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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Chantix® / Champix® / Varenicline Tartrate

PROTOCOL NO.: A3051075

PROTOCOL TITLE: A Phase 4, Multi-National, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Varenicline Compared to Placebo for Smoking Cessation Through Reduction

Study Center: A total of 61 centers took part in the study and enrolled subjects; 12 in the United States (US), 7 each in Taiwan and the United Kingdom (UK), 6 each in Canada, the Czech Republic, Germany, and Japan, 4 each in Australia and Mexico, and 3 in Egypt.

Study Initiation and Final Completion Dates: 19 July 2011 to 12 July 2013

Phase of Development: Phase 4

Study Objectives:

Primary Objective: To compare the efficacy of varenicline to placebo for smoking cessation during the last 10 weeks of treatment in subjects who were not willing/able to make an abrupt quit attempt but were willing to reduce their smoking with the ultimate goal of quitting.

Secondary Objective: Comparison of varenicline to placebo during the last 4 weeks of treatment and through the longer term follow-up phase to Week 52.

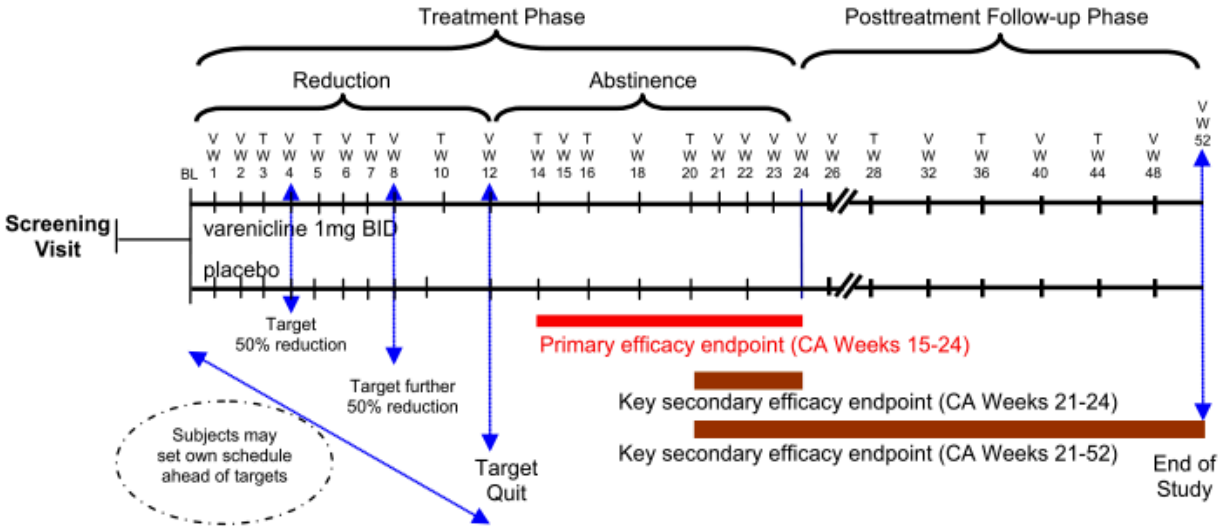
METHODS:

Study Design: This study was a Phase 4 (Phase 3 in Japan), randomized, double-blind, placebo-controlled, parallel-group, multicenter study designed to evaluate the efficacy and safety of varenicline in subjects who were not able to make an abrupt quit attempt but were willing to reduce their smoking with the ultimate goal of quitting.

After the screening phase (3 to 10 days), eligible subjects were randomized (1:1 ratio) to receive varenicline 1 mg BID or matching placebo for a 24-week double-blind treatment phase (Figure 1). During the first 12 weeks of treatment (ie, 12-week reduction phase), the subjects were expected to reduce the number of cigarettes smoked to 0, and brief smoking cessation counseling was provided at all visits from Baseline through to Week 12. Subjects were asked to reduce their smoking from the Baseline rate by at least 50% at Week 4, with a further 50% reduction in smoking rate from Week 4 to Week 8, with the goal of total abstinence at Week 12. The last cigarette was to be smoked prior to midnight on the day prior to the Week 12

Visit. Subjects could reduce their smoking rate faster if they so desired or could make a quit attempt at any time prior to Week 12 when they were ready. Subjects who reduced faster or quitted early were to continue dosing and visit participation as originally planned. After the 12-week reduction phase, subjects continued treatment from Week 12 to Week 24 (ie, 12-week abstinence phase), during which they were expected to be abstinent from smoking. At Week 24 or at early termination (ET), treatment was stopped and subjects were followed up for 28-weeks up to study completion at Week 52/ET.

Figure 1. Overview of Study Design



BID = twice daily; BL = baseline; CA = continuous abstinence; T = telephone contact; V = clinic visit; W = week.

The schedule of activities during the study is provided in Table 1 (Screening Visit to Week 12), Table 2 (Week 14 to Week 24), and Table 3 (Week 24/ET to Week 54/ET).

Table 1. Schedule of Activities: Screening Visit to Week 12

Protocol Activity	Screening	Treatment Phase										
		Baseline	Week 1	Week 2	Week 3 Tel-Visit	Week 4	Week 5 Tel-Visit	Week 6	Week 7 Tel-Visit	Week 8	Week 10 Tel-Visit	Week 12
Window			±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days
Informed consent	X											
Medical history	X											
Physical examination	X	X										
Vital signs and weight	X	X										X
Height	X											
Hematology	X											
Blood chemistry	X											
Pregnancy test[a]	X	X										X
Urine drug screen[b]	X	X										
12-Lead ECG[c]	X											
Registration/randomization		X										
Sample banking of exploratory research[d]	X											
Smoking history	X											
Tobacco Dependence Screener (TDS)	X											
Fagerstrom test	X											
Exhaled carbon monoxide (CO)	X	X	X	X		X		X		X		X
Nicotine Use Inventory (NUI)		X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and concomitant non-drug treatments	X	X	X	X		X		X		X		X
Concomitant drugs (for smoking cessation)	X	X	X	X		X		X		X		X
Dispense investigational product		X	X	X		X		X		X		X
Dosing record			X	X		X		X		X		X
Adverse events		X	X	X		X		X		X		X
NAEI		X	X	X		X		X		X		X
C-SSRS	X	X	X	X		X		X		X		X
SBQ-R	X											
PHQ-9		X		X		X		X		X	X	X
mCEQ[e]		X				X				X		X
MNWS		X				X				X		X
Smoking cessation counseling (up to 10 minutes)		X	X	X	X	X	X	X	X	X	X	X
Dispense “Clearing the Air” booklet		X										
Smoking log[f]		X	X	X								

Table 1. Schedule of Activities: Screening Visit to Week 12

C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; mCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; NAEI = Neuropsychiatric Adverse Event Interview; PHQ-9 = Patient Health Questionnaire-9; SBQ-R = Suicide Behaviors Questionnaire-Revised; Tel-Visit = telephone visit.

a. Dipstick at site.
b. Dipstick at site.
c. 12-lead electrocardiogram (ECG) at site.
d. Optional and only with signed consent.
e. Administered to only those subjects who smoked since the visit or since the last time they completed the form.
f. Dispense 2 weekly smoking logs at Week 2.

Table 2. Schedule of Activities: Week 14 to Week 24

Protocol Activity	Treatment Phase								
	Week 14 Tel-Visit	Week 15	Week 16 Tel-Visit	Week 18	Week 20 Tel-Visit	Week 21	Week 22	Week 23	Week 24
Window			**±3 Days**	**±3 Days**	**±3 Days**	**±3 Days**	**±3 Days**	**±3 Days**	**±3 Days**
Physical examination									X
Vital signs and weight									X
Pregnancy test[a]									X
Exhaled carbon monoxide (CO)		X		X		X	X	X	X
Nicotine Use Inventory (NUI)	X	X	X	X	X	X	X	X	X
Concomitant medications and concomitant non-drug treatments		X		X		X	X	X	X
Concomitant drugs (for smoking cessation)		X		X		X	X	X	X
Dispense investigational product		X		X		X	X	X	
Dosing record		X		X		X	X	X	X
Adverse events		X		X		X	X	X	X
NAEI		X		X		X	X	X	X
C-SSRS		X		X		X	X	X	X
PHQ-9	X		X	X	X		X		X
mCEQ[b]		X		X					X
MNWS		X		X					X
Smoking cessation counseling (up to 10 minutes)	X	X	X	X	X	X	X	X	X

C-SSRS = Columbia-Suicide Severity Rating Scale; mCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; NAEI = Neuropsychiatric Adverse Event Interview; PHQ-9 = Patient Health Questionnaire-9; Tel-Visit = telephone visit.

a. Dipstick at site.

b. Administered to only those subjects who smoked since the visit or since the last time they completed the form.

Table 3. Schedule of Activities: Week 24/ET to Week 52/ET

Protocol Activity	Treatment Phase	Posttreatment Follow-Up Phase								
	Week 24 or ET	Week 26	Week 28 Tel-Visit	Week 32	Week 36 Tel-Visit	Week 40	Week 44 Tel-Visit	Week 48	Week 52	Week 52 or ET
Window		**±7 Days**	**±3 Days**	**±7 Days**	**±3 Days**	**±7 Days**	**±3 Days**	**+±7 Days**	**±7 Days**	
Physical examination	X									
Vital signs and weight	X									
Pregnancy test[a]	X									
Exhaled carbon monoxide (CO)	X	X		X		X		X	X	X
Nicotine Use Inventory (NUI)	X	X	X	X	X	X	X	X	X	X
Concomitant medications and concomitant non-drug treatments	X	X		X		X		X	X	X
Concomitant drugs (for smoking cessation)	X	X		X		X		X	X	X
Dosing record	X									
Adverse events	X	X		X		X		X	X	X
NAEI	X	X		X		X		X	X	X
C-SSRS	X	X		X		X		X	X	X
PHQ-9	X	X		X		X		X	X	X
mCEQ[b]	X	X								
MNWS	X	X								
Smoking cessation counseling (up to 10 minutes)		X	X	X	X	X	X	X	X	X

C-SSRS = Columbia-Suicide Severity Rating Scale; ET = early termination; mCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; NAEI = Neuropsychiatric Adverse Event Interview; PHQ-9 = Patient Health Questionnaire-9; Tel-Visit = telephone visit.

a. Dipstick at site.

b. Administered to only those subjects who smoked since the last visit or since the last time they completed the form.

Number of Subjects (Planned and Analyzed): At least a total of approximately 1404 subjects (702 subjects per arm) at approximately 75 sites, were planned to be randomized and evaluated. A total of 1747 subjects were screened, 1510 subjects were randomized (760 to varenicline and 750 to placebo), and a total of 1493 subjects received at least 1 dose of study drug (751 varenicline and 742 placebo).

Diagnosis and Main Criteria for Inclusion: Male and female cigarette smokers (≥10 cigarettes per day during the past year and during the month prior to the Screening Visit, without a continuous period of abstinence of >3 months in the past year, and exhaled carbon monoxide (CO) >10 ppm at Screening), over the age of 18 years, not willing/able to quit smoking within the next month, but willing to reduce their smoking for a quit attempt within the next 3 months, were included in the study. Subjects with mild to moderate depression, anxiety, obsessive compulsive disorder, or phobias (eg, agoraphobia and social phobia) could be included if their condition was stable.

Excluded were subjects with a history of a suicide attempt or any suicidal behavior in the past 2 years, severe depression or anxiety, psychosis, panic disorder, bipolar disorder, post-traumatic stress disorder, schizophrenia, alcohol or substance abuse/dependence (except nicotine) unless in full remission for at least 12 months, or severe chronic obstructive pulmonary disease.

Study Treatment: Varenicline tartrate 0.5-mg film-coated tablets and matching placebo were supplied in bottles containing sufficient tablets for 10 days (ie, up to the next scheduled visit).

All subjects were randomized to either varenicline or placebo, and study drug administration was initiated with a titration period, as outlined in Table 4.

Table 4. Initiation of Study Drug Dosing With Titration Period

Treatment Group	Days 1 to 3	Days 4 to 7	Day 8	Week 2–Week 24
Blinded varenicline (or placebo)	0.5 mg QD (in the evening)	0.5 mg BID	1 mg BID	1 mg BID
	Week 1 drug supply in bottles			Week 2–24 drug supplies in bottles

BID = twice daily; QD = once a day.

Study drug was taken with 240 mL of water and it was recommended that subjects eat prior to dosing. It was recommended that there should be at least 8 hours between the morning and evening dosing. Subjects who had difficulties with tolerability (see stopping criteria below) were permitted to have the dose lowered temporarily or permanently to 0.5 mg BID. Dosing continued until the completion of the treatment phase at the Week 24 Visit.

Stopping Criteria: During the 24-week treatment phase, subjects were monitored for any clinically significant symptomatic changes, and appropriate referrals were made to ensure subject safety. The following individual dosing stopping criteria were followed:

- Dosing was required to be stopped if the clinician believed that continuing dosing would be detrimental to the subject's mental or physical health

- Dosing was required to be stopped if adverse events (AEs) including, but not limited to, agitation, hostility, depressed mood, changes in behavior or thinking that were not typical for the subject, were observed and, in the opinion of the clinician, made continued dosing detrimental to the subject's well-being or mental or physical health

- Dosing was required to be stopped immediately if the subject developed active suicidal ideation or suicidal behavior

Non-Permitted Concomitant Medications: Episodic and chronic use of the following concomitant medications was prohibited during the study:

- Any nicotine replacement therapy, including herbal medications

- Bupropion, naltrexone, insulin, nortriptyline, clonidine, theophylline, warfarin, herbals commonly used for anxiety or depression, over-the-counter/prescribed stimulants and anorectic agents

- Any steroids (oral/intravenous/intramuscular) except for inhaled and topical steroids, injectable steroids for local/intra-articular administration, and episodic short-term use of oral steroids

Efficacy Endpoints:

Primary Endpoint: CO confirmed continuous abstinence (CA) during the last 10 weeks of treatment (Figure 1), with CA defined as being abstinent from smoking and the use of any other nicotine products at the Week 15 visit through the Week 24 visit, as determined by direct questioning and supported by CO monitoring (exhaled CO ≤10 ppm); if exhaled CO was >10 ppm, measured at any clinic visit during Weeks 15-24, the subject was not counted as being continuously abstinent.

Key Secondary Endpoints:

- CO confirmed CA Week 21 through Week 24

- CO confirmed long-term CA Week 21 through Week 52

Other Secondary Endpoints:

- The 7-day point prevalence of smoking cessation (ie, subject's smoking status and other nicotine use, based on the "last 7 days" questions in the Nicotine Use Inventory [NUI]) at Weeks 12, 24, and 52

- The 4-week point prevalence of smoking cessation (ie, subject's smoking status and other nicotine use, based on the "last 4 weeks" questions in the NUI) at Week 52

Safety Evaluations: The safety assessments included the recording of observed, volunteered, or solicited AEs, regardless of treatment group or suspected causal relationship to the investigational product(s). In addition, suicidality was assessed with the Columbia-Suicide

Severity Rating Scale (C-SSRS) and the Suicide Behaviors Questionnaire-Revised (SBQ-R). The SBQ-R was self-administered by each subject at Screening and posed questions about past and future suicidality. The C-SSRS was conducted by an interviewer and posed questions about past suicidality (ie, lifetime history at Screening) and "since last visit" at subsequent clinic visits. Neuropsychiatric AEs observed, volunteered, or solicited through the Neuropsychiatric Adverse Event Interview (NAEI) were reported as AEs or serious AEs (SAEs) if they met the relevant criteria; causality assessments for such AEs reflected the consideration of study treatments, nicotine withdrawal, or other causes. In addition, the Patient Health Questionnaire (PHQ-9) elicited events potentially related to depression. Other safety assessments included physical examinations, weight assessments, vital signs, electrocardiogram (ECG), and blood safety tests (hematology and chemistry). ECG and blood tests were performed at Screening only, unless otherwise indicated.

Statistical Methods:

Analysis Sets: The full analysis set (FAS) was referred to as the intent-to-treat (ITT) population and was defined as all randomized subjects. The ITT population was the primary subject population for the efficacy analyses in this study. All Treated population was defined as all randomized subjects (ITT) who took at least 1 dose (partial or full) of study treatment. The subset of the ITT population known as the Completer population included all randomized subjects who took at least 1 dose (partial or full) of study treatment for at least 80% of the nominal duration of the active treatment phase of a study. The safety analysis set was the All Treated population and was the primary subject population for safety summaries and analyses in this study. All safety analyses were reported by the treatment received.

Efficacy Analysis: For the primary and key secondary efficacy endpoints analyses, a logistic regression model was used, which included treatment effect as the explanatory variable and investigative center as covariate. To evaluate the consistency of the efficacy in the primary and key secondary endpoints over demographic and other baseline characteristics, subgroup analyses were performed, when the number of subjects in the subgroups permitted. There were no imbalances in baseline data, and thus no additional analyses were performed. Adjusting for a country or region covariate instead of a center covariate was to be explored in the event of sufficient treatment-by-center interaction. There were no such significant interactions.

Other secondary efficacy endpoints were analyzed by using logistic regression, as described for the primary and key secondary endpoints. Change from Baseline in number of cigarettes per day was summarized daily from Day 1 to Day 28 and inferential statistical analyses of ≥50% and ≥75% reduction in average of number of cigarettes smoked was based on the logistic regression.

The Minnesota Nicotine Withdrawal Scale (MNWS) and the Modified Cigarette Evaluation Questionnaire (mCEQ) were summarized at each collection visit using descriptive statistics based on data from the ITT population. The analysis was a repeated measures analysis over time, with the post-treatment MNWS measure as the dependent variable, treatment group as the explanatory variable of interest, baseline MNWS measure, center and visit as covariates, and interaction of treatment by visit using post-treatment data collected at Weeks 4, 8, and 12.

Safety Analysis: The incidence and severity of all AEs and SAEs collected during the study and the incidence and severity of treatment-emergent AEs (TEAEs) and SAEs were tabulated. All AEs reported through Week 52 were coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 16.1). The incidence of all AEs reported during the study (through Week 52) was summarized by treatment group and by MedDRA system organ class (SOC), high level group term, and preferred term (PT).

In addition to the Sponsor's standard AE summaries and listings, a 3-tiered AE reporting approach was also utilized to provide additional summaries and analyses.

Tier-1: Prespecified Adverse Events of Special Clinical Interest: The Tier-1 list included all AEs in the suicidality standardized MedDRA query (SMQ) and the myocardial infarction SMQ. Data were summarized and analyzed (incidence rates, risk difference [RD], 95% confidence intervals [CIs], and p-value of the RD were to be reported).

Tier-2: Common Adverse Events: Tier-2 AEs were any observed PTs that were "common", ie, the AEs were reported by ≥5% of subjects in either treatment group, but the terms were not included in the list of Tier-1. Data were summarized and analyzed (incidence rates, RD, and 95% CIs were to be reported).

Tier-3: Infrequent Adverse Events: AEs that were not Tier-1 or Tier-2 AEs were categorized as Tier-3 AEs. Data were summarized; only incidence rates were to be reported.

RESULTS

Subject Disposition and Demography: A summary of subject disposition is presented in Table 5. A total of 1510 subjects were randomized into the study and comprised the All Randomized (ITT) population. A total of 1493 subjects took at least 1 dose of study drug and comprised the All Treated population. Overall, the rates of completion of the study were higher in the varenicline treatment group than in the placebo treatment group (73.6% versus [vs] 68.7%, respectively, for the All Randomized population).

Table 5. Subject Disposition

Number of Subjects (%)	Varenicline		Placebo	
	n	%	n	%
Screened=1747 subjects				
All Randomized or ITT population	760		750	
Treated	751	(98.8)	742	(98.9)
Completed treatment	540	(71.1)	492	(65.6)
Discontinued treatment	211	(27.8)	250	(33.3)
Completed study	559	(73.6)	515	(68.7)
Discontinued study	192	(25.3)	227	(30.3)
All Treated population	751		742	
Discontinuations from study	192	(25.6)	227	(30.6)
Subject died	1	(0.1)	0	-
Relation to study drug not defined	178	(23.7)	214	(28.8)
Insufficient clinical response	6	(0.8)	28	(3.8)
Lost to follow-up	76	(10.1)	81	(10.9)
No longer willing to participate in study	54	(7.2)	59	(8.0)
Other	39	(5.2)	43	(5.8)
Protocol violation	3	(0.4)	3	(0.4)
Related to study drug	12	(1.6)	9	(1.2)
Adverse event	12	(1.6)	9	(1.2)
Not related to study drug	1	(0.1)	4	(0.5)
Adverse event	1	(0.1)	4	(0.5)
Discontinuations from treatment	211	(28.1)	250	(33.7)
Subject died	1	(0.1)	0	-
Relation to study drug not defined	146	(19.4)	198	(26.7)
Did not meet entrance criteria	1	(0.1)	0	-
Insufficient clinical response	9	(1.2)	37	(5.0)
Lost to follow-up	50	(6.7)	61	(8.2)
No longer willing to participate in study	35	(4.7)	45	(6.1)
Other	47	(6.3)	52	(7.0)
Protocol violation	4	(0.5)	3	(0.4)
Related to study drug	53	(7.1)	40	(5.4)
Adverse event	53	(7.1)	40	(5.4)
Not related to study drug	11	(1.5)	12	(1.6)
Adverse event	11	(1.5)	12	(1.6)
Analyzed for efficacy				
All Randomized population	760	(100.0)	750	(100.0)
All Treated population	751	(98.8)	742	(98.9)
Completer population	564	(74.2)	513	(68.4)
Analyzed for safety				
Adverse events	751	(100.0)	742	(100.0)
Laboratory data[a]	13	(1.7)	3	(0.4)

The full analysis set was referred to as the intent-to-treat (ITT) population and included subjects who were randomized to study treatment. The All Treated population included all subjects who had been randomized and received at least 1 dose, including partial doses, of randomized study medication. All Randomized population (usually referred to as ITT) included subjects who are randomized into treatment in the study. All Completer population included all randomized subjects who took at least 1 dose (partial or full) of study treatment for at least 80% of the nominal duration of the active treatment phase of study.
ITT = intent-to-treat; n = number of subjects per category.
a. Laboratory testing was to be done only at the Screening Visit (within 3 to 10 days prior to randomization); however, laboratory testing was done at other visits at the Investigator's discretion.

Demographic characteristics for treated subjects in the study are summarized in Table 6 and were well balanced between the 2 treatment groups.

Table 6. Demographic Characteristics – All Treated Population

	Varenicline[a]			Placebo		
	Male (N=421)	Female (N=330)	Total (N=751)	Male (N=421)	Female (N=321)	Total (N=742)
Age category, n (%)						
<18 years	0	0	0	0	0	0
18 to 44 years	212 (50.4)	152 (46.1)	364 (48.5)	208 (49.4)	160 (49.8)	368 (49.6)
45 to 64 years	189 (44.9)	164 (49.7)	353 (47.0)	186 (44.2)	146 (45.5)	332 (44.7)
≥65 years	20 (4.8)	14 (4.2)	34 (4.5)	27 (6.4)	15 (4.7)	42 (5.7)
Age, years						
Mean (SD)	44.4 (11.9)	45.0 (11.8)	44.7 (11.8)	44.7 (12.2)	44.0 (11.9)	44.4 (12.0)
Range	19-78	20-79	19-79	18-78	19-73	18-78
Race, n (%)						
White	217 (51.5)	254 (77.0)	471 (62.7)	229 (54.4)	226 (70.4)	455 (61.3)
Black	20 (4.8)	14 (4.2)	34 (4.5)	20 (4.8)	27 (8.4)	47 (6.3)
Asian	129 (30.6)	46 (13.9)	175 (23.3)	130 (30.9)	47 (14.6)	177 (23.9)
Other	55 (13.1)	16 (4.8)	71 (9.5)	42 (10.0)	21 (6.5)	63 (8.5)
Weight, kg						
Mean (SD)	82.3 (17.5)	72.1 (19.4)	77.8 (19.0)	82.5 (19.4)	72.9 (19.3)	78.3 (19.9)
Range	45.5-170.0	36.0-177.9	36.0-177.9	45.0-178.7	43.0-150.5	43.0-178.7
Height, cm						
Mean (SD)	175.2 (7.4)	163.6 (7.4)	170.1 (9.4)	174.8 (8.2)	163.9 (6.7)	170.1 (9.3)
Range	155.0-196.0	135.9-185.0	135.9-196.0	150.0-198.0	141.0-180.0	141.0-198.0
Body mass index, kg/m^2						
Mean (SD)	26.7 (5.0)	26.9 (6.6)	26.8 (5.8)	26.9 (5.3)	27.1 (6.7)	27.0 (6.0)
Range	17.2-56.2	16.5-64.3	16.5-64.3	15.8-52.6	16.2-61.6	15.8-61.6

The All Treated population which was the safety analysis set included all subjects who had been randomized and received at least 1 dose, including partial doses, of randomized medication.
Body mass index was defined as weight/(height x 0.01)^2.
N = number of subjects in the treatment group; n = number of subjects per category; SD = standard deviation.
a. One subject was assigned to varenicline as a male but is in fact female.

The mean age at which subjects started smoking was identical in the varenicline and placebo groups (17.3 years) and the mean number of years for which the subjects had smoked was similar (26.7 and 26.5 years, respectively). The mean number of cigarettes smoked per day was also similar in both treatment groups, whether this was assessed since the subject started smoking (18.6 and 19.0 per day, varenicline and placebo groups, respectively), or over the last year (20.7 per day in both groups) or the last month (20.6 vs 20.8 per day, varenicline vs placebo groups, respectively) prior to baseline.

In the past year, the majority of subjects in both the varenicline and placebo groups had made no attempt to quit smoking (76.3% vs 81.6%, respectively). Based on lifetime serious attempts to quit smoking, the majority of subjects in the varenicline and placebo groups had made a serious attempt to quit smoking (82.8% vs 78.7%, respectively). The most common methods used were cold turkey (51.8% vs 48.6%, respectively) and nicotine patches (26.0% vs 24.4%, respectively). The mean longest period of abstinence since the subject starting smoking was longer in the varenicline than the placebo group (266.4 vs 206.4 days, respectively). However when focusing on the last year prior to Baseline, the mean longest period of abstinence was similar in the 2 treatment groups (3.6 vs 2.7 days, respectively). The last serious attempt to quit smoking was more recent for subjects in the varenicline group than in the placebo group (mean values of 469.1 vs 739.3 days prior to baseline, respectively).

The mean Fagerstrom total score was similar for subjects in the varenicline and placebo groups and consistent with moderate nicotine dependence (5.5 vs 5.6, where a higher score indicates greater nicotine dependence; range is 0-10).

At Screening, the lifetime incidences of suicidal behavior and/or ideation and of suicide attempt in the varenicline and placebo treatment groups were 8.7% vs 7.1% and 2.3% vs 1.9%, respectively (Table 7). At Baseline, 4 subjects (0.5%) in the placebo group had suicide ideation compared with none (0%) in the varenicline group.

Table 7. Summary of Columbia-Suicide Severity Rating Scale at Screening and Baseline - All Treated Population

Classification Category	Screening (Lifetime)		Baseline	
	Varenicline (N=751)	Placebo (N=742)	Varenicline (N=751)	Placebo (N=742)
Number assessed	751	742	751	742
Suicidal behavior and/or ideation	65 (8.7)	53 (7.1)	0	4 (0.5)
Suicidal behavior	20 (2.7)	15 (2.0)	0	0
Suicide attempt	17 (2.3)	14 (1.9)	0	0
Preparatory acts toward imminent suicidal behavior	9 (1.2)	6 (0.8)	0	0
Aborted attempt	2 (0.3)	3 (0.4)	0	0
Interrupted attempt	5 (0.7)	1 (0.1)	0	0
Preparatory act or behavior	5 (0.7)	4 (0.5)	0	0
Suicide ideation	58 (7.7)	51 (6.9)	0	4 (0.5)
Wish to be dead	50 (6.7)	39 (5.3)	0	4 (0.5)
Non-specific active suicidal thoughts	28 (3.7)	34 (4.6)	0	1 (0.1)
Active suicidal ideation with any methods (not plan) without intent to act	11 (1.5)	13 (1.8)	0	1 (0.1)
Active suicidal ideation with some intent to act without specific plan	8 (1.1)	9 (1.2)	0	0
Active suicidal ideation with specific plan and intent	5 (0.7)	9 (1.2)	0	0
Self-injurious behavior no suicidal intent	8 (1.1)	6 (0.8)	0	0

All Treated population (N) included all subjects who had been randomized and received at least 1 dose, including partial doses, of randomized study medication.

Efficacy Results:

Primary Endpoint Result:

Between Weeks 15 and 24, subjects treated with varenicline had a significantly higher continuous abstinence rate compared with placebo, as shown in Table 8.

Table 8. CO-Confirmed Continuous Abstinence Rate From Week 15 Through Week 24

Analyses Set	Varenicline		Placebo		OR (95% CI) vs Placebo	p-Value vs Placebo
	N	n (%)	N	n (%)		
ITT population	760	244 (32.1)	750	52 (6.9)	8.74 (6.09, 12.53)	<0.0001
All Treated population	751	244 (32.5)	742	52 (7.0)	8.74 (6.09, 12.55)	<0.0001
Completer population	564	225 (39.9)	513	45 (8.8)	9.78 (6.55, 14.60)	<0.0001

The intent-to-treat population included all randomized subjects. The All Treated population included all subjects who had been randomized and received at least 1 dose, including partial doses, of randomized study medication. The Completer population included all randomized subjects who took at least 1 dose (partial or full) of study treatment for at least 80% of the nominal duration of the active treatment phase of study.
The odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment and pooled center.
CI = confidence interval; CO = carbon monoxide; ITT = intent-to-treat; N = number of subjects in the analysis set; n = number of subjects who, at each visit from Week 15-24 (inclusive), reported no smoking and no use of other nicotine-containing products since the last study visit/last contact (on the NUI) and who did not have CO >10 ppm at any of these visits; OR = odds ratio; vs = versus.

Key Secondary Endpoint Results:

Between Weeks 21 and 24 and between Weeks 21 and 52, subjects treated with varenicline had a significantly higher continuous abstinence rate compared with placebo (Table 9).

Table 9. CO-Confirmed Continuous Abstinence Rates From Week 21 Through 24 and From Week 21 Through 52

Analyses Set	Varenicline		Placebo		OR (95% CI) vs Placebo	p-Value vs Placebo
	N	n (%)	N	n (%)		
CAR 21-24						
ITT population	760	287 (37.8)	750	94 (12.5)	5.66 (4.21, 7.61)	<0.0001
All Treated population	751	287 (38.2)	742	94 (12.7)	5.67 (4.21, 7.63)	<0.0001
Completer population	564	266 (47.2)	513	83 (16.2)	6.27 (4.50, 8.72)	<0.0001
CAR 21-52						
ITT population	760	205 (27.0)	750	74 (9.9)	4.02 (2.94, 5.50)	<0.0001
All Treated population	751	205 (27.3)	742	74 (10.0)	4.03 (2.95, 5.51)	<0.0001
Completer population	564	190 (33.7)	513	67 (13.1)	4.00 (2.85, 5.62)	<0.0001

The intent-to-treat population included all randomized subjects. The All Treated population included all subjects who had been randomized and received at least 1 dose, including partial doses, of randomized study medication. The Completer population included all randomized subjects who took at least 1 dose (partial or full) of study treatment for at least 80% of the nominal duration of the active treatment phase of study.
The odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment and pooled center.
CAR = continuous abstinence rate; CI = confidence interval; CO = carbon monoxide; ITT = intent-to-treat; N = number of subjects in the analysis set; n = number of subjects who, at each visit from Week 21 through 24 (inclusive) or Week 21 through 52 (inclusive), respectively, reported no smoking and no use of other nicotine-containing products since the last study visit/last contact (on the NUI) and who did not have CO >10 ppm at any of these visits; OR = odds ratio; vs = versus.

Other Secondary Endpoint Results:

Subjects treated with varenicline had a significantly higher prevalence of smoking cessation (ITT population, Table 10) based on the "last 7 days" questions on the NUI compared with placebo.

Table 10. Seven-Day Point Prevalence of Smoking Cessation at Weeks 12, 24, and 52 – ITT Population

	Varenicline		Placebo		OR (95% CI) vs Placebo	p-Value vs Placebo
	N	n (%)	N	n (%)		
Week 12	760	237 (31.2)	750	50 (6.7)	8.69 (6.03,12.51)	<0.0001
Week 24	760	328 (43.2)	750	131 (17.5)	4.58 (3.51,5.98)	<0.0001
Week 52	760	259 (34.1)	750	137 (18.3)	2.66 (2.05,3.44)	<0.0001

The intent-to-treat population included all randomized subjects.
The odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment and pooled center.
Missing CO was imputed as negative (CO ≤10 ppm).
CI = confidence interval; CO = carbon monoxide; ITT = intent-to-treat; N = number of subjects in the analysis set; n = number of subjects who reported no smoking and no use of other nicotine-containing products (at Weeks 12 and 24), or no use of other tobacco products (at Week 52) (on the Nicotine Use Inventory) in the past 7 days, and who did not have CO >10 ppm on that day (if measured); OR = odds ratio; vs = versus.

Subjects treated with varenicline had a significantly higher prevalence of smoking cessation (ITT population) based on the "last 4 weeks" questions in the NUI compared with placebo at Week 52 (Table 11).

Table 11. CO-Confirmed 4-Week Point Prevalence of Abstinence at Week 52 – ITT Population

	Varenicline	Placebo
N	760	750
Week 52: n (%)	249 (32.8)	130 (17.3)
Odds ratio (95% CI) vs placebo	2.67 (2.05, 3.47)	
p-Value vs placebo	<.0001	

ITT population included all randomized subjects.
Odds ratio and p-value were obtained from a logistic regression model including the main effects of treatment and pooled center.
CI = confidence interval; CO = carbon monoxide; ITT = intent-to-treat; N = number of subjects evaluated; n = number of subjects who reported no smoking and no use of other tobacco products (on the NUI) on the last 4 weeks of the study and who did not have CO >10 ppm measured during the time period; vs = versus.

Subgroup Analyses: In most subgroups for the primary and key secondary efficacy endpoints (ITT population), subjects who were treated with varenicline had a significantly higher continuous abstinence rate compared with subjects treated with placebo. However, for the race subgroups of Black and other, the results favored varenicline, but were not statistically significant, due to the small number of subjects in those categories.

Outcomes: Compared with placebo, varenicline significantly reduced the Weeks 4, 8, and 12 averages in terms of the Urge to Smoke scale (MNWS), Smoking Satisfaction domain (mCEQ), and Psychological Reward domain (mCEQ) (all $p<0.001$), according to the repeated measures analyses of such averages.

Safety Results: The percentages of TEAEs of all-causalities and treatment-related are summarized in Table 12.

Table 12. All Treatment-Emergent and Treatment-Related Solicited and Volunteered Adverse Events (All-Causalities) - All Treated Population

	Treatment-Emergent		Treatment-Related	
	Varenicline	**Placebo**	**Varenicline**	**Placebo**
Number of subjects[a] evaluable for AEs	751	742	751	742
Number of AEs	2168	1641	1078	597
Number (%) of subjects with AEs	618 (82.3)	538 (72.5)	446 (59.4)	289 (38.9)
Number (%) of subjects with SAEs	28 (3.7)	16 (2.2)	3 (0.4)	1 (0.1)
Number (%) of subjects with severe AEs	44 (5.9)	37 (5.0)	20 (2.7)	16 (2.2)
Number (%) of subjects discontinued treatment due to AEs	63 (8.4)	51 (6.9)	52 (6.9)	39 (5.3)
Number (%) of subjects discontinued study due to a AEs	13 (1.7)	12 (1.6)	12 (1.6)	9 (1.2)
Number (%) of subjects with dose reduced or temporary treatment discontinuation due to AEs	144 (19.2)	72 (9.7)	117 (15.6)	47 (6.3)

All Treated population included all subjects who were randomized and received at least 1 dose, including partial doses, of randomized study medication.
Except for the number of AEs, subjects were counted only once per treatment in each row.
SAEs - according to the Investigator's assessment.
AEs = adverse events; SAEs = serious adverse events.
a. Treatment-emergent adverse events included a first occurrence of an adverse event from the date of first dose of study drug up to 30 days after date of last dose of study drug.

Treatment-Emergent Adverse Events (All-Causalities): The most common (≥5% in either treatment group) all-causality TEAEs are summarized in Table 13. Among these most common all-causality TEAEs, the preferred terms that were at least twice as frequent in the varenicline vs placebo group were nausea (27.8% vs 9.0%, respectively) and constipation (5.1% vs 1.8%, respectively).

Table 13. Treatment-Emergent Solicited and Volunteered Non-Serious Adverse Events in ≥5% of Subjects in Either Treatment Group (All-Causalities) – All Treated Population

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term	Varenicline (N=751) n (%)	Placebo (N=742) n (%)
Number (%) of subjects evaluable for adverse events	751	742
Number (%) of subjects with adverse events	467 (62.2)	339 (45.7)
Gastrointestinal disorders	328 (43.7)	177 (23.9)
Constipation	38 (5.1)	13 (1.8)
Nausea	209 (27.8)	67 (9.0)
General disorders and administration site conditions	121 (16.1)	96 (12.9)
Fatigue	46 (6.1)	34 (4.6)
Irritability	39 (5.2)	30 (4.0)
Infections and infestations	265 (35.3)	257 (34.6)
Nasopharyngitis	98 (13.0)	89 (12.0)
Upper respiratory tract infection	63 (8.4)	63 (8.5)
Nervous system disorders	160 (21.3)	132 (17.8)
Headache	62 (8.3)	54 (7.3)
Psychiatric disorders	278 (37.0)	210 (28.3)
Abnormal dreams	86 (11.5)	43 (5.8)
Anxiety	52 (6.9)	65 (8.8)
Insomnia	80 (10.7)	51 (6.9)

All Treated population included all subjects who had been randomized and received at least 1 dose, including partial doses, of randomized study medication.
Subjects were only counted once per treatment for each row.
Includes subjects who experienced a non-serious adverse event from the date of first dose of study drug up to 30 days after the date of last dose of study drug.
Preferred terms with incidences ≥4.95% and <5% appear through rounding as 5, but do not make the cut-off point of ≥5%.
MedDRA (v16.1) coding dictionary applied.
MedDRA (v16.1) = Medical Dictionary for Regulatory Activities (version 16.1); N = number of subjects in each group; n = number of subjects with adverse events.

Treatment-Related Treatment-Emergent Adverse Events The most common (≥5% in either treatment group) treatment-related TEAEs are summarized in Table 14.

Table 14. Most Common (≥5% of Subjects in Either Treatment Group) Treatment-Emergent Solicited and Volunteered Adverse Events (Treatment-Related) - All Treated Population

Number (%) of Subjects With Adverse Events by: Preferred Term	Varenicline (N=751) n (%)	Placebo (N=742) n (%)
Subjects[a] with AEs	446 (59.4)	289 (38.9)
Nausea	194 (25.8)	50 (6.7)
Nasopharyngitis	1 (0.1)	0
Abnormal dreams	85 (11.3)	42 (5.7)
Insomnia	62 (8.3)	40 (5.4)
Upper respiratory tract infection	3 (0.4)	0
Headache	40 (5.3)	31 (4.2)
Anxiety	28 (3.7)	34 (4.6)
Fatigue	35 (4.7)	26 (3.5)
Irritability	27 (3.6)	20 (2.7)
Constipation	25 (3.3)	8 (1.1)

AEs and SAEs are not separated out.
All Treated population included all subjects who had been randomized and received at least 1 dose, including partial doses, of randomized study medication.
Subjects were only counted once per treatment for each row.
MedDRA (version 16.1) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each group; n = number of subjects with adverse events; SAEs = serious adverse events.
a. Includes subjects who experienced an adverse event from the date of first dose of study drug up to 30 days after the date of last dose of study drug.

Psychiatric Adverse Events: Both all-causality and treatment-related TEAEs in the psychiatric disorders SOC occurred more frequently in the varenicline treatment group than in the placebo treatment group: all-causality TEAEs, 37.0% vs 28.3%, respectively, and treatment-related TEAEs, 30.1% vs 20.5%, respectively. The most frequently occurring psychiatric AEs (≥5% of subjects in either treatment group; [all-causality, treatment-emergent]) that had a higher rate on varenicline compared with placebo were abnormal dreams (11.5% vs 5.8%) and insomnia (10.7% vs 6.9%). The all-causality, treatment-emergent, psychiatric AEs of anxiety and depression occurred more frequently on placebo than on varenicline (8.8% vs 6.9% and 4.7% vs 3.3%, respectively), whereas depressed mood occurred with similar frequency in both treatment groups (3.6% vs 3.5%, respectively).

The following psychiatric AEs (all-causality, treatment-emergent) were considered severe and occurred in 1 subject each unless noted otherwise:

- Varenicline group: abnormal dreams (2 subjects), depression, depression suicidal, insomnia, and panic attack
- Placebo treatment group: abnormal dreams (2 subjects), insomnia (2 subjects), agitation, alcoholism, anxiety, depression, and sleep disorder

Tier-1 Adverse Events: Across the entire 52-week study, there were Tier-1 prespecified AEs of special clinical interest within the suicide/self-injury SMQ and myocardial infarction SMQ. The number of suicide-related events was low, with 5 events reported by 4 subjects in the varenicline group and 5 events reported by 5 subjects in the placebo group (RD [95% CI]: -0.0021 [-0.0115, 0.0074]; p=0.668). The number of events in the myocardial infarction SMQ during this study

was also low and were reported by 1 subject in the varenicline group and 2 subjects in the placebo group (RD [95% CI]: -0.0017 [-0.0072, 0.0037]; p=0.529). Although the RDs of varenicline vs placebo were not statistically significant, given the low frequency of the events, no formal conclusion could be made from the results.

Tier-2 Adverse Events: Risk differences of observational time adjusted incidence rates for frequent all-causality TEAEs, computed as varenicline vs placebo, that did not include the null value in the 95% CI were observed for nausea (RD [95% CI]: 0.5641 [0.4521, 0.6760]), abnormal dreams (RD [95% CI]: 0.1366 [0.0672, 0.2060]), insomnia (RD [95% CI]: 0.0885 [0.0188, 0.1583]), and constipation (RD [95% CI]: 0.0734 [0.0318, 0.1150]). (95% CIs were provided to help gauge the precision of the estimate for risk difference. They were not adjusted for multiplicity and should be used for estimation purpose only).

All-Causality Serious Adverse Events: A summary of SAEs (all-causalities) reported during the study is presented in Table 16.

Table 15. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All-Causalities) – All Treated Population

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term	Varenicline (N=751) n (%)	Placebo (N=742) n (%)
Number (%) of subjects evaluable for adverse events	751	742
Number (%) of subjects with adverse events	28 (3.7)	16 (2.2)
Blood and lymphatic system disorders	1 (0.1)	0
Thrombocytopenia	1 (0.1)	0
Cardiac disorders	2 (0.3)	2 (0.3)
Angina pectoris	1 (0.1)	0
Myocardial infarction	0	2 (0.3)
Supraventricular tachycardia	1 (0.1)	0
Ear and labyrinth disorders	0	1 (0.1)
Vertigo	0	1 (0.1)
Gastrointestinal disorders	2 (0.3)	2 (0.3)
Gastritis	1 (0.1)	0
Ileus	0	1 (0.1)
Pancreatic cyst	1 (0.1)	0
Vomiting	0	1 (0.1)
General disorders and administration site conditions	2 (0.3)	1 (0.1)
Chest pain	1 (0.1)	1 (0.1)
Death	1 (0.1)	0
Infections and infestations	3 (0.4)	3 (0.4)
Acute tonsillitis	1 (0.1)	0
Cellulitis	0	1 (0.1)
Laryngitis	1 (0.1)	0
Lobar pneumonia	0	1 (0.1)
Lower respiratory tract infection	1 (0.1)	0
Peritonitis	0	1 (0.1)
Injury, poisoning and procedural complications	3 (0.4)	2 (0.3)
Contusion	0	1 (0.1)
Foetal exposure during pregnancy	1 (0.1)	1 (0.1)
Foot fracture	1 (0.1)	0
Rib fracture	0	1 (0.1)
Road traffic accident	0	1 (0.1)
Thermal burn	1 (0.1)	0
Metabolism and nutrition disorders	0	1 (0.1)
Diabetes mellitus inadequate control	0	1 (0.1)
Musculoskeletal and connective tissue disorders	4 (0.5)	2 (0.3)
Arthralgia	1 (0.1)	0
Back pain	1 (0.1)	0
Costochondritis	0	1 (0.1)
Intervertebral disc protrusion	1 (0.1)	1 (0.1)
Musculoskeletal chest pain	1 (0.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.3)	0
Bladder transitional cell carcinoma	1 (0.1)	0
Breast cancer	1 (0.1)	0
Prostate cancer	1 (0.1)	0
Nervous system disorders	4 (0.5)	1 (0.1)
Epilepsy	1 (0.1)	0
Intercostal neuralgia	1 (0.1)	0
Migraine	1 (0.1)	0
Presyncope	1 (0.1)	0
Ruptured cerebral aneurysm	0	1 (0.1)
Psychiatric disorders	4 (0.5)	1 (0.1)
Alcohol abuse	1 (0.1)	0
Alcoholism	0	1 (0.1)
Delirium tremens	1 (0.1)	0
Depression suicidal	1 (0.1)	0

Table 15. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All-Causalities) – All Treated Population

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term	Varenicline (N=751) n (%)	Placebo (N=742) n (%)
Intentional self-injury	1 (0.1)	0
Suicidal ideation	1 (0.1)	0
Renal and urinary disorders	1 (0.1)	0
Calculus ureteric	1 (0.1)	0
Reproductive system and breast disorders	2 (0.3)	1 (0.1)
Ovarian cyst	2 (0.3)	0
Ovarian haemorrhage	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders	1 (0.1)	1 (0.1)
Asthma	1 (0.1)	0
Pneumothorax	0	1 (0.1)
Skin and subcutaneous tissue disorders	0	1 (0.1)
Diabetic foot	0	1 (0.1)
Surgical and medical procedures	1 (0.1)	0
Hospitalisation	1 (0.1)	0
Vascular disorders	3 (0.4)	2 (0.3)
Aortic aneurysm rupture	1 (0.1)	0
Hypertension	1 (0.1)	1 (0.1)
Hypertensive crisis	1 (0.1)	0
Peripheral arterial occlusive disease	0	1 (0.1)

All Treated population included all subjects who had been randomized and received at least 1 dose, including partial doses, of randomized study medication.
Subjects were only counted once per treatment for each row.
Included subjects who experienced a serious adverse event from the date of first dose of study drug up to 30 days after the date of last dose of study drug.
MedDRA (v16.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each group; n = number of subjects with adverse events.

Treatment-Related Serious Adverse Events: A summary of treatment-related SAEs reported during the study is presented in Table 16.

Table 16. Treatment-Related Serious Adverse Events – All Treated Population

Serial Number/ Sex/Age (Years)[a]	Preferred Term	AE Onset Day[b]	AE Stop Day[c]	Action Taken (Study Drug)	Clinical Outcome
Varenicline Group					
1[d]/F/48	Hospitalization[d]	105	NA	Dose not changed	Unknown[d]
2/M/51	Presyncope	10	11	Dose not changed	Recovering/resolving/hospitalization
3/M/72	Death[e]	2	NA	Dose not changed	Fatal
4/M/47	Gastritis	139	198	Permanently withdrawn	Recovered/resolved/hospitalization
Placebo Group					
5[d]/M/27	Fetal exposure during pregnancy[d]	39	244	Permanently withdrawn	Resolved[d]

Causality was according to both the Investigator's and Sponsor's assessment (for all SAEs, except for death, both were the same).
AE = adverse event; F = female; M = male; NA = not applicable; OC = Oracle Clinical; SAE = serious adverse event; SDW = safety data warehouse.

a. Age at date of SAE onset.
b. AE onset study day was calculated as the SDW onset date minus the OC first active therapy date plus 1.
c. AE stop day was calculated as the SDW SAE stop date minus OC first active therapy date plus 1.
d. AE was noted as serious in the clinical database, but did not meet the criteria of serious in the safety database.
e. This SAE's causality was recorded as unrelated by the Investigator and related by the Sponsor.

Deaths: One death was reported in this study. The 72-year-old male subject who was smoking 40 cigarettes per day at the Baseline Visit, with relevant medical history of carcinoma of vocal cord, for which he had received 6 months of radiation therapy, and history of insomnia that was ongoing, had a fatal SAE of death on Day 8 (imputed from incomplete dates and times). There was no documented relevant psychiatric history. Ongoing concomitant medications included oral temazepam tablet 10 mg as needed for insomnia, paracetamol, and mometasone furoate nasal spray 100 µg twice daily for common cold from Day 8. No autopsy was done to confirm the date of death or its cause. The Investigator reported that the event was unrelated to varenicline treatment, concomitant drugs, or clinical trial procedure; to be conservative, the Sponsor considered the death as related.

Permanent Discontinuations due to Adverse Events: Table 17 presents a summary of discontinuations from the study due to AEs.

Table 17. Permanent Discontinuations From the Study due to Adverse Events – All Treated Population

Serial Number/Sex/Age[a]	AE Start/ Stop Day[b]	Preferred Term[c]	Severity/Outcome	Causality	SAE[d]
Varenicline Group					
1/F/42	2/5	Insomnia	Moderate/resolved	Study drug	No
2/F/43	129/168	Liver function test abnormal	Mild/resolved	Study drug	No
3/F/49	59/69	Mood swings	Moderate/resolved	Study drug	No
4/F/30	2/29	Depressed mood	Moderate/resolved	Study drug	No
5/F/51	1/3	Nausea	Moderate/resolved	Study drug	No
6/F/36	3/6	Irritability	Severe/resolved	Study drug	No
7/F/51	22/46	Irritability	Severe/resolved	Study drug	No
8/F/51	9/19	Dry mouth	Moderate/resolved	Study drug	No
	9/19	Nausea	Moderate/resolved	Study drug	No
	9/19	Dizziness	Moderate/resolved	Study drug	No
	9/19	Tremor	Moderate/resolved	Study drug	No
9/M/32	36/97	Nausea	Mild/resolved	Study drug	No
9/F/57	9/-	Abdominal distension	Mild/still present	Study drug	No
9/F/40	115/-	Depression	Severe/still present	Other-workplace stressor	No
10/F/39	11/13	Hostility	Moderate/resolved	Study drug	No
11/F/48	7/15	Nausea	Severe/resolved	Study drug	No
Placebo Group					
12/F/33	85/99	Vertigo	Severe/resolved	Other-exhaustion	Yes
	85/88	Vomiting	Severe/resolved	Other-exhaustion	Yes
13/F/30	85/86	Vertigo	Mild/resolved	Study drug	No
14/M/78	200/351	Guillain-Barre syndrome	Severe/resolved	Other-unknown, not related	Yes
15/F/55	8/12	Nausea	Moderate/resolved	Study drug	No
	8/12	Decreased appetite	Moderate/resolved	Study drug	No
	8/12	Insomnia	Moderate/resolved	Study drug	No
16/M/47	2/-	Fatigue	Mild/still present	Study drug	No
17/M/35	2/6	Dizziness	Mild/resolved	Study drug	No
18/M/47	35/38	Myocardial infarction	Severe/resolved	Other-underlying condition of obesity	Yes
19/F/48	8/8	Panic attack	Moderate/resolved	Study drug	No
20/F/64	42/45	Diarrhoea	Severe/resolved	Study drug	No
21/M/55	38/-	Decreased appetite	Mild/still present	Study drug	No
22/M/68	13/-	Tobacco abuse	Mild/still present	Study drug	No
	13/-	Therapeutic response unexpected	Mild/still present	Study drug	No
23/M/44	106/-	Bereavement	Moderate/still present	Other-death in family	No
24/M/33	84/-	Depression	Moderate/still present	Study drug	No

All Treated population included all subjects who had been randomized and received at least 1 dose, including partial doses, of randomized study medication.
AE = adverse event; F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.
a. Age at Screening in years.
b. Start Day and Stop Day were start and stop of AE relative to the start of treatment: first day of study treatment = Day 1.
c. All AEs were considered to be treatment-emergent, with the exception of Guillain-Barre syndrome (1 subject).
d. SAE was according to Investigator's assessment.

Dose Reductions and Temporary Discontinuations due to Adverse Events: Dose reductions or temporary discontinuations due to all-causality AEs were more common with varenicline than with placebo (144 [19.2%] vs 72 [9.7%], respectively.

Nausea was the only frequently occurring reason (≥2% in either treatment group) for dose reductions or temporary discontinuations due to AEs (7.2% with varenicline; 1.5% with placebo;

of the event of nausea, 7.1% in the varenicline group and 0.9% in the placebo group were considered to be treatment-related.

Vital Signs, Physical Findings, Laboratory Test and Other Observations Related to Safety:

Overall, 0.3% and 0.2% of subjects in the varenicline and placebo treatment groups, respectively, had an increase in sitting systolic blood pressure (SBP) defined as SBP >180 mm Hg and a change ≥20 mm Hg. A decrease in sitting SBP defined as SBP <90 mm Hg and a change ≤-20 mm Hg was observed for 0.6% and 0.2% of those in the varenicline and placebo treatment groups, respectively.

Overall, 0.6% and 0.2% of subjects in the varenicline and placebo treatment groups, respectively, had an increase in sitting diastolic BP (DBP) defined as DBP >105 mm Hg and a change ≥15 mm Hg. There were no decreases in sitting DBP.

Overall, 0% and 0.2% of subjects in the varenicline and placebo treatment groups, respectively, had a decrease in sitting pulse rate (PR) defined as <50 beats per minute and a change ≤-15 beats per minute. There were no changes in sitting PR meeting the definition for increase in PR.

Overall, 16.2% and 5.0% of subjects in the varenicline and placebo treatment groups, respectively, had a weight increase of >7%. A weight decrease of <-7% was observed for 1.6% and 1.7% of those in the varenicline and placebo treatment groups, respectively.

Significant changes from Screening in physical examination findings at Week 24 were rare in both treatment groups (varenicline, 1.2%; placebo, 1.3%).

Laboratory test abnormalities that were recorded as AEs included blood cholesterol increase for 1 subject in the varenicline treatment group and blood triglycerides increase for 1 subject in the varenicline treatment group; these AEs were considered mild in intensity.

Columbia-Suicide Severity Rating Scale:

During the study, treatment-emergent suicidal behavior and/or ideation was reported for 6 (0.8%) subjects in the varenicline group compared with 10 (1.4%) subjects in the placebo group (Table 18).

Table 18. Summary of Columbia-Suicide Severity Rating Scale During Treatment and During Follow-Up - All Treated Population

Classification Category	Treatment-Emergent		During Follow-Up	
	Varenicline (N=751)	Placebo (N=742)	Varenicline (N=751)	Placebo (N=742)
Number assessed	749	740	599	564
Suicidal behavior and/or ideation	6 (0.8)	10 (1.4)	5 (0.8)	3 (0.5)
Suicidal behavior	1 (0.1)	0	1 (0.2)	0
Completed suicide	0	0	0	0
Suicide attempt	1 (0.1)	0	0	0
Preparatory acts toward imminent suicidal behavior	0	0	1 (0.2)	0
Aborted attempt	0	0	0	0
Interrupted attempt	0	0	0	0
Preparatory act or behavior	0	0	1 (0.2)	0
Suicide ideation	6 (0.8)	10 (1.4)	5 (0.8)	3 (0.5)
Wish to be dead	5 (0.7)	8 (1.1)	4 (0.7)	3 (0.5)
Non-specific active suicidal thoughts	2 (0.3)	6 (0.8)	4 (0.7)	1 (0.2)
Active suicidal ideation with any methods (not plan) without intent to act	2 (0.3)	2 (0.3)	3 (0.5)	0
Active suicidal ideation with some intent to act without specific plan	0	0	0	0
Active suicidal ideation with specific plan and intent	1 (0.1)	0	0	0
Self-injurious behavior no suicidal intent	1 (0.1)	0	0	0

All Treated population (N) included all subjects who had been randomized and received at least 1 dose, including partial doses, of randomized study medication.

Patient Health Questionnaire:

During the study, PHQ-9 showed a low incidence of depressive symptoms of "moderately severe" and "severe" scores in both treatment groups. In the varenicline group, the incidence of "moderately severe" was 0.7% at Baseline and 0.7 % or less at each postbaseline visit while the incidence of "severe" was 0 at Baseline and 0.2% or less at each postbaseline visit. In the placebo group, the incidence of "moderately severe" was 0.3% at Baseline and 0.7 % or less at each postbaseline visit while the incidence of "severe" was 0.1% at Baseline and 0.4% or less at each postbaseline visit.

Table 19. Patient Health Questionnaire (PHQ-9) - All Treated Population

	Varenicline	Placebo	Mild		Moderate		Moderately Severe		Severe	
	N*	N*	Varenicline	Placebo	Varenicline	Placebo	Varenicline	Placebo	Varenicline	Placebo
Baseline	750	741	95 (12.7)	80 (10.8)	16 (2.1)	23 (3.1)	5 (0.7)	2 (0.3)	0	1 (0.1)
Week 2	734	726	68 (9.3)	50 (6.9)	14 (1.9)	10 (1.4)	1 (0.1)	0	0	0
Week 4	711	706	66 (9.3)	38 (5.4)	15 (2.1)	15 (2.1)	0	1 (0.1)	1 (0.1)	0
Week 6	697	678	63 (9.0)	45 (6.6)	9 (1.3)	6 (0.9)	0	2 (0.3)	1 (0.1)	0
Week 8	685	668	57 (8.3)	32 (4.8)	8 (1.2)	9 (1.3)	0	3 (0.4)	1 (0.1)	1 (0.1)
Week 10	671	641	32 (4.8)	30 (4.7)	5 (0.7)	2 (0.3)	0	3 (0.5)	1 (0.1)	0
Week 12	652	616	52 (8.0)	51 (8.3)	8 (1.2)	7 (1.1)	2 (0.3)	2 (0.3)	1 (0.2)	1 (0.2)
Week 14	646	592	32 (5.0)	16 (2.7)	3 (0.5)	4 (0.7)	0	1 (0.2)	0	1 (0.2)
Week 16	631	579	16 (2.5)	18 (3.1)	4 (0.6)	2 (0.3)	2 (0.3)	0	0	1 (0.2)
Week 18	623	572	49 (7.9)	40 (7.0)	7 (1.1)	7 (1.2)	2 (0.3)	4 (0.7)	0	2 (0.3)
Week 20	624	569	25 (4.0)	16 (2.8)	2 (0.3)	7 (1.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Week 22	591	545	33 (5.6)	37 (6.8)	1 (0.2)	8 (1.5)	1 (0.2)	2 (0.4)	0	0
Week 24	603	551	25 (4.1)	28 (5.1)	7 (1.2)	8 (1.5)	3 (0.5)	3 (0.5)	1 (0.2)	0
Week 26	589	539	34 (5.8)	31 (5.8)	5 (0.8)	7 (1.3)	4 (0.7)	2 (0.4)	0	2 (0.4)
Week 32	575	531	29 (5.0)	31 (5.8)	6 (1.0)	11 (2.1)	3 (0.5)	2 (0.4)	0	0
Week 40	554	512	25 (4.5)	20 (3.9)	4 (0.7)	12 (2.3)	1 (0.2)	3 (0.6)	1 (0.2)	1 (0.2)
Week 48	540	498	28 (5.2)	31 (6.2)	3 (0.6)	4 (0.8)	0	0	1 (0.2)	0
Week 52	557	514	20 (3.6)	24 (4.7)	1 (0.2)	4 (0.8)	2 (0.4)	2 (0.4)	0	0

All Treated population included all subjects who had been randomized and received at least 1 dose, including partial doses, of randomized study medication.
Percentages are based on the row total number N*.
Based on total score, categories were defined as 0-4 = 'none'; 5-9 = 'mild'; 10-14 = 'moderate'; 15-19 = 'moderately severe'; 20-27 = 'severe'.
The total score of PHQ was defined as the average score for the 8 non-missing items multiplied by 9 if the response to only 1 item is missing. However if the responses to >1 item were missing then the total score for that subject for that occasion was missing.
N* = number of subjects with assessment at the given week; PHQ = Patient Health Questionnaire.

Conclusions: Based on the results of the primary endpoint and all key secondary endpoints, this study provides the first placebo-controlled evidence that treatment with varenicline can benefit smokers who are unable to quit abruptly, but who are motivated to quit through a reduction approach.

Safety outcomes indicated that treatment with varenicline in this population was generally well tolerated with a safety profile that was consistent with previous varenicline studies and that no new safety concerns emerged from the study.