

ORIGINAL ARTICLE

# A double-blind study evaluating the long-term safety of varenicline for smoking cessation\*

Kathryn E. Williams, Karen R. Reeves, Clare B. Billing, Jr, Ann M. Pennington and Jason Gong

Pfizer Global Research & Development, Groton, CT, USA

*Address for correspondence:* Kathryn Williams, PhD, Pfizer Global Research & Development, Eastern Point Road, MS 8260-2529, Groton, CT 06340. Tel.: +1 860 441 6828; Fax: +1 860 715 9559; kathryn.e.williams@pfizer.com

*Key words:* Long-term – Point prevalence – Randomized controlled trial – Safety – Smoking cessation – Varenicline

## ABSTRACT

*Objective:* We assessed the safety of long-term varenicline administration for smoking cessation.

*Methods:* In this randomized, double-blind, multicenter trial, eligible adult smokers (18–75 years) who smoked an average of  $\geq 10$  cigarettes/day were randomized to either varenicline 1 mg twice daily (BID) or placebo for 52 weeks. Subjects made weekly clinic visits until week 8, and then every 4 weeks until week 52, with a follow-up visit at week 53. The target quit date was the morning of the week 1 clinic visit. Brief counseling was provided at each visit, and vital signs, adverse events (AEs), and smoking status were documented. Other laboratory measures were collected at specified visits.

*Results:* A total of 251 subjects were randomized to varenicline and 126 to placebo. Approximately half of the subjects in each arm completed the study (53.8% varenicline; 46.8%

placebo). Treatment-emergent AEs were observed in 96.4% of varenicline- and 82.5% of placebo-treated subjects during the study. Common varenicline-associated AEs were nausea (40.2%), abnormal dreams (22.7%), and insomnia (19.1%). Most AEs were considered mild or moderate in intensity. AEs leading to discontinuation of varenicline treatment included nausea (7.6%), insomnia (3.2%), and abnormal dreams (2.4%). A single varenicline-related serious AE, bilateral subcapsular cataracts, was observed. At week 52, 7-day point prevalence abstinence rates were 36.7% (varenicline) and 7.9% (placebo).

*Conclusions:* Varenicline 1 mg BID can be safely administered for up to 1 year. Varenicline was also a more effective smoking cessation aid than placebo throughout the study, supporting both its short- (12-week) and long-term (52-week) efficacy.

## Introduction

Cigarette smoking adversely affects most organs in the body, is responsible for causing many diseases, and reduces the overall health of smokers<sup>1</sup>. Smoking cessation is associated with immediate and long-term health benefits with an improvement in general health and a reduction in the risk for smoking-related diseases<sup>2,3</sup>.

Varenicline was recently approved to aid patients in attempts to quit smoking. Varenicline represents the first new prescription smoking cessation therapy since the approval of bupropion sustained release nearly a decade ago. Varenicline acts as a partial agonist at  $\alpha 4\beta 2$  nicotinic acetylcholine receptors in the brain. As an agonist, it has the potential to relieve or reduce craving and nicotine withdrawal symptoms in subjects who are quitting; and as an antagonist it has the potential to

\* The results have been presented in part as a poster presentation at the 12th Annual Meeting of the Society for Research on Nicotine and Tobacco, February 15–18, 2006, Orlando, Florida, USA – ClinicalTrials.gov number: NCT00143299

reduce the rewarding and reinforcing effects of nicotine in individuals who lapse<sup>4</sup>.

The recommended treatment regimen for supporting smoking cessation with varenicline is 1 mg twice daily for 12 weeks. An additional 12 weeks of treatment with varenicline was beneficial for smokers who had quit smoking by the end of an initial 12 weeks of treatment, with long-term abstinence rates significantly better than in those who did not receive the additional treatment<sup>5</sup>.

For some smokers, a longer period of support with pharmacotherapy may be necessary. The purpose of this study was to obtain safety information on cigarette smokers treated with varenicline for 52 weeks.

## Subjects and methods

### Study design

In this double-blind, multicenter clinical trial, subjects were randomized in a ratio of 2:1 to varenicline 1 mg twice daily (BID) or placebo to achieve approximately 250 subjects in the varenicline arm and 125 subjects in the placebo arm. Potential subjects, recruited via advertising in the local community, were first seen at a screening visit to determine study eligibility and obtain informed consent. Qualified subjects returned for a baseline visit  $\geq 3$  days and  $\leq 3$  weeks after screening. All subjects who continued to meet the entry criteria at the baseline visit were given an educational booklet on smoking cessation (*Clearing the Air: How to Quit Smoking ... and Quit for Keeps*, National Cancer Institute Publication 95-1647) and randomized to varenicline or placebo.

Treatment began on the evening of the baseline visit, with the target varenicline dose of 1 mg BID achieved through titration over the first week, as follows: 0.5 mg

once daily (QD) in the evening on days 1 to 3; 0.5 mg BID on days 4 to 7; and 1 mg BID starting on day 8. Subjects were encouraged to attempt to stop smoking on the target quit date (TQD) and remain abstinent from smoking and other nicotine use thereafter. The TQD was planned to coincide with the morning of the week 1 visit (7 to 10 days after the baseline visit; Figure 1), with the last cigarette before midnight the night before. Subjects attended clinic visits weekly on weeks 1 to 8, then every 4 weeks until week 52. A follow-up visit was scheduled at week 53 – 1 week after completion of treatment. Subjects who discontinued the study before week 52 had an early termination visit. Brief counseling (up to 10 minutes) was provided to all subjects at randomization and at each subsequent visit in accordance with the Agency for Healthcare Research and Quality (AHRQ) guidelines<sup>6</sup>.

The study was conducted between October 2003 and March 2005 at eight centers in the United States and one center in Australia. Approval for the study was obtained from the Independent Review Boards and/or Independent Ethics Committees of each study center before any subjects were enrolled. The study conformed to the ethical principles originating from the Declaration of Helsinki and in compliance with the International Conference on Harmonization Good Clinical Practices Guidelines.

### Study participants

Qualified subjects were male or female cigarette smokers, aged 18–75 years, who had smoked an average of  $\geq 10$  cigarettes per day during the past year, including the month before screening, with no period of abstinence  $> 3$  months. Women of childbearing potential were eligible if they were not nursing or pregnant, as determined by a negative serum pregnancy

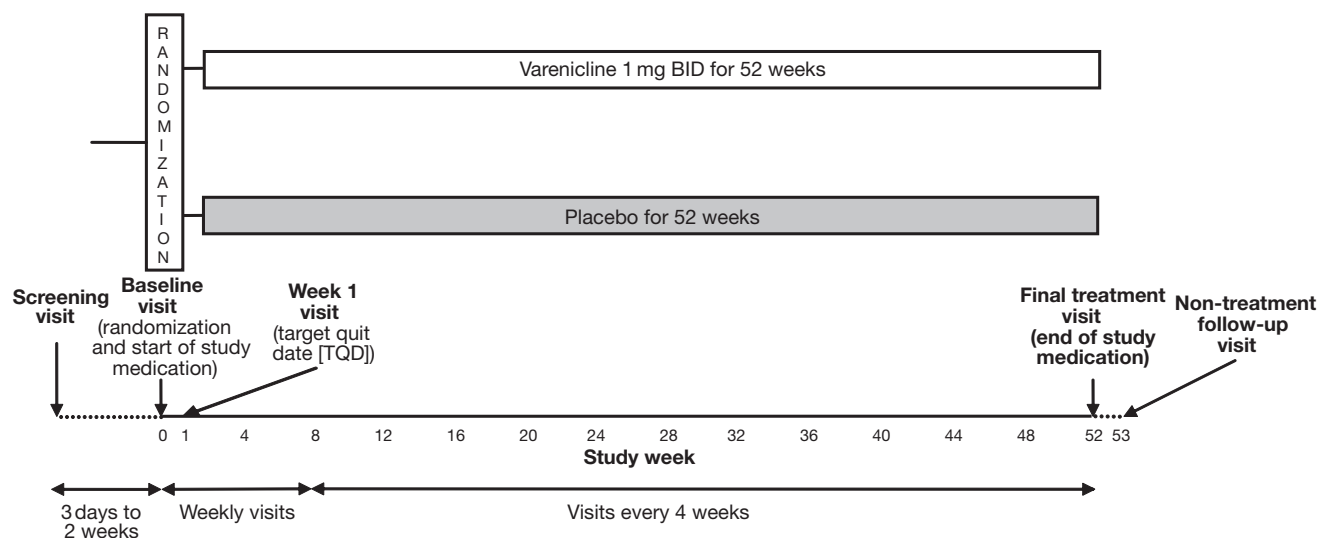


Figure 1. Study design

test ( $\beta$ -hCG) at screening and baseline, and were instructed and agreed to avoid pregnancy throughout the study by using adequate contraception. Additional inclusion criteria included access to an outpatient clinic setting for assessments; reasonable health status, as determined by a detailed medical history, full physical examination, 12-lead electrocardiogram (ECG), clinical laboratory tests; and body mass index (BMI) not < 15 and not > 38.

Individuals were excluded from study participation if they had clinically significant medical conditions, including a past or present history of cancer (other than treated basal or squamous cell skin carcinoma), a history of clinically significant cardiovascular diseases during the 6 months before screening or baseline, elevated liver enzymes, and a history of hypertension. Individuals with mild-to-moderate chronic obstructive pulmonary disease were eligible for inclusion. The use of tobacco products, other than cigarettes, within the past month or failure to agree to abstain from use of these products during study participation were also grounds for exclusion. Use of the following medications was prohibited during the study: antidepressants, antipsychotic agents, naltrexone, and nicotine replacement therapy (NRT).

## Study assessments

The primary evaluations of this study were for safety assessments, which were performed at each visit. Only one efficacy assessment, the 7-day point prevalence of abstinence, was conducted in this study and it was performed at every visit. Other assessments included collection of plasma samples at weeks 2, 12, 24, 36, and 52 for determination of study medication concentrations and for pharmacokinetic and pharmacodynamic analyses (results not reported) and an optional genotyping blood sample collected at baseline (results not reported). As well as conducting the safety assessments and other evaluations during study visits, time was allowed for up to 10 minutes of counseling.

## Safety assessments

At each visit after screening, observed or reported adverse events (AEs), concomitant medications, and vital signs (i.e., blood pressure and pulse rate) were documented. Additional safety evaluations were conducted at specified clinic visits during the treatment phase. At weeks 2, 12, 24, 36, and 52 (or upon early termination), a urine sample was collected and blood was drawn for the following tests: complete blood count with differential and platelet count and; blood chemistry, including albumin, alkaline phosphatase, bicarbonate,

blood urea nitrogen, calcium, chloride, cholesterol, creatinine, glucose, inorganic phosphorus, lactic dehydrogenase, potassium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, total bilirubin, total protein, and triglycerides. A complete physical examination including 12-lead ECG was conducted at screening or baseline and at weeks 24 and 52 (or upon early termination). An additional 12-lead ECG was obtained at week 2.

## Efficacy measures

The 7-day point prevalence of abstinence was measured. At each clinic visit, patients completed a questionnaire (the Nicotine Use Inventory) that consisted of oral self-reporting (yes/no) of smoking and use of other nicotine-containing products (e.g., nicotine patch, nicotine gum, nicotine nasal spray, nicotine inhaler, nicotine lozenge, pipe, cigars, chew, snuff) in the last 7 days. End-expiratory exhaled carbon monoxide (CO) concentration was also measured at each visit to confirm the subject's report.

As this trial was primarily a safety trial, no further efficacy analyses were performed.

## Data analysis

All analyses included all randomized subjects who took at least one dose of study medication. Demographic data, frequency of events, and mean changes from baseline for safety and efficacy data were summarized using descriptive statistics; no inferential statistics were applied to the study outcomes at any end point or time point. Laboratory measures were summarized as median change from baseline to the last observation; vital signs, and ECG parameters were summarized as the median change from baseline to the last observation and the mean change from baseline to each visit were summarized. Baseline values were defined as the last observation before the start of study medication.

Treatment-emergent AEs included adverse drug reactions, any illness with an onset occurring during the study, exacerbation of a previous illness, clinically significant changes in physical examination findings, and abnormal objective test findings (e.g., ECG, clinical laboratory value). No distinction was made between treatment-emergent AEs and symptoms that may have been caused by nicotine withdrawal. A serious AE was defined as one that resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in a persistent or significant disability or incapacity, or resulted in a congenital anomaly or birth defect at any dose. Investigators' terms for individual AEs were mapped to MedDRA Preferred Terms and summarized

by System Organ Class. All treatment-emergent AEs were summarized, regardless of the investigators' opinion regarding causality.

In the efficacy analysis, subjects who reported they had not smoked or used any nicotine-containing products and did not have a CO measurement > 10 ppm were considered responders for that 7-day period. Subjects who either missed a visit or whose nicotine use data were missing at a visit were considered smokers for that visit, and smokers who discontinued the study were considered smokers for subsequent visits regardless of their smoking status at their last recorded visit. The response rate was summarized as the 7-day point prevalence of abstinence at each visit. The 7-day point prevalence of abstinence for a given time point was defined as the proportion of all randomized and treated subjects abstaining from smoking during the preceding 7 days, as indicated by the subjects' responses to the interview questions and exhaled CO not > 10 ppm.

## Results

### Subject disposition

Subject disposition is summarized in Table 1. A total of 377 subjects were randomized in a 2:1 ratio – 251 to varenicline and 126 to placebo. Approximately half the subjects in both treatment groups completed the study (53.8%, varenicline; 46.8%, placebo). Among

varenicline-treated subjects, the most frequent reason for study withdrawal was AEs (25.9%); among placebo-treated subjects the most frequent reasons for withdrawal were refusal to continue study participation (15.9%) and lost to follow-up (15.1%). Subjects could remain in the study even if they discontinued study treatment.

### Subject demographic and baseline characteristics

Table 2 summarizes the demographic and baseline characteristics of the study population. The majority of the study population were white (88.6%) with males and females equally represented. The mean age was 48 years, with a range 18–75 years. The smoking history did not differ between treatment groups: subjects in both groups reported an average 30-year (range 4–57) smoking history. Subjects reported smoking an average of 23 cigarettes per day in the month before study entry. Mean scores (5.50/10 for varenicline; 6.05/10 for placebo) on the Fagerström Test for Nicotine Dependence<sup>7</sup> also indicate a similar degree of nicotine dependence in both treatment groups. The majority of subjects (92.0%, varenicline; 92.9%, placebo) had attempted to quit smoking one or more times in the past. Approximately half of all subjects (47.0%, varenicline; 52.3%, placebo) had tried the nicotine patch; approximately a quarter (25.9%, varenicline; 24.6%, placebo) had used nicotine gum; and more than one-third (33.1%, varenicline;

**Table 1.** Subject disposition

	Varenicline 1 mg BID	Placebo
Number screened, <i>N</i>	519	
Assigned to treatment, <i>n</i>	251	126
Treated, <i>n</i>	251	126
Completed study, <i>n</i> (%)	135 (53.8)	59 (46.8)
Discontinued study, <i>n</i> (%)	116 (46.2)	67 (53.2)
Adverse events	65 (25.9)	13 (10.3)
Lack of efficacy	0 (0.0)	6 (4.8)
Protocol deviations*	5 (2.0)	4 (3.2)
Pregnancy	1 (0.4)	0 (0.0)
Refusal to continue study	13 (5.2)	20 (15.9)
Lost to follow-up	25 (10.0)	19 (15.1)
Other†	7 (2.8)	5 (4.0)

\*Based on investigator decision. Included use of prohibited medications (three varenicline, one placebo), poor compliance with study medication (one varenicline, one placebo), poor compliance with study visits (one varenicline, two placebo)

†In the varenicline group, six subjects elected to discontinue for personal reasons and one subject did not meet entrance criteria post-randomization; in the placebo group, four subjects relocated and one subject was withdrawn because of poor visit compliance

41.2%, placebo) had used bupropion as a smoking cessation aid before study entry (Table 2).

### Treatment duration

The duration of treatment in the overall study population is summarized in Table 3. The duration of treatment was calculated from the first through the last day of treatment, inclusive, without deducting for missed doses. A total of 121 subjects took varenicline for >51 weeks; the median duration of varenicline exposure was 348 days. Excess exposure to varenicline (i.e., 95 subjects with >52 weeks of varenicline treatment) may have occurred because of incremental visit delays over the course of the study.

### Safety results

Almost all subjects (96.4%, varenicline; 82.5%, placebo) experienced treatment-emergent AEs (all causality) during the 52-week study. All-causality AEs that occurred in  $\geq 5\%$  of varenicline-treated subjects and that were more frequent in varenicline- than placebo-treated subjects are summarized in Table 4. Frequently occurring AEs among varenicline-treated subjects were nausea (40.2%), abnormal dreams (22.7%), and insomnia (19.1%). AEs were mostly transient. The onset of gastrointestinal (nausea, dyspepsia, constipation, flatulence, vomiting) and psychiatric (abnormal dreams, insomnia) AEs occurred mostly during the first 4 weeks of treatment and new onsets of

**Table 2.** Baseline demographic characteristics and smoking history

	Varenicline 1 mg BID (n = 251)	Placebo (n = 126)
Sex at birth, n (%)		
Male	127 (50.6)	61 (48.4)
Female	124 (49.4)	65 (51.6)
Age (years)		
Mean (SD)	48.2 (12.3)	46.6 (12.1)
Range	18–75	18–74
Race, n (%)		
White	218 (86.9)	116 (92.1)
Black	18 (7.2)	6 (4.8)
Asian	1 (0.4)	0 (0.0)
Other	14 (5.6)	4 (3.2)
Number of years subject smoked		
Mean	30.7	29.9
Range	4–57	6–57
Number of cigarettes smoked daily over past month		
Mean	23.2	23.4
Range	10–90	10–50
Previous serious quit attempts, n (%)		
None	20 (8.0)	9 (7.1)
$\geq 1$	231 (92.0)	117 (92.9)
Methods used to quit smoking during previous attempts (%)		
Nicotine patch	47.0	52.3
Nicotine gum	25.9	24.6
Bupropion	33.1	41.2
Longest period of abstinence in past year (days)		
Mean	7.75	8.12
Range	0–90	0–90
Fagerström test for Nicotine Dependence Score*		
n	250	126
Mean (SD)	5.50 (2.07)	6.05 (1.94)

\*Fagerström scores range from 1 to 10, with higher scores indicating greater nicotine dependence

these AEs after week 4 were relatively infrequent. The incidence of AEs decreased over time. The majority of AEs were reported as mild or moderate in intensity.

Study medication was permanently discontinued because of AEs in 71 (28.3%) varenicline-treated subjects and 13 (10.3%) placebo-treated subjects. The three AEs most often leading to permanent discontinuation of varenicline treatment were nausea

(19 subjects, 7.6%), insomnia (eight subjects, 3.2%), and abnormal dreams (six subjects, 2.4%); no other AE contributed to varenicline treatment discontinuation in >2% of subjects.

Eighteen subjects experienced serious AEs during the study (15 varenicline-treated; three placebo-treated). Many of the serious AEs were cardiovascular conditions known to be comorbid with cigarette smoking and the

**Table 3.** Duration of treatment

Duration	Varenicline 1 mg BID ( <i>n</i> = 251) <i>n</i> (%)	Placebo ( <i>n</i> = 126) <i>n</i> (%)
> 12 weeks (≥ 85 days)	192 (76.5)	91 (72.2)
> 24 weeks (≥ 169 days)	154 (61.4)	72 (57.1)
> 51 weeks (≥ 358 days)	121 (48.2)	54 (42.9)
> 52 weeks (≥ 365 days)	95 (37.8)	43 (34.1)
Median duration (days)	348	255
Range (days)	5–413	8–379

**Table 4.** Most frequent all-causality treatment-emergent adverse events\*

Adverse event	Varenicline 1 mg BID ( <i>n</i> = 251) <i>n</i> (%)	Placebo ( <i>n</i> = 126) <i>n</i> (%)
Gastrointestinal disorders		
Nausea	101 (40.2)	10 (7.9)
Dyspepsia	33 (13.1)	3 (2.4)
Constipation	31 (12.4)	9 (7.1)
Flatulence	31 (12.4)	12 (9.5)
Vomiting	17 (6.8)	2 (1.6)
Infections and infestations		
Upper respiratory tract infection	34 (13.5)	12 (9.5)
Sinusitis	17 (6.8)	8 (6.3)
Influenza	15 (6.0)	3 (2.4)
Psychiatric disorders		
Abnormal dreams	57 (22.7)	9 (7.1)
Insomnia	48 (19.1)	12 (9.5)
Nervous system disorders		
Dysgeusia	27 (10.8)	3 (2.4)
Dizziness	19 (7.6)	6 (4.8)
Musculoskeletal and connective tissue disorders		
Arthralgia	18 (7.2)	7 (5.6)
Back pain	16 (6.4)	6 (4.8)
All other system organ classes		
Weight increase	17 (6.8)	5 (4.0)
Hypertension	15 (6.0)	5 (4.0)
Increased appetite	13 (5.2)	4 (3.2)

\*Only includes events that occurred at an incidence (all causalities) of ≥5% in the varenicline treatment group and were more frequent in varenicline-treated than placebo-treated subjects

medical histories of many of these subjects documented conditions that may have contributed to the events. Only one of the serious AEs was considered related to varenicline treatment by the study investigators – bilateral subcapsular cataracts, diagnosed on treatment day 125. This subject discontinued treatment on day 169. Two other varenicline-treated subjects discontinued treatment because of a serious AE: one with coronary artery disease discontinued on day 191 and one with a myocardial infarction discontinued on day 7. One placebo-treated subject with a pulmonary embolism discontinued treatment on day 14. No deaths were reported during the study.

### Laboratory values, vital signs, and ECG changes

The median changes from baseline to the last observation in hematology and serum chemistry laboratory parameter values were small and comparable between groups; clinically significant laboratory test abnormalities occurred infrequently. Two subjects in the varenicline group discontinued treatment for elevations in liver enzymes; one with elevated AST and one with elevated ALT. Another varenicline-treated subject discontinued treatment for decreased potassium levels. Two additional varenicline-treated subjects had bilirubin values meeting the criteria for clinically significant deviations, but did not discontinue treatment. Both had elevated bilirubin values at screening.

Median changes in blood pressure and heart rate from baseline to last observation, as well as mean changes from baseline to each visit, were small and indicated no differences between treatment groups. Clinically significant changes in vital signs were noted only sporadically. Heart rate-associated AEs occurred in six varenicline-treated subjects: two with bradycardia and four with tachycardia. One episode of tachycardia was a serious AE; however, it was not considered treatment-related by the investigator. In this case, varenicline was

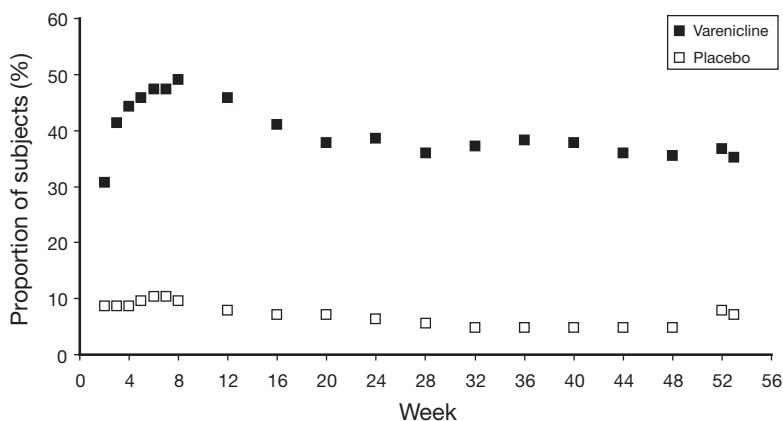
temporarily discontinued during hospitalization, the event resolved, and the subject completed the study treatment. No varenicline-treated subject had a QTc (Bazett or Fridericia correction)  $\geq 480$  ms.

### Changes in body weight

The median change in body weight from baseline to last observation was 2.09 kg for 248 varenicline-treated versus 0.67 kg for 124 placebo-treated subjects. To better understand the relationship between weight gain and long-term smoking status, subjects were classified as consistent non-smokers, intermittent smokers, or consistent smokers according to whether they met abstinence criteria at all, some, or none of the 7-day point prevalence abstinence assessments from week 8 to their last observation in the study. Median weight changes in the varenicline group were 3.18 kg in the consistent non-smokers ( $n = 65$ ), 3.53 kg in the intermittent smokers ( $n = 90$ ), and 0.79 kg in the consistent smokers ( $n = 57$ ). The pattern was similar in the placebo group with median weight changes of 1.02 kg in the consistent non-smokers ( $n = 4$ ), 3.35 kg in the intermittent smokers ( $n = 14$ ), and 0.45 kg in the consistent smokers ( $n = 84$ ).

### Efficacy results

The CO-confirmed, 7-day point prevalence abstinence rates for each visit are shown in Figure 2. The highest point prevalence rates in the varenicline group were observed between weeks 5 and 12, ranging from 45.8% to 49.0%; the highest rates in the placebo group were observed between weeks 5 and 8 and ranged from 9.5% to 10.3%. Point prevalence rates for varenicline remained fairly constant between weeks 24 and 52, ranging from 35.5% to 38.6%, and were 36.7% at the end of the treatment period; point prevalence rates for placebo over the same period ranged from 4.8% to 7.9%, and were 7.9% at week 52. For both treatment groups,



**Figure 2.** CO-confirmed 7-day point prevalence of abstinence data for varenicline 1 mg BID ( $n = 251$ ) and placebo ( $n = 126$ )

the abstinence rates were slightly lower 1 week after discontinuation of study medication (week 53): 35.1%, varenicline; 7.1%, placebo. This may be accounted for, in part, by subjects who did not return for the follow-up visit, and were consequently considered to be smokers.

## Discussion

Safety analyses from this study indicate that varenicline is well-tolerated and can be used safely for long-term administration of up to 1 year. The subjects included in this study had, on average, smoked for the past 30 years, and were smoking more than one pack of cigarettes per day. The demographics of the population represented in this study (similar proportions of males and females, predominantly white) are consistent with those of the smoking populations of the countries in which the study was conducted (USA and Australia)<sup>8,9</sup>.

Approximately half of the subjects in each group completed the study. Although more varenicline- (25.9%) than placebo-treated (10.3%) subjects discontinued participation due to AEs, the median duration of treatment was longer with varenicline. Most subjects reported at least one AE during this 1-year study (96.4% varenicline, 82.5% placebo), predominantly gastrointestinal disorders (71.3% varenicline, 38.1% placebo). AEs (all causality) with the highest incidences in the varenicline group were nausea, abnormal dreams, and insomnia. Other AEs reported for  $\geq 5\%$  varenicline subjects, with an incidence more than twice that of placebo were dyspepsia, vomiting, dysgeusia, and influenza. There were no deaths during the study. One serious AE, bilateral subcapsular cataracts, was attributed to study medication. There were no clinically important hematology or serum chemistry findings and no notable changes in blood pressure, heart rate, or ECG parameters.

Although not an objective of this study, abstinence was assessed at each study visit as a secondary end point. The 7-day point prevalence of abstinence rate with varenicline treatment was never lower than 35.1% after week 2, and was as high as 49% at week 8. In comparison, the 7-day point prevalence of abstinence rate with placebo ranged from 4.8% to 10.3% over the duration of the study. Although the highest response rate achieved with varenicline was not sustained, there did not appear to be any attenuation of effect, as abstinence rates remained relatively consistent, between 35% and 38%, from week 20 until week 53. The pattern of abstinence observed during the first 12 weeks was consistent with the point prevalence rates observed in the varenicline 12-week smoking cessation studies<sup>10,11</sup>.

Other smoking cessation therapies, various NRTs and bupropion, are also available and are generally well-tolerated. The most common AE for the nicotine

transdermal patch are application site reactions, itching, and insomnia. The rate of discontinuation from the nicotine transdermal patch in clinical trials due to poor local skin tolerability has been reported at between 7% and 9%<sup>12</sup>. For nicotine gum, the most common AEs are jaw fatigue and gastrointestinal symptoms<sup>13</sup>, while the nicotine inhaler and spray also cause local irritation<sup>3</sup>. NRTs can sustain tolerance and physical dependence in some users<sup>13</sup>. The most common AEs associated with use of bupropion SR are insomnia and gastrointestinal (dry mouth, nausea, constipation)<sup>14,15</sup>. Bupropion is also associated with a small increase in the risk of seizures<sup>15</sup>.

Comparative data among the available pharmacotherapy agents for smoking cessation is limited. The 7-day point prevalence abstinence rate with varenicline treatment observed in this study was greater than the average reported in a meta-analysis of clinical trial results using NRTs for smoking cessation<sup>16</sup>. This increment in efficacy may be attributable to differences in the mechanism of action of the two therapies. NRTs, by means of the agonist effect of nicotine at the  $\alpha 4\beta 2$  nicotinic acetylcholine receptor, provide relief from withdrawal symptoms and tobacco cravings<sup>3</sup>. Conversely, varenicline was designed as a partial agonist (with agonist and antagonist effects) and may also reduce the rewarding effects of smoking in subjects who lapse during treatment<sup>4,17</sup>.

There are several limitations to this analysis that should be noted. No attempt was made to distinguish between AEs associated with the study drugs and those symptoms that are associated with nicotine withdrawal. For many symptoms, subjective signs of nicotine withdrawal, such as nausea and insomnia, overlap with some of the AEs attributed to study drugs<sup>18,19</sup>. Efficacy studies of 12 weeks' treatment with varenicline have established that varenicline reduces withdrawal symptoms, as measured by the Minnesota Nicotine Withdrawal Scale (MNWS),<sup>10,11</sup> but since the MNWS was not administered during this trial it is not possible to determine the impact of varenicline on withdrawal symptoms or their overlap with reported AEs.

In addition, no statistical analyses were performed to compare varenicline efficacy or safety parameters with placebo. Most efficacy trials of smoking cessation pharmacotherapies use a more conservative measure of abstinence – the continuous abstinence rate over a specified time period – instead of the 7-day point prevalence of abstinence data reported here. In this safety trial, the 7-day point prevalence of abstinence results provide an indication of abstinence and although rates are similar to those observed in other trials of varenicline, it is not possible to draw firm conclusions regarding the efficacy of 52 weeks of treatment of varenicline versus placebo based on the data reported here. Future trials of long-term treatment with

varenicline should evaluate efficacy measures including continuous abstinence rates, craving and withdrawal symptoms, and the reinforcing effects of any cigarettes smoked while on treatment.

## Conclusions

Results of this safety trial indicate that varenicline 1 mg BID can be safely administered for up to 1 year. Gastrointestinal symptoms, insomnia, and abnormal dreams are AEs that occur most frequently. These commonly reported symptoms were rarely rated as severe and infrequently resulted in discontinuation of varenicline. In addition, varenicline was a more effective smoking cessation aid compared with placebo throughout the study duration supporting both its short- (12-week) and long-term (52-week) efficacy.

## Acknowledgments

**Declaration of interest:** Kathryn E. Williams, Karen R. Reeves, Clare B. Billing, Jr, Ann M. Pennington, and Jason Gong are all employees of Pfizer and were involved in designing the study, data monitoring, data management, statistical analysis, and interpretation of the results, as well as the drafting, editing, and reviewing of this manuscript.

The authors would like to thank the study investigators (Dr Daniel E. Bechard, McGuire VA Medical Center, Richmond, VA, USA; Dr Brian T. Brock, Lederach Family Medicine, Harleysville, PA, USA; Dr Clinton N. Corder, COR Clinical Research LLC, Oklahoma City, OK, USA; Dr Daniel S. Fuleihan, Cardiovascular Specialists, PC, DBA-New York Heart Center, Syracuse, NY, USA; Dr Lydia R. Lawson, Lovelace Scientific Resources Incorporated, Albuquerque, NM, USA; Dr Leslie P. Moldauer, Radiant Research, Denver, CO, USA; Dr Anthony D. Puopolo, Milford Emergency Associates Inc, Milford, MA, USA; Dr Anne-Marie Southcott, Queen Elizabeth Hospital, Woodville South, SA, Australia; and Dr Selwyn J. Spangenthal, Charlotte Lung and Health Center, Charlotte, NC, USA) for their valuable contribution to the conduct of the study.

The study was funded by Pfizer (Clinical Trials Identification Number: NCT00143299). Editorial support for the development of this manuscript

was provided by Paul Littlebury, PhD, and Abegale Templar, PhD, at Envision Pharma, and funded by Pfizer.

## References

1. The health consequences of smoking: a report of the Surgeon General. Rockville, MD: US Department of Health and Human Services, Public Health Service, Office of the Surgeon General, 2004
2. The health benefits of smoking cessation: a report of the Surgeon General. Rockville, MD: US Department of Health and Human Services, Centers for Disease Control, 1990
3. Henningfield JE, Fant RV, Buchhalter AR, et al. Pharmacotherapy for nicotine dependence. *CA Cancer J Clin* 2005;55:281-99; quiz 322-3, 5
4. Coe JW, Brooks PR, Vetelino MG, et al. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. *J Med Chem* 2005;48:3474-7
5. Tonstad S, Tonnesen P, Hajek P, et al. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA* 2006;296:64-71
6. Fiore MC, Bailey WC, Cohen SJ, et al. Treating tobacco use and dependence: Clinical practice guideline. Rockville, MD: US Department of Health and Human Services. Public Health Service, 2000
7. Fagerström KO. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. *Addict Behav* 1978;3:235-41
8. Hughes JR. Data to estimate the similarity of tobacco research samples to intended populations. *Nicotine Tob Res* 2004;6:177-9
9. AIHW. 2001 National Drug Strategy Household Survey: Detailed findings. Canberra: AIHW (Drug Statistics Series No.11); 2002. Report No.: cat. no. PHE 41
10. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006;296:47-55
11. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006;296:56-63
12. Abelin T, Ehrsam R, Buhler-Reichert A, et al. Effectiveness of a transdermal nicotine system in smoking cessation studies. *Methods Find Exp Clin Pharmacol* 1989;11:205-14
13. Henningfield JE. Nicotine medications for smoking cessation. *N Engl J Med* 1995;333:1196-203
14. Aubin HJ. Tolerability and safety of sustained-release bupropion in the management of smoking cessation. *Drugs* 2002;62(Suppl 2): 45-52
15. Zyban. Summary of product characteristics. Research Triangle Park, North Carolina, USA: GlaxoSmithKline, 2001
16. Fiore MC, Smith SS, Jorenby DE, et al. The effectiveness of the nicotine patch for smoking cessation. A meta-analysis. *JAMA* 1994;271:1940-7
17. Rollema H, Chambers LK, Coe JW, et al. Pharmacological profile of the alpha4beta2 nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. *Neuropharmacology* 2007;in press
18. Ward MM, Swan GE, Jack LM. Self-reported abstinence effects in the first month after smoking cessation. *Addict Behav* 2001;26:311-27
19. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. Washington: American Psychiatric Association, 1995

CrossRef links are available in the online published version of this paper:

<http://www.cmrojournal.com>

Paper CMRO-3831\_3, *Accepted for publication*: 21 February 2007

*Published Online*: 05 March 2007

doi:10.1185/030079907X182185