

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-714**

**STATISTICAL REVIEW(S)**

# Statistical Review and Evaluation

NDA 20-714

Date of review: 15 October 1996

By: Thomas Permutt

Name of drug: Nicotine inhaler

Applicant: Pharmacia

Indication: Smoking cessation

Documents reviewed: volumes 1.1, 1.27, 1.32, 1 May 1996

(received HFD-170 3 May 1996)

medical officers' reviews

Project manager: Bonnie McNeal

Medical reviewers: A. W. Longmire, M.D.; C. Q. Li, M.D.

## Introduction

The nicotine inhaler is a new dosage form for nicotine for smoking cessation, consisting of a reusable plastic tube in which a plug containing nicotine is fitted. By sucking on the tube the patient "inhales" gaseous nicotine, but most of it is absorbed in the mouth and throat rather than reaching the lungs.

The efficacy and safety of the product were studied in six placebo-controlled trials. The trials were reviewed in detail by the medical officers. This review will focus on the integrated interpretation of the results of the six trials.

## Overview of efficacy

The six controlled studies were of similar design and had the same primary measure of outcome. Complete abstinence from smoking had to be reported by the patient for four weeks, starting two weeks after the beginning of treatment. Confirmation by a concentration less than 10 ppm of carbon monoxide in expired air was required. Otherwise, or if patients dropped out, they were considered as not abstinent. This has been the measure of efficacy in smoking cessation trials for all previously approved products. All but five patients randomized were included in the primary analysis; the five received no treatment.

All patients	active successes	placebo successes	p-value
Sachs, U.S.	37/112 (37%)	33/111 (33%)	1.0
Glover, U.S.	36/129 (28%)	28/112 (25%)	0.6
Tønnesen, 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 last four studies showed a statistically significant treatment effect, but the first two failed to do so. In such a case a quantitative assessment of the overall strength of evidence may be useful, as intuitive methods may be misleading. A variety of methods are reasonable, and I do not think the choice among them is critical here. I did a Mantel-Haenszel test. This is the test sometimes described as a test of the "common odds ratio," but it is a valid test of the hypothesis that the odds ratios in all strata are 1 against the alternative that at least some are different from 1. The chi-square (1 d.f.) is 35, giving a microscopic p-value. Thus, from a statistical point of view, the combined evidence is very strong that the inhaler is effective at least in some circumstances. There are also plausible explanations, discussed in detail by the medical officers, for differences among the studies, mainly related to variation in dose and compliance.

## Demographics and subset analyses

Each of the six studies enrolled both men and women in roughly equal numbers. A total of 132 patients over age 60 were treated. From 89 percent (Schneider) to 100 percent (Glover, Hjalmarson) of the patients were white (race was apparently not recorded in Tønnesen's study).

Separate analyses of efficacy were carried out for men, for women, and for patients over 60.

Men	active successes	placebo successes	p-value
Sachs, U.S.	16/50 (32%)	18/51 (35%)	0.7
Glover, U.S.	15/33 (28%)	9/50 (18%)	0.2
Tønnesen, Denmark	23/60 (38%)	6/51 (12%)	0.002
Hjalmarson, Sweden	20/47 (43%)	12/42 (29%)	0.2
Leischow, U.S.	35/63 (46%)	6/47 (13%)	<0.0005
Schneider, U.S.	33/72 (46%)	18/69 (26%)	0.02

Reviewer's table, after sponsor's Table 14, p. 10-2508-11. P-values from chi-square test.

Women	active successes	placebo successes	p-value
Sachs, U.S.	21/62 (34%)	19/60 (32%)	0.8
Glover, U.S.	21/76 (28%)	19/62 (31%)	0.7
Tønnesen, Denmark	30/83 (36%)	20/89 (22%)	0.048
Hjalmarson, Sweden	37/76 (49%)	29/82 (35%)	0.09
Leischow, U.S.	26/59 (44%)	9/64 (14%)	<0.0005
Schneider, U.S.	16/40 (40%)	8/42 (19%)	0.04

Reviewer's table, after sponsor's Table 14, p. 10-2508-11. P-values from chi-square test.

The Mantel-Haenszel chi-square statistics are 22 for men and 14 for women (1 d.f.). Again, these correspond to p-values with too many zeroes to be taken literally. Clearly, the inhaler was effective both for men and for women.

Over 60	active successes	placebo successes	p-value
Sachs, U.S.	6/12 (50%)	3/12 (25%)	0.2
Glover, U.S.	2/3 (67%)	2/7 (28%)	0.3
Tønnesen, Denmark	4/7 (57%)	6/15 (40%)	0.5
Hjalmarson, Sweden	8/20 (40%)	3/12 (25%)	0.4
Leischow, U.S.	4/12 (33%)	2/10 (20%)	0.5
Schneider, U.S.	5/11 (45%)	4/11 (36%)	0.7

Reviewer's table, after sponsor's Table 10, p. 10-2499. My calculations of percentages and p-values. Because of the small numbers, the chi-square test is rather a crude approximation, but not so much as to affect the conclusions.

The numbers of patients over 60 were too small in any one study to produce statistical significance, but the trend was consistently in favor of the active product. The Mantel-Haenszel test gave a p-value just under 0.05. Thus, there is considerable evidence that the nicotine inhaler is effective for smokers over 60.

Separate analyses were also done for the subsets of patients who reported smoking less than or more than 20 cigarettes per day. The Mantel-Haenszel p-values were again very small. Thus, the inhaler was effective both for heavier and lighter smokers.

≤20 cigarettes/day	active successes	placebo successes	p-value
Sachs, U.S.	18/54 (33%)	20/53 (38%)	0.6
Glover, U.S.	14/53 (26%)	14/52 (27%)	1.0
Tønnesen, Denmark	45/110 (41%)	21/103 (20%)	0.001
Hjalmarson, Sweden	41/79 (52%)	31/88 (35%)	0.03
Leischow, U.S.	28/51 (55%)	10/54 (19%)	<0.0005
Schneider, U.S.	23/46 (50%)	15/58 (26%)	0.01

Reviewer's table, after sponsor's Table 14, p. 10-2508-11. P-values from chi-square test.

> 20 cigarettes/day	active successes	placebo successes	p-value
Sachs, U.S.	19/58 (33%)	17/58 (29%)	0.7
Glover, U.S.	22/76 (29%)	14/60 (23%)	0.5
Tønnesen, Denmark	8/33 (24%)	5/37 (14%)	0.2
Hjalmarson, Sweden	16/44 (36%)	10/36 (28%)	0.4
Leischow, U.S.	22/60 (37%)	5/57 (9%)	<0.0005
Schneider, U.S.	26/66 (39%)	11/53 (21%)	0.03

Reviewer's table, after sponsor's Table 14, p. 10-2508-11. P-values from chi-square test.

## Conclusions and recommendations

The nicotine inhaler has been shown to be more effective than placebo in helping cigarette smokers stop smoking. Safety is discussed in the medical officers' reviews; there do not appear to be any special concerns about safety. The application is approvable from the standpoint of statistics.

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