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

PROTOCOL NO.: A3051095

PROTOCOL TITLE: Phase 4, Prospective, Multi-National, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Smoking Cessation With Varenicline Tartrate Compared With Placebo in the Setting of Patient Self-Selected (Flexible) Quit Date

Study Centers: A total of 33 centers in 14 countries took part in the study and enrolled subjects; 1 each in Argentina, Brazil, France, Italy, Mexico and the United Kingdom (UK), 2 each in Canada, the Czech Republic, Germany, Hungary, the Republic of Korea and Taiwan, 3 in China, and 12 in United States (US).

Study Initiation and Final Completion Dates: 26 September 2008 to 10 December 2009

Phase of Development: Phase 4

Study Objectives:

Primary Objective:

- To compare 12 weeks of treatment with varenicline 1 mg twice daily (BID) to placebo for smoking cessation in the setting of a subject self-selected quit date (before Week 5 visit), and to evaluate continuous abstinence (CA) from smoking for 12 weeks after the treatment period.

Secondary Objectives:

- To compare treatments for decreasing the Urge to Smoke, Smoking Satisfaction and the Psychological Reward from smoking over time in subjects in the US by analyses of the results from the Minnesota Nicotine Withdrawal Scale (MNWS) and the Modified Cigarette Evaluation Questionnaire (mCEQ) questionnaires, respectively.

- To gather safety data for 12 weeks of treatment with varenicline 1 mg BID or placebo followed by 12 weeks of nontreatment follow-up, and to evaluate safety and tolerability when used in the setting of a subject self-selected quit date.

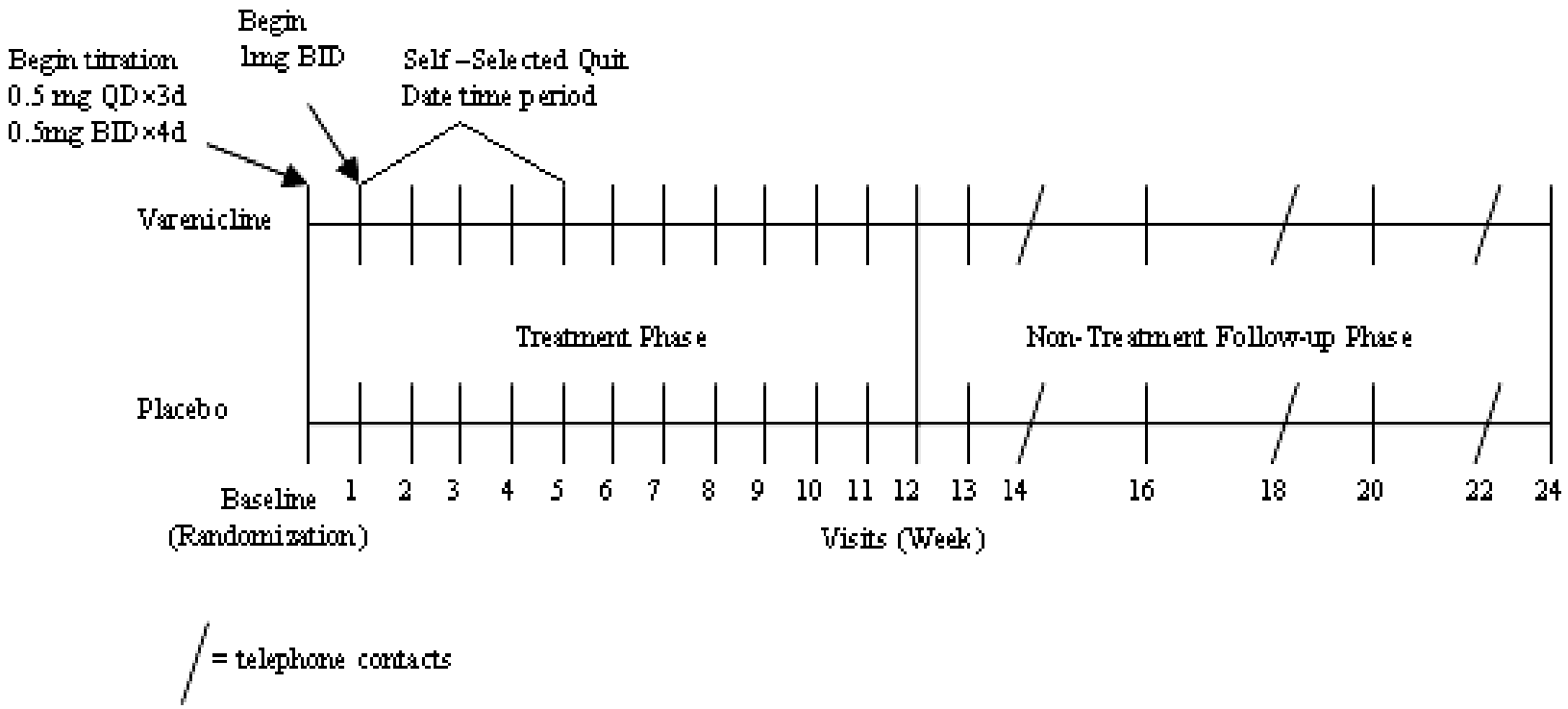
METHODS

Study Design: This was a randomized, double-blind, placebo-controlled, multinational study comparing the efficacy and safety of varenicline 1 mg BID with placebo for smoking cessation.

The study consisted of a 12-week treatment phase followed by a 12-week nontreatment phase for a total study duration of 24 weeks (Figure 1). The subjects were to be randomized in a 3:1 ratio to receive either varenicline (1-week titration followed by 11 weeks of 1 mg BID treatment) or placebo. Blinded study medication was discontinued at the Week 12 visit and was followed by a nontreatment period to Week 24. Subjects were to self-select a quit date to occur between Day 8 (the date of dose escalation to 1 mg BID) and the Week 5 visit day. The Week 1 visit occurred at the end of the first week of treatment. Subjects were to return for clinic visits at Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 during the treatment period. During the nontreatment follow-up, subjects were to return for visits at Weeks 13, 16, 20 and 24, and were contacted by phone at Weeks 14, 18 and 22. Each subject received brief smoking cessation counseling, consistent with the Agency for Healthcare Research and Quality guidelines or similar local guidelines at each clinic visit and at each telephone contact starting with the baseline visit. At the baseline visit, subjects also received an educational booklet about smoking cessation.

Specific procedures and assessments are shown in the schedule of activities in Table 1 for the treatment phase and in Table 2 for the nontreatment follow-up phase.

Figure 1. Study Design



BID = twice daily; d = day; QD = once daily.

Table 1. Schedule of Activities for the Treatment Phase

Visit Protocol Activity	Screening Visit	Baseline Visit	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	ET 12 [a]	Day of First Quit Attempt [b]
Informed consent[c]	X															
Demographic, medical, alcohol use/smoking history, height and temperature	X															
Physical exam	X													X	X	
Weight	X	X												X	X	
Fagerström test	X	X														X
Heart rate, sitting blood pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood chemistry, hematology (fasting)	X													X	X	
Urinalysis	X													X	X	
hs-CRP	X													X	X	
Serum cotinine	X													X	X	
Serum pregnancy test[d]	X													X	X	
ECG	X													X	X	
Urine drug screen	X															
Study drug dispensed		X	X	X	X	X	X	X	X	X	X	X	X			
Dosing records			X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Exhaled CO		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Nicotine use inventory			X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacogenomics sample[e]	X															
AEs and SAEs[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Counseling (AHRQ guidelines)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1. Schedule of Activities for the Treatment Phase

Visit Protocol Activity	Screening Visit	Baseline Visit	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	ET 12 [a]	Day of First Quit Attempt [b]
Urine cotinine[g]		X	X	X	X	X	X									
Smoking log[h]	X	X	X	X	X	X	X									
Plan and quit questionnaire		X	X	X	X	X	X									
mCEQ[i]		X	X	Xj	X	X	X	X	X	X	X	X	X	X	X	
MNWS[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PHQ-9	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

AE = adverse event; AHRQ = Agency for Healthcare Research and Quality; CO = carbon monoxide; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; FTND = Fagerström test for nicotine dependency; hs-CRP = high-sensitivity C-reactive protein; mCEQ = modified Cigarette Evaluation questionnaire; MNWS = Minnesota Nicotine Withdrawal scale; PHQ-9 = Patient Health Questionnaire; SAE = serious adverse event; Wk = week.

a. Early Termination (ET) 12, if early termination is before the Week 12 visit.
b. To occur between Day 8 and day prior to Week 5 Visit. The responses on the FTND should reflect consideration of the days just prior to the first attempt.
c. Must be signed prior to any protocol procedures being performed.
d. All females unless surgically sterilized or at least 2 years postmenopausal.
e. Optional-separate consent required.
f. All adverse events were collected from informed consent to the last subject visit.
g. Urine cotinine to be measured only while subject is continuing to smoke up to Week 5.
h. Dispense at Screening and weekly through Visit 4. To be kept by the subject while continuing to smoke up to Week 5.
i. Collected only in subjects recruited in the United States.
j. Administered daily during Week 2.

Table 2. Schedule of Activities for the Nontreatment Follow-Up Phase

Visit Protocol Activity	Week 13 Clinic	Week 14 Phone	Week 16 Clinic	Week 18 Phone	Week 20 Clinic	Week 22 Phone	Week 24 Clinic	ET 24[a] Clinic
Nicotine use inventory	X	X	X	X	X	X	X	X
Vital signs (heart rate, sitting blood pressure)	X		X		X		X	X
Exhaled carbon monoxide	X		X		X		X	X
Concomitant medications	X	X	X	X	X	X	X	X
Adverse events and serious adverse events	X	X	X	X	X	X	X	X
Counseling (AHRQ)	X	X	X	X	X	X	X	X
Blood chemistry, hematology, fasting							X	X
Urinalysis							X	X
ECG							X	X
Weight							X	X
Serum cotinine							X	X
hs-CRP							X	X
PHQ-9	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X

AHRQ = Agency for Healthcare Research and Quality; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; hs-CRP = high-sensitivity C-reactive protein; PHQ-9 = Patient Health Questionnaire.

a. If early termination was before the Week 24 visit.

Number of Subjects (Planned and Analyzed): A sample size of 652 subjects was planned for enrollment into this study. A total of 831 subjects were screened and 659 were assigned to treatment in a 3:1 ratio: 493 in varenicline treatment group and 166 in placebo. Of these, 486 and 165 subjects were treated with at least 1 dose of varenicline and placebo, respectively.

Of 659 subjects; 224 were randomized in the US, 58 in China, 56 in Germany, 43 in the UK, 38 in the Republic of Korea, 37 in Hungary, 36 each in the Czech Republic and Taiwan, 30 in Canada, 24 in Mexico, 20 each in France and Italy, 19 in Argentina, and 18 in Brazil.

Diagnosis and Main Criteria for Inclusion: Subjects were eligible for enrollment into the study if they were current cigarette smokers between 18 and 75 years of age, inclusive, and motivated to stop smoking. Subjects had to have smoked an average of at least 10 cigarettes per day before entering the study. Subjects were excluded if they had active psychiatric disease, or severe/unstable cardiovascular or pulmonary disease. If a subject had current or recent treatment to stop smoking or was previously treated with varenicline they were excluded from study.

Study Treatment: Subjects were randomized to receive either blinded varenicline or placebo. Subjects randomized to varenicline were titrated to the full dose during the first week in the following manner: 0.5 mg once daily (QD) x 3 days followed by 0.5 mg BID x 4 days, and then 1 mg BID for 11 weeks.

Treatment began from the Week 1 bottle on the day after the baseline visit. For the first 3 days of the Week 1 dosing period, subjects took one 0.5 mg tablet per day at the same time each day, either morning or evening; for the next 4 days, this increased to two 0.5 mg tablets per day, 1 in the morning and 1 in the evening. On study Day 8, subjects increased their dose to 1 mg BID. If Day 8 was before the Week 1 visit, this could have been administered using two 0.5 mg tablets in the morning and two 0.5 mg tablets in the evening (using the Week 1 bottle). At the Week 1 and subsequent visits, subjects were given the respective bottles of 1 mg varenicline or placebo and were instructed to take two 1 mg tablets daily, 1 in the evening and 1 in the morning.

Dosing was advised to occur with approximately 240 ml of water and it was recommended that subjects took their medication with food. At least 8 hours between the morning and evening dosing was recommended.

During the nontreatment follow-up period from Week 13 to Week 24, subjects did not receive study medication. Tablets (blinded varenicline or placebo) were supplied in bottles containing sufficient tablets for 1 week. Varenicline was supplied as 0.5 mg tablets for the first week and 1.0 mg tablets for the remaining 11 weeks of the study treatment period.

Efficacy Endpoints:

Primary Endpoint: The 4-week continuous abstinence rate (CAR) for Weeks 9-12 (ie, the proportion of subjects who were able to maintain complete abstinence from cigarette smoking and other nicotine use, with end-expiratory exhaled CO measurements ≤10 ppm, for the planned last 4 weeks of treatment).

Secondary Endpoints: Continuous abstinence (CA) from smoking from Week 9 through Week 24 (ie, the proportion of subjects who were able to maintain CA from cigarette smoking for Weeks 9 through 24).

Additional secondary efficacy endpoints were long-term quit rate (LTQR) through Week 24 (defined as the proportion of subjects who had successfully quit during the treatment phase of the study based on the 4-week CAR from Week 9 through Week 12 and who had no more than 6 days of smoking during the nontreatment phase of the study), 7-day point prevalence of nonsmoking at Weeks 12 and 24 (defined as the proportion of subjects who were able to maintain CA from cigarette smoking for the 7 days prior to Week 12 and Week 24, respectively) and 4-week point prevalence of nonsmoking at Week 24 (defined as the proportion of subjects who were able to maintain CA from cigarette smoking for the 4 weeks prior to Week 24).

Additionally, other secondary endpoints included the results from the MNWS and the mCEQ. The MNWS was used to assess craving and nicotine withdrawal symptoms. The rewarding effects associated with smoking were measured with the mCEQ. The MNWS and the mCEQ were administered at Baseline and weekly through Week 12 to subjects enrolled in the US centers only.

Safety Evaluations: Safety was evaluated based on adverse events (AEs), vital signs, physical examination, body weight and height, electrocardiograms (ECGs), and laboratory test results. Throughout the study, the Columbia Suicide Severity Rating Scale (C-SSRS) was administered to evaluate suicidal ideation and behavior. The Patient Health Questionnaire (PHQ-9) was used at each clinic visit or telephone assessment to evaluate depression.

Statistical Methods:

All Subjects Population: All subjects who received at least 1 dose, including partial doses, of randomized study medication.

Evaluable Subjects Population: All subjects who took at least 14 days of study medication in the first 21 days of the study.

Intention-to-treat (ITT) Population: All subjects who were randomized to study treatment were included in the ITT population.

Completers Population: All subjects who had at least 80% treatment compliance.

The All Subjects population was the primary population for efficacy and safety analyses in this study. Analyses of the Evaluable Subjects population, Completers population, and ITT population were intended to support the robustness of the conclusions made on the All Subjects population.

Mean, median, standard deviation, and range were used to summarize continuous variables, and counts and percentages were used to summarize categorical variables. For binary efficacy endpoints, statistical inference was based on logistic regression models with the main effect of treatment as the explanatory variable and investigative center as covariate. This statistical methodology was used for analyzing the primary and key secondary efficacy data.

All statistical testing was 2-sided and used a 0.05 level of significance. In order to preserve the type I family-wise error rate of 0.05, a step-down procedure was used for the analysis of the primary and key secondary endpoint. The hierarchy of comparisons was 1) the 4-week CQR for Weeks 9 through 12 and then 2) the CA at Week 24 for Weeks 9 through 24. Statistical significance was declared for each hypothesis in the ordered list until a p-value >0.05 was obtained, at which point the hypothesis was declared to not be statistically significant. The p-values for analyses of the secondary endpoints, other than the key secondary endpoint, were reported with no adjustments for multiplicity.

The All Subjects population were included in the safety analysis. Safety data were presented using descriptive statistics.

RESULTS

Subject Disposition and Demography: A summary of subject disposition and subjects analyzed is presented in Table 3. Of the 831 subjects who were screened for study participation, 659 were assigned to treatment; 486 subjects received varenicline and 165 subjects received placebo. Eight subjects were randomized but did not receive treatment.

Subjects were encouraged to remain in the study if they discontinued treatment in order to provide data for smoking status and other outcomes. Hence, there were 2 separate presentations on subject disposition, 1 representing treatment, and 1 representing the entire study.

All subjects who received study drug treatment were included in the primary analysis population for efficacy and safety (All Subjects population).

Table 3. Subject Disposition and Subjects Analyzed

Number (%) of Subjects	Varenicline	Placebo
Screened=831		
Assigned to study treatment	493	166
Treated	486	165
Completed study	425 (87.4)	141 (85.5)
Discontinued study	61 (12.6)	24 (14.5)
Completed study treatment period[a]	442 (90.9)	142 (86.1)
Discontinued study in treatment period	44 (9.1)	23 (13.9)
Completed treatment[b]	425 (87.4)	131 (79.4)
Discontinued treatment[c]	61 (12.6)	34 (20.6)
Related to study drug	24 (4.9)	14 (8.5)
Adverse event	23 (4.7)	11 (6.7)
Lack of efficacy	1 (0.2)	3 (1.8)
Not related to study drug	37 (7.6)	20 (12.1)
Adverse event	1 (0.2)	2 (1.2)
Lost to follow up	9 (1.9)	10 (6.1)
Subject no longer willing to participate in study	18 (3.7)	6 (3.6)
Other	9 (1.9)	2 (1.2)
Discontinued treatment, but stayed in study[d]	17 (3.5)	11 (6.7)
Completed follow-up period	0	10 (6.1)
Discontinued study in follow-up period	17 (3.5)	1 (0.6)
Not related to study drug	17 (3.5)	1 (0.6)
Lost to follow up	8 (1.6)	0
Subject no longer willing to participate in study	7 (1.4)	1 (0.6)
Other	2 (0.4)	0
Analyzed for efficacy[e]		
All Subjects[f]	486 (98.6)	165 (99.4)
Evaluable Subjects[g]	468 (94.9)	160 (96.4)
Completer Subjects[h]	425 (86.2)	130 (78.3)
ITT (all randomized subjects)[i]	493 (100.0)	166 (100.0)
Analyzed for safety[j]		
Adverse events[k]	486 (100.0)	165 (100.0)
Laboratory data[l]	444 (91.4)	144 (87.3)

ITT = intent-to-treat.

a. Refers to subjects who remained in the study until Week 12 regardless of treatment exposure.
b. Refers to subjects who took study medication up to Week 12.
c. Discontinuations from the study could occur during the treatment period or during the post-therapy follow-up period, ie, subjects discontinuing treatment were not necessarily also discontinuing the study.
d. Subjects could discontinue from treatment and remain in the study.
e. Percentages based on ITT population.
f. The All Subjects population was defined as all subjects who received at least 1 dose of study drug. This was the primary efficacy analysis population.
g. The Evaluable Subjects group was defined to be a subset of the All Subjects population, who took at least 14 days of study drug in the first 21 days of the study.
h. The Completers population was defined as the subset of the All Subjects population, who had at least 80% treatment compliance.
i. The ITT population was defined as all randomized subjects.
j. Percentages based on All Subjects population.
k. Adverse events were analyzed for the All Subjects population.
l. Laboratory data were analyzed for all subjects who had at least 1 postbaseline laboratory value.

The demographic characteristics for the All Subjects population are presented in Table 4.

Overall, subjects in the varenicline and placebo groups had been smoking for an average of 26.0 years and 24.6 years, respectively. About one-third of the subjects in each group never had made a serious quit attempt.

Table 4. Demographic and Baseline Characteristics (All Subjects Population)

	Varenicline N=486	Placebo N=165
Gender, n (%)		
Male	293 (60.3)	99 (60.0)
Female	193 (39.7)	66 (40.0)
Age, n (%)		
18-44	248 (51.0)	93 (56.4)
45-64	209 (43.0)	64 (38.8)
≥65	29 (6.0)	8 (4.8)
Mean ± SD	43.9±12.55	43.2±12.22
Range	18–75	18–72
Race, n (%)		
White	331 (68.1)	112 (67.9)
Black	31 (6.4)	8 (4.8)
Asian	103 (21.2)	36 (21.8)
Other	21 (4.3)	9 (5.5)
Weight (kg)		
Mean ± SD	76.5±15.74	78.5±17.08
Range	46.0–133.6	48.1–148.8
Body mass index (kg/m^2)[a]		
Mean ± SD	26.2±4.33	26.7±4.66
Range	16.8–38.0	19.3–38.7
Height (cm)		
Mean ± SD	170.5±8.97	171.0±9.23
Range	145.0–197.0	144.0–203.0
Smoking history		
Total number of years subject smoked		
Mean	26.0	24.6
Range	2–57	2–59
Average number of cigarettes per day over last month		
Mean	21.3	21.4
Range	10–70	10–65
Longest period of abstinence (days) in past year		
Mean	4.4	4.7
Range	0–90	0–90
Number of lifetime serious quit attempts, n (%)[b]		
None	159 (32.7)	60 (36.4)
One	150 (30.9)	45 (27.3)
Two	65 (13.4)	24 (14.5)
Three or more	112 (23.0)	36 (21.8)
Fagerström test for nicotine dependence, total score[c]		
Mean ± SD	5.6±2.21	5.4±2.12

N = total number of subjects in the respective treatment group; n = number of subjects with respective characteristic; SD = standard deviation.

a. Body mass index was calculated as weight in kg/height in m^2.
b. Any method. Calculated field, which represents the number of quit attempts and/or types used.
c. Total score ranges from 0 to 10. Higher scores indicate greater degree of dependence.

The median duration of treatment was 83 days for both the varenicline and placebo treatment groups and most subjects were exposed for 61 to 90 days for both the varenicline and placebo treatment groups. Treatment duration was defined as the total number of dosing days from the first dose day to (and including) the last dose day of study treatment.

Efficacy Results:

Primary Endpoint Result:

Four-Week Continuous Abstinence Rate/Continuous Quit Rate for Weeks 9-12: In the All Subjects population, the 4-week CQR for Weeks 9 through 12 was statistically significantly greater for varenicline than placebo with an odds ratio of 6.03 and corresponding 95% CI of 3.80 and 9.56 ($p < 0.0001$) (Table 5).

Results of the Weeks 9 through 12 CQR analyses for the Evaluable Subjects (varenicline: 260 subjects [55.6%], placebo: 32 [20.0%]; odds ratio [OR]: 6.24), Completer Subjects (varenicline: 256 subjects [60.2%], placebo: 29 [22.3%]; OR: 6.66), and ITT (All Randomized Subjects) (varenicline: 262 subjects [53.1%], placebo: 32 [19.3%]; OR: 5.93) populations support the robustness of the results for the All Subjects' analysis (all $p < 0.0001$).

Secondary Endpoints Results: The results are presented in Table 5.

Continuous Abstinence From Smoking From Week 9 Through Week 24: The CAR from Week 9 to Week 24 was statistically significantly higher in the varenicline group than the placebo group. At Week 24, the CAR was 35.2% for varenicline and 12.7% for placebo ($p < 0.0001$) (Table 5).

Results of the analyses for the Evaluable Subjects (varenicline: 170 subjects [36.3%], placebo: 21 [13.1%]; OR: 4.54), Completer Subjects (varenicline: 167 subjects [39.3%], placebo: 19 [14.6%]; OR: 4.62), and ITT (All Randomized Subjects) (varenicline: 171 subjects [34.7%], placebo: 21 [12.7%]; OR: 4.42) populations supported the results for the All Subjects population, with a statistically significant difference between the varenicline and placebo groups in the CAR from Weeks 9 to 24 for all populations (all $p < 0.0001$).

Long-Term Quit Rate Through Week 24: At Week 24, the LTQR was statistically significantly higher for varenicline compared with placebo (40.7% versus 14.6%, respectively; $p < 0.0001$) (Table 5).

Results of the analyses for the Evaluable Subjects, Completer Subjects, and ITT (All Randomized Subjects) populations supported the results for the All Subjects population, with a statistically significant difference between the varenicline and placebo groups in the LTQR from Week 9 through Week 24 for each population (all $p < 0.0001$).

Seven-day Point Prevalence of Nonsmoking at Weeks 12 and 24: At Weeks 12 and 24, a statistically significantly higher number of subjects in the varenicline group reported abstinence in the previous 7 days compared with subjects in the placebo group.

At the end of the treatment phase (Week 12), 289 (59.5%) subjects in the varenicline group compared with 40 (24.2%) subjects in the placebo group reported abstinence in the previous 7 days ($p < 0.0001$). At Week 24, 209 (43.0%) subjects in the varenicline group reported abstinence in the previous 7 days compared with 29 (17.6%) subjects in the placebo group ($p < 0.0001$) (Table 5).

Results of the 7-day point prevalence of abstinence analyses for the ITT (All Randomized Subjects) population were consistent with the results for the All Subjects' analysis.

Four-Week Point Prevalence of Nonsmoking at Week 24: At Week 24, a statistically significantly higher number of subjects in the varenicline group reported abstinence in the previous 4 weeks compared with subjects in the placebo group (204 [42.0%] subjects versus 28 [17.0%] subjects; p <0.0001) (Table 5).

Results of the 4-week point prevalence of abstinence analyses for the ITT (All Randomized Subjects) population were consistent with the results for the All Subjects' analysis.

Table 5. Overview of Primary and Secondary Efficacy Endpoints (All Subjects Population)

Endpoint	Varenicline N=486	Placebo N=165	Odds Ratio (95% CI) Versus Placebo	p-Value
Primary Endpoint:				
4-week CQR Weeks 9 to 12, n (%)[a]	262 (53.9)	32 (19.4)	6.03 (3.80, 9.56)	<0.0001
Secondary Endpoints:				
CAR from Week 9 to Week 24, n (%)[b]	171 (35.2)	21 (12.7)	4.45 (2.62, 7.55)	<0.0001
LTQR at Week 24, n (%)[c]	198 (40.7)	24 (14.6)	4.91 (2.96, 8.13)	<0.0001
CO-confirmed 7-day point prevalence of abstinence, n (%)[d]				
At Week 12	289 (59.5)	40 (24.2)	5.66 (3.66, 8.75)	<0.0001
At Week 24	209 (43.0)	29 (17.6)	4.12 (2.58, 6.58)	<0.0001
CO-confirmed 4-week point prevalence of abstinence at Week 24, n (%)[e]	204 (42.0)	28 (17.0)	4.14 (2.58, 6.67)	<0.0001

Odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment and pooled center.
CA = continuous abstinence; CI = confidence interval; CO = carbon monoxide; CQR = continuous quit rate; LTQR = long term quit rate; N = total number of subjects in respective treatment group.

a. Number of subjects who, at each visit from Weeks 9 through 12 (inclusive), reported no smoking and no use of other nicotine-containing products since the last study visit (on the Nicotine Use Inventory) and who did not have CO >10 ppm since the last study visit.
b. Number of subjects who at each contact from Weeks 9 to 24 reported no smoking and no use of other nicotine containing products (treatment phase) or tobacco products (nontreatment phase) since the last study contact (on the Nicotine Use Inventory) and who did not have CO >10 ppm at the clinic visit.
c. Number of subjects who were responders for the primary endpoint and who had no more than 6 days of smoking from Week 12 through Week 24.
d. Number of subjects who at the given visit, reported no smoking and no use of other nicotine-containing products (treatment phase) or tobacco products (nontreatment phase) in the last 7 days and who did not have CO >10 ppm on that day.
e. Number of subjects who reported no smoking and no use of other tobacco products in the last 4 weeks and who did not have CO >10 ppm at the visit.

Minnesota Nicotine Withdrawal Scale and Modified Cigarette Evaluation Questionnaire: At all weekly time points from Week 1 through Week 12, MNWS scores for Urge to Smoke and mCEQ scores for Satisfaction were lower for varenicline than for placebo, but only marginally lower for mCEQ Psychological Reward (Table 6).

Table 6. MNWS and mCEQ; Repeated Measures Analysis - MNWS - Urge to Smoke and mCEQ - Smoking Satisfaction and Psychosocial Reward (All Subjects Population - US Only)

	Varenicline N=163			Placebo N=56		
MNWS: Week 1-12 Average[a]	**Mean**	**SE**	**95% CI**	**Mean**	**SE**	**95% CI**
Least square	1.2	0.06	1.09, 1.31	2.0	0.09	1.78, 2.14
Difference from placebo	-0.8	0.11	-0.97, -0.55			
p-Value[b]	<0.0001					
mCEQ: Week 1-12 Average						
Subscale satisfaction[c]						
Least square	2.2	0.08	2.07, 2.39	2.8	0.13	2.56, 3.06
Difference from placebo	-0.6	0.15	-0.87, -0.29			
p-Value[d]	0.0001					
Subscale psychological reward[c]						
Least square	1.9	0.07	1.77, 2.03	2.1	0.11	1.92, 2.35
Difference from placebo	-0.2	0.12	-0.48, 0.01			
p-Value[d]	0.0602					

CI = confidence interval; mCEQ = modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; N = number of subjects in respective treatment group; SE = standard error; US = United States of America.

a. Individual scores ranged from 0 to 4, where 0 = not at all, 1 = slight, 2 = moderate, 3 = quite a bit, 4 = extreme.
b. Inferential statistics obtained from a repeated-measures model over time with the postbaseline MNWS measure as the dependent variable, treatment group as the explanatory variable of interest, baseline MNWS measure, pooled center, and visit as covariates, and interaction of treatment by visit.
c. Individual scores ranged from 1 to 7, where 1 = not at all, 2 = very little, 3 = a little, 4 = moderately, 5 = a lot, 6 = quite a lot, 7 = extremely.
d. Inferential statistics obtained from a repeated-measures model over time with the postbaseline mCEQ measure as the dependent variable, treatment group as the explanatory variable of interest, baseline mCEQ measure, pooled center, and visit as covariates, and interaction of treatment by visit.

Safety Results:

An overview of treatment-emergent AEs (TEAEs) is provided in Table 7. The incidence of all-causality TEAEs was 71.6% of varenicline-treated subjects and 53.9% of placebo-treated subjects. The incidence of TEAEs considered to be related to study drug was higher in the varenicline group than in the placebo group (56.6% varenicline-treated subjects versus 36.4% placebo-treated subjects).

Table 7. Overview of Treatment-Emergent Adverse Events (All Subjects Population)

Number (%) of Subjects	Varenicline N=486	Placebo N=165
Adverse events[a]		
All-causality	348 (71.6)	89 (53.9)
Treatment-related	275 (56.6)	60 (36.4)
Discontinuations due to adverse events[b]		
All-causality	24 (4.9)	13 (7.9)
Treatment-related	23 (4.7)	11 (6.7)
Dose reductions or temporary discontinuations of study drug due to adverse events		
All-causality	53 (10.9)	5 (3.0)
Treatment-related	44 (9.1)	4 (2.4)
Serious adverse events		
All-causality	6 (1.2)	1 (0.6)
Treatment-related	1 (0.2)	1 (0.6)
Severe adverse events		
All-causality	43 (8.8)	18 (10.9)
Treatment-related	20 (4.1)	8 (4.8)

Adverse events and serious adverse events are not separated out.
Includes data up to 30 days after last dose of study drug.
Subjects were counted only once per treatment in each row.
N = total number of subjects in respective treatment group.
a. Adverse events and serious adverse events are not separated out.
b. Includes discontinuations from the study or from treatment.

All-Causality Treatment-Emergent Adverse Events: All-causality TEAEs that occurred in ≥2% of subjects in either treatment group are summarized in Table 8.

For both treatment groups, all-causality TEAEs occurred with the greatest incidence in the system organ class (SOC) of gastrointestinal disorders, psychiatric disorders, infections and infestations, and nervous system disorders. In the varenicline group, the most frequently reported TEAEs were nausea, abnormal dreams, headache, insomnia, and nasopharyngitis. In the placebo group, the most frequently reported AEs were headache, nausea, nasopharyngitis, and dizziness.

Table 8. Treatment-Emergent Adverse Events (All-Causalities) Reported by ≥2% of Subjects in Any Treatment Group (All Subjects Population)

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term (MedDRA v12.1)	Varenicline N=486	Placebo N=165
Number (%) of subjects with adverse events	297 (61.1)	79 (47.9)
Gastrointestinal disorders	182 (37.4)	29 (17.6)
Abdominal pain	6 (1.2)	4 (2.4)
Abdominal pain upper	14 (2.9)	0
Constipation	23 (4.7)	5 (3.0)
Diarrhoea	11 (2.3)	3 (1.8)
Dry mouth	18 (3.7)	3 (1.8)
Dyspepsia	13 (2.7)	2 (1.2)
Nausea	142 (29.2)	15 (9.1)
Toothache	6 (1.2)	6 (3.6)
Vomiting	19 (3.9)	1 (0.6)
General disorders and administration site conditions	35 (7.2)	9 (5.5)
Fatigue	23 (4.7)	3 (1.8)
Irritability	14 (2.9)	6 (3.6)
Infections and infestations	85 (17.5)	29 (17.6)
Bronchitis	12 (2.5)	1 (0.6)
Influenza	19 (3.9)	6 (3.6)
Nasopharyngitis	34 (7.0)	14 (8.5)
Rhinitis	7 (1.4)	4 (2.4)
Sinusitis	8 (1.6)	4 (2.4)
Upper respiratory tract infection	13 (2.7)	4 (2.4)
Investigations	17 (3.5)	3 (1.8)
Weight increased	17 (3.5)	3 (1.8)
Metabolism and nutrition disorders	11 (2.3)	5 (3.0)
Increased appetite	11 (2.3)	5 (3.0)
Musculoskeletal and connective tissue disorders	21 (4.3)	8 (4.8)
Arthralgia	6 (1.2)	4 (2.4)
Back pain	15 (3.1)	4 (2.4)
Nervous system disorders	74 (15.2)	31 (18.8)
Disturbance in attention	11 (2.3)	6 (3.6)
Dizziness	8 (1.6)	8 (4.8)
Headache	55 (11.3)	20 (12.1)
Somnolence	11 (2.3)	2 (1.2)
Psychiatric disorders	120 (24.7)	24 (14.5)
Abnormal dreams	61 (12.6)	5 (3.0)
Anxiety	4 (0.8)	5 (3.0)
Depressed mood	5 (1.0)	5 (3.0)
Depression	4 (0.8)	5 (3.0)
Insomnia	43 (8.8)	6 (3.6)
Sleep disorder	20 (4.1)	6 (3.6)
Respiratory, thoracic and mediastinal disorders	14 (2.9)	5 (3.0)
Cough	14 (2.9)	5 (3.0)

Subjects were only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (v12.1) coding dictionary applied.
MedDRA (v12.1) = Medical Dictionary for Regulatory Activities (version 12.1); N = total number of subjects in respective treatment group.

Treatment-Emergent Treatment-Related Adverse Events: Treatment-related TEAEs that occurred in ≥2% of subjects in any treatment group are summarized in Table 9.

For both treatment groups, treatment-related TEAEs occurred with the greatest incidence in the SOC of gastrointestinal disorders, psychiatric disorders, and nervous system disorders. The most frequently reported treatment-emergent treatment-related AEs among the varenicline-treated subjects were nausea (28.0% of subjects), abnormal dreams (12.6%), headache (8.6%), and insomnia (8.2%). The most frequently reported treatment-emergent treatment-related AEs among the placebo-treated subjects were nausea and headache (9.1% each), dizziness (4.2%), and abnormal dreams, insomnia, and sleep disorder (3.0% each).

Table 9. Treatment-Emergent Treatment-Related Adverse Events Reported by ≥2% of Subjects in Any Treatment Group (All Subjects Population)

Number (%) of Subjects With Adverse Events by System Organ Class Preferred Term (MedDRA v12.1)	Varenicline N=486	Placebo N=165
Gastrointestinal disorders	176 (36.2)	22 (13.3)
Constipation	13 (2.7)	3 (1.8)
Dyspepsia	10 (2.1)	1 (0.6)
Nausea	136 (28.0)	15 (9.1)
Vomiting	15 (3.1)	1 (0.6)
Dry mouth	18 (3.7)	3 (1.8)
General disorders and administration site conditions	41 (8.4)	8 (4.8)
Fatigue	19 (3.9)	3 (1.8)
Irritability	11 (2.3)	3 (1.8)
Metabolism and nutrition disorders	16 (3.3)	1 (0.6)
Increased appetite	10 (2.1)	0
Nervous system disorders	73 (15.0)	28 (17.0)
Headache	42 (8.6)	15 (9.1)
Disturbance in attention	10 (2.1)	4 (2.4)
Dizziness	7 (1.4)	7 (4.2)
Somnolence	11 (2.3)	2 (1.2)
Psychiatric disorders	127 (26.1)	24 (14.5)
Depression	3 (0.6)	4 (2.4)
Abnormal dreams	61 (12.6)	5 (3.0)
Insomnia	40 (8.2)	5 (3.0)
Sleep disorder	18 (3.7)	5 (3.0)

AEs and SAEs are not separated out.
Subjects were only counted once per treatment in each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (v12.1) coding dictionary applied.
AE = adverse event; MedDRA (v12.1) = Medical Dictionary for Regulatory Activities (version 12.1); N = total number of subjects in respective treatment group; SAE = serious adverse events.

Serious Adverse Events (SAEs) and Deaths:

Treatment-emergent SAEs (all-causalities) are summarized by system organ class and preferred term in Table 10. There were 6 (1.2%) subjects in the varenicline group and 1 (0.6%) subject in the placebo group with SAEs that occurred during the treatment period or up to 28 days after the treatment phase. Two of the SAEs were considered treatment-related (syncope in 1 subject in the varenicline group and suicidal ideation in 1 subject in the placebo group). Syncope was assessed as treatment-related by the Investigator but as not related to treatment by the Sponsor. All SAEs resolved or were resolving by the end of the study. The SAEs syncope in the varenicline group and suicidal ideation in the placebo group led to discontinuation of the study.

No deaths were reported during the study.

Table 10. Treatment-Emergent Serious Adverse Events (All-Causalities) - All Subjects Population

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term (MedDRA v12.1)	Varenicline	Placebo
Number of subjects evaluable for adverse events	486 (100)	165 (100)
Number of subjects with adverse events	6 (1.2)	1 (0.6)
Musculoskeletal and connective tissue disorders	2 (0.4)	0
Intervertebral disc protrusion	2 (0.4)	0
Nervous system disorders	2 (0.4)	0
Carotid artery stenosis	1 (0.2)	0
Syncope	1 (0.2)	0
Psychiatric disorders	0	1 (0.6)
Suicidal ideation	0	1 (0.6)
Renal and urinary disorders	1 (0.2)	0
Calculus ureteric	1 (0.2)	0
Pyelocaliectasis	1 (0.2)	0
Ureteric obstruction	1 (0.2)	0
Vascular disorders	1 (0.2)	0
Peripheral arterial occlusive disease	1 (0.2)	0

Subjects were only counted once per treatment in each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (v12.1) coding dictionary applied.
AE = adverse event; MedDRA (v12.1) = Medical Dictionary for Regulatory Activities (version 12.1).

Permanent Discontinuations due to Adverse Events: Incidence of AEs resulting in permanent discontinuation of study medication (all-causalities) is summarized in Table 11.

Table 11. Incidence of Treatment-Emergent Adverse Events Resulting in Permanent Discontinuation of Study Medication (All-Causalities) - All Subjects Population

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term (MedDRA v12.1)	Varenicline	Placebo
Number of subjects evaluable for adverse events	486 (100)	165 (100)
Gastrointestinal disorders	8 (1.6)	0
Abdominal pain upper	1 (0.2)	0
Dyspepsia	1 (0.2)	0
Nausea	5 (1.0)	0
Vomiting	1 (0.2)	0
General disorders and administration site conditions	3 (0.6)	0
Irritability	3 (0.6)	0
Injury, poisoning and procedural complications	1 (0.2)	0
Lower limb fracture	1 (0.2)	0
Musculoskeletal and connective tissue disorders	0	1 (0.6)
Intervertebral disc protrusion	0	1 (0.6)
Nervous system disorders	3 (0.6)	5 (3.0)
Amnesia	1 (0.2)	0
Disturbance in attention	0	2 (1.2)
Headache	1 (0.2)	1 (0.6)
Migraine	0	1 (0.6)
Somnolence	0	1 (0.6)
Syncope	1 (0.2)	0
Psychiatric disorders	7 (1.4)	7 (4.2)
Abnormal dreams	1 (0.2)	0
Aggression	1 (0.2)	0
Anxiety	0	1 (0.6)
Depressed mood	0	2 (1.2)
Depression	1 (0.2)	2 (1.2)
Insomnia	2 (0.4)	0
Major depression	1 (0.2)	0
Nightmare	1 (0.2)	0
Obsessive-compulsive disorder	0	1 (0.6)
Suicidal ideation	0	1 (0.6)
Reproductive system and breast disorders	1 (0.2)	0
Vulvovaginal dryness	1 (0.2)	0
Skin and subcutaneous tissue disorders	1 (0.2)	0
Rash	1 (0.2)	0

Subjects were only counted once per treatment in each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (v12.1) coding dictionary applied.
AE = adverse event; MedDRA (v12.1) = Medical Dictionary for Regulatory Activities (version 12.1).

Incidence of TEAEs resulting in dose reductions or temporary discontinuations (all-causalities) from the study are summarized in Table 12.

Table 12. Incidence of Treatment-Emergent Adverse Events Resulting in Dose Reductions or Temporary Discontinuations (All-Causalities) - All Subjects Population

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term (MedDRA v12.1)	Varenicline	Placebo
Number of subjects evaluable for adverse events	486 (100)	165 (100)
Cardiac disorders	1 (0.2)	0
Palpitations	1 (0.2)	0
Ear and labyrinth disorders	0	1 (0.6)
Vertigo	0	1 (0.6)
Eye disorders	1 (0.2)	0
Cataract	1 (0.2)	0
Gastrointestinal disorders	24 (4.9)	0
Abdominal distension	2 (0.4)	0
Abdominal pain	1 (0.2)	0
Diarrhoea	1 (0.2)	0
Dyspepsia	3 (0.6)	0
Gastrooesophageal reflux disease	1 (0.2)	0
Nausea	15 (3.1)	0
Vomiting	1 (0.2)	0
General disorders and administration site conditions	5 (1.0)	0
Asthenia	1 (0.2)	0
Chest pain	1 (0.2)	0
Face oedema	1 (0.2)	0
Fatigue	2 (0.4)	0
Feeling abnormal	1 (0.2)	0
Infections and infestations	9 (1.9)	1 (0.6)
Bronchitis	1 (0.2)	0
Diverticulitis	1 (0.2)	0
Gastroenteritis	1 (0.2)	0
Gastrointestinal viral infection	2 (0.4)	0
Influenza	1 (0.2)	1 (0.6)
Nasopharyngitis	2 (0.4)	0
Tooth abscess	1 (0.2)	0
Investigations	1 (0.2)	0
Blood pressure increased	1 (0.2)	0
Metabolism and nutrition disorders	1 (0.2)	0
Decreased appetite	1 (0.2)	0
Nervous system disorders	5 (1.0)	3 (1.8)
Dizziness	1 (0.2)	0
Headache	2 (0.4)	0
Memory impairment	2 (0.4)	1 (0.6)
Migraine	0	1 (0.6)
Somnolence	0	1 (0.6)
Psychiatric disorders	11 (2.3)	1 (0.6)
Affect lability	1 (0.2)	0
Agitation	1 (0.2)	0
Apathy	1 (0.2)	0
Depersonalisation	1 (0.2)	0
Dissociation	1 (0.2)	0
Insomnia	4 (0.8)	1 (0.6)
Libido decreased	1 (0.2)	0
Nightmare	1 (0.2)	0
Panic attack	1 (0.2)	0
Panic reaction	0	1 (0.6)
Skin and subcutaneous tissue disorders	1 (0.2)	0
Angioedema	1 (0.2)	0
Vascular disorders	1 (0.2)	0
Angiopathy	1 (0.2)	0

Table 12. Incidence of Treatment-Emergent Adverse Events Resulting in Dose Reductions or Temporary Discontinuations (All-Causalities) - All Subjects Population

Subjects are only counted once per treatment in each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (v12.1) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

Columbia-Suicide Severity Rating Scale Results: The results of the C-SSRS are presented in Table 13.

A history of suicide attempt, self-injurious behavior, or suicidal ideation was reported at Screening more often in the varenicline group compared to the placebo group. Two of the subjects in the varenicline group also reported non-suicidal, self-injurious behavior and suicidal ideation, respectively, at Baseline. The protocol allowed the inclusion of subjects with a history of suicidal ideation or behavior if it had occurred more than 5 years prior to the Baseline Visit. For 1 subject, a deviation from this inclusion criterion was reported.

During the postbaseline assessments, there were 2 subjects in each treatment group that had suicidal ideation. None of these subjects had a positive answer for suicidal ideation or behavior at Baseline. Suicidal ideation was documented as an AE for these subjects. It was noticed, after the database was locked and released, that 1 subject did not have an AE reported by the Investigator for this postbaseline assessment which was later clarified by the Investigator that this was a clerical error and that this subject had no suicidal ideation at any time during the study period.

Table 13. Columbia-Suicide Severity Rating Scale (All Subjects Population)

Number (%) of Subjects	Varenicline N=486			Placebo N=165		
	Suicide Attempt	Self-Injurious Behavior, Non-Suicidal Intent	Suicidal Ideation	Suicide Attempt	Self-Injurious Behavior, Non-Suicidal Intent	Suicidal Ideation
Screening (lifetime)	2 (0.4)	3 (0.6)	15 (3.1)	0	1 (0.6)	2 (1.2)
Baseline	0	1 (0.2)	1 (0.2)	0	0	0
Any postbaseline assessment	0	0	2 (0.4)	0	0	2 (1.2)
No at Baseline and yes at any postbaseline visit	0	0	2 (0.4)	0	0	2 (1.2)

N = number of subjects in respective treatment group.

Patient Health Questionnaire-9 Depression Severity Category Results: The vast majority of subjects had a categorization of none at Screening and Baseline, as required by the protocol inclusion criteria. In the varenicline group, 6 subjects (1.3%) had mild symptoms and 1 subject (0.2%) had moderately severe symptoms at Screening; 5 subjects (1.0%) had mild symptoms, and 1 subject (0.2%) each had moderate and moderately severe symptoms at Baseline. In the placebo group 1 subject (0.6%) had mild symptoms at Screening and 1 subject (0.6%) at Baseline. These subjects were considered protocol deviators.

Table 14 shows shifts in depression severity category from Baseline to the postbaseline visit with the worst postbaseline assessment. Most frequently, shifts from none at Baseline to a postbaseline assessment of mild were reported (54 subjects [11.1%] in the varenicline group and 25 subjects [15.2%] in the placebo group). No allocation to the depression category severe occurred at any study visit for either treatment.

Table 14. PHQ-9: Shift in Depression Severity Category From Baseline to Worst Postbaseline Assessment (All Subjects Population)

	Varenicline N=486 n (%)	Placebo N=165 n (%)
Any increase in severity from Baseline[a]	65 (13.4)	29 (17.6)
None at Baseline to worst postbaseline		
Mild	54 (11.1)	25 (15.2)
Moderate	8 (1.6)	3 (1.8)
Moderately severe	3 (0.6)	0
Severe	0	0
Any at Baseline with increased severity postbaseline	0	1 (0.6)[b]

A total of 479 subjects in the varenicline group and 160 subjects in the placebo group had a baseline PHQ-9 assessment and at least 1 postbaseline assessment.
N = number of subjects in respective treatment group; n = number of subjects in the respective category; PHQ-9 = Patient Health Questionnaire-9.
a. Percentages are in reference to treatment group total.
b. From mild to moderate.

Other Safety Related Findings: The results from laboratory, body weight, vital signs, ECG, and physical examination analyses did not raise any safety concerns.

Conclusions:

This 12-week study comparing varenicline 1 mg BID with placebo for smoking cessation in the setting of a subject self-selected quit date with a 12-week follow-up period demonstrated that:

- Varenicline treatment compared to placebo treatment resulted in statistically significantly higher abstinence rates as measured by the primary efficacy endpoint CO-confirmed 4-week CQR. Varenicline treatment also achieved statistically significantly higher abstinence rates as evidenced by the parameters CAR Weeks 9 to 24, LTQR at Week 24, 7-day point prevalence of abstinence at Weeks 12 and 24, and the 4-week point prevalence of abstinence at Week 24. Varenicline statistically significantly reduced the Urge to Smoke based on the MNWS and the Satisfaction from Smoking based on the mCEQ, when compared to placebo.

- Varenicline was safe and well tolerated. There were relatively few discontinuations due to AEs. The most frequently occurring AE in the varenicline group assessed as treatment-related was nausea, which was generally mild to moderate in intensity and infrequently resulted in treatment discontinuation. The majority of SAEs were not assessed as treatment-related.