Smoking Cessation With Varenicline, a Selective α4β2 Nicotinic Receptor Partial Agonist

Results From a 7-Week, Randomized, Placebo- and Bupropion-Controlled Trial With 1-Year Follow-up

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Background: Currently available smoking cessation therapies have limited success rates. Varenicline tartrate is a novel, selective nicotinic receptor partial agonist developed specifically for smoking cessation. This study evaluated the efficacy, tolerability, and safety of 3 varenicline doses for smoking cessation. Bupropion hydrochloride was included as an active control.

Methods: A phase 2, multicenter, randomized, double-blind, placebo-controlled study of healthy smokers (18-65 years old). Subjects were randomized to varenicline tartrate, 0.3 mg once daily (n=128), 1.0 mg once daily (n=128), or 1.0 mg twice daily (n=127), for 6 weeks plus placebo for 1 week; to 150-mg sustained-release bupropion hydrochloride twice daily (n=128) for 7 weeks; or to placebo (n=127) for 7 weeks.

Results: During the treatment phase, the continuous quit rates for any 4 weeks were significantly higher for varenicline tartrate, 1.0 mg twice daily (48.0%; $P<.001$) and 1.0 mg once daily (37.3%; $P<.001$), than for placebo (17.1%). The bupropion rate was 33.3% ($P=.002$ vs placebo). The carbon monoxide–confirmed continuous quit rates from week 4 to week 52 were significantly higher in the varenicline tartrate, 1.0 mg twice daily, group compared with the placebo group (14.4% vs 4.9%; $P=.002$). The bupropion rate was 6.3% ($P=.60$ vs placebo). Discontinuation owing to treatment-emergent adverse events was 15.9% for bupropion, 11.2% to 14.3% for varenicline, and 9.8% for placebo. No dose-related increases occurred in adverse events for varenicline.

Conclusions: Varenicline tartrate demonstrated both short-term (1 mg twice daily and 1 mg once daily) and long-term efficacy (1 mg twice daily) vs placebo. Varenicline was well tolerated and may provide a novel therapy to aid smoking cessation.

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Group Information: The members of the Varenicline Study Group are listed at the end of this article.

CIGARETTE SMOKING REmains the world's leading cause of preventable death,[1] contributing to 5 million premature deaths in 2000,[2] which is estimated to increase to 10 million by 2020.[1] Surveys show that most smokers want to quit,[3] but most attempts are unaided, with success rates of only 3% to 5% at 1 year.[3] Current pharmacotherapies, such as nicotine replacement therapy (NRT), bupropion hydrochloride, and nortriptyline hydrochloride, have shown moderate success, typically doubling short-term quit rates vs placebo,[4-7] with success at 1 year averaging approximately 7% to 30%, depending on the level of adjunctive behavioral counseling.[8,9] Consequently, additional, more efficacious smoking cessation medications are needed.

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Varenicline tartrate is a novel, nonnicotine agent developed expressly for smoking cessation. It is a selective nicotinic acetylcholine receptor partial agonist that binds specifically at the α4β2 nicotinic receptor subtype.[10] The α4β2 receptor is thought to mediate the rewarding properties of nicotine by modulating the release of dopamine in the nucleus accumbens.[11-13] Cytisine, a plant-derived α4β2 partial agonist used for many years as a smoking cessation aid in eastern Europe,[14] provided a structural starting point for the development of the higher-affinity varenicline. The agonist effect of oral varenicline on dopamine release is 35% to 60% of that observed with nicotine,[10] theoretically sufficient to attenuate craving and withdrawal without producing its own dependence syndrome. The

See also pages 1547, 1553, and 1571

slower release of dopamine with varenicline compared with smoking would also reduce any potential for abuse.[10] Varenicline also has a competitive antagonist effect on nicotine due to a substantially higher affinity for the α4β2 receptor.[10] Starting therapy 1 week before the target quit day could potentially lead to at least partial extinction of smoking behavior by blocking the rewarding effects of smoked nicotine.[15,16] In addition, the blockade of reward could reduce the chance that a "slip" while still undergoing treatment would lead to a full-blown relapse.

The current study was part of a phase 2 program conducted to select the optimal dose for larger-scale, phase 3 studies. The primary objectives were to assess the efficacy, tolerability, and safety of 3 doses of varenicline administered for 6 weeks. A bupropion arm was included as an active control.

METHODS

STUDY DESIGN

This randomized, multicenter, double-blind, parallel-group, placebo- and active-controlled phase 2 clinical trial was conducted at 7 US sites from February 21, 2000, to January 3, 2003. Before the start of the study, a randomization list was computer generated using a method of randomly permuted blocks and a pseudorandom number generator. Investigators assigned medication to subjects in numerical order of acceptance into the study. Randomized subjects received 1 of 3 varenicline tartrate dose regimens (0.3 mg once daily, 1.0 mg once daily, or 1.0 mg twice daily), sustained-release bupropion hydrochloride (150 mg twice daily), or matched placebo. Varenicline doses were selected on the basis of tolerability data from phase 1 studies, and subjects were dosed for 6 weeks, receiving blinded placebo during week 7 to preserve treatment blinding. Bupropion, the primary, non–nicotine-based treatment currently prescribed for smoking cessation, was included as an active control. In accordance with US labeling recommendations, bupropion hydrochloride was dosed for 7 weeks, with titration from 150 mg once daily (days 1-3) to 150 mg twice daily through week 7. All subjects took study medication for 1 week before attempting to quit smoking on day 8 of the study.

During the 7-week treatment phase, subjects visited the study site weekly for efficacy and safety evaluations and up to 10 minutes of standardized, individual smoking cessation counseling from trained staff. Subjects were also given the *Clearing the Air: How to Quit Smoking . . . and Quit for Keeps*[17] smoking-cessation booklet at the baseline visit.

After completing the 7-week treatment phase, subjects had the option to participate in the non–drug treatment phase, which continued through week 52. Continuing subjects had clinic visits at weeks 12, 24, and 52, where vital signs and smoking status were assessed, along with additional brief smoking cessation and relapse prevention counseling. Subjects were also contacted by telephone every 4 weeks beginning with week 16 and assessed for their use of cigarettes, other forms of tobacco, or any other smoking cessation products since the previous study contact.

STUDY POPULATION

Subjects were male and female smokers between 18 and 65 years old who were in general good health as determined by a detailed medical history, limited physical examination, electrocardiogram (ECG), and clinical laboratory tests. Subjects were required to have smoked an average of 10 cigarettes per day during the previous year, without a period of abstinence of more than 3 months. Exclusion criteria were major depression requiring treatment within the past year; history of panic disorder, psychosis, or bipolar disorder; history of anorexia nervosa or bulimia; treatment with bupropion within the past year; history of seizures or cardiovascular disease; uncontrolled hypertension; history of clinically significant allergic, hematologic, renal, endocrine, pulmonary, hepatic, gastrointestinal, or neurologic disease; alcohol or other drug abuse within the past year; or use of NRT within the past 3 months. Subjects who discontinued use of study medication prematurely were allowed to remain in the study.

This study was conducted in compliance with the Declaration of Helsinki. The study protocol and amendments were approved by the institutional review board for each site, and before study entry, all subjects signed informed consent forms approved by the sponsor and the site institutional review board.

EFFICACY ASSESSMENT

Subjects kept daily diaries of the number of cigarettes smoked from baseline through week 7. Exhaled carbon monoxide (CO)levels were measured at each clinic visit through week 52, using a breath CO monitor (Bedfont EC_{50} Micro III Smokerlyzer, Bedfont USA, Medford, NJ). At each clinic and telephone visit beginning with week 1, subjects were asked whether they had smoked in the previous 7 days and since the previous visit.

The primary efficacy measure was the continuous quit rate (CQR) for any 4 weeks, defined as abstinence for any consecutive 28-day period during the treatment phase (determined by diary data). This measure was chosen to give the best possibility of detecting an efficacy signal in this early phase 2 study. Secondary efficacy measures included the CO-confirmed (≤10 ppm) 4-week CQR for weeks 4 to 7, as well as CQRs from week 4 to weeks 12, 24, and 52. Subjects who dropped out for any reason were considered to be smokers at all subsequent time points. Craving was assessed with the urge to smoke item of the Minnesota Nicotine Withdrawal Scale (MNWS)[18] and the 10-item Brief Questionnaire of Smoking Urges (QSU-Brief).[19] Withdrawal was evaluated using the remaining 8 items of the MNWS. The MNWS and QSU-Brief data were collected daily for the first 2 weeks and at each weekly visit through week 7.

The Modified Cigarette Evaluation Questionnaire (mCEQ) assesses the reinforcing effects of smoking through 12 questions that collectively make up 5 subscales: smoking satisfaction, psychological reward, enjoyment of respiratory tract sensations, craving relief, and aversion. Subjects completed the mCEQ daily through week 1 and at each weekly visit through the week 7 visit if they had smoked since the previous visit.[15,20]

Body weight was evaluated at each weekly visit during the treatment phase and summarized separately for smokers and "cessators" (subjects who did not smoke any cigarettes from the target quit date to the day of measurement, based on the daily smoking diary). Inferential analyses were not performed.

SAFETY ASSESSMENTS

Assessments of adverse events (AEs), clinical laboratory measures, vital signs, a 12-lead ECG, and a physical examination were conducted. The AEs were recorded during each weekly visit. Serious AEs were reported from randomization through 30 days after the last dose of study medication. Those AEs that occurred after 30 days were reported if the investigator considered them related to the study medication. Samples for clinical laboratory evaluation were collected at screening, base-

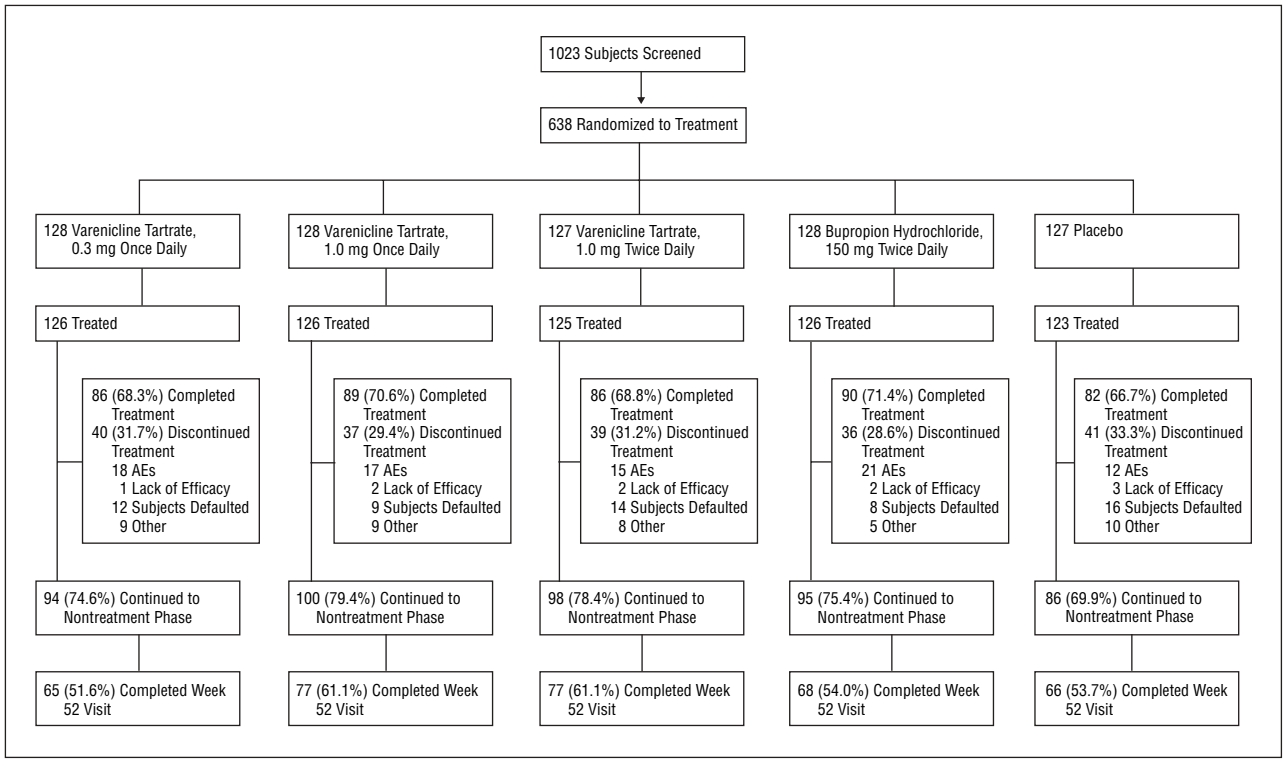

Figure 1. Patient disposition. Adverse events (AEs) were laboratory abnormalities considered AEs and treatment-emergent and non–treatment-emergent AEs. Other indicates protocol violation, subject failed to meet entry criteria, noncompliance, and personal reasons.

line, and weeks 1, 2, 4, 6, and 7. Limited physical examinations were conducted at screening or baseline and at the week 7 visit.

STATISTICAL ANALYSIS

Sample size (approximately 125 per treatment group) was determined by detecting a clinically meaningful difference in response rates for active treatment vs placebo (assuming 38% vs 20%, respectively) on the primary efficacy variable with 80% power ($\alpha = .05$, 2-tailed). Analyses are reported here for the all subjects population (those who reported taking ≥1 dose of study medication) for each treatment group vs placebo. The study was not powered for statistical analyses comparing varenicline with bupropion. All significance tests were 2-tailed using an overall level of significance of $\alpha = .05$. For the primary end point, the Dunnett adjustment for multiple comparisons was used to preserve the family-wise type I error rate at $\alpha = .05$. No adjustments for multiple comparisons were made for secondary end points. Four-week CQRs and other binary response rates were analyzed using a logistic regression model, including treatment and center, and testing was performed with the likelihood ratio χ^2 test. Odds ratios (ORs) and 95% confidence intervals (CIs) reported for each active treatment group vs placebo are the least squares mean estimates from the logistic regression model. For continuous end points (MNWS, QSU-Brief, and mCEQ), inferential analyses were performed using an analysis of variance model, including baseline value of the end point as a covariate and the fixed effects of treatment and center.

RESULTS

SUBJECT DISPOSITION

Subject disposition for the treatment phase is shown in **Figure 1**. A total of 638 subjects were randomized to treatment. Twelve subjects did not take any study medication (2 in each active treatment group, 4 in the placebo group); 626 subjects were therefore included in the all subjects population and evaluated for safety and efficacy. The percentage of subjects who completed 7 weeks of study medication was similar for each group. The most frequent reasons for study discontinuation during the treatment phase were AEs and subject default (ie, withdrew consent, lost to follow-up). Of the subjects treated, 75.6% across treatment groups entered the nontreatment phase. Of those who were continuously quit from weeks 4 to 7, only 1 subject (in the placebo group) did not continue onto the nontreatment phase. Of those in the treatment group, 56.4% completed the week 52 visit.

PATIENT CHARACTERISTICS

Demographic and baseline characteristics for the all subjects population at screening are given in **Table 1**. Smoking history and dependence were similar across treatment groups; subjects represented a population of smokers with a mean consumption of approximately 20 cigarettes per day for an average of 24 years. Forty-four percent had previously used transdermal NRT. The frequency of previous bupropion use ranged from 13.0% to 20.6% across treatment groups.

EFFICACY RESULTS

The 4-week CQRs were significantly higher for varenicline tartrate, 1.0 mg twice daily (48.0%; OR, 4.71; 95% CI, 2.60-8.53; $P<.001$) and 1.0 mg once daily (37.3%; OR, 2.97; 95% CI, 1.63-5.40; $P<.001$), vs placebo (17.1%) and

Table 1. Demographic Characteristics and Smoking History at Screening

Characteristic	Varenicline Tartrate 0.3 mg Once Daily (n = 126)	Varenicline Tartrate 1.0 mg Once Daily (n = 126)	Varenicline Tartrate 1.0 mg Twice Daily (n = 125)	Bupropion Hydrochloride, 150 mg Twice Daily (n = 126)	Placebo (n = 123)
Male, %	50.0	43.7	50.4	45.2	52.0
Age, mean ± SD, y	41.9 ± 10.6	42.9 ± 10.5	41.9 ± 9.8	40.5 ± 10.8	41.6 ± 10.4
White, %	88.1	88.1	85.6	83.3	87.8
Body mass index, mean ± SD*	25.8 ± 4.3	25.8 ± 4.0	25.6 ± 4.1	26.1 ± 4.1	26.5 ± 4.5
Fagerström score, mean ± SD†	5.7 ± 2.1 (n = 125)	5.5 ± 2.0 (n = 123)	5.6 ± 2.0 (n = 122)	5.2 ± 1.9 (n = 126)	5.5 ± 2.3 (n = 120)
Smoking history, mean ± SD, y	24.6 ± 10.9	25.4 ± 11.1	23.4 ± 10.0	23.4 ± 10.9	23.9 ± 10.6
No. of cigarettes smoked per day, mean ± SD	20.3 ± 7.7	20.1 ± 7.8	18.9 ± 6.9	19.5 ± 6.9	21.5 ± 8
Previous serious quit attempts, %					
0	6.3	7.1	4.8	9.5	10.6
≥1	93.6	92.9	95.2	90.5	89.5
Longest period of abstinence in past year, mean ± SD, d	6.28 ± 15.2	6.55 ± 14.6	5.73 ± 12.1	6.46 ± 15.0	7.63 ± 18.5

*Body mass index is calculated as weight in kilograms divided by the square of height in meters.
†Fagerström Test of Nicotine Dependence assesses the severity of nicotine addiction ranging from 0 (minimum dependence) to 11 (maximum dependence).

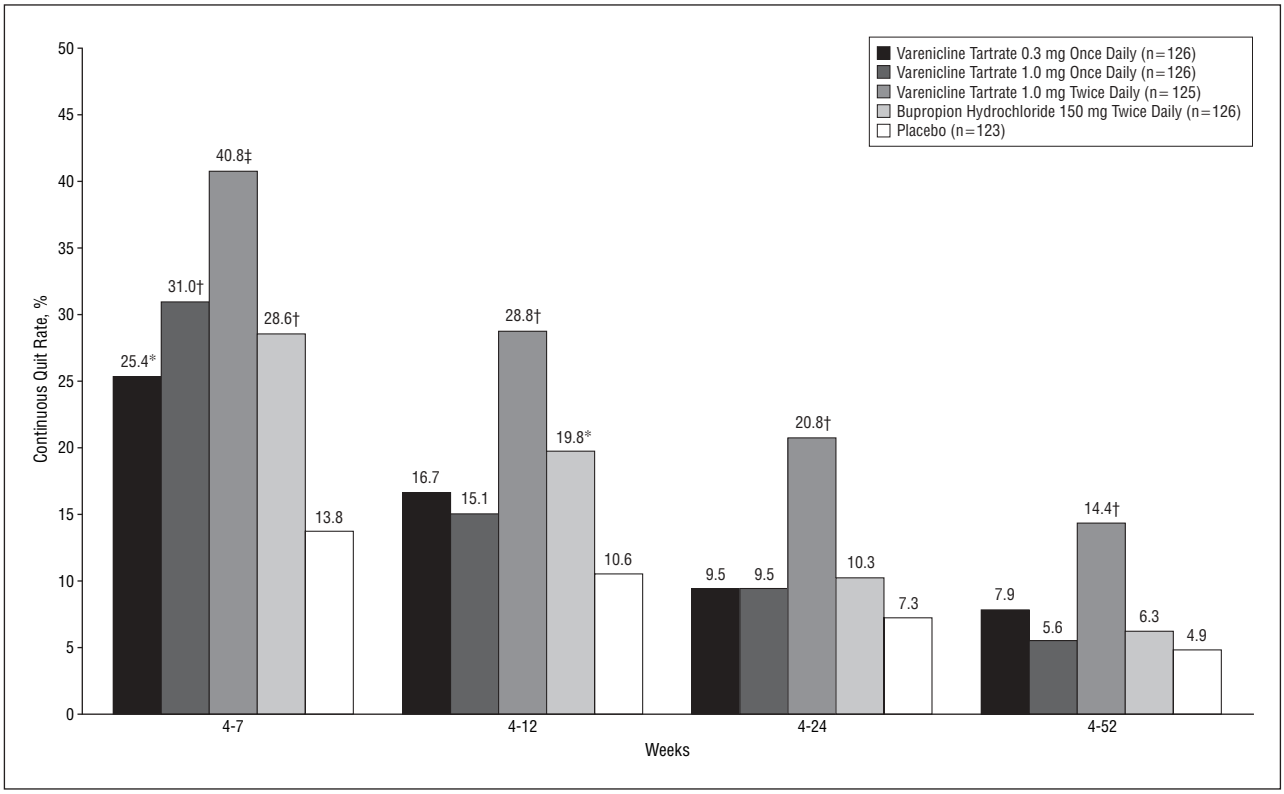

Figure 2. Carbon monoxide–confirmed continuous quit rates for the all-subjects population. *$P \leq .05$. †$P \leq .01$. ‡$P \leq .001$.

for bupropion (33.3%; OR, 2.53; 95% CI, 1.38-4.63; $P = .002$) vs placebo. The response rate increased with increasing dose of varenicline. Although the response rate for varenicline tartrate, 0.3 mg once daily, was numerically higher than placebo (28.6%; OR, 1.97; 95% CI, 1.07-3.65; $P = .03$), it did not reach statistical significance after applying the Dunnett adjustment for multiple comparisons (the Dunnett correction for 4 contrasts vs control requires $P < .015$ for significance at $\alpha = .05$).

Similar results were seen for the CO-confirmed CQRs from weeks 4 to 7, with quit rates increasing with increasing varenicline dose. Quit rates for all 3 varenicline doses and for bupropion were statistically superior to that of placebo (**Figure 2**). Response rates were 3 times greater for varenicline tartrate, 1.0 mg twice daily, vs placebo compared with a bupropion response rate of approximately twice that of placebo.

Figure 2 also shows the rates of CO-confirmed CQRs from week 4 to weeks 12, 24, and 52. The CQRs for the varenicline tartrate, 1.0 mg twice daily, group were significantly higher than that for the placebo group at each time point. By week 52, the response rate had more than

Table 2. Craving Assessments: Mean Change From Baseline to Weeks 1 to 7*

Group	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7†
MNWS item 1‡								
Varenicline tartrate								
0.3 mg (n = 126)	2.7	−0.76	−0.73	−1.15	−1.45	−1.53§	−1.66	−1.53
1.0 mg once daily (n = 126)	2.7	−0.97‖	−1.03§	−1.27§	−1.59§	−1.49	−1.83§	−1.50
1.0 mg twice daily (n = 126)	2.7	−1.14¶	−1.19‖	−1.57¶	−1.81¶	−1.88¶	−2.04¶	−1.61
Bupropion hydrochloride, 150 mg twice daily (n = 126)	2.7	−0.78	−0.88	−1.16	−1.53§	−1.64‖	−1.70	−1.68‖
Placebo (n = 123)	2.6	−0.66	−0.73	−0.95	−1.26	−1.23	−1.51	−1.23
QSU-Brief total score#								
Varenicline tartrate								
0.3 mg (n = 126)	28.8	−5.10	−5.52	−8.08	−10.78	−11.44	−11.59	−11.52
1.0 mg once daily (n = 126)	27.0	−6.30	−9.46§	−10.10§	−11.97	−11.72	−13.04	−13.42
1.0 mg twice daily (n = 126)	28.7	−7.00§	−10.71‖	−12.72§	−14.08‖	−13.24§	−14.94‖	−14.38‖
Bupropion hydrochloride, 150 mg twice daily (n = 126)	26.9	−5.85	−9.18§	−10.51§	−11.91	−13.22§	−13.98§	−14.46‖
Placebo (n = 123)	29.0	−3.91	−6.22	−7.13	−10.28	−10.21	−11.06	−11.36

Abbreviations: MNWS, Minnesota Nicotine Withdrawal Scale; QSU-Brief, Brief Questionnaire of Smoking Urges.

*Mean change is the least squares mean from the analysis of variance model, including baseline value as a covariate and the fixed effects for treatment and center.

†Varenicline groups were not receiving medication for 1 week at the week 7 visit.

‡Each item on the MNWS is rated on a 0 to 4 ordinal response scale (0 indicates not at all; 1, slight; 2, moderate; 3, quite a bit; and 4, extreme).

§$P<.05$.

‖$P<.01$.

¶$P<.001$ for comparison with placebo for changes from baseline.

#In the version of the QSU-Brief used in the present study, subjects rated their strength of agreement with each of the 10 items on a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). The Total Craving Score is created by averaging all 10 items to provide a total urge score. Higher scores indicate greater intensity of the subject's urge to smoke.

Table 3. Modified Cigarette Evaluation Questionnaire Subscales: Mean Change From Baseline to Week 1*

Group	Satisfaction	Psychological Reward	Enjoyment of Respiratory Tract Sensations	Craving Reduction	Aversion
Varenicline tartrate					
0.3 mg (n = 125)					
Baseline	13.0	17.8	2.7	5.1	2.8
Mean change	−3.44	−6.2	−0.51	−1.11	−0.09
1.0 mg once daily (n = 125)					
Baseline	12.6	17.7	2.7	4.9	2.9
Mean change	−3.77	−6.10	−0.74	−1.10	0.42
1.0 mg twice daily (n = 125)					
Baseline	13.1	18.4	2.7	5.2	2.8
Mean change	−4.82†	−6.87	−0.84‡	−1.24	0.82§
Bupropion hydrochloride, 150 mg twice daily (n = 125)					
Baseline	13.1	17.1	2.5	5.1	2.7
Mean change	−4.02	−6.87	−0.60	−1.18	0.00
Placebo (n = 123)					
Baseline	12.9	18.8	2.8	4.9	3.0
Mean change	−3.20	−6.52	−0.55	−1.09	0.03‡

*The modified version of the Cigarette Evaluation Questionnaire has 12 items that are rated on a 7-point scale ranging from 1 (not at all) to 7 (extremely). Higher scores indicate greater intensity of each smoking effect after smoking. Mean change is the least squares mean from the analysis of variance model, including baseline value as a covariate and the fixed effects for treatment and center.

†$P<.001$.

‡$P<.05$.

§$P<.01$ for comparison with placebo for changes from baseline.

tripled. The rate for bupropion was significantly higher than that for placebo only at week 12.

Craving, as assessed with both MNWS item 1 and the QSU-Brief total score, was consistently reduced with varenicline tartrate, 1.0 mg twice daily, compared with placebo, reaching statistical significance at all weekly time points (**Table 2**). Bupropion reduced craving compared with placebo, although the differences reached statistical significance at fewer weekly time points across the 2 instruments. In general, withdrawal symptom scores were mild in all treatment groups, as measured by the composite score for MNWS items 2 to 9, with no clear treatment effect on composite score change from baseline.

Table 3 gives the mCEQ scores by treatment group at week 1, the day before quit day. This time point was chosen because it shows the potential effects of 1 week of receiving treatment while virtually the

Table 4. Incidence of Adverse Events (AEs) Occurring in 10% or More of Any Treatment Group

	Subjects, %				
		Varenicline Tartrate			
COSTART Preferred Term	Placebo (n = 123)	0.3 mg Once Daily (n = 126)	1.0 mg Once Daily (n = 126)	1.0 mg Twice Daily (n = 125)	Bupropion Hydrochloride, 150 mg Twice Daily (n = 126)
Any AE	87.8	90.5	88.1	92.0	89.7
Discontinuations owing to AEs	9.8	14.3	12.7	11.2	15.9
Nausea	18.7	17.5	37.3	52.0	21.4
Insomnia	22.0	19.8	27.0	35.2	45.2
Headache	26.8	27.0	27.0	24.0	30.2
Abnormal dreams	8.1	7.9	11.1	15.2	11.9
Taste perversion	7.3	8.7	14.3	15.2	11.1
Irritability	9.8	11.9	13.5	12.0	11.1
Respiratory tract infection	25.2	25.4	14.3	12.0	15.9
Asthenia	8.1	10.3	7.9	10.4	7.1
Dyspepsia	7.3	7.9	6.3	8.8	11.1
Increased appetite	5.7	14.3	10.3	8.0	7.1
Constipation	4.1	6.3	6.3	5.6	13.5
Dry mouth	5.7	3.2	8.7	5.6	11.9

Abbreviation: COSTART, Coding Symbols for Thesaurus of Adverse Reaction Terms.

entire sample was still smoking. The varenicline tartrate, 1.0 mg twice daily, group demonstrated statistically significant differences from placebo on 3 subscales: smoking satisfaction, enjoyment of respiratory tract sensations, and aversion. The other treatment groups did not show any significant differences on any of the subscales. Interpretation of the aversion subscale may be confounded for varenicline because 1 of the 2 items measures nausea, an AE reported more frequently for patients taking varenicline compared with those taking placebo.

Mean weight gain from baseline to week 7 was generally greater among cessators than smokers. Among cessators, mean weight gain was numerically higher in the placebo group (+4.00 kg, n=10) compared with the active treatment groups: varenicline tartrate, 0.3 mg once daily (+2.47 kg, n=15), 1.0 mg once daily (+2.14 kg, n=14), and 1.0 mg twice daily (+1.96 kg, n=24), and bupropion (+1.68 kg, n=22).

SAFETY AND TOLERABILITY

Table 4 gives the treatment-emergent AEs that occurred in 10% or more of subjects in any of the active treatment groups. Varenicline was safe and well tolerated at all 3 doses. The frequency of discontinuations related to treatment-emergent AEs was lowest among the placebo-treated subjects (9.8%) and highest in the bupropion group (15.9%). In the varenicline treatment groups, the rate of discontinuation due to treatment-emergent AEs does not appear to be dose related. The AEs that occurred most frequently among varenicline-treated subjects were nausea, insomnia, headache, abnormal dreams, and taste perversion. The incidence of these AEs increased with increasing dose, except for headache. Nausea was mild to moderate in severity and typically transitory (median duration ≤12 days), with most episodes beginning within the first week of treatment across all varenicline groups. Discontinuation owing to nausea was low: for varenicline tartrate, 1.6% in the 0.3 mg once daily group, 0.8% in the 1.0 mg once daily group, and 4.0% in the 1.0 mg twice-daily group; for bupropion, 0.8%; and for placebo, 0.0%. Depression was not observed as an AE with varenicline treatment. No deaths occurred during the study. During the treatment phase, only 1 patient in the varenicline tartrate, 1.0 mg twice daily, group experienced a serious AE (transient ischemic attacks in a subject with mild stenosis of the ipsilateral common carotid artery), whereas 4 subjects in the bupropion group experienced serious AEs (persistent intermittent bloody diarrhea, syncope, and convulsion [2 subjects]). All serious AEs were considered by the investigator to be possibly related to the study drug.

Results of clinical laboratory tests, ECGs, and vital signs demonstrated no safety issues of concern. The frequency of clinically significant laboratory test abnormalities was low and similar across all treatment groups.

COMMENT

In this study, varenicline, in combination with brief behavioral counseling, was highly efficacious for short- and long-term smoking cessation compared with placebo. Efficacy improved as the dose increased, with varenicline tartrate, 1.0 mg twice daily, providing the highest rates of continuous abstinence across all treatment groups, including bupropion. Moreover, varenicline tartrate, 1.0 mg twice daily, significantly reduced craving and several aspects of smoking reinforcement compared with placebo, supporting the hypothesized agonist and antagonist qualities of this selective α4β2 nicotinic receptor partial agonist. Varenicline exhibited a good safety and tolerability profile across all doses.

The approximate tripling of response rates observed for varenicline tartrate, 1.0 mg twice daily, compares favorably with previously reported studies for NRT and bu-

propion where brief behavioral counseling was also included. Meta-analyses of NRT typically find a doubling of success rates vs placebo at the end of treatment and at 1 year.[5] Although bupropion exhibited the previously reported doubling of continuous abstinence from weeks 4 to 7,[21-23] why it did not demonstrate significant separation from placebo after week 12 is unclear. One potential limitation was the inclusion of subjects who had been previously exposed to bupropion. Two phase 3 studies[24,25] that included only bupropion-naïve smokers and were appropriately powered to compare varenicline with bupropion have been completed.

Future studies will investigate whether a longer treatment period with varenicline would increase quit rates. In this study, the rate of relapse (smoking ≥1 puff) from week 7 to week 12 for continuous quitters from weeks 4 to 7 was similar for varenicline tartrate, 1.0 mg twice daily (29.3%), compared with bupropion (27.4%) and somewhat greater than placebo (21.4%). Relapse prevention remains a continuing challenge for any smoking cessation treatment.

The patient-reported data from the MNWS, QSU-Brief, and mCEQ support the hypothesis that varenicline's partial agonist and antagonist mode of action would also reduce the craving and the reinforcing effects of smoking. Varenicline tartrate, 1.0 mg twice daily, demonstrated a consistent and significant reduction in craving vs placebo over 2 separate patient-reported assessments. Moreover, although subjects were still smoking during the first week of treatment, only varenicline tartrate, 1.0 mg twice daily, was effective in reducing the reinforcing effects of smoking as measured by the smoking satisfaction and enjoyment of respiratory tract sensations subscales of the mCEQ. These reward blockade effects may promote at least partial extinction of smoking behavior during the prequit period and prevent a postquit slip from providing enough reward to trigger a full-blown relapse. Other novel treatments that combine agonist and antagonist effects are being investigated. Rose et al[15,26,27] have demonstrated that a combination of nicotine and mecamylamine hydrochloride, a nicotine receptor antagonist, can increase smoking abstinence rates. Buprenorphine hydrochloride, an opioid receptor partial agonist, has also demonstrated effectiveness for treating opioid dependence.[28]

Varenicline was safe and well tolerated at all 3 doses. Discontinuation rates for each dose were similar to those seen in the placebo and bupropion groups. Nausea was a frequent AE but was mainly transient and mild to moderate in severity and infrequently led to discontinuation of study medication.

In summary, varenicline is a novel nonnicotine agent designed specifically for smoking cessation. In this study, varenicline tartrate, 1.0 mg twice daily, effectively helped subjects quit smoking, with response rates 3 times higher than those for placebo while demonstrating a good tolerability profile in this population of smokers who on average had smoked approximately 20 cigarettes per day for approximately 24 years. Efficacy was maintained in the non–drug treatment phase through week 52. The significant reductions in craving and in some of the rewarding effects of smoking seen with varenicline tartrate, 1.0 mg twice daily, may assist in promoting abstinence and preventing relapse.

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