Retreatment With Varenicline for Smoking Cessation in Smokers Who Have Previously Taken Varenicline: A Randomized, Placebo-Controlled Trial

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The efficacy and safety of retreatment with varenicline in smokers attempting to quit were evaluated in this randomized, double-blind, placebo-controlled, multicenter trial (Australia, Belgium, Canada, the Czech Republic, France, Germany, the United Kingdom, and the United States). Participants were generally healthy adult smokers (≥10 cigarettes/day) with ≥1 prior quit attempt (≥2 weeks) using varenicline and no quit attempts in ≤3 months; they were randomly assigned (1:1) to 12 weeks' varenicline (*n* = 251) or placebo (*n* = 247) treatment, with individual counseling, plus 40 weeks' nontreatment follow-up. The primary efficacy end point was the carbon monoxide–confirmed (≤10 ppm) continuous abstinence rate for weeks 9–12, which was 45.0% (varenicline; *n* = 249) vs. 11.8% (placebo; *n* = 245; odds ratio: 7.08; 95% confidence interval: 4.34, 11.55; *P* < 0.0001). Common varenicline group adverse events were nausea, abnormal dreams, and headache, with no reported suicidal behavior. Varenicline is efficacious and well tolerated in smokers who have previously taken it. Abstinence rates are comparable with rates reported for varenicline-naive smokers.

Tobacco dependence continues to kill an estimated 5 million tobacco users each year worldwide.[1] Most smokers would like to quit,[2] and many make several quit attempts each year.[3] However, few are able to achieve permanent or long-term abstinence (≥6 months) from smoking with a single quit attempt.[4] This chronic cycling of periods of tobacco use followed by periods of abstinence and periods of relapse[5] in highly dependent smokers has resulted in such tobacco dependence being defined as a chronic disease.[2,6] Treatment guidelines encourage clinicians to prescribe/recommend medications plus counseling for each quit attempt.[6] Repeated medication-assisted quit attempts can result in progressively greater abstinence over time.[5] Even if increasing the frequency of quit attempts per year does not result in long periods of abstinence, these attempts may still be clinically important by reducing exposure to toxicants in tobacco smoke and improving lung function.[4]

In countries with long-standing tobacco control policies and declining prevalence of smoking, an increasing proportion of continuing smokers accessing smoking cessation medications have a history of previous quit attempts with these medications.[7] In medical conditions for which multiple medication options are available for treatment, there may be more flexibility for the clinician to recommend/prescribe a drug different from the one used earlier, but smoking cessation medications approved by national regulatory agencies are generally limited to nicotine replacement therapies (NRTs), bupropion, and varenicline.[6,8–10] Development and approval of new therapies have been slow. The most recent approvals were for bupropion (1997) and varenicline (2006).[11]

Switching from one form of NRT to another,[12,13] or from NRT to bupropion,[14] may increase the likelihood of abstinence with the next quit attempt, but there are few medications to try before retreatment with one of these medications is the only option remaining. There are limited data to guide clinical decisions for subsequent treatments with smoking cessation medications. Long-term abstinence rates (6 months) for previous nicotine patch users retreated with various forms of NRT range from 0 to 6.4%.[15–17] The 6-month abstinence rate for the one bupropion retreatment

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study was 12%.[18] A recent study tested repeated 6-month cycles of treatment with bupropion (7 weeks) or NRT (nicotine patches; 6 weeks) in smokers who failed to achieve abstinence at the end of initial treatment. Abstinence rates measured as 7-day point prevalence at the end of three consecutive retreatment cycles were 12.4, 16, and 15.9%, respectively. The report did not specify whether participants opted for repeated treatment with the same medication for each cycle.[19] Although both NRT and bupropion have been shown to be efficacious for retreatment, abstinence rates are more than threefold lower for NRTs and twofold lower for bupropion compared with initial treatment with those drugs.[6] With the approval of varenicline, an additional medication candidate for retreatment became available, but studies that provide clinician guidance for retreatment have not been conducted. This study evaluates the efficacy and safety of retreatment with varenicline in smokers who had taken varenicline for ≥2 weeks in a previous smoking cessation attempt.

RESULTS

Participant disposition

Of the 593 participants screened, 498 were randomized to varenicline ($n = 251$) or placebo ($n = 247$). A total of 494 participants

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ The majority of smokers seeking cessation treatment make repeated quit attempts, but little evidence-based guidance exists for choosing medications for retreatment.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ Is varenicline effective in smokers who used it in their previous quit attempt but are now smoking again or were unable to stop smoking in their previous attempt?

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ Varenicline is effective and well tolerated in smokers who have previously taken it, generating long-term sustained abstinence rates comparable to rates reported for varenicline-naive smokers.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✓ Clinicians can feel confident in recommending varenicline to patients who have failed to achieve abstinence or relapsed to smoking after their previous treatment with the medication but are open to using it again.

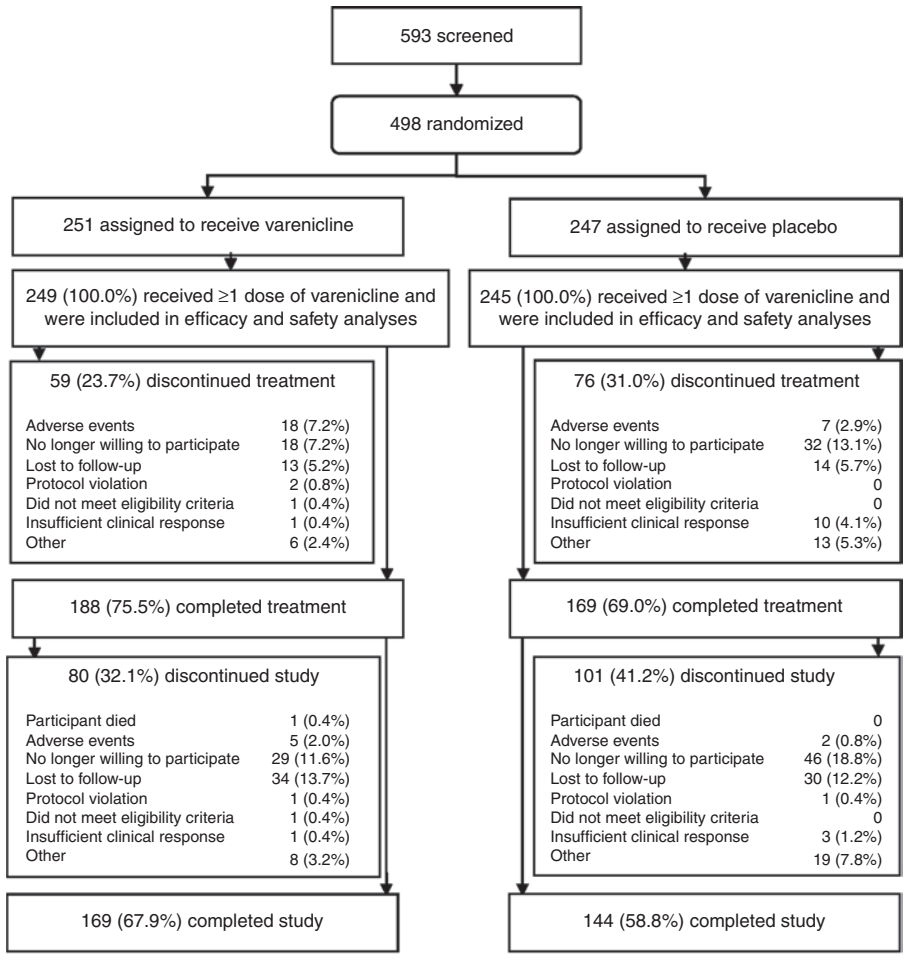

Figure 1 Participant disposition.

Table 1 Participant characteristics at baseline

	Varenicline (*N* = 249)	Placebo (*N* = 245)
Demographic characteristics		
Sex, *n* (%)		
Male	124 (49.8)	121 (49.4)
Female	125 (50.2)	124 (50.6)
Age (years)		
Mean (SD)	47.7 (11.4)	47.3 (11.3)
Range	23–75	20–73
Race, *n* (%)		
White	236 (94.8)	224 (91.4)
Black	10 (4.0)	12 (4.9)
Asian	2 (0.8)	7 (2.9)
Other	1 (0.4)	2 (0.8)
Body mass index (kg/m^2)		
Mean (SD)	27.7 (5.4)	27.3 (5.6)
Range	17.0–47.7	16.8–55.2
Most frequent current medical history, *n* (%)		
Hypertension	36 (14.5)	44 (18.0)
Hypercholesterolemia	36 (14.5)	36 (14.7)
Seasonal allergy	25 (10.0)	24 (9.8)
Smoking characteristics		
Fagerström Test for Nicotine Dependence[a] total score		
Mean (SD)	5.4 (2.0)	5.7 (2.0)
Total number of years subject smoked		
Mean (SD)	30.2 (12.06)	30.0 (11.69)
Average number of cigarettes per day in the past year		
Mean (SD)	19.9 (7.24)	21.4 (7.67)
Longest period of abstinence (days) in the past year		
Mean (SD)	28.6 (53.20)	23.8 (46.68)
Number of serious[b] quit attempts in lifetime, *n* (%)		
Attempts by any method		
One	20 (8.0)	25 (10.2)
Two	37 (14.9)	48 (19.6)
Three or more	192 (77.1)	172 (70.2)
Attempts with varenicline[c]		
One[c]	211 (84.7)	207 (84.5)
Two or more	37 (14.9)	37 (15.1)
Number of serious[b] quit attempts in the past year, *n* (%)		
Attempts by any method		
None	131 (52.8)	124 (50.8)
One	96 (38.7)	99 (40.6)
Two	15 (6.0)	13 (5.3)
Three or more	6 (2.4)	8 (3.3)
Attempts with varenicline		
None	40 (33.3)	30 (24.8)
One	79 (65.8)	90 (74.4)
Two or more	1 (0.8)	1 (0.8)

N, number of participants who received ≥1 dose of study drug, including partial doses; *n*, number of participants with the given characteristic.

[a]The Fagerström Test for Nicotine Dependence has been renamed the Fagerström Test for Cigarette Dependence[20] since this trial was conducted. [b]A serious quit attempt was defined as any attempt lasting >24 h. [c]There was one participant in each treatment arm who had a quit attempt with varenicline, but the attempts were not considered serious quit attempts with varenicline because the participants used two methods concurrently, and the attempts were listed for the other method.

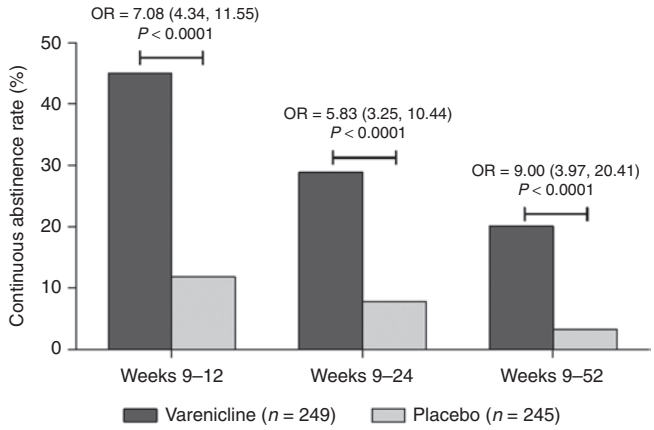

Figure 2 Continuous abstinence rates (CARs), defined as the percentage of participants remaining continuously abstinent from week 9 to each in-clinic visit through week 52. ORs shown are for CAR during weeks 9–12 (primary end point) and for CARs during weeks 9–24 and 9–52 (secondary end points). CI, confidence interval; *N*, number of participants who received ≥1 dose, including partial doses, of randomized study drug; OR, odds ratio.

took at least one dose of varenicline (*n* = 249) or placebo (*n* = 245) and were included in both the main efficacy analyses and the safety analyses. Details of total participant disposition for the trial are provided in **Figure 1**.

Baseline characteristics

Participant baseline characteristics were similar for the two treatment groups (**Table 1**). Overall, 93% of participants were Caucasian, mean age was 47.5 years, participants had smoked a mean of 20 cigarettes/day for an average of 30 years, and mean Fagerström Test for Nicotine Dependence (now known as the Fagerström Test for Cigarette Dependence)[20] scores were 5.6. Most participants (74%) reported three or more previous lifetime attempts to quit smoking, and all had made one or more quit attempts with varenicline.

Efficacy

The following results are for those participants who took at least one dose of study drug (varenicline *n* = 249; placebo *n* = 245). Participants retreated with varenicline had significantly greater continuous abstinence rates (CARs) than those treated with placebo for weeks 9–12 (45.0 vs. 11.8%; odds ratio (OR) = 7.08 (95% confidence interval (CI): 4.34, 11.55), $P < 0.0001$), weeks 9–24 (28.9 vs. 7.8%; OR = 5.83 (95% CI: 3.25, 10.44), $P < 0.0001$), and weeks 9–52 (20.1 vs. 3.3%; OR = 9.00 (95% CI: 3.97, 20.41), $P < 0.0001$; **Figure 2**). For the primary end point of CAR for weeks 9–12, there was no interaction effect of treatment by pooled study center ($P = 0.8407$).

The CARs for weeks 9–12 for all the randomized (intent-to-treat) population were 44.6% for varenicline vs. 11.7% for placebo (OR = 6.96 (95% CI: 4.27, 11.33), $P < 0.0001$) and for the completers population (participants with >80% compliance with study medication), they were 56.4% for varenicline vs. 15.4% for placebo (OR = 8.99 (95% CI: 5.16, 15.67), $P < 0.0001$; **Supplementary Table S1** online). More participants in the varenicline group (77.7%) vs. the placebo group (70.9%)

Table 2 Participants with adverse events occurring in ≥5% of either treatment group

	Varenicline (*N* = 249)	Placebo (*N* = 245)	Risk difference	95% confidence interval	
	n (%)	*n* (%)		Lower limit	Upper limit
Participants with ≥1 adverse event	188 (75.5)	155 (63.3)			
Participants with:					
Nausea	66 (26.5)	22 (9.0)	0.8867	0.5685	1.2048
Abnormal dreams	36 (14.5)	8 (3.3)	0.4680	0.2610	0.6749
Headache	26 (10.4)	24 (9.8)	0.0119	−0.2085	0.2324
Nasopharyngitis	19 (7.6)	17 (6.9)	0.0124	−0.1676	0.1923
Upper respiratory tract infection	19 (7.6)	17 (6.9)	0.0131	−0.1661	0.1924
Insomnia	17 (6.8)	10 (4.1)	0.1002	−0.0552	0.2556
Diarrhea	15 (6.0)	10 (4.1)	0.0657	−0.0831	0.2145
Constipation	13 (5.2)	7 (2.9)	0.0864	−0.0464	0.2193
Fatigue	13 (5.2)	6 (2.4)	0.1011	−0.0277	0.2299
Sleep disorder	13 (5.2)	5 (2.0)	0.1176	−0.0074	0.2427

Risk difference is computed as varenicline vs. placebo and is in subject-year units. 95% Confidence intervals are not adjusted for multiplicity and are provided to help gauge the precision of the estimate for risk difference and should be used for estimation purposes only. Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA; v15.1; http://www.meddra.org/). AEs were reported during treatment plus 30 days.

N, number of participants who received ≥1 dose, including partial doses, of randomized study drug. Treatment-emergent adverse events are defined as those occurring from the date of first dose of study drug until 30 days after the date of the last dose of study drug.

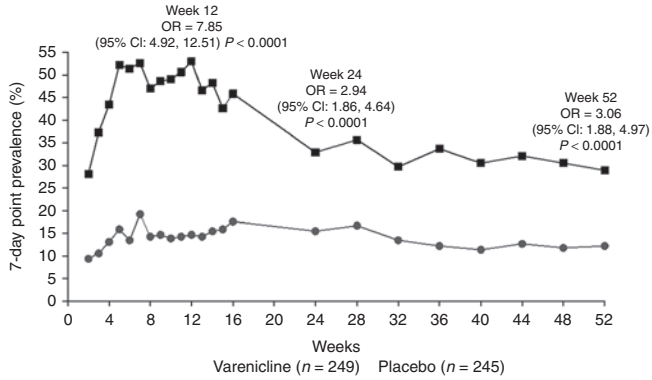

Figure 3 Mean 7-day point prevalence of abstinence, defined as the percentage of participants remaining abstinent from cigarette smoking and use of other nicotine and/or tobacco products in the previous 7 days. CI, confidence interval; *N*, number of participants who received ≥1 dose, including partial doses, of randomized study drug; OR, odds ratio.

complied with study medication (i.e., received any dose of study drug for >80% of the planned number of days in the study), and the median duration of treatment was 84 days in both treatment groups.

The primary efficacy end point of CAR for weeks 9–12 was further examined in exploratory subgroup analyses controlling separately for smoking cessation history and baseline characteristics. The analysis model included the main effect of treatment, one covariate (including one of the subgroup characteristics in the model separately), and the treatment by covariate interaction effect. There were no significant treatment by subgroup interactions in this exploratory analysis (all $P > 0.09$), and results can be generalized to all subgroups. CARs are listed by subgroup in (**Supplementary Table S2** online).

In addition, the 7-day point prevalence abstinence rate was significantly higher for varenicline vs. placebo at week 12 (53.0 vs. 14.7%; OR = 7.85; 95% CI: 4.92, 12.51; $P < 0.0001$), week 24 (32.9 vs. 15.5%; OR = 2.94; 95% CI: 1.86, 4.64; $P < 0.0001$), and week 52 (28.9 vs. 12.2%; OR = 3.06; 95% CI: 1.88, 4.97; $P < 0.0001$).

Safety and tolerability

Adverse events (AEs) were similar to those reported in previous varenicline trials of participants who were naive to varenicline. AEs occurred in 188 (75.5%) of those retreated with varenicline and in 155 (63.3%) of those treated with placebo and were generally mild or moderate in both groups. The numbers of treatment discontinuations due to AEs were 18 (7.2%) and 7 (2.9%) for varenicline and placebo, respectively. Dose reductions or temporary discontinuations were 31 (12.4%) for varenicline and 11 (4.5%) for placebo. Common AEs occurring in ≥5% of those receiving varenicline vs. placebo were nausea (26.5 vs. 9.0%), abnormal dreams (14.5 vs. 3.3%), and headache (10.4 vs. 9.8%; Table 2). One cardiac AE (palpitations) occurred in one (0.4%) varenicline participant. Six cardiac AEs occurred in four (1.6%) placebo participants: acute coronary syndrome, angina pectoris, coronary artery disease, congestive cardiac failure, and palpitations (two participants).

The most frequent treatment-emergent psychiatric AEs, occurring in ≥2% of varenicline vs. placebo participants, were abnormal dreams (14.5 vs. 3.3%), insomnia (6.8 vs. 4.1%), sleep disorder (5.2 vs. 2.0%), depressed mood (3.2 vs. 0.4%), agitation (2.0 vs. 0.4%), depression (2.0 vs. 0.8%), and nightmare (2.0 vs. 0.8%). Suicidal ideation was reported on the Columbia Suicide Severity Rating Scale (C-SSRS)[21] for three (1.2%) varenicline and no placebo participants during the treatment phase and for two (1.2%) varenicline and no placebo participants during follow-up. Of the three varenicline participants with suicidal ideation during the treatment phase, one had a positive lifetime history on the C-SSRS. Similarly, one of the two varenicline participants with suicidal ideation during the nontreatment follow-up period had a lifetime history of self-injurious behavior on the C-SSRS. At baseline, no participant in either group had any suicidal behavior or ideation. There were no reports of suicidal behavior on the C-SSRS during drug treatment or follow-up phases for either group. No AEs related to suicidal ideation or behavior were reported.

Treatment-emergent serious AEs (SAEs) were reported for 7 (2.8%) varenicline participants: knee arthroplasty, pyelonephritis, intervertebral disc protrusion, ankle fracture, chest pain, and drug hypersensitivity (1 reaction to amoxicillin and 1 reaction to hair dye). For placebo, 4 (1.6%) treatment-emergent SAEs were reported: acute coronary syndrome, ligament rupture,

hyperventilation, and drug hypersensitivity. Of these, only chest pain reported in one varenicline participant (day 1 of dosing) was attributed to study drug. During post-drug follow-up, one death was reported for one varenicline participant (~31 weeks after the last dose of study drug). The cause of death on the death certificate was recorded as acute and chronic alcoholism. Death was not attributed to the study drug.

DISCUSSION

In this first randomized trial of retreatment with varenicline for smoking cessation, varenicline was shown to be efficacious. The end-of-treatment CAR for varenicline (45%) was more than 3.8 times greater than that for placebo (11.8%) for both men and women. AEs reported were consistent with those reported in the varenicline label,[22] and no suicidal behaviors were reported. Abstinence rates are consistent with varenicline abstinence rates across previous studies in diverse and varenicline-naive populations (**Supplementary Table S3** online)[23–36] and are in contrast to the lower retreatment abstinence rates with NRTs[15–17] and bupropion.[18]

The relapse curve after varenicline retreatment was similar to relapse curves observed in other trials that have included supportive counseling.[15–18,23] Seven-day point prevalence abstinence rates were significantly greater for varenicline vs. placebo at all points. Abstinence peaked for varenicline at week 12 (last week of dosing) and then declined steadily to week 52, as observed in treatment-naive trials. Placebo point prevalence rates peaked earlier, at week 7, and remained somewhat flat until the end of the study (**Figure 3**). The varenicline CAR was sixfold greater than that for placebo at 52 weeks. Our data suggest that although retreatment with varenicline is effective in attaining and maintaining smoking abstinence (remission), the risk of relapse and the need for additional courses of treatment will likely continue for many chronic smokers. This retreatment paradigm provides an additional treatment approach to that provided by varenicline maintenance therapy, which extends continuous varenicline treatment from 3 to 6 months to aid in maintaining abstinence.[34]

The study posed some unique challenges. All participants had earlier exposure to the medicine being investigated. Participants and site staff were not encouraged to guess treatment assignments, but some participants may have assumed that they were assigned placebo based on earlier varenicline experience and, consequently, discontinued study participation. However, the completion rate for placebo participants was similar to placebo completion rates for varenicline-naive participants in approval or pivotal trials.[23,24] Because the trial recruited smokers who were willing to try varenicline again, our results may not be generalizable to all smokers who have tried varenicline previously.

This study has several strengths. The trial was designed to answer practical clinical questions about retreating patients with varenicline. Participants were generally healthy, but there were fewer exclusions for cardiovascular disease and cancers, resulting in a somewhat more diverse population than in pivotal varenicline trials.[23,24] Although the study was not designed to assess the efficacy or safety of varenicline in smokers with a current psychiatric diagnosis, additional assessments to ensure participant safety and collect uniform data regarding suicidal ideation and behavior were conducted.

In summary, varenicline is efficacious and well tolerated in smokers who have previously taken varenicline. Clinicians can feel confident in recommending varenicline for patients who have failed to achieve abstinence or relapsed to smoking after previous treatment with varenicline.

METHODS

Study design. This was a phase IV, double-blind, placebo-controlled, randomized, parallel-group, two-arm, multicenter clinical study with a 12-week drug treatment phase and a 40-week postdrug treatment follow-up phase. The trial was conducted in accordance with the Declaration of Helsinki[37] and the International Conference on Harmonisation Good Clinical Practice Guidelines[38] between 10 December 2010 and 2 November 2012 in Australia (four centers), Belgium (four centers), Canada (four centers), the Czech Republic (three centers), France (three centers), Germany (five centers), the United Kingdom (five centers), and the United States (seven centers). The institutional review board and/or independent ethics committee at each site approved the study protocol. Written informed consent was obtained from all participants before any procedures were performed.

Setting and participants. Eligible participants were 18 years of age or older, smoked 10 or more cigarettes/day during the 4 weeks before screening, had an exhaled carbon monoxide (CO) value >10 parts per million (ppm) at screening, had no quit attempts in the previous 3 months, had previously taken varenicline for 2 or more weeks, with the last dose taken ≥3 months before screening, and were motivated to stop smoking. Participants were recruited via advertising and patient lists. Key exclusion criteria included any previous significant adverse reaction to varenicline; previous participation in a varenicline study, severe chronic obstructive pulmonary disease; recent (<5 years) history of cancer (except cured basal cell or squamous cell carcinoma of the skin); clinically significant cardiovascular disease or cerebrovascular disease in the previous 2 months; history of a suicide attempt or any suicidal behavior in the past 2 years or current suicidal ideation identified by the C-SSRS[21] at screening or baseline; current depression self-reported at screening or with a diagnosis of depression or treatment with antidepressants during the previous 12 months recorded in medical history; lifetime diagnosis of psychosis, panic disorder, other anxiety disorders, or bipolar disorder; active alcohol or substance abuse/dependence (except nicotine) within the past 12 months; or any severe medical or psychiatric condition or laboratory abnormality that would make the participant inappropriate for the study. Additional exclusions included use of NRT, bupropion, or other smoking cessation aids during treatment; use of investigational drugs in the 30 days before the baseline visit and during the study; and use of other tobacco products, electronic cigarettes, marijuana, or illegal or street drugs at any time during the study (those who used tobacco products, marijuana, or street drugs during the study were instructed not to, but were not discontinued from the study; a protocol deviation was recorded for such use). Women of childbearing potential were included provided that they were not pregnant or breastfeeding and agreed to avoid pregnancy and practice effective contraception from the start of the study drug treatment through 30 days after the last dose of the study drug.

Interventions and follow-up. Eligible participants were randomly assigned to receive either varenicline or placebo at a 1:1 ratio for 12 weeks of drug treatment using computer-generated block randomization within each site. Dosing was titrated: 0.5 mg/day for days 1–3, 0.5 mg twice daily for days 4–7, and 1 mg twice daily through the end of week 12. Compliance with dosing was obtained by pill counts and participant self-report at each visit during the drug treatment period.

Participants were then followed in a 40 week nondrug follow-up phase. Clinic visits were at screening, baseline, and weeks 1, 2, 3, 4, 6, 8, 9, 10, 11, and 12 during drug treatment; and at weeks 13, 16, 24, 32, 40, 48, and 52 during follow-up. Brief telephone visits occurred at weeks 5, 7, 14, 20, 28, 36, and 44. Individual counseling (≤10 min) based on the US Agency for Healthcare Research and Quality guideline[6] was provided to all participants at clinic and telephone visits, beginning with the baseline visit, to assist in developing coping strategies for achieving and maintaining abstinence. Participants were to set a target quit date to coincide with the week 1 visit. Dosing could be reduced to 0.5 mg twice daily for participants who were unable to tolerate the recommended dose. Those who discontinued the study drug were encouraged to remain in the study and complete the remaining visits.

Suicidal ideation and behavior were assessed with the Suicidal Behaviors Questionnaire–Revised (SBQ-R)[39] at screening and the C-SSRS[21] at screening and at each clinic visit. No other standard psychiatric assessments were conducted by sites. Additional safety assessments were required for participants who were considered at risk based on their responses on the C-SSRS.

Efficacy measures. Smoking abstinence was assessed by self-report of no smoking (not even a puff) and no use of nicotine-containing products since the last study visit/last contact, confirmed by an exhaled CO value of ≤10 ppm at clinic visits. The primary efficacy end point was the CO-confirmed CAR for the last 4 weeks of treatment (weeks 9–12). The key secondary efficacy end point was CO-confirmed CAR for weeks 9–52. Other secondary end points were CO-confirmed CAR for weeks 9–24 and 7-day point prevalence abstinence (report of no smoking, not even a puff, for the previous 7 days) at weeks 12, 24, and 52.

AEs. All observed or participant-reported AEs were recorded in electronic case report forms and followed to resolution or to the end of the study. AEs that were determined to be life threatening, that resulted in death, hospitalization, significant disability/incapacity, or a congenital anomaly/birth defect, or that were considered important medical events were classified as SAEs. Summaries of AEs include events of all causalities that occurred during treatment and up to 30 days after treatment.

Statistical analysis. The primary efficacy (CAR weeks 9–12) and safety analyses were performed on the all-participants population, which included all randomized participants who took ≥1 dose of study drug, including partial doses. Additional analyses of CAR at weeks 9–12 were performed for the all-randomized (intent-to-treat) population and the completers population (participants with >80% compliance with study medication, as measured by having any dose of study drug for >80% of the planned number of days in the study) (**Supplementary Table S1** online). A sample size of 490 participants randomized to varenicline or placebo in a 1:1 ratio was estimated to provide ≥90% power for a comparison of varenicline vs. placebo using a two-group continuity-corrected two-sided χ^2 test at the 0.05 significance level for the primary end point (CAR for weeks 9–12), assuming an OR of 3.36 with a placebo CAR of 12% and a varenicline CAR of 31%. It was also estimated to provide 80% power for the treatment comparison in the key secondary end point (CAR for weeks 9–52) for an OR of at least 2.55 with a 6% CAR in the placebo group and 14% in the varenicline group.

In the case of a missed visit or visits during the primary evaluation period (weeks 9–12), a participant was defined as abstinent if the participant reported no smoking or use of nicotine products "since the last contact/visit" at the visit after the missing visit or visits. Missing CO measurements were imputed as negative (i.e., as ≤10 ppm), therefore not disqualifying the participant from being considered abstinent. However, those who missed all visits during weeks 9–12 were considered smokers. Numbers of participants with missing CO measurements during weeks 9–12 are shown (**Supplementary Table S4** online).

Participants who discontinued the study were assumed to be smokers from the point of discontinuation through the end of the study. In computing abstinence rates, those who discontinued the study were included in the denominator, but not in the numerator, regardless of their last smoking status evaluation.

CARs for weeks 9–12, 9–24, and 9–52, and 7-day point prevalence abstinence at weeks 12, 24, and 52 were analyzed using a logistic regression model that included treatment and pooled study center as independent variables. Small study centers were pooled for model convergence. The final analysis results were based on the main effects model, regardless of the statistical significance of the treatment by pooled study center interaction.

For the C-SSRS, percentages of participants with "yes" answers for the Columbia Classification Algorithm of Suicide Assessment categories[21] were calculated for screening (lifetime), baseline, and treatment phase (and 30 days after), and during follow-up (post-treatment) and by treatment group.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

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AUTHOR CONTRIBUTIONS

D.G., P.H., L.P., K.N., L.-J.T, T.D.M., and J.T. wrote the manuscript. D.G., P.H., and J.T. designed the research. D.G., P.H., L.P., K.N., L.-J.T, T.D.M., and J.T. analyzed the data.

CONFLICT OF INTEREST

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