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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Chantix® / Champix® / / Varenicline tartrate (generic name)

PROTOCOL NO.: A3051139

PROTOCOL TITLE: A Phase 4 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Re-Treatment With Varenicline in Subjects who are Currently Smoking, and who Have Previously Taken Varenicline

Study Centers: A total of 36 centers took part in the study and randomized subjects; 4 each in Australia, Belgium, Canada and the Czech Republic, 3 in France, 5 each in Germany and the United Kingdom, and 7 in the United States

Study Initiation Date and Final Completion Dates: 10 December 2010 to 02 November 2012

Phase of Development: Phase 4

Study Objectives: The primary objective of this study was to compare the efficacy and safety of re-treatment with varenicline with placebo for smoking cessation for the last 4 weeks of a 12-week treatment period (continuous abstinence rate; CAR 9-12).

The key secondary objective was to compare the efficacy of varenicline with placebo from Week 9 to the end of the long-term nontreatment follow-up period at Week 52 (CAR 9-52).

Additional secondary efficacy objectives included:

- Comparing smoking abstinence at the 24-week time point (CAR 9-24) between the varenicline and placebo treatment groups;
- Comparing the 7-day point prevalence of smoking abstinence at specific time points (Weeks 12, 24 and 52) between the varenicline and placebo treatment groups.

METHODS

Study Design: This study was a Phase 4, randomized, double-blind, placebo-controlled, parallel group, 2-arm, multicenter study designed to evaluate the efficacy and safety of re-treatment with varenicline in subjects who had been smoking (for at least 4 weeks), and who had taken varenicline for a smoking cessation attempt in the past (for a total treatment duration of a minimum of 2 weeks), at least 3 months previously.

Screening Period (Approximately 3 to 10 Days): During this period, subjects attended a clinic Screening visit at which their eligibility for participation in the study was evaluated, the consent form was signed, samples were collected for laboratory tests, and a 12-lead electrocardiogram (ECG) was performed. Subjects who met all eligibility criteria for randomization at the Baseline clinic visit then entered the active treatment period.

12-Week Treatment Period: During this double-blind treatment period, subjects attended the clinic for weekly visits, except at Weeks 5 and 7, where contact was made by telephone. All efficacy and safety evaluations were undertaken at the clinic visits. Data for the nicotine-use inventory (NUI) were also collected for the weeks where there was telephone contact. Brief counseling (≤10 minutes) was provided at all weekly time points from Baseline through Week 12. All subjects randomized to receive varenicline were titrated to the full dose during the first week in the following manner: 0.5 mg once daily (QD) for 3 days, 0.5 mg twice daily (BID) for 4 days, then 1 mg BID for the following 11 weeks. Study drug (varenicline or placebo) was dispensed at clinic visits only; subjects received sufficient study drug at Weeks 4 and 6 for the study period between Weeks 4 and 6, and Weeks 6 and 8, respectively, given that subjects did not attend clinic visits at Weeks 5 and 7. Dosing records were checked at clinic visits only.

40-Week Nontreatment Period (Follow-Up to Week 52): Study drug was discontinued at Week 12, and subjects continued into the nontreatment follow-up period. Clinic visits were at Weeks 13, 16, 24, 32, 40, 48, and 52. Telephone contact was made at Weeks 14, 20, 28, 36, and 44. Brief counseling (≤10 minutes) continued to be provided from Week 13 through to Week 52, at each clinic visit or telephone contact.

Table 1 summarizes the schedule of activities from the Screening visit to Week 12/End of Treatment and Table 2 summarizes the schedule of activities from Week 13 to Week 52 (Nontreatment Follow-Up Period).

Table 1 Schedule of Activities: Screening Visit to Week 12/End of Treatment

Protocol Activity	Screen[a]	BL	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	ET 12
Visit Window		**3-10 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**NA[b]**
Clinic visit	X	X	X	X	X	X		X		X	X	X	X	X	X
Telephone contact							X		X						
Informed consent[c]	X														
Medical and smoking history	X														
Demography	X														
Physical examination	X													X	X
Vital signs (HR, BP)	X	X												X	X
Weight	X													X	X
Height	X														
Fagerström test	X														
Exhaled carbon monoxide	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	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X	X	X	X		X		X	X	X	X		
Complete dosing record and collect unused medication bottles			X	X	X	X		X		X	X	X	X	X	X

Table 1 Schedule of Activities: Screening Visit to Week 12/End of Treatment

Protocol Activity	Screen[a]	BL	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	ET 12
Visit Window		**3-10 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**+/-±3 Days**	**NA[b]**
Concomitant drug and non drug treatments	X	X	X	X	X	X		X		X	X	X	X	X	X
ECG (local)	X														
CBC, blood chemistry (central)	X														
Pregnancy test (dipstick at site)[d]	X	X												X	X
Urine drug screen (dipstick at site)[e]	X	X													
Counseling (≤10 minutes)		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
SBQ-R	X														

BL = baseline; BP = blood pressure; C-SSRS = columbia suicide severity rating scale; CBC = complete blood count; ECG = electrocardiogram; ET = early termination, if not occurring at Week 12; HR = heart rate; SBQ-R = suicide behaviors questionnaire-revised; W = week.

a. Screening Visit occurred approximately 3 to 10 days before Baseline.
b. NA - For subjects who withdrew from the study, the ET 12 visit was to take place at the next scheduled visit, or as soon as could be arranged.
c. The informed consent form was required to be signed prior to the performance of any protocol procedures.
d. Required for all females unless surgically sterilized or ≥2 years postmenopausal. Pregnancy tests could have been repeated as per request of Independent Ethics Committee/ Institutional Review Board, or if required by local regulations.
e. Urine drug screen could have been repeated as needed at the Investigator's discretion.

Table 2 Schedule of Activities: Week 13 to Week 52 (Nontreatment Follow-Up Period)

Protocol Activity	W 13	W 14	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	ET 52
Visit Window	+/- 7 Days	+/- 7 Days	+/- 7 Days	+/- 7 Days	+/- 7 Days	+/- 7 Days	+/- 7 Days	+/- 7 Days	+/- 7 Days	+/- 7 Days	+/- 7 Days	+/- 7 Days	NA[a]
Clinic visit	X		X		X		X		X		X	X	X
Telephone contact		X		X		X		X		X			
Exhaled carbon monoxide	X		X		X		X		X		X	X	X
Nicotine-use inventory	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant drugs (for smoking cessation)	X		X		X		X		X		X	X	X
Counseling (≤10 minutes)	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X		X		X		X		X		X	X	X

C-SSRS = columbia suicide severity rating scale; ET = early termination; if not occurring at Week 52; NA = not applicable; W = week.

a. NA - For subjects who withdrew from the study, the ET 52 visit was to take place at the next scheduled visit, or as soon as could be arranged.

Number of Subjects (Planned and Analyzed): The study was planned to randomize 490 subjects, with 245 subjects per treatment group. A total of 498 subjects (44 in Australia, 27 in Belgium, 67 in Canada, 45 in the Czech Republic, 19 in France, 69 in Germany, 93 in the United Kingdom and 134 in the United States) were randomized into the study and were analyzed as the All Randomized population (251 subjects, varenicline; 247 subjects, placebo). A total of 494 subjects received ≥1 dose of study drug and were analyzed as the Safety Analysis Set (249 subjects, varenicline; 245 subjects, placebo).

Diagnosis and Main Criteria for Inclusion: Subjects were female or male adult cigarette smokers, who had previously attempted to stop smoking on ≥1 occasion with varenicline for a treatment duration of at least 2 weeks, with the last varenicline dose taken ≥3 months prior to Screening. Subjects were enrolled irrespective of whether they failed to stop smoking during the previous attempt(s) supported by varenicline, or whether they succeeded, but subsequently relapsed. Subjects who had not tolerated varenicline well previously, who had a current or prior medical or psychiatric history, who had previously participated in clinical trials of varenicline, and subjects who had participated in another smoking cessation trial within the last 3 months or other drug trial within the last 30 days were excluded from the study.

Subjects must have smoked an average of ≥10 cigarettes (cigarettes only) per day during the past 4 weeks, with an exhaled carbon monoxide (CO) >10 parts per million (ppm) at Screening.

Study Treatment: Details of study drug administration with oral varenicline tablet(s) (as well as for placebo) are shown in Table 3.

Table 3 Study Drug Administration

Study Day	Daily Dosing	Total Daily Dose
Days 1 to 3	1 x 0.5 mg tablet (evening)	0.5 mg
Days 4 to 7	2 x 0.5 mg tablet (1 in the morning and 1 in the evening)	1.0 mg
Day 8 (ie, at Week 1 visit)	4 x 0.5 mg tablet (2 in the morning and 2 in the evening)	2.0 mg
Weeks 1 to12 (Starting Day 9)	4 x 0.5 mg tablet (2 in the morning and 2 in the evening)	2.0 mg

Study drug administration with matching placebo was the same as that described above for varenicline tablet(s). Subjects received 12 weeks of active treatment.

Efficacy Endpoints:

Primary Efficacy Endpoint: CAR 9-12, confirmed by exhaled CO ≤10 ppm.

Key Secondary Endpoint: CAR 9-52, confirmed by CO exhaled.

Additional secondary efficacy endpoints were: CAR 9-24, confirmed by CO exhaled; 7-day point prevalence of smoking cessation at Weeks 12, 24, and 52.

Safety Evaluations: Safety evaluations included adverse events (AEs), vital signs (heart rate and blood pressure), and weight. Suicidal behavior and ideation was assessed using the Suicidal Behaviors Questionnaire Revised and the Columbia Suicide Severity Rating Scale (C-SSRS).

Statistical Methods:

Efficacy: The All Subjects population, defined as all subjects who had received ≥1 dose, including partial doses, of randomized study drug, was the primary subject population for efficacy analyses in this study. To support conclusions made for the All Subjects population, the primary endpoint and key secondary endpoint analyses were also performed in the All Randomized population and the Completers population. The All Randomized population (usually referred to as the intent-to-treat population) included all subjects who were randomized into treatment in the study. The Completers population included subjects in the All Subjects population who had ≥80% treatment compliance as measured by having any dose of study medication for ≥80% of the planned number of days in the study.

The primary endpoint of CAR 9-12 was based on the weekly reports of cigarette and nicotine use "since the last contact/visit". A subject was not considered a responder for the CO-confirmed 4-week continuous quit rate for Weeks 9 to 12 if the expired CO was >10 ppm at any time point during this period. CAR 9-52 was defined as all subjects who remained abstinent from the period defining the primary endpoint, Weeks 9 through 12, through the end of the study (Week 52).

Logistic regression models were used in the efficacy analyses. The model included treatment and center as independent (explanatory and covariate) variables. In addition, an expanded logistic regression model was used to test for the treatment by center interaction effect for the primary and secondary key efficacy endpoints.

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 the key secondary endpoints. The treatment comparison was performed first for CAR 9-12, and second for CAR 9-52.

Safety: The Safety Analysis Set was the same as the Full Analysis Set (FAS) (All Subjects population) in this study, which is defined above. Any AEs occurring after the start of study drug and ≤30 days post treatment were considered treatment-emergent (ie, lag period as 30 days). The incidence of all AEs reported during the study was summarized by treatment group and by Medical Dictionary for Regulatory Activities (MedDRA; version 15.1) system organ class (SOC), high-level group term, and preferred term per the sponsor's standard AE summaries and listings.

Vital signs data were summarized by treatment group (change from Baseline at Week 12 and categorical data); significant changes from Screening at Week 12 in physical examination findings were summarized. Suicidal behavior and ideation (using the C-SSRS) were summarized at screening (lifetime), at Baseline, and for incidents occurring during active treatment and follow-up periods.

RESULTS

Subject Disposition and Demography: A summary of the subject disposition is provided in Table 4.

Table 4 Subject Disposition

Number of Subjects (%)	Varenicline		Placebo	
	n	%	n	%
Screened, 593 subjects				
Randomized to study treatment	251	--	247	--
Treated	249	(100.0)	245	(100.0)
Completed treatment	188	(75.5)	169	(69.0)
Completed study	169	(67.9)	144	(58.8)
Discontinued study	80	(32.1)	101	(41.2)
Subject died	1	(0.4)	0	0
Relation to study drug not defined	74	(29.7)	99	(40.4)
Did not meet entrance criteria	1	(0.4)	0	0
Insufficient clinical response	1	(0.4)	3	(1.2)
Lost to follow-up	34	(13.7)	30	(12.2)
No longer willing to participate in study	29	(11.6)	46	(18.8)
Other	8	(3.2)	19	(7.8)
Protocol violation [a]	1	(0.4)	1	(0.4)
Related to study drug	5	(2.0)	1	(0.4)
Adverse event	5 [b]	(2.0)	1	(0.4)
Not related to study drug	0	0	1	(0.4)
Adverse event	0	0	1	(0.4)
Discontinued treatment	59	(23.7)	76	(31.0)
Relation to study drug not defined	41	(16.5)	69	(28.2)
Did not meet entrance criteria	1	(0.4)	0	0
Insufficient clinical response	1	(0.4)	10	(4.1)
Lost to follow-up	13	(5.2)	14	(5.7)
No longer willing to participate in study	18	(7.2)	32	(13.1)
Other	6	(2.4)	13	(5.3)
Protocol violation [a]	2	(0.8)	0	0
Related to study drug	17	(6.8)	5	(2.0)
Adverse event	17	(6.8)	5	(2.0)
Not related to study drug	1	(0.4)	2	(0.8)
Adverse event	1	(0.4)	2	(0.8)

The Safety Analysis Set (same as the All Subjects population) included all subjects who received ≥1 dose, including partial doses, of randomized study drug.

a. Per the source tables, this was referred to as a protocol "violation", which was a "reasons for withdrawal" category in the Case Report Form.

b. Among the 5 subjects in the varenicline group who discontinued from the study due to an adverse event, for 1 subject, there is a discrepancy between source listings as to the reason for the subject's discontinuation. Subject discontinuations from study indicates that this subject discontinued due to an adverse event; however, listing of adverse events does not include an AE for this subject with an action of discontinuation. Thus, this table lists 5 subjects with a discontinuation due to an AE in the varenicline group.

Demographics were well balanced between the 2 treatment groups. Most subjects were white and approximately half were female; in both treatment groups, the mean age of subjects was approximately 47 years and the mean body mass index was approximately 27 kg/m^2.

Efficacy Results:

Primary Efficacy Endpoint: For the primary endpoint (All Subjects), treatment with varenicline resulted in significantly higher CAR 9-12 (CO confirmed) than placebo, as indicated in Table 5.

Table 5 Primary Endpoint: CAR from Week 9 through Week 12

Analyses Set	Varenicline		Placebo		OR (95% CI) vs Placebo	p-value vs Placebo
	N	n (%)	N	n (%)		
All Subjects population	249	112 (45.0)	245	29 (11.8)	7.08 (4.34, 11.55)	<0.0001
All Randomized population	251	112 (44.6)	247	29 (11.7)	6.96 (4.27, 11.33)	<0.0001
Completers population	195	110 (56.4)	175	27 (15.4)	8.99 (5.16, 15.67)	<0.0001

The All Subjects population included all subjects who received ≥1 dose, including partial doses, of randomized study drug. The All Randomized population included all subjects randomized to treatment in the study. The Completers population included subjects who had at least 80% treatment compliance, as measured by having any dose of study drug for at least 80% of the planned number of days in the study. OR's 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; N = number of subjects in the analysis set; n = number of subjects who, at each visit from Week 9 to 12 (inclusive), reported no smoking and no use of other nicotine-containing products since the last study visit/last contact (on the Nicotine Use Inventory) and who did not have CO >10 ppm at any of these visits; OR = odds ratio.

Key Secondary Endpoint: Results were consistent for the key secondary objective of CAR 9-52 (CO confirmed; All Subjects), with significantly more responders in the varenicline group compared with the placebo group (20.1% versus 3.3%, respectively; OR, 9.00; p <0.0001). Table 6 shows key secondary endpoint: CAR from Week 9 through Week 52.

Table 6. Key Secondary Endpoint: CAR From Week 9 Through Week 52

Analyses Set	Varenicline		Placebo		OR (95% CI) vs Placebo	p-value vs Placebo
	N	n (%)	N	n (%)		
All Subjects population	249	50 (20.1)	245	8 (3.3)	9.00 (3.97, 20.41)	<0.0001
All Randomized population	251	50 (19.9)	247	8 (3.2)	8.92 (3.94, 20.24)	<0.0001
Completers population	195	49 (25.1)	175	8 (4.6)	8.53 (3.68, 19.75)	<0.0001

The All Subjects population included all subjects who received ≥1 dose, including partial doses, of randomized study drug. The All Randomized population included all subjects randomized to treatment in the study. The Completers population included subjects who had at least 80% treatment compliance, as measured by having any dose of study drug for at least 80% of the planned number of days in the study. OR's 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; N = number of subjects in the analysis set; n = number of subjects who, at each visit from Week 9 through Week 52, reported no smoking (Weeks 9 through 52) and no use of other nicotine-containing products (Weeks 9 through 12), or no use of other tobacco products (Weeks 13 through 52), since the last study visit/last contact (on the Nicotine Use Inventory) and who did not have CO >10 ppm at any of these visits; OR = odds ratio

Other Secondary Endpoints and Other Efficacy Endpoints: Results for the other secondary endpoints and other efficacy endpoints, as well as those based on other populations (All Randomized and Completers populations), were consistent with and supportive of the primary and key secondary endpoint results. Table 7 presents CAR from Week 9 through Week 24 and Table 8 presents 7-day point prevalence of smoking cessation at Week 2 through Week 12, Week 24, and Week 52 (All Subjects).

Table 7. CAR From Week 9 Through Week 24

Analyses Set	Varenicline		Placebo		OR (95% CI) vs Placebo	p-value vs Placebo
	N	n (%)	N	n (%)		
All Subjects population	249	72 (28.9)	245	19 (7.8)	5.83 (3.25, 10.44)	<0.0001
All Randomized population	251	72 (28.7)	247	19 (7.7)	5.69 (3.19, 10.16)	<0.0001
Completers population	195	70 (35.9)	175	17 (9.7)	6.52 (3.43, 12.39)	<0.0001

The All Subjects population included all subjects who received ≥1 dose, including partial doses, of randomized study drug. The All Randomized population included all subjects randomized to treatment in the study. The Completers population included subjects who had at least 80% treatment compliance, as measured by having any dose of study drug for at least 80% of the planned number of days in the study. OR's 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; N = number of subjects in the analysis set; n = number of subjects who, at each visit from Weeks 9 through 24, reported no smoking (Weeks 9 through 24) and no use of other nicotine-containing products (Weeks 9 through 12), or no use of other tobacco products (Weeks 13 through 24), since the last study visit/last contact (on the Nicotine Use Inventory) and who did not have CO >10 ppm at any of these visits; OR = odds ratio.

Table 8. Seven-Day Point Prevalence of Smoking Cessation at Week 2 Through Week 12, Week 24, and Week 52 (All Subjects)

Week	Varenicline (N=249)	Placebo (N=245)	OR (95% CI) vs Placebo	p-value vs Placebo
	n (%)			
Week 2	70 (28.1)	23 (9.4)	5.04 (2.84, 8.94)	<0.0001
Week 3	93 (37.3)	26 (10.6)	5.57 (3.37, 9.19)	<0.0001
Week 4	108 (43.4)	32 (13.1)	5.85 (3.64, 9.40)	<0.0001
Week 5	130 (52.2)	39 (15.9)	6.66 (4.24, 10.44)	<0.0001
Week 6	128 (51.4)	33 (13.5)	8.39 (5.18, 13.60)	<0.0001
Week 7	131 (52.6)	47 (19.2)	5.32 (3.47, 8.18)	<0.0001
Week 8	117 (47.0)	35 (14.3)	6.43 (4.01, 10.30)	<0.0001
Week 9	121 (48.6)	36 (14.7)	6.32 (3.99, 9.99)	<0.0001
Week 10	122 (49.0)	34 (13.9)	7.02 (4.39, 11.22)	<0.0001
Week 11	126 (50.6)	35 (14.3)	7.15 (4.50, 11.37)	<0.0001
Week 12	132 (53.0)	36 (14.7)	7.85 (4.92, 12.51)	<0.0001
Week 24	82 (32.9)	38 (15.5)	2.94 (1.86, 4.64)	<0.0001
Week 52	72 (28.9)	30 (12.2)	3.06 (1.88, 4.97)	<0.0001

Weeks 2 to 4, 6, 8 to 12, 24, and 52 were all carbon-monoxide-confirmed visits. The All Subjects population included all subjects who received ≥1 dose, including partial doses, of randomized study drug. OR's and p-values were obtained from a logistic regression model including the main effects of treatment and pooled center.
CI = confidence interval; N = number of subjects in the analysis set; n= number of subjects meeting specified criterion; OR = odds ratio.

Subgroup Analyses: For the primary endpoint of CAR 9-12, as well as for the key secondary endpoint of CAR 9-52, a significant treatment effect with varenicline versus placebo was consistently observed across demographic subgroups (ie, gender and age) and across subgroups by smoking history and smoking cessation history.

Safety Results:

Treatment-emergent AEs are summarized in Table 9.

Table 9. Treatment-Emergent Adverse Events (All-Causality and Treatment-Related) – Safety Analysis Set

	Varenicline (N=249)				Placebo (N=245)			
	All-Causality		Treatment-Related		All-Causality		Treatment-Related	
	No. of Subjects (%)							
Subjects evaluable for AEs	249				245			
Number of AEs[a]	591		295		395		115	
Subjects with								
AEs[a]	188	(75.5)	136	(54.6)	155	(63.3)	65	(26.5)
SAEs	8	(3.2)	1	(0.4)	4	(1.6)	0	--
Severe AEs	17	(6.8)	10	(4.0)	12	(4.9)	3	(1.2)
Discontinued treatment due to AEs	18	(7.2)	17	(6.8)	7	(2.9)	5	(2.0)
Discontinued the study due to AEs	4	(1.6)	3	(1.2)	2	(0.8)	1	(0.4)
Dose reduction or temporary discontinuation due to AEs[a]	31	(12.4)	22	(8.8)	11	(4.5)	6	(2.4)

The Safety Analysis Set (same as the All Subjects population) included all subjects who received ≥1 dose, including partial doses, of randomized study drug. This table includes subjects who experienced an AE from the date of first dose of study drug ≤30 days after the date of the last dose of study drug. SAEs were according to the Investigator's assessment. MedDRA (v15.1) coding was applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; No. = number; N = total number of subjects SAE = serious adverse event

a. Two additional subjects with AEs (1 AE per subject, both in the placebo group) were reported after the database was released. Both AEs were treatment-emergent, nonserious, and not severe; 1 of the AEs (nausea) was treatment related and 1 of the AEs (dental surgery) resulted in a temporary discontinuation of the study drug.

Table 10 presents most common (reported by ≥5% of subjects in either treatment group) treatment-emergent AEs (all-causality and treatment-related).

Table 10. Most Common (≥5% of Subjects in Either Treatment Group) Treatment-Emergent Adverse Events (All-Causality and Treatment-Related) – Safety Analysis set

	Varenicline (N=249)				Placebo (N=245)			
MedDRA Preferred Term	**All-Causality**		**Treatment-Related**		**All-Causality**		**Treatment-Related**	
	No. of Subjects (%)							
Subjects with AEs [a]	188	(75.5)	136	(54.6)	155	(63.3)	65	(26.5)
Subjects with Nausea [a]	66	(26.5)	63	(25.3)	22	(9.0)	14	(5.7)
Abnormal dreams	36	(14.5)	36	(14.5)	8	(3.3)	6	(2.4)
Headache	26	(10.4)	14	(5.6)	24	(9.8)	12	(4.9)
Nasopharyngitis	19	(7.6)	1	(0.4)	17	(6.9)	1	(0.4)
Upper respiratory tract infection	19	(7.6)	0	--	17	(6.9)	1	(0.4)
Insomnia	17	(6.8)	13	(5.2)	10	(4.1)	7	(2.9)
Diarrhea	15	(6.0)	7	(2.8)	10	(4.1)	4	(1.6)
Constipation	13	(5.2)	10	(4.0)	7	(2.9)	4	(1.6)
Fatigue	13	(5.2)	7	(2.8)	6	(2.4)	2	(0.8)
Sleep disorder	13	(5.2)	12	(4.8)	5	(2.0)	4	(1.6)

Preferred terms in this table are sorted by frequency of all causality AEs in the varenicline treatment group.
The Safety Analysis Set (same as the All Subjects population) included all subjects who received ≥1 dose, including partial doses, of randomized study drug. This table includes subjects who experienced an AE from the date of first dose of study drug ≤30 days after the date of the last dose of study drug. MedDRA (v15.1) coding was applied.
AE/SAE results are not separated out.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects
a. After the database was released, 2 additional subjects with AEs (1 AE per subject, both in the placebo group) were reported, of these, only 1 AE (nausea, treatment related) was experienced by ≥5% of subjects in either treatment group, and therefore should have been included in this table.

Both all-causality and treatment-related AEs in the psychiatric disorders SOC occurred more frequently as a whole in the varenicline versus the placebo treatment group. The most frequently occurring all-causality psychiatric AEs in the varenicline group were all less frequent in the placebo group; these included abnormal dreams, insomnia, sleep disorder (see Table 10 above for frequency), and depressed mood (all-causality – varenicline 3.2%, placebo 0.4%; treatment-related – varenicline 2.4%, placebo 0.4%).

In addition to psychiatric AEs, assessment of suicidal behavior and ideation (assessed using the CSSR-S) indicated that no subject had an incident of suicidal behavior or ideation that was considered as an AE during the study. At Screening, the lifetime history of suicidal ideation or behavior was somewhat greater for the varenicline group (6.4%) compared to the placebo group (2.9%). During the treatment period, 3 varenicline (1.2%) and no placebo subjects expressed suicidal ideation. During the non-treatment period, 2 varenicline (1.0%) and no placebo subjects expressed suicidal ideation.

The percentage of subjects with serious AEs was low for both treatment groups, but was higher with varenicline than with placebo (3.2% versus 1.6%, respectively). Serious AEs are summarized in Table 11.

Table 11. Serious Adverse Events

Subject Number	Sex/Age (Years) [a]	MedDRA (v15.1) Preferred Term	AE Onset Day [b]	AE Stop Day [c]	Action Taken (Study Drug)	Causality [d]	Clinical Outcome
Pre-randomization							
1	M/49	Angina unstable	NA	NA	NA (pre-rand)	NA	Recovered/Resolved/Hospitalization
Varenicline							
1	M/58	Knee arthroplasty	112	112	Post-therapy	Unrelated	Recovered/Resolved/Hospitalization
2	F/63	Carotid arteriosclerosis	191	193	Post-therapy	Unrelated	Recovered/Resolved/Hospitalization
3	F/33	Pyelonephritis	15	28	Dose not changed	Unrelated	Recovered/Resolved/Important medical event
4	F/67	Intervertebral disc protrusion	78	88	Dose not changed	Unrelated	Recovered/Resolved/Important medical event
5	M/60	Intervertebral discitis	113	243	Post-therapy	Unrelated	Recovered/Resolved with sequel/Hospitalization
6	F/72	Ankle fracture	82	122	Dose not changed	Unrelated	Recovered/Resolved/Hospitalization
7	M/76	Non-small cell lung cancer Stage IIIA	337	NA	Post-therapy	Unrelated	Not recovered/Not resolved/Important medical event
8	F/58	Alcoholism	301	NA	Post-therapy	Unrelated	Fatal
9	F/53	Chest pain	1	4	Temp withdrawal	Related	Recovered/Resolved/Hospitalization
10	F/66	Hypersensitivity [e]	57	59	Temp withdrawal [e]	Unrelated [e]	Recovered/Resolved/Hospitalization
11	M/33	Anal abscess	259	261	Post-therapy	Unrelated	Recovered/Resolved/Hospitalization
12	F/31	Hypersensitivity	111	130	Post-therapy	Unrelated	Recovered/Resolved/Hospitalization
13 [f]	M/53	Rotator cuff repair	341	343	Post-therapy	Unrelated [f]	Resolved [f]
Placebo							
1	F/56	Appendicitis	217	221	Post-therapy	Unrelated	Recovered/Resolved/Hospitalization
2	F/48	Ovarian cyst	140	251	Post-therapy	Unrelated	Recovered/Resolved/Hospitalization
3	M/58	Acute coronary syndrome	22	30	Perm withdrawal	Unrelated	Recovered/Resolved/Hospitalization: life-threatening
4	M/35	Ligament rupture	70	75	Dose not changed	Unrelated	Recovered/Resolved/Hospitalization
5	F/33	Ovarian cyst	341	385	Post-therapy	Unrelated	Recovered/Resolved/Hospitalization
6	F/64	Pneumonia	188	212	Post-therapy	Unrelated	Recovered/Resolved/Hospitalization
7	F/73	Hyperventilation	117	117	Post-therapy	Unrelated	Not recovered/Not resolved/Important medical event
8	M/54	Dizziness	249	250	Post-therapy	Unrelated	Recovered/Resolved/Hospitalization
9	F/61	Hypersensitivity	74	81	Dose not changed	Unrelated	Recovered/Resolved/Life-threatening

Table 11. Serious Adverse Events

Subject Number	Sex/Age (Years) [a]	MedDRA (v15.1) Preferred Term	AE Onset Day [b]	AE Stop Day [c]	Action Taken (Study Drug)	Causality [d]	Clinical Outcome

Two additional SAEs were reported for non-subjects: an exposure via semen and an exposure via pregnancy. Medical Dictionary for Regulatory Activities (MedDRA version 15.1) coding was applied.

AE = adverse event; NA = not applicable; OC = Oracle Clinical; perm = permanent; rand = randomization; SAE = serious adverse event; SDW = safety data warehouse; temp = temporary.

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. Causality was according to both the Investigator's and sponsor's assessment (for all SAEs, both were the same).
e. This SAE was also recorded in a second row which indicates "No Data" for causality; this second row refers to the amoxicillin to which the subject reacted
f. AE was noted as serious in the clinical database, but did not meet the criteria of serious in the safety database.

A total of 6 subjects discontinued from the study as summarized in Table 12. Dose reductions or temporary discontinuations due to all-causality AEs were more common with varenicline than with placebo (12.4% vs 4.5%, respectively).

Nausea was the only frequently occurring reason (≥5% in either treatment group) for dose reductions or temporary discontinuations due to AEs (5.6% with varenicline; 0.4% with placebo); all such events of nausea were considered treatment-related.

Table 12. Permanent Discontinuations From the Study Due to Adverse Events – Safety Analysis Set

Subject Number	Sex/Age (years)[a]	AE Start/ Stop Day[b]	Preferred Term	Severity/ Outcome	Causality	SAE[c]
Varenicline Treatment Group						
1	M/60	8/129	Dermatitis allergic	Moderate/ resolved	Study drug	No
2	F/52	4/6	Diarrhea	Moderate/ resolved	Study drug	No
3	F/44	17/21	Sleep disorder	Moderate/ resolved	Study drug	No
4	F/53	2/5	Depression	Moderate/ resolved	Study drug	No
Placebo Treatment Group						
1	F/63	11/15	Diarrhea	Severe/resolved	Other illness (viral gastroenteritis)	No
2	M/45	7/16	Mood altered	Moderate/ resolved	Study drug	No

The Safety Analysis Set (same as the All Subjects population) included all subjects who received ≥1 dose, including partial doses, of randomized study drug. All AEs were treatment emergent. The Medical Dictionary for Regulatory Activities (MedDRA version 15.1) coding was applied.
AE = adverse event; F = female; M = male; SAE = serious adverse event.
a. Age at Screening.
b. AE start and stop days were relative to the start of treatment, which was defined as Day 1.
c. SAE was according to Investigator's assessment.

One death was reported in this study. The 58-year-old female subject, with a relevant past medical history of depression, had a fatal SAE of alcoholism on Day 301, during the post-treatment follow-up period. The subject did not disclose a history of alcoholism at study entry or at any time during the conduct of the study. In this study, the subject had received treatment with varenicline 1 mg BID for 83 days.

Concurrent with her fatal SAE, and also during the post-treatment period, the subject also experienced a nonserious, treatment-related AE of flat affect (on Day 109, which was considered ongoing until the date of death); this AE of flat affect was considered mild in intensity.

The subject was smoking 21 cigarettes per day at the Baseline visit and reported smoking 10 cigarettes per day at the Week 40 visit, just prior to the subject's death due to alcoholism.

Both the Investigator and the sponsor assessed the causality of the fatal SAE of alcoholism as not related to the study drug (cause of death was acute and chronic alcoholism).

Vital signs data and weight change from Baseline at Week 12 results were similar between treatment groups.

CONCLUSIONS:

- For the primary endpoint (All Subjects), treatment with varenicline resulted in significantly higher CAR 9-12 (CO confirmed) than placebo (45.0% versus 11.8%, respectively; OR, 7.08; p <0.0001).
- For the key secondary objective (All Subjects), treatment with varenicline resulted in significantly higher CAR 9-52 (CO confirmed) than placebo (20.1% versus 3.3%, respectively; OR, 9.00; p <0.0001).
- Efficacy results for the other secondary endpoints and other efficacy endpoints, as well as those using other populations (All Randomized and Completers populations), and the subgroup analyses, were consistent with and supportive of those with the primary and key secondary endpoint analyses.
- This study provides the first placebo-controlled evidence that re-treatment with varenicline can benefit smokers who either failed to quit on varenicline or relapsed after taking it.
- Safety data indicated that:
    - Re-treatment with varenicline was generally well-tolerated, with a safety profile consistent with previous studies of treatment-naïve subjects.
    - Re-treatment with varenicline did not reveal any new safety concerns.