking Cessation Clinic Sahlgren's Hospital Röda Stråket 6 S-413 45 Gothenburg Sweden

Title: **The Nicotine Inhaler (Nicohaler) in Smoking Cessation. A Long-Term Double-Blind Randomized Clinical Evaluation.**

Summary

This was a double-blind placebo controlled, single center efficacy trial with the Nicotine Inhaler in smoking cessation. The main study objective was to determine if nicotine inhaler is more effective as treatment of tobacco dependence. There were 247 subjects enrolled in the study. Dosing of the inhaler was self-titrated at least 4 inhalers per day and was used whenever the subject felt an urge to smoke. Self-reported rates of complete abstinence verified by CO levels < 10 ppm were measured. The primary outcome variable was complete abstinence from week 2 to week 6.

The Nicotine Inhaler treatment showed significant higher complete abstinence rate from 2 weeks through 12 months as compared to the control group: 46% vs. 33% at 6 weeks, 37% vs. 22% at 3 months, 35% vs. 19% at 6 months, and 29% vs. 18% at 12 months. The study, however, provided only supportive evidence of efficacy of Nicotine Inhaler as an aid to smoking cessation because of the enrolment problem. Twenty-three quitters (or 40% quitters) in the active group and 14 quitters (or 34% quitters) in the placebo group had a baseline CO < 10 ppm. It is impossible to classify them as smoking cessation successes or failures based upon their exhaled CO levels at week 6. The differences in

quit rates between the two groups were marginally insignificant (P=0.056) after adjusting the problem.

The inhaler was associated with irritant side effects in the mouth, the throat and with coughing. No unusual risks emerged.

Material Reviewed - Primary (Electronic) Data

Background

Nicotine replacement as an aid to smoking cessation is a well accepted and established treatment. The inhaler is a plastic tube containing a plastic plug impregnated with nicotine and menthol. The total released nicotine content in an inhaler is about 5 mg. About half of the released nicotine is absorbed. The subject has to work harder to get the nicotine out of the inhaler compared to smoking, while the inhaler last longer than an ordinary cigarette. The placebo inhaler contains about 1.0 mg of l-menthol. The primary objective of this study was to investigate whether there are any differences in smoking cessation success rates between active Nicohaler and placebo inhaler when used in conjunct with group counseling.

Protocol

This was a randomized double-blind parallel phase III clinical trial of two nicotine inhaler (NIN) treatment regimens: NIN active and NIN placebo. Active or placebo treatment was given for 3 months with a possibility for tapering between 3 and 6 months. The subjects were followed up to 12 months. Expired carbon monoxide levels were utilized to corroborate subject reports of smoking cessation. Subjects were recruited by a newspaper ad in a local paper, and by television notices. Entry into the study was open to patients meeting the inclusion and exclusion criteria.

Inclusion Criteria

- Age: 20 years or older
- Daily smoker, 3 years or more, cigarette consumption > 9 cigarettes/day
- Having made at least one serious attempt to quit smoking, by using nicotine chewing gum.
- However, the subject should have been smoking during the last 12 months.
- Indicating willingness to follow through with protocol requirements
- Informed consent that complies with current regulations
- Ability to read, write and speak Swedish

Exclusion Criteria

- Severe or symptomatic cardiovascular disease such as acute myocardial infarction and active angina pectoris (more than four attacks per month).
- Pregnancy
- Breast-feeding
- Requirement of any form of regular psychotropic medication
- Abuse of alcohol or any other drug during the last 12 months
- Use of any current smokeless form of tobacco and nicotine replacement therapy during the last 12 months.
- Suffering from acute medical illness

Treatment Plan

Dosage Regimen

Nicotine Inhaler or Placebo Inhaler at self-titrated doses. Subjects were instructed to use at least 4 inhalers per day on an ad libitum basis, whenever they felt an urge to smoke. The same inhaler could be used 3 to 5 times before switching to a new one. The first week they were recommended to use the inhalers as frequently as possible in order to adjust to the use and sensation. If a subject had difficulties in controlling withdrawal symptoms, he/she would be encouraged to increase the dose. In addition the inhalation technique was reviewed.

At entry an instructual video tape and written instruction on the inhaler concept and explanation of the use was provided. Group therapy was given during the first 6 weeks of treatment in conjunction with individual visits.

Duration of Treatment

Inhaler treatment was intended to continue (individual ad lib dose) for 3 months. Smoke-free subjects who do not need any further treatment were still included in the study. After 3 months of treatment, a tapering period could be initiated for up to 3 months. Extra office visits were permitted for study medication delivery for subjects during the tapering period. Subjects received medication for tapering and were instructed to taper on an individual basis. Follow-up was scheduled for 12 months.

Study visits: Before the first scheduled visit, subjects who answered the ads were called to the clinic and screened for possible eligibility. The next visit was Visit 1 (1 week before Quit-Day) for completion of questionnaires and baseline measures. From Visit 2 (Quit - Day) and on visits were scheduled after day 3-5 (Visit 3), 1 week (Visit 4), 2 weeks (Visit 5), 3 weeks (Visit 6), 6 weeks (Visit 8), 12 weeks (Visit 9), 26 weeks (Visit 10), and 52 weeks (Visit 11). The individual visits lasted about 20 minutes and group sessions lasted about 1 hour. Visit 7, between 3 and 6 weeks was a group lecture about smoking, smoking

cessation and health benefit by quitting smoking. Subjects were informed that slips were no longer permitted after Visit 5.

Treatment Withdrawal Criteria: (1) Subjects with severe reactions and subjects who reject further treatment were to be withdrawn from treatment. (2) Subjects who were smoking at Visit 6 or later, or who do not return to the clinic in spite of two request to do so, (either by phone or mail) were regarded as failures and withdrawn from the trial.

Primary outcome variable: Smoking cessation rate of Nicotine Inhaler vs placebo. For review purposes abstinence was defined as complete abstinence (no slips allowed) for at least 4 weeks from week 2 to week 6 and must be confirmed by exhaled CO < 10 ppm. Slips (occasional smoking) during the first two weeks of treatment were allowed.

Secondary outcome variables: Assessments of withdrawal symptoms and Fagerström Tolerance Questionnaire (FTQ).

Safety outcome variables: Findings of experiences from specific questions recorded in a diary through 6 weeks as well as open-ended questions about any problems experienced throughout the study period.

Usage assessment: Daily use of inhalers were recorded in a diary through 6 weeks. They were also asked to estimate their remaining stock of unused inhalers at each follow-up visit through 6 months.

Statistical analyses: Subjects were randomized at Visit 1, 1 week before, Quit-day. Subjects were included in the analysis if they were given medication at Visit 2 (Quit-day). Quit rates were analyzed using Chi-square test.

RESULTS:

Subject Demographics: The demographics of the subjects randomized to treatment are given in Table 1. The demographical characteristics were comparable between groups.

Table 1. Subject Characteristics at Baseline - Demographics

	Active(N=123)	Placebo(N=124)	P-value
	Mean (SD) (Low - High)	Mean (SD) (Low - High)	
Age(Years)	48 (10.6) (27-74.4)	47 (9.5) (23.6-71.2)	0.425
% Female	61.8	66.1	0.563
% Caucasian	100	100	
% neg med hx	4.9	8.1	0.448
Weight(kg)	72.8 (15.3) (40-129.2)	70.9 (12.8) (49.8-117.6)	0.274
Height(cm)	171.3 (8.6) (153-196)	170.5 (9) (146-190)	0.494
Years smoking	30 (10.3) (6-60)	28.9 (8.7) (10-55)	0.375
Cig/day	21.7 (8.1) (10-55)	21 (7.8) (8-60)	0.480
Total daily nicotine(mg)	25.4 (13.4) (1.5-88)	22.3 (11.1) (2.4-72)	0.049
FTQ(Max score=11)	7.3 (1.9) (2-11)	7 (1.8) (2-11)	0.203
Exhaled CO(ppm)	13.8 (9.2) (0-51)	14.4 (8.9) (1-48)	0.575
Cotinine(saliva ng/ml)	367.9 (139.6) (54.6-786)	409.5 (176.2) (38.2-859)	0.065

* Data are extracted from the sponsor's reports. P-values are provided by the sponser based on two-sided unpaired t-test or Pearson's Chi-square test with continuity correction when applicable or Fishers exact test(F) when expected count in one or more cell is less than 5.

Baseline Medical Conditions:
Concurrent medical problems and medications are listed in the following Table 2 and 3:

TABLE 2. Current Medical Problems at Baseline

	No. of reported medical problems(No. of subjects reporting)		
Category	Active(N=123)	Placebo(N=124)	Total
Pulmonary	43 (39)	51 (44)	94 (83)
Cardiovascular	91 (74)	91 (69)	182 (143)
Gastrointestinal	57 (57)	47 (47)	104 (104)
Metabolic/Endocrine	24 (21)	25 (22)	49 (43)
Musculo-Skeletal	60 (57)	56 (52)	116 (109)
Allergic	40 (40)	39 (39)	79 (79)
Miscellaneous	29 (23)	14 (14)	43 (37)
Total	344 (117)	323 (114)	667 (231)

* Data are extracted from the sponsor's reports

TABLE 3. Current Medication at Baseline

	No. of reported medications(No. of subjects reporting)		
Category	Active(N=123)	Placebo(N=124)	Total
Pulmonary	3 (1)	7 (4)	10 (5)
Cardiovascular	21 (16)	19 (15)	40 (31)
Gastrointestinal	4 (4)	4 (4)	8 (8)
Metabolic/Endocrine	22 (17)	28 (20)	50 (37)
Musculo-Skeletal	7 (4)	12 (6)	19 (10)
Allergic	2 (2)	10 (5)	12 (7)
Miscellaneous	21 (17)	10 (9)	31 (26)
Total	80 (51)	90 (45)	170 (96)

* Data are extracted from the sponsor's reports

Primary Efficacy Analysis:
The number, percentage and odds ratio of subjects completely abstinent from week 2 are shown in the graph below and Table 4:

Continous Cessation, No Slip Allowed

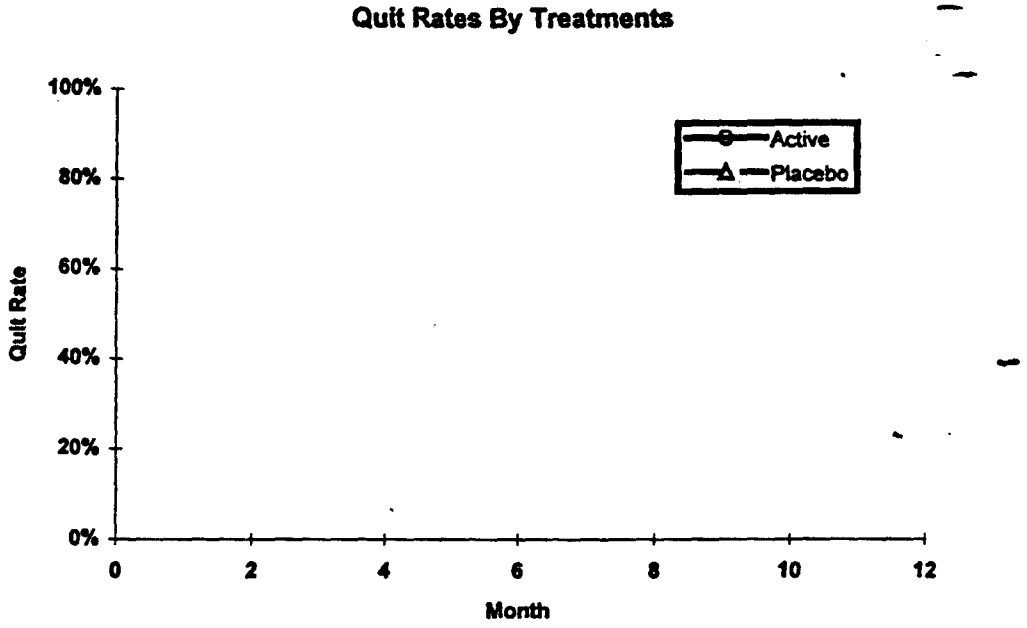


Table 4. Quit Rates and Odds Ratio by Treatment Group

Time	**Active (N=123) %**	**Placebo (N=124) %**	**P-value**	**Odds Ratio**	*Odds Ratio Lower 95% CI*	*Odds Ratio Upper 95% CI*
6 Weeks	46.3 (57)	33.1 (41)	0.033	1.83	1.07	3.16
3 Months	36.6 (45)	21.8 (27)	0.010	2.32	1.30	4.21
6 Months	35.0 (43)	18.6 (23)	0.004	2.65	1.45	4.94
12 Months	28.5 (35)	17.7 (22)	0.046	2.00	1.08	3.79

* Odds Ratios were estimated by using logistic regression method in JMP, and were adjusted by age, sex, years of smoking, cigarrette per day, FTQ, weight, and CO level at baseline. CO level was a significant variable in the logistic model. P-values are based on Chi-Square with continuity correction, but they are not corrected for multiple comparisons.

The Nicotine Inhaler treatment showed significant higher complete abstinence rate from 2 weeks through 12 months as compared to the control group: 46% vs. 33% at 6 weeks, 37% vs. 22% at 3 months, 35% vs. 19% at 6 months, and 29% vs. 18% at 12 months. This study yielded estimates that the odds ratios of quitting smoking were about two times (OR=1.83 to 2.65) greater for those with the active treatment than for persons with placebo. The odds ratios were adjusted by baseline characteristics such as age, number of years of smoking and CO level.

Verification of Smoking Cessation Data

Review of the electronic data supplied by the sponsor revealed that all subjects, regardless of treatment assignment, recorded as abstinent for longer than 6 week had biochemical verification after week 6. However, 23 quitters in the active group and 14 quitters in the placebo group had a baseline CO < 10 ppm (Table 5). Their baseline cotinine levels indicated that they were smokers, and they met the inclusion criterion of cigarette consumption > 9 cigarettes per day. The question here is how to classify them as smoking cessation successes or failures based upon biochemical verification. Obviously, exhaled CO level will not be very useful under this condition. Cotinine levels provide an alternative method in the placebo group to estimate quit rates for they were not consuming nicotine. These results can then be extrapolated to the active group.

Table 5. List of Quitters with Baseline CO < 10 ppm

ID #	treatment (Placebo=14 Active=23)	Self-Reported Quitting at wk6	CO baseline	CO wk6	Cotin Baseline	Cotin wk6	Cig/day
	placebo	yes	7	2	387.3	6.6	20
	placebo	yes	9	3	203	0	20
	placebo	yes	9	4	264		20
	placebo	yes	4	3	239		15
	placebo	yes	2	1	387.3	17.2	15
	placebo	yes	5	1	223	3.5	10
	placebo	yes	5	3	251	13	12
	placebo	yes	6	1	55.9	5.8	20
	placebo	yes	8	5	387.3		10
	placebo	yes	3	2	387.3	4.4	20
	placebo	yes	7	1	157	5	10
	placebo	yes	3	2	38.2	7.4	8
	placebo	yes	7	1	260	5.3	20
	placebo	yes	4	1	307	368	10
	active	yes	3	2	201	8.6	15
	active	yes	7	5	626	5.5	20
	active	yes	5	4	114	7.1	10
	active	yes	9	3	387.3	58.3	15
	active	yes	5	3	546	13.8	18
	active	yes	2	3	117	18.1	15
	active	yes	1	3	353	77.8	40
	active	yes	5	3	180	4.4	20
	active	yes	2	1	394	349	20
	active	yes	6	0	387.3	48.5	15
	active	yes	0	2	391	396	10
	active	yes	9	1	302	133	20
	active	yes	7	3	313		15
	active	yes	8	2	242	47.6	20
	active	yes	6	2	210	32.4	10
	active	yes	4	1	387.3	0	11
	active	yes	5	2	385	68.1	17
	active	yes	9	4	387.3	0	10
	active	yes	6	3	398	157	20
	active	yes	7	2	387.3	11.1	20
	active	yes	6	4	387.3	73.2	20
	active	yes	8	2	348	5.4	20
	active	yes	7	3	238	278	30

* Data is derived from the sponsor's electronic data sets.

A saliva cotinine value of 30 ng/ml or less has been used to validate non-smoking status in many studies. Anyone who does not provide a saliva sample at follow-up will be classified as a smoker. Therefore, four self-reported quitters with the low baseline CO level in the placebo group or 28.6% (4/14) can be grouped into smokers based upon their cotinine values at week 6 (Table 6). Applying the deception rate of 28.6% to the active group, 6 subjects (28.6% x 23) may not quit smoking. The estimated quit rates at week 6, therefore, are 29.8% (37/124) in the placebo group, and 41.5% (51/123) in the active group. The differences between the two groups are marginally insignificant (P=0.056).

Table 6. Estimated Quit Rates at Week 6 by Treatment Groups

	Placebo (N=124)		Active (N=123)		P-value
	N	%	N	%	
Sponsor's Quit Rate	41	33.1%	57	46.3%	0.033
Subjects w Baseline CO < 10 ppm	14		23		
Estimated Non-quitters and Deception Rate	4	28.6% (4/14)	6 (23 x 28.6%)		
Estimated Quit Rate	37 (41 - 4)	29.8%	51 (57 - 6)	41.5%	0.056

The data in Table 7 suggest that quitters tend to be those who smoked less with lower continine or CO level than non-quitters. The results suggest that the nicotine inhaler treatment increases the chance to quit, but it is not as effective for heavy smokers.

Table 7. Baseline Smoking Characteristics of Quitters by Treatment Groups

	Active		Placebo	
	Quitter N=57	Non-Quitter N=66	Quitter N=41	Non-Quitter N=83
Age	47.4	48.5	47.8	46.6
% Female	60%	60%	70%	60%
Smoking Years	29.5 (9.9)	30.5 (10.8)	29.2 (8.7)	28.8 (8.8)
Cigarettes/Day	20.6 (6.6)	22.6 (9.2)	19.9 (8.2)	21.5 (7.6)
FTQ Score	7.0 (1.9)	7.6 (2.0)	6.7 (1.8)	7.2 (1.8)
CO (ppm)	11.9 (7.3)	15.3 (10.4)	13.4 (8.5)	14.9 (9.1)
Cotinine (saliva ng/ml)	355 (130)	378 (147)	353 (169)	437 (174)

Who will quit smoking and what is the chance of quitting? Examining smoking clusters may provide an answer. The smoking *clusters are grouped by baseline smoking characteristics* based on Ward's method (in JMP). In Ward's minimum variance method the distance between two clusters is the ANOVA sum of squares between the two clusters added up over all the vaiables. The chart below and Table 8 show quit rates by the smoking clusters and smoking characteristics of each cluster.

Quit Rate (%) by Smoking Clusters

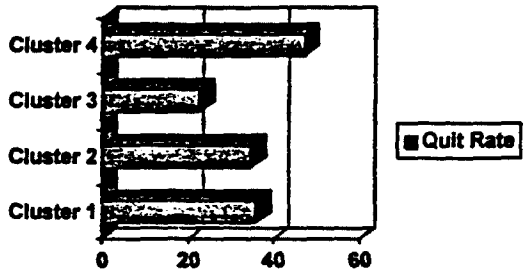


Table 8. Quit Rate and Baseline Smoking Characteristics (Mean±SD) by Clusters

	Cluster 1 (N=53)	Cluster 2 (N=23)	Cluster 3 (N=44)	Cluster 4 (N=123)
Quit Rate (%)	35.9	34.8	22.7	47.2
Cotinine (ng/ml)	383 (140)	462 (157)	477 (152)	338 (134)
CO (ppm)	10.4 (5.9)	15.1 (5.1)	27.6 (9.3)	10.6 (5.3)
Cigeretes/Day	18.4 (4.4)	37.1 (8.9)	23.2 (5.8)	18.4 (4.7)
FTQ	7.0 (1.8)	9.2 (1.2)	8.3 (1.2)	6.3 (1.6)
Craving	2.0 (0.9)	3.0 (1.1)	1.9 (1.4)	2.3 (1.2)

Craving Categories: 0=Not at all; 1=Somewhat; 2=Moderately so; 3=Very much so; 4=Markedly/Extremely so.

The clusters provide to clinicians valuable information about possible cessation rates once a few smoking characteristics are known. For example, approximately 50% of smokers quit smoking if they smoked less than a pack of cigarrette per day with a cotinine < 350 ng/ml and CO < 11 ppm (cluster 4), but the cessation rate may be reduced to 35% if the FTQ score was 7.0 (Cluster 1). Cluster 2 and Cluster 3 present another interesting comparison. Both groups had a high nicotine intake. Persons in cluster 2, however, smoked nearly 2 packs a day with the highest craving and FTQ score among the clusters, and one-third of the smokers in cluster 2 quit smoking. In contrast, cluster 3 presents a

"hard core" of heavy smokers indicated by the highest cotinine AND CO levels. Less than a quarter of smokers in cluster 3 achieved smoking cessation.

Abstinent and Slips

Slips (occasional smoking) during the first two weeks of treatment were allowed. Slip rates and CO levels by treatment outcomes are presented in the charts below and Table 9.

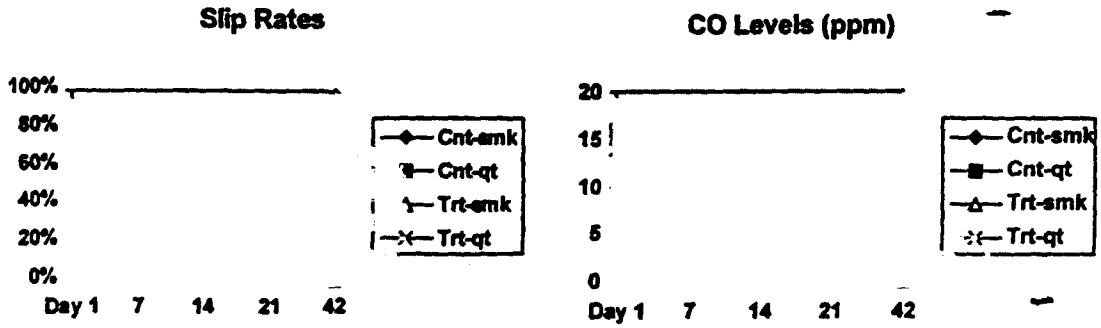


Table 9. Slip Rates and CO levels by Treatment Outcomes

	Placebo-Smokers N=83		Placebo-Quitters N=41		Active-Smokers N=66		Active-Quitters N=57	
Day	Slip %	CO ppm	Slip %	CO ppm	Slip %	CO ppm	Slip %	CO ppm
1	47.0	15.6	4.9	16	40.9	15.1	3.5	14
7	72.3	10.3	4.9	3.0	48.5	11.7	8.8	4.7
14	75.9	12.4	9.8	2.7	60.6	9.7	3.5	3.5
21	79.5	13.8	0		71.2	10.5	0	
42	97.6	14.5	0		93.9	13.6	0	

The data in Table 9 show that about 10% of the quitters in both active and placebo groups smoked occasionally during the first two weeks of treatment. Note that the CO values between 7-14 days were less than 10 ppm among quitters, which suggests that the CO levels checked at a 7-day interval may not sensitive to detect occasional slips.

Patient Accounting:

285 subjects were seen for the screen visit. Of these, 247 (89 men and 158 women) were eligible and willing to participate in the trial. At visit 1, they attended the first session and were randomized to the two treatment groups (123 to active inhaler, 124 to placebo). All 247 subjects were included in both the safety database and the efficacy analysis.

Subjects who did not return for a visit for reasons other than starting smoking were classified as dropouts. Forty-two (42) patients were dropouts at week 6: eighteen patients

from the active treatment group, twenty-four patients from the placebo group. Table 1 shows the disposition of patients by treatment days.

Table 10. Disposition of Patients (Number of Patients)

Days	-7	Quit day	3-5	7	14	21	42	90
Active(N=123)								
Dropout	0	0	3	6	10	12	18	19
Reason for dropout								
Protocol violation	0	0	1	2	4	4	6	6
Non-compliance	0	0	0	1	1	1	2	2
Severe adverse experience	0	0	1	1	1	2	4	5
Lost to follow-up	0	0	1	2	4	5	6	6
Other reasons	0	0	0	0	0	0	0	0
Placebo(N=124)								
Dropout	0	0	4	10	16	20	24	30
Reason for dropout								
Protocol violation	0	0	3	7	12	13	14	17
Non-compliance	0	0	1	1	2	3	3	3
Severe adverse experience	0	0	0	1	1	1	1	1
Lost to follow-up	0	0	0	1	1	2	5	8
Other reasons	0	0	0	0	0	1	1	1

* Data are extracted from the sponsor's reports

Safety Outcome Analysis

Subjects were specifically asked about the occurrence of Local effects. The results from specific questions as well as from open ended questions and severity of Local effects; Irritation in Mouth and Throat, and Coughing are presented in Table 11 and 12.

Table 10. Irritation in mouth and throat

Day	3-5	7	14	21	42	90	180	365
Active(N=123)								
Nn	22 (18%)	21 (17%)	18 (15%)	15 (12%)	11 (9%)	6 (5%)	3 (2%)	3 (2%)
n	18	17	13	12	10	6	3	3
Mean(Severity)	1	1	1.2	1.1	1.1	1.2	1	1
Placebo(N=124)								
Nn	6 (5%)	8 (7%)	7 (6%)	5 (4%)	6 (5%)	0	0	0
n	4	7	5	4	5	0	0	0
Mean(Severity)	1	1	1	1	1			

Nn = Number of subjects reporting the adverse events; n = Number of subjects reporting the severity.

* Data are extracted from the sponsor's reports

Table 12. Coughing

Day	3-5	7	14	21	42	90	180	365
Active(N=123)								
Nn	33 (27%)	25 (20%)	20 (16%)	9 (7%)	6 (5%)	1	1	0
n	29	21	18	8	5	1	1	0
Mean(Severity)	1	1	1	1	1	1	1	
Placebo(N=124)								
Nn	3 (2%)	2 (2%)	3 (2%)	1 (1%)	1 (1%)	0	0	0
n	3	2	1	0	0	0	0	0
Mean(Severity)	1	1	1					

Nn = Number of subjects reporting the adverse events; n = Number of subjects reporting the severity.

* Data are extracted from the sponsor's reports

Table 11 and Table 12 show that about 20% of patients reported the irritation in the first few weeks of the active treatment as compared to 5-8% in placebo. Coughing occurred in similar frequencies. Table 13 lists the increased adverse events (≥5%) in the treatment group.

Table 13. Selected Adverse Events by Treatment Group

	Active (N=123)		Placebo (N=124)	
Adverse Events	N	%	N	%
Headache	79	64%	62	50%
Sweating Increased	65	53%	51	41%
Somnolence	82	67%	71	57%
Pharyngitis	18	15%	8	6%
Nervousness	96	78%	87	70%
Dyspepsia	13	11%	5	4%
Nausea	13	11%	8	6%
Stomatitis	13	11%	8	6%

* Data are extracted from the sponsor's reports

Withdrawn from Study due to Adverse Event

Eight (8) subjects were withdrawn from the study due to an adverse event, five (5) on active treatment and three (3) on placebo treatment. These are described in Table 14.

TABLE 14. Subjects Withdrawn from Study due to Adverse Event

Subject No. Active	Visit (week)	Adverse Event (AE)
	Day 3-5	Nausea
	3	Hearth failure due to irregular pulse
	6	Pain/burn in throat
	12	Nausea
	6	Corrosive symptoms in mouth
Subject No. Placebo	**Visit (week)**	**Adverse Event (AE)**
	3	Illness
	26	Ulcer
	1	Blood pressure falling too much

* Data are extracted from the sponsor's reports

Seven (7) subjects discontinued permanently their treatment due to an adverse event, five (5) on active treatment and two (2) on placebo treatment. These are described in Table 15.

TABLE 15. Permanent Discontinuation of Treatment due to Adverse Events

Subject No. Active	Week/day	Event
	6	Taste of plastic
	1	Nausea
	day 3-5	Nausea
	2	Irritating cough and sore throat
	12	Nausea, taste bad, burn in mouth
Subject No. Placebo	**Week/day**	**Event**
	26	Stomach ulcer
	3	Lump in throat

* Data are extracted from the sponsor's reports

Eleven (11) subjects discontinued temporarily their treatment due to an adverse event, seven (7) on active treatment and four (4) on placebo treatment. These are described in Table 16. Out of these seven (7) subject, one subject on placebo medication later also permanently discontinued treatment.

TABLE 16. Temporary Discontinuation of Treatment due to Adverse Events

Subject No. Active	Week/day	Event
	1	Taste bad, burns in throat
	12	Can't stand them
	day 3-5	Cause pain in stomach
	day 3-5	Cold
	2	Nausea
	6	Pain in teeth
	2	They hurts in mouth, pain on tongue, dry mouth, corrosive symptoms in mouth, corrosive symptoms on lips
Subject No. Placebo	**Week/day**	**Event**
	6	Gastric ulcer
	1	Hurts to much in mouth to use them
	2	Caused irritability
	3	Cold

* Data are extracted from the sponsor's reports

The most frequently reported reasons for study withdrawal in the Nicotine Inhaler treated group were local irritation effects such as sore throat, throat irritating, coughing and headache.

Serious Adverse Event:

No serious adverse event was reported during the study.

Comments

This study was the fourth clinical trial intended to provide further evidence to support the primary efficacy claim. There were major changes in study design to enhance the trial sensitivity, including increased medication dose, patient selection, minimum of educational intervention, and pilot study.

A lesson learned from the previous studies is that the degree of nicotine substitution should be high enough to achieve complete abstinence. The study, therefore, doubled its minimal recommended dose from 2 inhalers to 4 inhalers per day in the treatment plan. As a result, research subjects who used ≥ 4 inhalers per day in the treatment group increased significantly: 85% in study 4 vs 17%, 57%, and 40% in study 1-3, respectively. It is not surprising that study 4 achieved the highest cessation rate among the four studies because of the high dose of medication.

The study had made an important change in inclusion criteria, i.e., only patients who used nicotine chewing gum before would be recruited. This criteron was not applied in the previous studies. The patient's experience with nicotine replacement might enhance the acceptance of the inhaler as a device in smoking cessation, and may contribute to the high use of the inhaler in the study.

An open-lable, pilot study on active medication was performed prior to study 4. The pilot study provided the therapists an opportunity to acquainte to the protocol and the product. For example, the concept of how to use the inhaler is thought to be very important. The previous studies used a tape to teach inhaler use. This study, however, employed personal demonstration. The Principal Investigator or her designees instructed subjects on how to use the inhaler correctly.

It is well documented in literature that educational intervention is an effective treatment component in smoking cessation programs. A minimum of supportive intervention would lower quit rate in placebo, thus it would augment the difference between treatment and control groups. This study adopted such a strategy. The subjects in study 4 did not receive any self-help materials, and counseling intensity was less intense than those in study one and two. The "minimum intervention" approach might have enhanced the trial sensitivity.

The increased trial sensitivity has also made sample size less critical. The study was designed to detect a difference between active and placebo rates of 30% vs 15% with 80% power and α=0.05 using a one-tailed test. A total of 247 subjects were recruited. With a sample size of N(Active)=123 and N(Placebo)=124 the difference in rates between the two groups must be about 10 points in order to be significant. The quit rate in the active group was 13 points higher than the rate in placebo (46% vs 33%). The power, however, is only 68% based on the quit rates observed in the study, which mean there is a 68% chance that the cessation effect in this study will be 10 points or more and significant. By the same token there is a 32% chance (beta) that the effect in the study will be less than 10 points and not significant. Fortunately (for the sponsor), the study demonstrated the efficacy of the inhaler although the statistical power is not opitimal.

The major flaw in this study is the enrolment of 84 smokers (34% of the research subjects) with a baseline CO < 10 ppm. Usually, a typical non-smoker will produce a carbon monoxide recording of less than 10 ppm (corrected for ambient carbon monoxide). Smokers range from 10 ppm in a non-inhaler to well over 75 ppm in heavy smokers. A carbon monoxide reading of < 10 ppm was used to categorise the subject as a quitter in this study. As a result, the 84 smokers might become "instinctive" quitters before the use of the inhalers, which creates a real dilemma in assessing the treatment effect. The " instinctive" quitters were not evenly distributed in the active and placebo group. Twenty-three quitters (or 40% quitters) in the active group and 14 quitters (or 34% quitters) in the placebo group had a baseline CO < 10 ppm. The estimated abstinence at week 6 based upon cotinine level is marginally insignificant (29.8% vs. 41.5%, P=0.056) between the placebo and active group. The strength of the efficacy evidence reported by the sponsor, therefore, is diminished greatly because of the study flaw.

Conclusions:

The study provided supportive evidence of efficacy of Nicotine Inhaler as an aid to smoking cessation because of the enrolment problem.

The recommended minimum dose of 4 inhaler per day is appropriate.

Approximately 10% of the quitters may smoke occasionally during the first two weeks of treatment, and CO levels checked at a 7-day interval are not sensitive to detect occasional slips.

The smoking clusters may provide clinicians valuable information about cessation rates once a few smoking characteristics (i.e., CO and cotinine level, cigarrette per day, and FTQ) are known.

The inhaler was associated with irritant side effects in the mouth, the throat and with coughing. No unusual risks emerged.

Chang Q Li 11/6/96

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Medical Officer

E Douglas Kramer 11-6-96

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Peer Medical Officer

NDA 20-714

cc:
Orig. NDA 20-714
Div. File
HFD-170/Kramer/Ross/Doddapaneni/Geyer/Permutt/McNeal
HFD-344

Medical Review

Sponsor	Pharmacia
Drug	Nicotine Inhaler
Received	May 3,1996
Reviewer	AW Longmire
Peer	E D Kramer
Study:	5, CTN: 92NNIN002
Investigator:	Scott Leischow, PhD
Location:	The University of Arizona Health Sciences Center 1435 N Fremont Street Tucson, AZ, USA

Title: **The Nicotine Inhaler in Smoking Cessation. A Double-Blind Randomised Clinical Evaluation**

SUMMARY:

This study is almost identical in design and results to study 92NNIN003 done by Dr NG Schneider in the previous review. The studies will be reviewed in the same format to facilitate comparison. Study 92NNIN003 will be referred to as the Schnieder study and differences in design or results will be *accented with italics.*
This was a double-blind placebo controlled single center efficacy trial using the nicotine inhaler for smoking cessation. Healthy motivated subjects self-titrated from 4 to 20 inhalers per day for 3 months and the dose was tapered from 3 to 6 months. Self-reported rates of complete abstinence from week 2 through 1 year were verified by CO levels < 10 ppm. The complete abstinence rates with nicotine inhaler treatment were significant at all time-points from 2 weeks through 6 months compared to placebo:

45% vs. 14% at 6 weeks,
31% vs. 8% at 3 months,
20% vs. 6% at 6 months,
and 11% vs. 5% at 12 months.

Throat/mouth irritation and cough were higher on active drug in the first week of treatment.

STUDY DESCRIPTION:

Subjects: Subjects were adults ≥ 21 years old who had been smoking ≥ 10 cigarettes per day for ≥ 3 years and motivated to quit smoking. They were recruited by a newspaper ad in a local paper, and television notices. Members of the same household or close friends were not allowed to participate in the study. Persons with a medical illness e.g. diabetes mellitus or symptomatic cardiac disease, were excluded.

Treatment: Subjects were instructed to use the inhaler on an ad libitum basis from 4 - 20 inhalers per day. The first week they were instructed to use the inhalers as

frequently as possible in order to adjust to the use and sensation. Inhaler use was recommended for 3 months. At 3 months, if the inhaler was still being used, the number of inhalers were tapered for up to 6 months and no inhaler was allowed after 6 months. Follow-up was scheduled for 12 months. At entry, an instruction video tape was shown and written instruction on the inhaler concept was given. Group therapy was not given but subjects had an instructional video and written instructions at entry and individual counselling sessions at week 1, 2, 3, and 6.

Study visits: Before the first scheduled visit, subjects who answered the ads were called to the clinic and screened for possible eligibility. The next visit was Visit 0 (2 weeks before Quit-Day) for completion of questionnaires and baseline measures. From Visit 1 (Day before Quit-Day) visits were scheduled after day 2 (Visit 2), 1 week (Visit 3), 2 weeks (Visit 4), 3 weeks (Visit 5) 6 weeks (Visit 6), 12 weeks (Visit 7), 26 weeks (Visit 8) and 52 weeks (Visit 9). CO, cotinine, diary, and weight were documented at each visit.

Primary outcome: Smoking cessation rate of nicotine inhaler vs. placebo. As in the Schneider study, abstinence was defined as complete abstinence (no "slips" allowed) for at least 4 weeks from week 2 to week 6 and was confirmed by exhaled CO < 10 ppm. Failure was assumed if subjects dropped out or reported any use of cigarettes.

Secondary outcome: Assessments of subjective parameters such as withdrawal symptoms, acceptability and self-perceived helpfulness.

Safety outcome: Events were tabulated from open-ended questions and a 19 item Withdrawal Symptom Questionnaire (p 08-0003929) at each visit

Usage assessment: Daily use of inhalers were recorded in a diary through 6 weeks. They were also asked to estimate their remaining stock of unused inhalers at each follow-up visit through 6 months.

Statistical analyses: Subjects were randomised at Visit 1, Day Before Quit-Day. Subjects were included in the analysis if they were given medication at Visit 1. An interim report was allowed under the protocol and was performed at 3 months without disclosing the individual treatment code. The quit rates were calculated by chi square with continuity correction.

RESULTS:

All subjects recruited by newspaper and television notices between November 1992 and March 1993, were screened for suitability, eligibility and for inclusion in the trial. In order to achieve a minimum of 220 randomised subjects, 267 subjects were seen for the Baseline visit. Of these, 222 were eligible and willing to participate in the trial. At visit 1, they attended the first session and were randomised and assigned subject numbers.
All 222 subjects were included in both safety database and the efficacy analysis.

Demographics: The demographics of the subjects randomised to treatment are given in the following Table 1. *There were more females (53 vs 36 %) and less black subjects (1 vs 7 %) than in the Schneider study.*

TABLE 1
Subjects Characteristics at Baseline - Demographic

	Active (N=112) Mean (SD)	Placebo (N=111) Mean (SD)
% Female	53	58
% White	95	91
% Black	1	0
Age	44 (12)	46 (12)
Weight (kg)	73 (16)	73 (16)
Cig /day	26 (11)	26 (9)
Cotinine (sal)	358(151)	326(122)
FTQ	6.9(1.8)	6.9 (1.7)
CO	25 (11)	22 (8)

The table values are supplied by the sponsor. P-values are from 2-sided unpaired t-test with continuity correction when applicable. The # cig/day, CO (This was from visit 0), age, and FTC, were verified by electronic data.

Concurrent medical problems and medications are listed below:

Current Medical Problems at Baseline

# problems(# subjects) Category	Active(N=111)	Placebo(N=111)	Total
Pulmonary	15 (11)	15 (11)	30 (26)
Cardiovascular	32 (28)	24 (22)	56 (50)
Gastrointestinal	24 (24)	22 (19)	46 (40)
Metabolic/Endocrine*	30 (26)	30 (21)	60 (47)
Musculo-Skeletal	55 (40)	80 (55)	135(95)
Allergic	37 (36)	28 (27)	65 (63)
Miscellaneous	134(74)	134(73)	268(147)
Total	327(99)	333(97)	660(196)

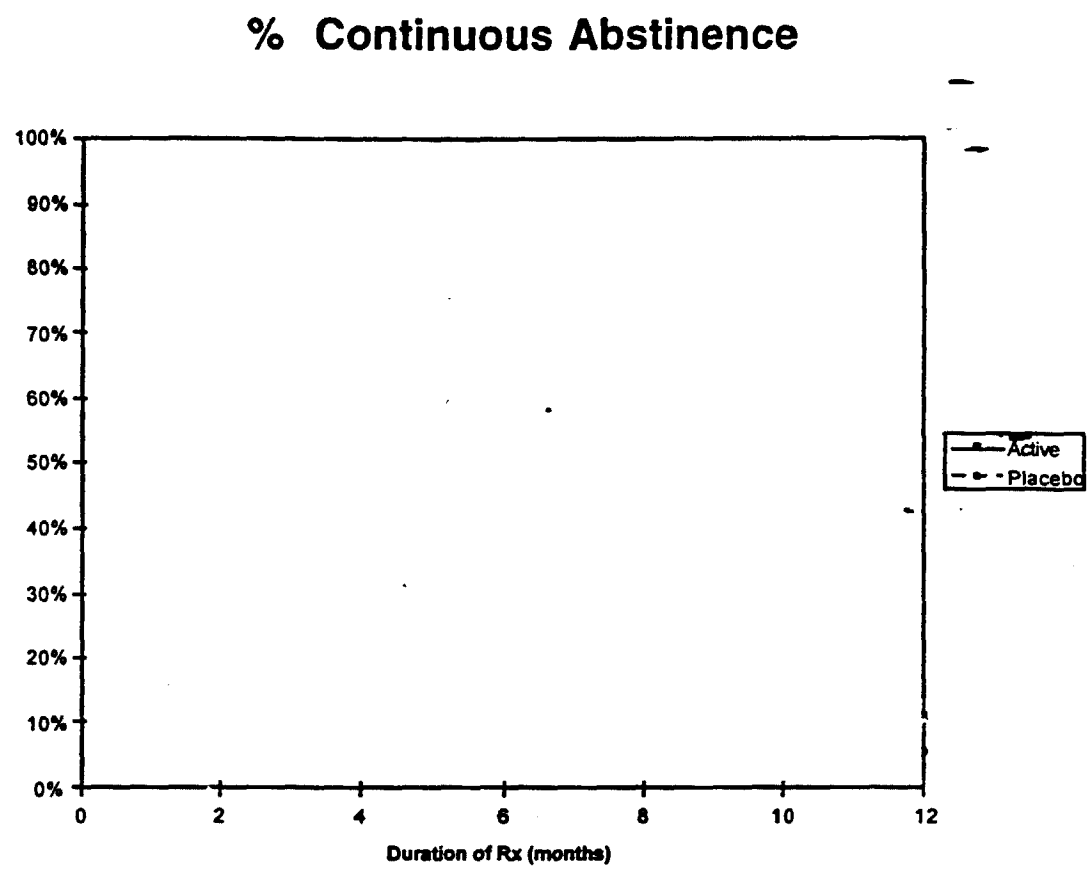
Table from the sponsor's summary report
*Diabetics were excluded from this study.

Current Medication at Baseline

# medications(# subjects) Category	Active(N=111)	Placebo(N=111)	Total
Pulmonary	2 (2)	3 (2)	5 (4)
Cardiovascular	7 (6)	8 (8)	15 (14)
Gastrointestinal	7 (4)	7 (6)	14 (10)
Metabolic/Endocrine	20 (16)	21 (15)	41 (31)
Musculo-Skeletal	19 (16)	22 (17)	41 (33)
Allergic	12 (7)	7 (6)	19 (13)
Miscellaneous	151 (62)	168 (65)	319 (127)
Total	218 (78)	236 (76)	454 (154)

Table from the sponsor's summary report

Primary Efficacy Analysis: The number and percentage of subjects completely abstinent from week 2 is shown below:



	Duration of Rx	6 weeks	3 months	6 months	12 months
Active N=111	# Quit Cigs	50	34	22	12
	% Quit Cigs	**45%**	**31%**	**20%**	**11%**
Placebo N =111	# Quit Cigs	15	9	7	6
	% Quit Cigs	**14%**	**8%**	**6%**	**5%**
	P value	**<0.005**	**<0.005**	**<0.005**	**0.22**

Data display made from sponsor's electronic data set s5demo.xls. P-values are by chi-square with continuity correction. All subjects were treated for 6 weeks. Inhalattions were recommended at 4--20 Inhalers /day until 3 months but then were required to begin tapering and no inhaler use was allowed after 6 months.

Validation of abstinence: Of the 50 subjects listed above as abstinent on active inhalers in this study, all had biochemically verified abstinence (CO<10 with no slips reported) at the 3 and 6 week visits. Thirteen subjects reported slips, and 3 of them had elevated CO levels prior to week 2. One additional subject who denied slipping had an

elevated CO prior to week 2. No subjects have missing data prior to week 6. Of the 15 placebo subjects, none have CO>=10 at any time, 4 reported slips prior to week 2, and none have missing data prior to week 6. All subjects in both groups listed as abstinent by the sponsor after week 6 had biochemically verified abstinence. Light smokers were allowed in the study as smokers if they smoked 10 cig /day or more. This allowed Seven of the above quitters and 6 nonquitters to begin with a CO < 10 but the results are still significant when corrected for this.

Secondary Outcome Analysis: Craving for cigarettes was assessed with the question "How do you feel now in regards to your desire /urge to smoke" on a 5-point categorical scale (Not at all = 0, Extremely so = 4). Differences in craving are shown in Table 5.

Craving

Day	BL(pre-Quit)	7	14	21	42
Active(N=111)					
N	111	96	85	79	67
Mean craving	2.86	2.08	1.73	1.49	1.16
Placebo(N=111)					
N	111	71	54	43	25
Mean craving	2.83	2.48	2.22	1.77	1.72
P-value (Craving)	0.838	0.021	0.011	0.183	0.02

p values from two sided unpaired t test

Table from the sponsor's summary report

In this trial, *unlike in the Schneider study, there was less craving at 7 and 14 days on active drug.*

SAFETY

Serious Adverse Events

One subject on active medication experienced a serious adverse event. Subject _ was a male, age 33, who experienced chest pain after 4 months in the study and was hospitalised for 1 day. Symptoms resolved after that day and the subject continued in the study using the inhalers up to his 6 months' visit. He was abstinent from Quit-Day on. The sponsor did not consider this event related to the study drug and I agree.

Bronchospasm and Asthma

A specific search for the terms bronchospasm and asthma found 3 subjects.

active	Bronchospasm all visits to 6 wks	BL meds-none BL Dx murmur
active	Bronchospasm day 365	BL med- propranolol
placebo	Asthma day 2, 180, 365	BL med - none BL Dx Asthma Lupus

There were 2 subjects with bronchospasm in the Schneider study, both in the placebo group. There is insufficient exposure of this product in the asthmatic population for meaningful comment.