A Randomized, Placebo-Controlled Trial of Varenicline, a Selective $\alpha_4\beta_2$ Nicotinic Acetylcholine Receptor Partial Agonist, as a New Therapy for Smoking Cessation in Asian Smokers

Shih-Tzu Tsai, MD[1]; Hong-Jun Cho, MD, PhD[2]; Huey-Shinn Cheng, MD[3]; Cheol-Hwan Kim, MD, PhD[4]; Kuang-Chieh Hsueh, MD[5]; Clare B. Billing Jr., MS[6]; and Kathryn E. Williams, PhD[6]

[1]Department of Community Medicine, Buddhist Tzu Chi General Hospital and Tzu Chi University College of Medicine, Hualien, Taiwan; [2]Department of Family Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [3]Department of Internal Medicine, Chang-Gung Memorial Hospital, Chang-Gung University College of Medicine, Kwei-shan, Taiwan; [4]Department of Family Medicine, InJe University Seoul Paik Hospital, Seoul, Republic of Korea; [5]Department of Family Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; and [6]Pfizer Global Research & Development, Groton, Connecticut

ABSTRACT

Background: Rates of smoking in East Asian men range from >35% to >60%, and are increasing in women and the young.

Objective: This study evaluated the efficacy and tolerability of 1 mg BID varenicline, a novel $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, for smoking cessation in smokers in Taiwan and Korea.

Methods: A randomized, double-blind, placebo-controlled, 12-week treatment, 12-week follow-up trial was conducted at 5 sites each in Korea and Taiwan. Eligible subjects, smoking ≥10 cigarettes/d, received brief smoking-cessation counseling and were randomly assigned in a 1:1 ratio to varenicline 1 mg BID (titrated during the first week) or placebo. Smoking status was established by self-report and confirmed at clinic visits by end-expiratory carbon monoxide ≤10 ppm. The primary end point was continuous abstinence rate (CAR) during the last 4 weeks of treatment. Secondary end points included CAR from weeks 9 to 24 and 7-day point prevalence (PP) of abstinence at weeks 12 and 24. Craving, withdrawal, and smoking satisfaction were determined by the Minnesota Nicotine Withdrawal Scale, the Brief Questionnaire of Smoking Urges, and the modified Cigarette Evaluation Questionnaire. Observed or volunteered adverse-event data were recorded at clinic visits.

Results: Overall, 126 subjects (84.9% male) received varenicline, and 124 (92.7% male) received placebo. Subjects were aged 21 to 73 years (mean age, 39.7 and 40.9 years for varenicline and placebo groups, respectively), and the mean (range) body weights were 69.0 (44.8–110.0) kg and 71.4 (45.5–102.0) kg, respectively. Subjects had smoked for 3 to 52 years (mean, 20.2 and 22.1 years in the varenicline and placebo groups, respectively). Subjects had smoked a mean of 23 cigarettes/d over the past month, with 51.6% (varenicline) and 46.0% (placebo) having made 1 or more prior serious quit attempts. Smoking-cessation rates at the end of treatment were 59.5% with varenicline versus 32.3% with placebo ($P < 0.001$). CARs through 12 weeks post-treatment (weeks 9–24) were 46.8% with varenicline and 21.8% with placebo ($P < 0.001$). The 7-day PP was 67.5% with varenicline versus 36.3% with placebo at week 12, and 57.1% versus 29.0% with placebo at week 24 (both, $P < 0.001$). Treatment-emergent, all-causality adverse events with an incidence ≥5% for

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varenicline were nausea (43.7% for varenicline vs 11.3% placebo), insomnia (15.1% vs 13.7%), increased appetite (7.9% vs 6.5%), constipation (7.1% vs 2.4%), anxiety (5.6% vs 2.4%), and abnormal dreams (5.6% vs 0.8%). Adverse events resulted in <10% treatment discontinuations overall.

Conclusion: Varenicline was an efficacious and well-tolerated pharmacotherapy for smoking cessation in this group of Asian smokers over a 12-week treatment period, and its effects persisted for a further 12-week follow-up period. (*Clin Ther*. 2007;29: online)

Key words: smoking cessation, varenicline, Asian smokers, nicotinic partial agonist.

INTRODUCTION

Tobacco smoking is the most prevalent modifiable risk factor for morbidity and mortality due to cancer, cardiovascular, and respiratory disease.[1] It is estimated that almost 5 million individuals die prematurely of diseases caused by chronic tobacco smoking each year.[2] In Western populations (North America, Western Europe), smoking prevalence varies between <20% to 40% in men and <20% to 30% in women.[2] In contrast, smoking prevalence in East Asians, and in particular East Asian men, ranges from >35% (Vietnam) to >60% (China, Korea, Taiwan).[1-4] Smoking has been claimed to contribute to 30.1%, 37.3%, and 26.7% of all-cause mortality, cancer mortality, and cardiovascular mortality, respectively, in Korean men.[5] In Taiwan, it also accounted for 27% of deaths in men aged between 35 and 69 years in 2001, a figure that is likely to increase even if smoking rates remain at present levels.[6]

Currently available smoking-cessation therapies approved in Taiwan and Korea are limited to sustained-release (SR) bupropion and various forms of nicotine-replacement therapy (NRT).[7,8] Bupropion SR was approved in the United States as a smoking-cessation aid in 1997,[9] and NRT provides an alternative source of nicotine to tobacco and has been found to reduce withdrawal and craving symptoms.[10] However, both agents have limitations. Bupropion is associated with a low incidence (0.1%) of seizures,[11] while adherence to NRT has been reported to be low—only 16% of a sample of 1051 Chinese smokers used NRT for at least 4 weeks.[12] An alternative nonnicotine therapy that directly targets the mechanism believed to underlie the craving, withdrawal, and reinforcement properties of nicotine would clearly benefit Asian smokers wishing to quit.

The reinforcing nature of nicotine is thought to be mediated through activation of nicotinic acetylcholine receptors (nAChR) in the ventral tegmental area of the brain, a region frequently associated with addiction. One of the most abundant mammalian brain nAChRs is the subtype containing $\alpha_4\beta_2$ subunits,[13] and evidence from transgenic animal studies supports the necessary and sufficient role of the $\alpha_4\beta_2$ nAChR in the reinforcing effects of nicotine.[14]

Varenicline, a selective $\alpha_4\beta_2$ nAChR partial agonist, has been developed for smoking cessation.[15,16] The partial agonist properties of the compound may reduce craving and withdrawal symptoms by activating the $\alpha_4\beta_2$ nAChRs, but with a diminished potential for dopamine release in the mesolimbic system (40%–60% of the nicotine response).[16] The antagonist properties of varenicline may reduce the reward experienced by those who relapse back to smoking during therapy, thereby increasing the likelihood of reestablishing abstinence.

In a large (N = 1027), randomized, double-blind, placebo-controlled, 52-week study of smoking cessation conducted in the United States,[17] varenicline 1 mg BID for 12 weeks was associated with significantly improved continuous abstinence rates (CARs) compared with bupropion SR 150 mg BID and placebo. CARs for the last 4 weeks of treatment were 43.9% with varenicline compared with 17.6% for placebo ($P < 0.001$) and 29.8% for bupropion SR ($P < 0.001$). At the end of 1 year of treatment, 23.0% of varenicline-treated smokers remained continuously abstinent compared with 10.3% of the placebo group ($P < 0.001$) and 14.6% taking bupropion SR ($P = 0.004$). A second identically designed study in 1025 subjects showed similar results, with a CAR at treatment end of 44.0% for varenicline versus placebo (17.7%; $P < 0.001$) and bupropion SR (29.5%; $P < 0.001$), and at study end of 21.9% for varenicline versus placebo (8.4%; $P < 0.001$) and bupropion SR (16.1%; $P = 0.057$).[18]

Since more than three quarters of the smokers in these Western trials were of white ethnic origin and <3% were Asian, the properties of varenicline have not been fully evaluated in Asian smokers. This study was designed to assess the efficacy and tolerability of varenicline compared with placebo for smoking cessation in smokers from 2 Asian countries, Taiwan and Korea. Both of these countries have smoking preva-

lence in men >60%[2] and substantial health burden from smoking-related diseases.[5,6]

The primary objective of this study was to assess the CAR during the last 4 weeks of a 12-week period of treatment with varenicline 1 mg BID or placebo. Secondary objectives included measurements of long-term abstinence from smoking during a 12-week non-treatment follow-up period, for a total study duration of 24 weeks, as well as evaluations of nicotine craving, withdrawal, and reinforcement.

SUBJECTS AND METHODS

Study Design

A randomized, double-blind, placebo-controlled, multicenter clinical trial (ClinicalTrials.gov Identification Number: NCT00141167) in Korea (5 sites) and Taiwan (5 sites) was conducted between February 2005 and March 2006. This study was conducted in accordance with the Declaration of Helsinki[19] and in compliance with independent review boards or independent ethics committees, informed consent regulations, and International Conference on Harmonization and Good Clinical Practice Guidelines.[20] In addition, all local regulatory requirements were followed.

Subjects

Male and female smokers aged between 18 and 75 years, who had smoked ≥10 cigarettes/d during the past year, with no period of abstinence >3 months in the past year, and who were motivated to stop smoking were screened and were eligible for inclusion into the study if they met all study entry criteria. Women of childbearing potential were included provided that they were not pregnant or breastfeeding and had agreed to practice effective contraception. Participating subjects were required to give written informed consent and to attend all clinic visits for study assessments during treatment and nontreatment phases. Study exclusion criteria included a past or present history of a serious or unstable clinical disease requiring treatment (including cardiovascular, cerebrovascular, endocrine, gastrointestinal, and pulmonary disease; significant hepatic or renal impairment; and neurologic or psychiatric disorders). Other exclusion criteria were a body mass index <15 or >38 kg/m^2, body weight <45 kg, and a history of drug (except nicotine) or alcohol abuse.

Interventions

Subjects who were qualified to enter the study completed the Fagerström Test for Nicotine Dependence (FTND)[21] at the screening visit, and were scheduled to return between 3 and 14 days later for a baseline visit (week 0). During the baseline visit, subjects set a target quit date (TQD; the date at which subjects were to initiate abstinence from smoking) to coincide with the week-1 visit and received a translated version of an educational booklet on smoking cessation.[22] At baseline and at each subsequent visit during the treatment phase, subjects were provided with up to 10 minutes of counseling, in accordance with a translated version of the 2000 US Agency for Healthcare Research and Quality Guidelines (formerly the US Agency for Health Care Policy and Research).[23]

The varenicline dosage of 1 mg BID was achieved using a titration scheme over the course of 1 week (0.5 mg QD for 3 days followed by 0.5 mg BID for 4 days), with full dosage starting at the end of the first week of dosing. During the treatment phase, subjects made a total of 9 clinic visits (baseline and weeks 1, 2, 3, 4, 6, 8, 10, and 12) for assessments of self-reported smoking or other nicotine use, and smoking-cessation counseling. End-expiratory carbon monoxide (CO) was measured at each clinic visit. In addition, subjects received 5 brief telephone contacts (up to 5 minutes), which included smoking-cessation counseling (TQD + 3 days, weeks 5, 7, 9, and 11). Posttreatment follow-up included 4 further clinic visits (weeks 13, 16, 20, and 24) interspersed with 3 telephone contacts (weeks 14, 18, and 22). The Minnesota Nicotine Withdrawal Scale (MNWS)[24,25] and the Brief Questionnaire of Smoking Urges (QSU-Brief)[26,27] instruments, designed to measure nicotine craving and withdrawal, were self-administered at baseline and weeks 1 to 4, 6, and 12 (and week 13 for MNWS only). Additionally, the modified Cigarette Evaluation Questionnaire (mCEQ),[28,29] designed to assess the rewarding effects of smoking, was completed at weeks 1 to 4 and 6 by individuals who had smoked since their previous visit. All questionnaires had linguistically validated translations into Mandarin Chinese and Korean. Language validation was by consecutive back-and-forth translations by native speakers of the target language who were also fluent in English, with concomitant monitoring of conceptual content. However, the content and factor structure of the translated questionnaires were not independently validated in Taiwan or Korea.

Efficacy Outcomes

Primary End Point

The primary end point was the CAR for weeks 9 to 12, which was defined as no reported smoking (not even a puff) or other nicotine use during the final 4 weeks of treatment, verified by end-expiratory CO levels of ≤10 ppm.

Secondary End Points

Secondary end points included end-expiratory CO-confirmed CAR for weeks 9 to 24, 7-day point prevalence (PP) of abstinence at week 12 and week 24, and analyses of craving, withdrawal symptoms, and reinforcing effects. The 7-day PP at week 12 and week 24 was defined as the proportion of subjects who were continuously abstinent for the 7 days preceding these clinic visits (verified by end-expiratory CO measurements at the clinic visits). The analyses of craving and withdrawal were based on scores on the 9 items of the MNWS, rated on a 5-point scale from 0 (not at all) to 4 (extreme), and the 10 items of the QSU-Brief, rated on a 7-point scale from 1 (strongly disagree) to 7 (strongly agree). The analysis of reinforcement was based on scores on the 11 items of the mCEQ, rated on a 7-point scale of 1 (not at all) to 7 (extremely).

Statistics

An estimated 125 subjects per group was planned to provide ≥99% power to detect a difference in the primary end point between the varenicline and placebo groups at a significance level of 0.05 (assumed odds ratio [OR] of ≥3.7 over placebo rate of 15%).[30] This sample size also provided ≥90% power to detect a difference in CAR through week 24 (assumed OR of 3.6 over placebo rate of 8%). Eligible subjects were randomized, using the method of randomly permuted blocks (block size = 4), and assigned to receive varenicline or placebo in a ratio of 1:1. Investigators obtained subject identification numbers and study drug assignments via a Web- and telephone-based drug-management system that assigned subjects at the baseline visit in the order in which they were deemed eligible for treatment. Knowledge of treatment assignments was withheld from those directly involved with the operation of the study, including study subjects, study investigators and their staffs, and sponsor personnel involved in clinical operations.

Analyses of efficacy were conducted on all subjects who received ≥1 dose, including partial doses, of randomized study medication. Adherence to treatment was checked by counting leftover tablets at weekly clinic visits during the treatment period. Measures of abstinence were treated as binary data and analyzed using a logistic regression model that included treatment and center. Subjects were classified as responders or nonresponders for each parameter and time point, and analyses were of responder rates (n = responders/N = treated). Subjects who dropped out of the study were classified as nonresponders for the remainder of the study. Craving, withdrawal symptoms, and reinforcement measures were treated as continuous data and repeated-measures analyses compared varenicline with placebo over time in a model including the post-treatment measure (ie, MNWS, QSU-Brief, and mCEQ) as the dependent variable, the treatment group as the explanatory variable of interest, baseline measure, center, and visit as covariates, and interaction of treatment by visit. Model estimates of the mean effect were obtained by contrasting the mean of weeks 1 to 6 between drug and placebo.

Tolerability Assessments

Complete physical examinations were conducted at the screening or baseline visit and at week 12. Vital signs and physical measurements were determined either at screening or baseline (height and body temperature) or at all clinic visits in both the treatment and nontreatment follow-up phases (body weight, blood pressure, and heart rate after 5 minutes in the sitting position and after 2 minutes standing, using an automated, semiautomated, or manual sphygmomanometer on the dominant arm). Laboratory tests to determine clinical abnormalities were completed at screening and at the week-12 visit (or at the time of early termination) and included blood chemistry (including measurements of liver function), complete blood count, and urinalysis. A 12-lead electrocardiogram (ECG) was obtained at the screening visit and week 12. All observed or self-reported adverse events (AEs) were recorded on case-report forms and followed up until resolved or to the study end. The severity, duration, date of onset, action taken, and the suspected relationship to study drug of all AEs were recorded at each visit. AEs at any dose that resulted in death, were life-threatening, required hospitalization, or resulted in significant disability were classified as serious AEs.

RESULTS

Subject Disposition

Of the 287 smokers screened, a total of 250 smokers (126 varenicline and 124 placebo) from 10 centers were randomized and treated (**Figure 1**). Of the screened smokers, 37 were found to be noneligible to enter the study on the basis of the study exclusion criteria, particularly having a past or present serious or unstable clinical disease requiring treatment. Study completion rates were 95.2% in the varenicline group and 94.4% in the placebo group. The numbers of subjects discontinuing during the 12-week treatment phase of the study were 4 (3.2%) and 3 (2.4%) in the varenicline and placebo groups, respectively. The reasons for discontinuation were AEs in 2 varenicline subjects, refusal to participate further in 2 varenicline and 2 placebo subjects, and loss to follow-up in 1 placebo subject. The numbers of subjects discontinuing during the 12-week, nontreatment, follow-up phase were 2 (1.6%) in the varenicline group and 4 (3.2%) in the placebo group. The reasons for discontinuation were loss to follow-up for the 2 varenicline subjects and refusal to participate further for the 4 placebo subjects.

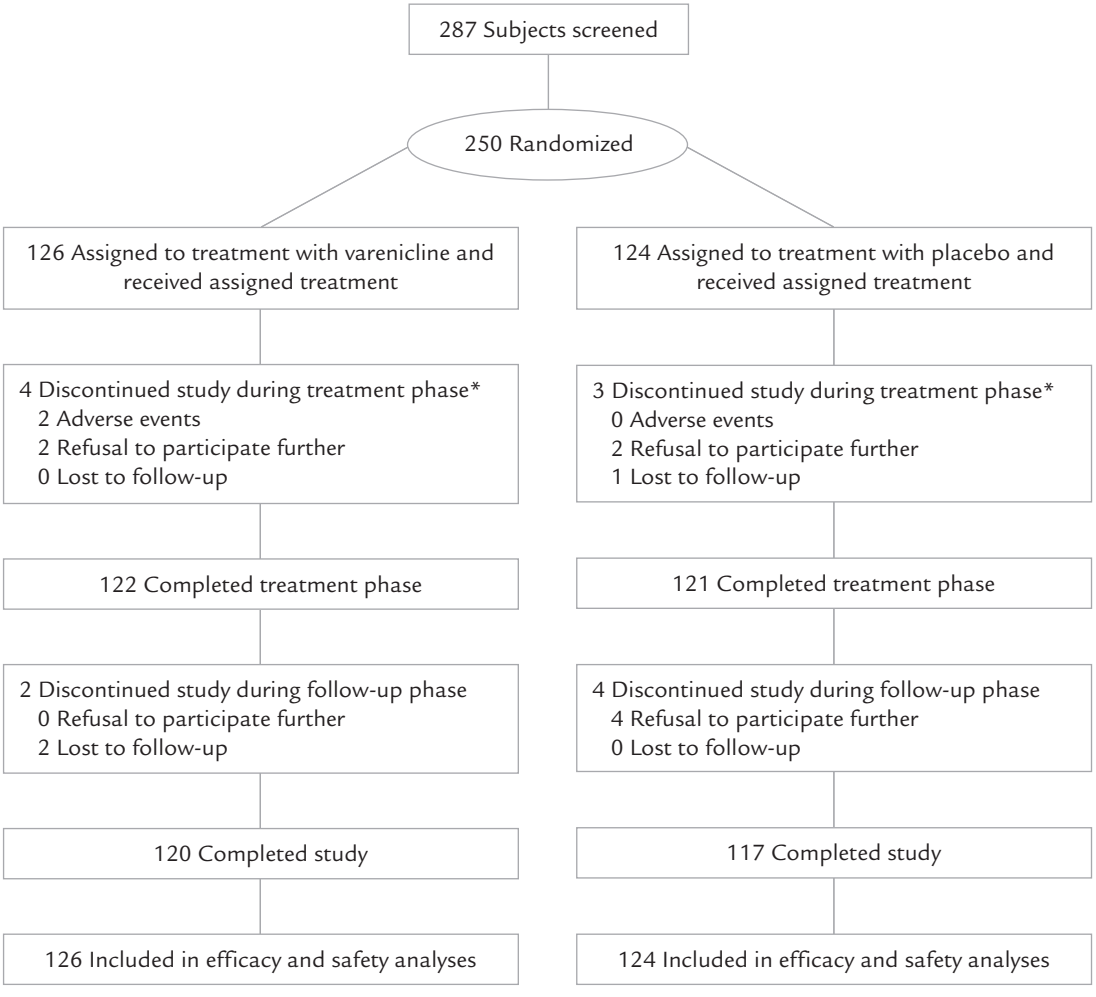

Figure 1. Subject disposition throughout the study. *Subjects could discontinue study medication but remain in the study.

Baseline Characteristics

Treatment groups were similar with respect to baseline demographic characteristics and smoking history (**Table I**). Overall, the majority of the study subjects were male, 84.9% in the varenicline group and 92.7% in the placebo group, while women made up 15.1% of the varenicline group and 7.3% of the placebo group. The mean (range) body weights were 69.0 (44.8–110.0) kg and 71.4 (45.5–102.0) kg, respectively. On the FTND, varenicline subjects had a mean score of 5.2 and placebo subjects a mean score of 5.0 out of a possible total of 10. Although smokers with a past or present serious or unstable clinical disease requiring treatment were excluded from the study, there were nonserious comorbidities recorded among the subjects and the most frequently occurring of these was hyperlipidemia, which was present in 10.3% and 7.3% of the varenicline and placebo groups, respectively.

Primary Efficacy End Point–Continuous Abstinence at Treatment End

The CAR for weeks 9 to 12 (**Figure 2**) was significantly higher with varenicline compared with placebo (59.5% vs 32.3%; OR [95% CI] = 3.22 [1.89–5.47]; $P < 0.001$). Evaluation of an expanded logistics model confirmed no significant treatment-by-center or treatment-by-country interaction, supporting the generalization of the combined results across the 2 countries in which this study was conducted.

Table I. Baseline subject characteristics.

Variable	Varenicline 1 mg BID (n = 126)	Placebo (n = 124)
Sex, no. (%)		
Male	107 (84.9)	115 (92.7)
Female	19 (15.1)	9 (7.3)
Age, y		
Mean (SD)	39.7 (9.3)	40.9 (11.1)
Range	21–62	23–73
Weight, kg		
Mean (SD)	69.0 (11.5)	71.4 (10.5)
Range	44.8–110.0	45.5–102.0
Height, cm		
Mean (SD)	169.4 (7.0)	170.5 (6.5)
Range	153.9–186.5	154.7–189.9
No. of years of smoking, mean (SD)	20.2 (3–45)	22.1 (3–52)
No. of cigarettes/d in past month, mean (range)	23.4 (10–60)	22.7 (10–60)
Prior serious quit attempts,* no. (%)		
None	61 (48.4)	67 (54.0)
1	42 (33.3)	27 (21.8)
≥2	23 (18.3)	30 (24.2)
Longest period of abstinence in past year, mean (range), d	5.5 (0–90)	4.9 (0–90)
Fagerström Test for Nicotine Dependence score,† mean (SD)	5.2 (2.4)	5.0 (2.3)

*Number of quit attempts and/or number of quit methods used.
†Scores range from 0 to 10, with higher scores indicating greater nicotine dependence.

Secondary Measures of Abstinence

Varenicline was also significantly more efficacious than placebo for the CAR for weeks 9 to 24 (46.8% vs 21.8%, respectively; OR [95% CI] = 3.38 [1.91–5.99]; $P < 0.001$), a key secondary end point in this study (**Figure 2**). No significant treatment-by-center or country interaction was detected.

The 7-day PP at the end of treatment (week 12) showed that nearly twice as many subjects in the varenicline group were abstinent in the previous 7 days than in the placebo group (67.5% vs 36.3%, respectively; OR [95% CI] = 3.80 [2.23–6.48]; $P < 0.001$) (**Figure 3**). Similarly, at study end (week 24), 57.1% of varenicline subjects reported abstinence in the previous 7 days compared with 29.0% of the placebo subjects (OR [95% CI] = 3.40 [1.99–5.82]; $P < 0.001$). Rates of 7-day PP were higher for varenicline than for placebo at all assessment points.

Questionnaire-Based Craving, Withdrawal, and Reinforcement Measures

For the MNWS, results of the repeated-measures analysis found that varenicline was associated with a significant reduction in craving compared with placebo, as measured by the Urge to Smoke item (**Figure 4**). For the mean effect over weeks 1 to 6, the least squares (LS) mean difference from placebo was –0.40 (95% CI, –0.57 to –0.23; $P < 0.001$). Differences between varenicline and placebo on the other MNWS subscales (Negative Affect, Restlessness, Insomnia, Increased Appetite) did not reach statistical significance.

Consistent with the MNWS Urge to Smoke measure, varenicline was associated with a significant reduction in craving relative to placebo, as measured by the QSU-Brief total score (**Figure 5**). For the mean effect over weeks 1 to 6, the LS mean difference from placebo was –0.39 (95% CI, –0.60 to –0.17; $P < 0.001$).

In subjects who smoked during treatment, varenicline was associated with a significant reduction in the reinforcing effects of smoking compared with placebo, as measured on the Smoking Satisfaction subscale of the mCEQ (**Figure 6**). For the mean effect over weeks 1 to 6, the LS mean difference was –0.39 (95% CI, –0.67 to –0.10; $P = 0.008$). Differences between the varenicline and placebo groups for the remaining subscales (Psychological Reward, Enjoyment of Respiratory Tract Sensations, Craving Reduction, Aversion), did not reach statistical significance.

Tolerability

The percentage of subjects who experienced all-causality, treatment-emergent AEs in the varenicline

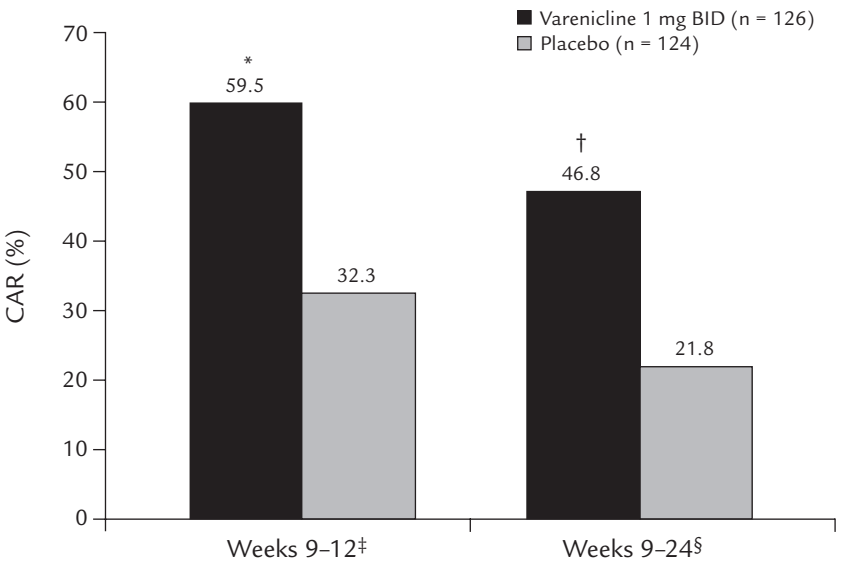

Figure 2. Continuous abstinence rate (CAR). *Odds ratio (95% CI) = 3.22 (1.89–5.47), $P < 0.001$; †odds ratio (95% CI) = 3.38 (1.91–5.99), $P < 0.001$; ‡CAR during last 4 weeks of treatment period; §CAR to end of study (including the last 4 weeks of the treatment period and the 12-week nontreatment follow-up period).

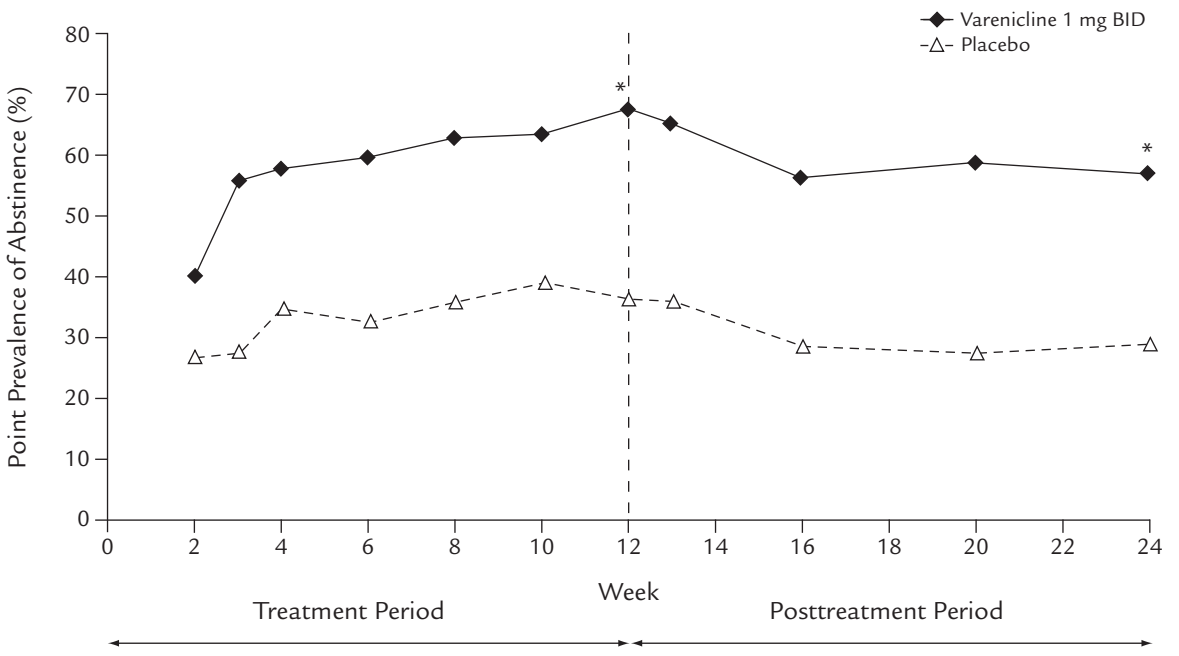

Figure 3. 7-Day point prevalence of abstinence. Subjects who did not provide an assessment at any time point were considered nonresponders for that time point. *$P < 0.001$.

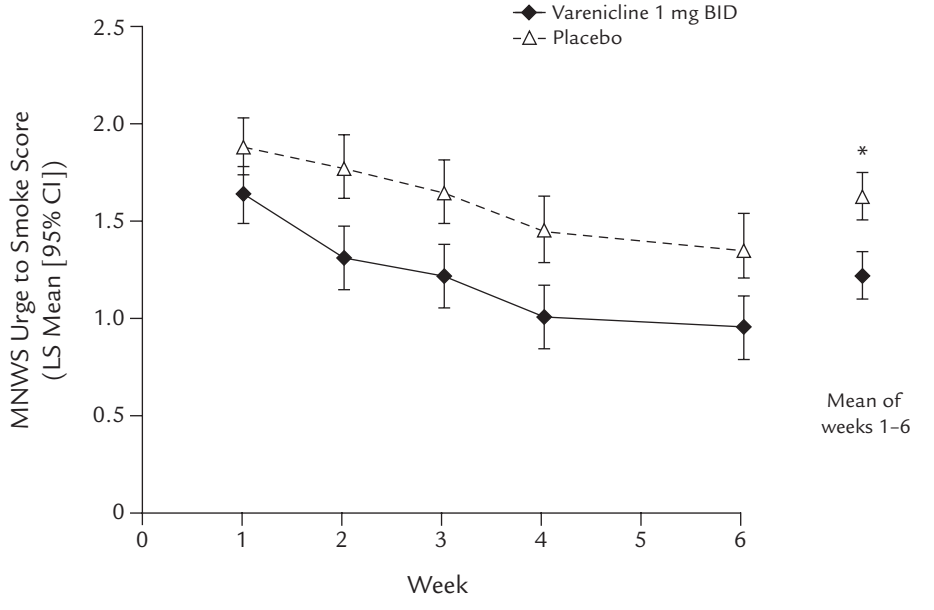

Figure 4. Reduction in craving, as measured on the Minnesota Nicotine Withdrawal Scale (MNWS) Urge to Smoke item. Higher scores indicate greater intensity in the urge to smoke. LS = least squares. *$P < 0.001$.

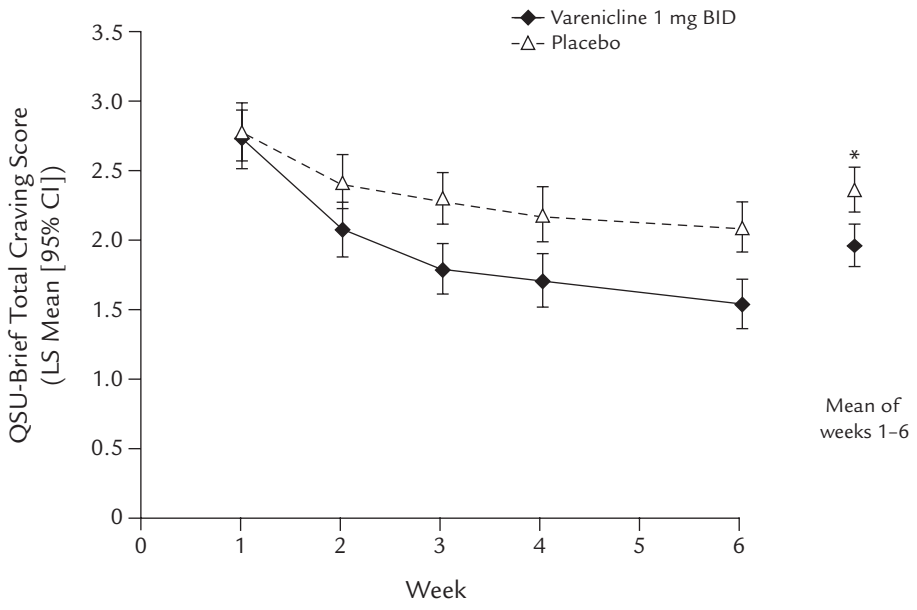

Figure 5. Reduction in craving, as measured using the Brief Questionnaire of Smoking Urges (QSU-Brief) total craving score. Higher scores indicate greater intensity of symptoms. LS = least squares. *$P < 0.001$.

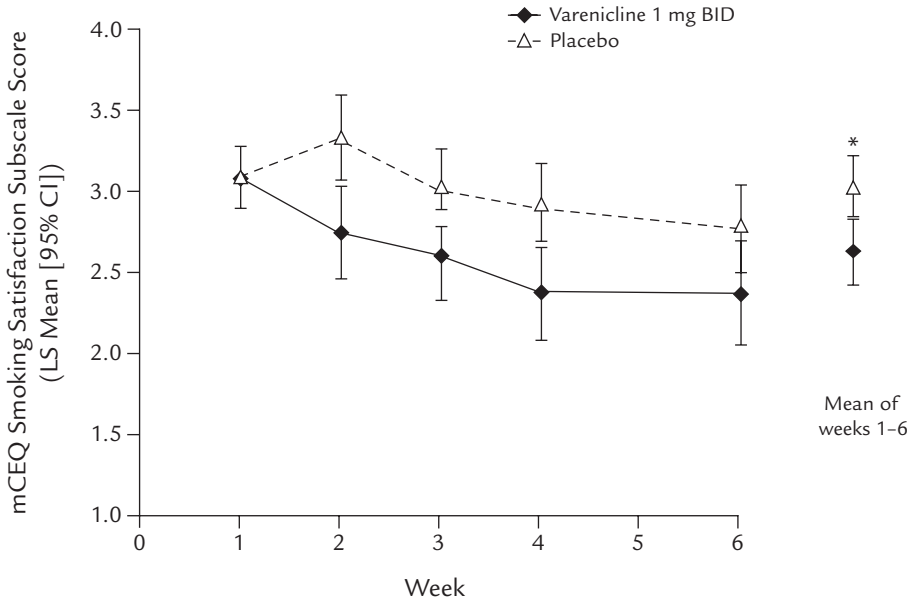

Figure 6. Reduction in reinforcement in subjects who reported smoking since the previous visit, as measured on the Modified Cigarette Evaluation Questionnaire (mCEQ) Smoking Satisfaction subscale. Higher scores indicate greater intensity of smoking satisfaction. LS = least squares. *$P = 0.008$.

group was 86.5% and in the placebo group was 79.0% (**Table II**). AEs occurring in ≥5% of varenicline-treated subjects were nausea (43.7% varenicline vs 11.3% placebo), insomnia (15.1% vs 13.7%), increased appetite (7.9% vs 6.5%), constipation (7.1% vs 2.4%), anxiety (5.6% vs 2.4%), and abnormal dreams (5.6% vs 0.8%), with nausea being the most frequently reported AE with varenicline (**Table III**). AEs were reported to be of mild or moderate intensity, except in 8.7% and 4.8% of the subjects in the varenicline and placebo groups, respectively, who had AEs rated as severe. Nausea (reported as severe by 4 subjects in the varenicline group) was the only AE so rated in >1 subject in either treatment group. In the varenicline group, the other AEs of severe intensity were abnormal dreams, anorexia, anxiety, flatulence, insomnia, nicotine dependence, peritonitis/appendicitis, pyelonephritis, and rash (1 subject each). Eight (6.3%) varenicline-treated subjects and 1 (0.8%) placebo subject permanently discontinued study medication as a result of AEs (**Table II**). In the varenicline group these were moderate constipation and nausea in 1 subject; severe unstable angina in 1 subject; mild ear pain, epigastric discomfort, nausea, and vomiting in 1 subject; moderate nausea with mild headache and insomnia in 1 subject; severe rash in 1 subject; severe peritonitis and appendicitis in 1 subject; severe acute pyelonephritis in 1 subject; and severe flatulence in 1 subject. Moderate somnolence and mild depression were reported in 1 placebo-group subject.

Six subjects experienced serious AEs while receiving treatment or within 28 days of the last dose in this study: 3 in the varenicline group and 3 subjects in the placebo group (**Table II**). One serious AE in the varenicline group was considered possibly treatment related: unstable angina in a 47-year-old man with a history of intermittent chest pain, hypertension, and hyperlipidemia that resulted in varenicline treatment discontinuation on day 53. On investigation the subject was found to have 80% to 90% occlusion of both the left circumflex and right coronary arteries. Other serious AEs in the varenicline group included peritonitis/acute appendicitis and acute pyelonephritis (1 subject each). Serious AEs in the placebo group were all injuries associated with traffic accidents (3 subjects).

Clinically significant elevations in liver function values for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) occurred in 1 varenicline subject (AST and ALT levels on day –5 of 34 and 58 U/L, rising to AST 114 U/L on day 135 and ALT 168 U/L on day 161) and 1 placebo subject (AST and ALT levels on day –7 of 20 and 25 U/L, rising to AST 81 U/L and ALT 160 U/L on day 91). There were no permanent discontinuations of study medication as a result of laboratory test abnormalities, and there were no evident clinically significant changes in vital signs and ECG findings. None of the varenicline subjects had corrected QT (QTc) (Fridericia correction) values >450 milliseconds, and no subjects had QTc increases of ≥60 milliseconds from baseline.

Table II. Summary of treatment-emergent, all-causality adverse events (AEs) (no. [%]).

Variable	Varenicline 1 mg BID (n = 126)	Placebo (n = 124)
Subjects with any AEs	109 (86.5)	98 (79.0)
Treatment discontinuations due to AEs	8 (6.3)	1 (0.8)
Dose reductions or temporary discontinuations due to AEs	14 (11.1)	9 (7.3)
Nonfatal serious AEs*	3 (2.4)	3 (2.4)

*Serious AEs occurring during treatment or within 28 days after the last dose of treatment.

Table III. Treatment-emergent adverse events* occurring in ≥5% of varenicline-treated subjects compared with placebo (no. [%]).

Adverse Event	Varenicline 1 mg BID (n = 126)	Placebo (n = 124)
Nausea	55 (43.7)	14 (11.3)
Insomnia	19 (15.1)	17 (13.7)
Increased appetite	10 (7.9)	8 (6.5)
Constipation	9 (7.1)	3 (2.4)
Anxiety	7 (5.6)	3 (2.4)
Abnormal dreams	7 (5.6)	1 (0.8)

*Defined as adverse events that began or increased in severity during study drug treatment or up to 7 days after the last dose.

Mean (SE) increases in body weight during the 12-week treatment period were 1.17 (0.20) kg in the varenicline group and 0.66 (0.16) kg in the placebo group. As smoking cessation is known to be associated with weight gain, subjects who had been abstinent in weeks 9 to 12 were considered separately, and in these subjects weight gain was similar between the varenicline (1.29 [0.28] kg) and placebo (1.59 [0.27] kg) groups.

DISCUSSION

Varenicline has only recently gained marketing approval in the United States and Europe as well as other countries, and all studies to date have been conducted by the sponsor. Thus, the present study is the first, randomized, double-blind, placebo-controlled study to evaluate the effect of varenicline in conjunction with brief smoking cessation counseling in Taiwanese and Korean smokers. Varenicline was associated with significantly greater CARs from smoking compared with placebo among these Taiwanese and Korean smokers, with approximately doubled quit rates both during weeks 9 to 12, the last 4 weeks of treatment (59.5% vs 32.3%) and for weeks 9 to 24, which included an additional 12 weeks posttreatment (46.8% vs 21.8%).

A limitation of the study design was that inclusion was limited to relatively healthy subjects, excluding smokers with unstable disease or an illness requiring concurrent treatment. Few female smokers were included in the study, although the proportion of women was representative of the female smoking prevalence in these countries. For example, the adult smoking rate in Taiwan (2001) was 4.3% in women and 46.5% in men, with women making up 8.5% of all smokers.[3] In Korea (2001), the smoking rate was 5.4% in women and 61.8% in men, with women making up 8.0% of all smokers.[4] Data from 4 smoking-cessation trials conducted from 1988 to 2000 have suggested that abstinence rates in men and women were not significantly different[31] and varenicline efficacy has been found to be similar in men and women.[17] Although the questionnaires used for assessment of subjective outcomes (eg, MNWS) had linguistically validated translations, the instruments themselves have not been validated in Asian smokers. The study was of 24 weeks' duration, but its outcome was consistent with those of 2 Western studies of 52 weeks' duration.[17,18]

The CARs in both the varenicline and placebo groups were numerically higher in this study than those observed in the comparable Western studies. For example, end-of-treatment CARs were 60% versus 44% for varenicline and 32% versus 18% for placebo.[17,18] However, the treatment effect, as evident from the OR of quitting on varenicline compared with placebo is similar: the OR (95% CI) for the primary end point of CAR for weeks 9 to 12 in this study was 3.22 (1.89–5.47) and the ORs in the Western studies were 3.85 (2.69–5.50)[17] and 3.85 (2.70–5.50).[18] Similarly, for the secondary end point of CAR for weeks 9 to 24, the OR (95% CI) in this study was 3.38 (1.91–5.99) and the ORs in the Western studies were 2.83 (1.91–4.19)[17] and 3.68 (2.42–5.60).[18] Although there is some pharmacogenetic evidence that decreased capacity to metabolize nicotine may play a role in an increased ability to abstain from smoking, it appears unlikely, based on studies in subjects of several ethnicities,[32,33] that there are relevant pharmacogenetic differences between Western and Korean or Taiwanese smokers that would explain the finding of this study. One noteworthy difference with the Western studies is that ~50% of the participants in this present study were making their first serious quit attempt, compared with ~15% making their first serious quit attempt in one of the Western studies.[18] The study retention rate at the 12-week end-of-treatment assessment time point was numerically higher in this study, at >96%, than those in the Western studies (70% and 68%).[17,18]

The results from 3 patient-reported outcome questionnaires, the MNWS, QSU-Brief, and mCEQ, supported a partial agonist–antagonist mechanism of action for varenicline. The craving-reducing effect of varenicline, as evidenced by the significant reductions compared with placebo in both the MNWS Urge to Smoke subscale and the QSU-Brief total craving score, is consistent with an agonist property. The reduction in the smoking satisfaction in subjects who lapsed during the treatment, which is measured by the mCEQ Smoking Satisfaction subscale, is consistent with an antagonist property. Similar effects were observed in the Western studies.[17,18] These results suggest that varenicline may have the potential to improve the likelihood of smokers to permanently abstain from smoking.

Overall, varenicline was generally well tolerated, with 6.3% of subjects discontinuing treatment due to any AE, which is comparable with rates in the Western trials (10.5% and 8.6%, respectively).[17,18]

Mild or moderate nausea was the most common all-causality AE (43.7% and 11.3% in the varenicline and placebo groups, respectively). Despite the reported rate of nausea being numerically higher in this study than in the Western studies (both, ~30%), possibly due to lower baseline body weights (mean body weights of Asian subjects were between 14.5 and 16.5 kg lower than those of the Western subjects), the treatment-discontinuation rates due to nausea were comparable, at ≤3% across the 3 studies. This result implies a favorable tolerability profile of varenicline with regard to AEs in this 24-week study in Taiwanese and Korean smokers.

CONCLUSIONS

The results of this study suggest that varenicline is an efficacious therapy in Taiwanese and Korean smokers motivated to quit smoking. Treatment with varenicline for 12 weeks was associated with improved smoking-abstinence rates measured during the last 4 weeks of treatment, as well as long-term abstinence in a 12-week, nontreatment, follow-up period compared with placebo. Varenicline was generally well tolerated, with mild or moderate nausea as the most common AE.

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Address correspondence to: Hong-Jun Cho, MD, PhD, Department of Family Medicine, Asan Medical Center, University of Ulsan College of Medicine, 388-1, Pungnap-2dong, Songpa-gu, Seoul, 138-736, Republic of Korea. E-mail: hjcho@amc.seoul.kr