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

PROTOCOL NO.: A3051049

PROTOCOL TITLE: A 12-Week, Double-Blind, Placebo-Controlled, Multicenter Study With a 40 Week Follow-Up Evaluating the Safety and Efficacy of Varenicline Tartrate 1 mg BID for Smoking Cessation in Subjects With Cardiovascular Disease

Study Centers: A total of 39 centers took part in the study and enrolled subjects: 4 each in Canada, the United Kingdom, and Republic of Korea; 3 each in the United States, Germany, and France; 2 each in Netherlands, Brazil, Australia, Denmark, Argentina, Czech Republic, Greece, Taiwan, and Mexico.

Study Initiation Date and Final Completion Date: 20 February 2006 to 18 August 2008

Phase of Development: Phase 3b

Study Objectives: The primary efficacy objective of this study was a comparison of 12 weeks of treatment with varenicline 1 mg twice daily (BID) to placebo for smoking cessation in subjects with cardiovascular disease and to evaluate continuous abstinence 40 weeks after the treatment period.

The safety objective was to gather safety data in subjects with cardiovascular disease treated with varenicline 1 mg BID or placebo for 12 weeks followed by a 40-week nontreatment follow-up period.

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled, multicenter study with a 12-week treatment period followed by a 40-week nontreatment period for a total study duration of 52 weeks. A total of 700 subjects were planned to be randomized in a ratio of 1:1 to receive either varenicline (1 week titration followed by 11 weeks of 1 mg BID dosing) or placebo. Blinded study medication was discontinued at the Week 12 visit and subject's smoking status was followed through the nontreatment period to Week 52.

All subjects were to set a target quit date (TQD) to coincide with the Week 1 visit, which occurred at the end of the first week of the treatment phase. All subjects were instructed to quit smoking at midnight preceding the day of the Week 1 visit. Subjects returned for weekly clinic visits during the treatment period. During the nontreatment follow-up, subjects

returned for visits at Weeks 13, 16, 24, 32, 40, 48, and 52, and were contacted by telephone at Weeks 14, 20, 28, 36, and 44.

All subjects received smoking cessation counseling in accordance with Agency for Healthcare Research and Quality (AHRQ) guidelines or similar local guidelines, at each clinic visit and telephone contact starting with the Baseline visit.

A schedule of the study assessments for the treatment period (Screening visit – Week 12) is provided in Table 1 and for the nontreatment follow-up period (Week 13 visit – Week 52 visit) in Table 2.

Table 1. Assessments: Treatment Phase - Screening Visit – Week 12 Visit

Assessment / Procedure	Screening	BL	Wk 1	TQD +3	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12 ET12[a]
Informed consent[b]	X														
Medical history	X														
Physical examination	X														X
Temperature, height, weight	X														
Heart rate, blood pressure, weight	X	X	X				X				X				X
Waist measurement		X					X				X				X
End-expiratory 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
Fagerström test (FTND)	X														
Smoking log dispensed		X	X		X										
All adverse events		X	X		X	X	X	X	X	X	X	X	X	X	X
Dispense study drugs		X[c]	X[c]		X	X	X	X	X	X	X	X	X	X	
All subjects stop smoking (TQD)			X												
Dosing record			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
Electrocardiogram	X														X
Serum cotinine	X														
Blood chemistry; CBC with differential	X (fasting or non-fasting)														X (fasting)
C-Reactive protein, lipid profile, fibrinogen		X													X
Genotyping sample[d]		X													
HbA1c	X[e]	X[f]													X
Serum pregnancy test[g]	X														
Urinalysis (dipstick)	X														
Urine albumin/creatinine ratio		X													X
Urine drug screen[h]	X														
Counseling (AHRQ guidelines)		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1. Assessments: Treatment Phase - Screening Visit – Week 12 Visit

Assessment / Procedure	Screening	BL	Wk 1	TQD +3	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12 ET12[a]
Brief telephone contact				X											

AHRQ = Agency for Healthcare Research and Quality; BL = Baseline; CBC = complete blood count; ET = early termination; FTND = Fagerstrom Test for Nicotine Dependence; HbA1c = hemoglobin A1c; IRB = Institution Review Board: IEC = Independent Ethics Committee; TQD = target quit date; Wk = week.

a. If ET was before the Week 12 visit.
b. Had to be signed prior to any protocol procedures being performed.
c. At BL visit, 0.5 mg titration bottle (or placebo to match) dispensed; At Week 1-11 visits, 1 mg twice daily bottles (or placebo to match) dispensed.
d. Optional; separate consent form required.
e. Diabetic subjects only.
f. All subjects, except diabetics.
g. All females, unless surgically sterilized or at least 2 years postmenopausal. If IRB/IEC or local laws required, an additional pregnancy test could be done.
h. Could be performed at other visits at Investigator's discretion or similar local guidelines.

Table 2. Assessments: Nontreatment Follow-Up Phase – Week 13 Visit – Week 52 Visit

Assessment / Procedure	Wk 13	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	ET52[a]
Clinic visit	X		X		X		X		X		X	X	X
Phone contact		X		X		X		X		X			
Heart rate, blood pressure, weight	X				X				X			X	X
Waist measurement					X				X			X	X
Physical examination												X	X
Electrocardiogram												X	X
Fasting blood chemistry; CBC with differential; C-Reactive Protein, lipid profile, fibrinogen, urine albumin/creatinine ratio												X	X
HbA1c												X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
All adverse events	X	X											
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
End-expiratory 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
Counseling (AHRQ)	X	X	X	X	X	X	X	X	X	X	X	X	X

AHRQ = Agency for Healthcare Research and Quality or similar local guidelines; CBC = complete blood count; HbA1c = hemoglobin A1c; ET = early termination; Wk = week.

a. If ET was before the Week 52 visit.

Number of Subjects (Planned and Analyzed): A total of 700 subjects were planned to be randomized to varenicline or placebo in a 1:1 ratio. Of the total 714 subjects who were randomized to receive study treatment, 703 subjects were treated (353 received varenicline and 350 received placebo). In the varenicline and placebo groups, all treated subjects (353 and 350 subjects, respectively) were included in the All Subjects population used for efficacy and safety analyses.

Diagnosis and Main Criteria for Inclusion: Subjects were eligible to be included in this study if they were male or female current smokers (smoked an average of 10 cigarettes per day), between the ages of 35 and 75 years, inclusive, with stable, documented cardiovascular disease, other than hypertension (eg, coronary artery disease, peripheral vascular disease [PVD], or cerebrovascular disease).

Study Treatment: Treatments administered included placebo or varenicline (1-week titration, followed by 11 weeks of 1 mg oral BID dosing) administered for 12 weeks. A summary of the dose titration schedule is provided in Table 3.

Table 3. Dose Titration Schedule

<table>
<tr><th>Treatment Group</th><th>Study Days 1 to 3</th><th>Study Days 4 to 7</th><th>Study Day 8</th><th>Week 1 – Week 12</th></tr>
<tr><td rowspan="2">Blinded varenicline (or placebo)</td><td>One 0.5 mg tablet daily in the morning</td><td>One 0.5 mg tablet in the morning and one 0.5 mg tablet in the evening</td><td>Two 0.5 mg tablets in the morning and one 1.0 mg tablet in the evening (from bottle dispensed at Week 1)</td><td>One 1.0 mg tablet in the morning and one 1.0 mg tablet in the evening</td></tr>
<tr><td colspan="3">Week 1 bottle</td><td>Week 2-12 bottles</td></tr>
</table>

Efficacy Endpoints:

Primary Endpoint: The primary endpoint was the 4-week Continuous Quit Rate (CQR) 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 carbon monoxide (CO) measurements ≤10 ppm, for the planned last 4 weeks of treatment.

Secondary Endpoints:

Key Secondary Endpoints:

- Continuous Abstinence (CA) from Week 9 through Week 52
- Long-Term Quit Rate (LTQR) from Week 9 through at Week 52 (defined as the proportion of subjects who had successfully quit during the treatment phase of the study and who have had no more than 6 days of smoking during the nontreatment phase of the study).

Other Secondary Endpoints:

- Seven-day Point Prevalence of nonsmoking at Weeks 12, 24 and 52
- CA from Week 9 through Week 24
- LTQR from Week 9 through Week 24
- Four-week Point Prevalence of nonsmoking at Week 52

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (heart rate, blood pressure), 12- lead electrocardiograms (ECGs), adverse events (AEs), safety laboratory tests, physical examinations, body weight, height, and waist circumference, and inflammatory markers.

Cardiovascular Adverse Events: The following cardiovascular events were reviewed and adjudicated by an independent cardiovascular event adjudication committee to confirm the diagnosis of the events:

- Nonfatal myocardial infarction
- Any hospital admission for chest pain
- Hospitalization for angina pectoris
- Need for coronary revascularization
- Resuscitated cardiac arrest
- Hospitalization for congestive heart failure
- Fatal, nonfatal stroke or transient ischemic attack
- Any diagnosis of PVD in a subject not previously diagnosed as having PVD or any admission for a procedure for the treatment of PVD
- Death from any cause

These events were adjudicated using a standard events manual under blinded conditions.

Statistical Methods: The population sets analyzed in the study included:

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

Evaluable Population: The Evaluable Subjects group was a subset of the All Subjects population who took at least 14 days of study medication in the first 21 days of the study. A

day of randomized study medication was defined as a calendar day during which the subject received any dose of study medication (either AM, PM, or both of the planned BID doses).

Completer Population: The subset of the All Subjects population known as Completers applied to the efficacy evaluation of the primary and key secondary endpoints only, and was defined as the subset of the All Subjects population who had at least 80% treatment compliance as measured by having any dose of study medication for 80% of the planned number of days in the study.

The intent of the primary analysis was to evaluate the hypothesis that varenicline is superior to placebo for smoking cessation after 12 weeks of treatment. The primary endpoint in the study for the evaluation of the primary efficacy hypothesis was based on a CO confirmed 4-week continuous quit rate (CQR), with the 4 weeks being counted from Weeks 9 through 12, inclusive. The secondary efficacy endpoints were categorized as key secondary and other secondary efficacy endpoints.

A logistic regression model was fitted to the primary endpoint and key secondary binary endpoints and included the main effects of treatment group and center as independent variables.

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 2 key secondary endpoints. The hierarchy of comparisons were: 1) the 4-week CQR for Weeks 9 through 12, 2) CA at Week 52, and 3) the LTQR through Week 52. 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.

Descriptive statistics, such as the mean, median, standard deviation, and range for continuous variables, and counts and percentages for categorical variables were completed to summarize most data.

All other statistical testing was 2-sided and used a 0.05 level of significance. Nominal p-values were reported for secondary analyses, as long as the primary endpoint was met, with no adjustments for the analysis of multiple secondary endpoints.

Safety data were summarized using descriptive statistics.

RESULTS

Subject Disposition and Demography: A summary of subject evaluation groups is provided in Table 4. A total of 714 smokers were randomized (ie, assigned to study treatment), 11 subjects were randomized, but not treated. The reasons for subjects being randomized, not treated included no longer willing to participate in the study (5 subjects), protocol violation (3 subjects), lost to follow-up (1 subject), and other (2 subjects). A total of 703 subjects were treated with at least 1 dose of study medication (353 varenicline, 350 placebo). A total of 85.6% varenicline and 82.6% placebo subjects completed the study. The most common reason for discontinuation from the study was that the subject was no

longer willing to participate in the study (22 [6.2%] varenicline and 34 [9.7%] placebo) (Table 4).

Table 4. Subject Evaluation Groups

Number (%) of Subjects		Varenicline	Placebo
Screened:	858		
Assigned to study treatment:	714		
Treated		353	350
Completed treatment		293 (83.0)	286 (81.7)
Discontinued treatment		60 (17.0)	64 (18.3)
Completed study		302 (85.6)	289 (82.6)
Discontinued study		51 (14.4)	61 (17.4)
Subject died		2 (0.6)	5 (1.4)
Related to study drug		7 (2.0)	7 (2.0)
Adverse event		7 (2.0)	5 (1.4)[a]
Lack of efficacy		0	2 (0.6)
Not related to study drug		42 (11.9)	49 (14.0)
Adverse event		1 (0.3)	0
Lost to follow-up		14 (4.0)	10 (2.9)
Other		5 (1.4)	5 (1.4)
Subject no longer willing to participate in study		22 (6.2)	34 (9.7)

a. One subject discontinued the study due to treatment-related malaise and treatment-unrelated emphysema and was only included in the related to study drug row.

A summary of data sets analyzed is provided in Table 5.

Table 5. Data Sets Analyzed

Number (%) of Subjects		Varenicline	Placebo
Assigned to study treatment:	714		
Treated		353	350
Evaluated for efficacy			
All subjects		353 (100.0)	350 (100.0)
Evaluable subjects		338 (95.8)	338 (96.6)
Completer subjects		289 (81.9)	287 (82.0)
Analyzed for safety			
Adverse events		353 (100.0)	350 (100.0)
Laboratory data		316 (89.5)	303 (86.6)

Demographic characteristics were generally similar between the treatment groups. The majority of subjects in each group were male (266/353 [75.4%] varenicline and 287/350 [82.0%] placebo) (Table 6).

Treatment groups were well balanced with respect to smoking history. Subjects in the varenicline group smoked an average of 22.2 cigarettes per day over the past month and had been smoking for an average of 40.0 years. Subjects in the placebo group smoked an average of 22.9 cigarettes per day over the past month and had been smoking for an average of 39.1 years.

Table 6. Demographic Characteristics – All Subjects

Number (%) of Subjects	Varenicline (N=353)	Placebo (N=350)
Gender		
Male	266 (75.4)	287 (82.0)
Female	87 (24.6)	63 (18.0)
Age (years)		
<55	132 (37.4)	152 (43.4)
55-65	159 (45.0)	145 (41.4)
>65	62 (17.6)	53 (15.1)
Mean	57.0	56.0
SD	8.6	8.4
Range	34-76	35-75
Race		
White	284 (80.5)	282 (80.6)
Black	3 (0.8)	2 (0.6)
Asian	30 (8.5)	30 (8.6)
Other	36 (10.2)	36 (10.3)
Weight (kg)		
Mean	79.7	81.7
SD	15.3	15.2
Range	47.0-122.0	45.0-137.0
Body Mass Index (kg/m^2)		
Mean	27.5	27.9
SD	4.4	4.4
Range	18.3-42.5	17.0-39.3
Height (cm)		
Mean	169.9	171.0
SD	8.9	7.9
Range	145.0-196.0	147.0-191.0

N = number of subjects; SD = standard deviation.

Efficacy Results:

Overview of Efficacy Results: In the All Subjects population, the primary efficacy parameter, CO-confirmed 4-week CQR for the last 4 weeks of treatment, was significantly higher for the varenicline treatment group (47.3%) than for the placebo group (14.3%) ($p<0.0001$).

The differences between the varenicline and placebo groups were statistically significant for the key secondary parameters of CA Weeks 9-24 and LTQR Week 52, as well as for the other secondary efficacy parameters. An overview of efficacy is presented in Table 7.

Table 7. Overview of Efficacy (All Subjects)

Endpoint	Varenicline (N=353) n (%)	Placebo (N=350) n (%)	Odds Ratio (95% CI)	p-Value
4-week CQR Weeks 9-12	167 (47.31)	50 (14.29)	6.05 (4.13, 8.86)	<0.0001
CA Weeks 9-24	100 (28.33)	34 (9.71)	3.86 (2.51, 5.93)	<0.0001
CA Weeks 9-52	70 (19.83)	26 (7.43)	3.19 (1.97, 5.18)	<0.0001
LTQR Week 52	80 (22.66)	34 (9.71)	2.82 (1.82, 4.38)	<0.0001
7-day PP of abstinence				
Week 12	192 (54.39)	65 (18.57)	5.97 (4.17, 8.56)	<0.0001
Week 24	124 (35.13)	57 (16.29)	2.93 (2.03, 4.23)	<0.0001
Week 52	102 (28.90)	62 (17.71)	1.93 (1.34, 2.77)	0.0003
4-wk PP of abstinence Week 52	99 (28.05)	57 (16.29)	2.05 (1.41, 2.97)	0.0001

CA = continuous abstinence; CI = confidence interval; CQR = continuous quit rate; N = total number of subjects; n = number of subjects in specified category; PP = point prevalence; LTQR = long term quit rate; wk = week.

Primary Endpoints:

CO-Confirmed 4-Week Continuous Quit Rate: In the All Subjects population, the CO-confirmed 4-week CQR for the last 4 weeks (ie, Weeks 9-12) of treatment was significantly higher for varenicline (47.3%) than for the placebo (14.3%) (p<0.0001) (Table 7).

Results of the analyses for the Evaluable and Completer populations supported the results for the All Subjects population, with a statistically significant difference between the varenicline and placebo groups in the CO-confirmed 4-week CQR for Weeks 9-12 (p<0.0001 and p<0.0001, respectively).

Secondary Endpoints:

Continuous Abstinence Rate: The continuous abstinence rate (CAR) from Week 9 through Week 52, a key secondary endpoint, was statistically significantly higher for varenicline (19.8%) than for placebo (7.43%) (p<0.0001) (Table 7).

Results of the analyses for the Evaluable and Completer populations supported the results for the All Subjects population, with a statistically significant difference between the varenicline and placebo groups in the CAR from Week 9-52 (p<0.0001 and p<0.0001, respectively).

Long-Term Quit Rate: The LTQR, a key secondary endpoint, was statistically significantly higher for varenicline compared with placebo at Week 52 (22.7% vs 9.71%, respectively, p<0.0001) (Table 7).

Results of the analyses for the Evaluable and Completer populations were consistent with the results for the All Subjects population, with a statistically significant difference between the varenicline and placebo groups in the LTQR at Week 24 and Week 52 (p<0.0001 and p<0.0001, respectively).

Seven-Day Point Prevalence of Abstinence: At the end of the treatment phase (Week 12), 192 subjects (54.4%) in the varenicline group compared with 65 subjects (18.6%) in the placebo group reported abstinence in the previous 7 days ($p<0.0001$). At Week 24, 35.1% of subjects in varenicline group reported abstinence in the previous 7 days compared with 16.3% in the placebo group ($p<0.0001$). At Week 52, 28.9% varenicline-treated subjects reported abstinence in the previous 7 days compared with 17.7% of the placebo-treated subjects ($p=0.0003$; Table 7).

Four-week Point Prevalence of nonsmoking at Week 52: The 4-week point prevalence of nonsmoking at Week 52, was statistically significantly higher for varenicline compared with placebo (28.1% vs 16.3%, respectively, $p=0.0001$) (Table 7).

Safety Results:

Overview of Safety Results: An overview of treatment-emergent AEs for All Subjects is provided in Table 8. There was a greater percentage of subjects in the varenicline than in the placebo group that reported treatment-emergent, all-causality AEs (81.6% and 64.9%, respectively) and treatment-related AEs (64.6% and 43.7%, respectively).

Table 8. Overview of Treatment-Emergent Adverse Events (All Subjects)

Number (%) of Subjects	Varenicline (N=353)	Placebo (N=350)
	n (%)	n (%)
Adverse events (AEs)		
All causality	288 (81.6)	227 (64.9)
Treatment related	228 (64.6)	153 (43.7)
Discontinued due to AEs		
All causality	8 (2.3)	5 (1.4)
Treatment related	7 (2.0)	5 (1.4)
Dose reductions or temporary discontinuations due to AEs		
All causality	47 (13.3)	16 (4.6)
Treatment related	37 (10.5)	8 (2.3)
Serious adverse events (SAEs)		
All causality	23 (6.5)	21 (6.0)
Treatment related	4 (1.1)	4 (1.1)

Data on AEs include both non-serious and serious AEs (ie, AEs and SAEs are not separated out).
Includes data up to 30 days after the last dose of study drug.
N = total number of subjects; n = number of subjects in specified category.

All Causality and Treatment Related Adverse Events: A summary of treatment-emergent (all-causality) and treatment related AEs reported by ≥2% of varenicline subjects at a frequency greater than placebo for All Subjects is provided in Table 9. The system organ classes with the most reported treatment-emergent AEs included Gastrointestinal Disorders (177 [50.1%] varenicline and 90 [25.7%] placebo), Psychiatric Disorders (102 [28.9%] varenicline and 60 [17.1%] placebo), and Nervous System Disorders (93 [26.3%] varenicline and 78 [22.3%] placebo). The most common treatment-emergent AE was nausea (104 [29.5%] varenicline and 30 [8.6%] placebo). Other AEs reported by at least 5% of varenicline subjects included vomiting, constipation, diarrhea, dyspepsia, insomnia, abnormal dreams, headache, dizziness, and fatigue. The system organ classes with the most

reported treatment-emergent, treatment-related AEs included the Gastrointestinal Disorders (155 [43.9%] varenicline and 73 [20.9%] placebo), Psychiatric Disorders (81 [22.9%] varenicline and 41 [11.7%] placebo), and Nervous System Disorders (71 [20.1%] varenicline and 55 [15.7%] placebo). The most common treatment-emergent, treatment-related AE was nausea (98 [27.8%] varenicline and 26 [7.4%] placebo). Most AEs were mild or moderate in intensity. There were no AEs reported of suicide or suicide ideation by any subject during the study.

Table 9. Treatment-Emergent All Causality Adverse Events Reported by ≥2% of Subjects in the Varenicline Group and at a Frequency Greater Than Placebo (All Subjects)

System Organ Class Adverse Event (MedDRA v11.0 Preferred Term)	All Causality		Treatment-Related	
	Varenicline (N=353) n (%)	Placebo (N=350) n (%)	Varenicline (N=353) n (%)	Placebo (N=350) n (%)
Gastrointestinal disorders	177 (50.1)	90 (25.7)	155 (43.9)	73 (20.9)
Nausea	104 (29.5)	30 (8.6)	98 (27.8)	26 (7.4)
Vomiting	29 (8.2)	4 (1.1)	24 (6.8)	3 (0.9)
Constipation	23 (6.5)	7 (2.0)	18 (5.1)	5 (1.4)
Diarrhea	22 (6.2)	18 (5.1)	16 (4.5)	10 (2.9)
Dyspepsia	19 (5.4)	12 (3.4)	14 (4.0)	8 (2.3)
Abdominal pain, upper	15 (4.2)	9 (2.6)	13 (3.7)	7 (2.0)
Dry mouth	13 (3.7)	7 (2.0)	11 (3.1)	6 (1.7)
Flatulence	8 (2.3)	7 (2.0)	8 (2.3)	7 (2.0)
Abdominal distension	7 (2.0)	3 (0.9)	7 (2.0)	3 (0.9)
Psychiatric disorders	102 (28.9)	60 (17.1)	81 (22.9)	41 (11.7)
Insomnia	42 (11.9)	23 (6.6)	34 (9.6)	17 (4.9)
Abnormal dreams	28 (7.9)	6 (1.7)	28 (7.9)	6 (1.7)
Sleep disorder	12 (3.4)	5 (1.4)	11 (3.1)	5 (1.4)
Nicotine dependence	9 (2.5)	5 (1.4)	0	0
Nervous system disorders	93 (26.3)	78 (22.3)	71 (20.1)	55 (15.7)
Headache	45 (12.7)	39 (11.1)	36 (10.2)	28 (8.0)
Dizziness	22 (6.2)	16 (4.6)	17 (4.8)	10 (2.9)
Dysgeusia	16 (4.5)	8 (2.3)	16 (4.5)	7 (2.0)
General disorders and administration site conditions	59 (16.7)	40 (11.4)	39 (11.0)	26 (7.4)
Chest pain	9 (2.5)	8 (2.3)	0	0
Fatigue	25 (7.1)	14 (4.0)	18 (5.1)	8 (2.3)
Edema peripheral	7 (2.0)	4 (1.1)	0	0
Musculoskeletal and connective tissue disorders	42 (11.9)	36 (10.3)	0	0
Back pain	14 (4.0)	9 (2.6)	0	0
Respiratory, thoracic and mediastinal disorders	34 (9.6)	39 (11.1)	0	0
Dyspnea	10 (2.8)	4 (1.1)	0	0
Skin and subcutaneous tissue disorders	23 (6.5)	17 (4.9)	0	0
Hyperhidrosis	7 (2.0)	5 (1.4)	0	0
Cardiac disorders	23 (6.5)	19 (5.4)	0	0
Angina pectoris	13 (3.7)	7 (2.0)	0	0

AEs include both non-serious and serious AEs (ie, AEs and SAEs are not separated out).
Includes data up to 30 days after the last dose of study drug.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects with adverse events; SAEs = serious adverse events; v = version.

Cardiovascular Adverse Events: Cardiovascular AEs of interest in this study appear in several system organ classes and therefore selected MedDRA preferred terms of interest in the Cardiac Disorders, Nervous System Disorders, and Psychiatric System Disorders system organ classes are presented in Table 10.

The most common treatment-emergent AEs in selected cardiovascular AEs (occurring in at least 5 total subjects) were angina pectoris (13 [3.7%] varenicline and 7 [2.0%] placebo), hypertension (5 [1.4%] varenicline and 9 [2.6%] placebo), and palpitations (2 [0.6%] varenicline and 4 [1.1%] placebo). Dyspnea (in the Respiratory, Thoracic, and Mediastinal Disorders system organ class), occurred at a slightly greater frequency among the varenicline than placebo subjects (10 [2.8%] varenicline and 4 [1.1%] placebo); however, chronic obstructive pulmonary disease was also more prevalent in the varenicline group (past history, 2 varenicline and 2 placebo; present history 36 varenicline and 26 placebo). None of the selected cardiovascular AEs led to treatment discontinuation. In general, there was a low incidence of cardiovascular events in each treatment group and there were no differences between treatment groups in the numbers or types of cardiovascular events. Cardiovascular AEs that led to treatment discontinuation included acute myocardial infarction, angina pectoris (2 subjects), arrhythmia, cardiac failure, myocardial infarction, cerebrovascular accident, arteriosclerosis, and hypertension in 1 varenicline subject each and atrial fibrillation, cardiogenic shock, cardiovascular disorder, and palpitations in 1 placebo subject each. In general, there was a low incidence of cardiovascular events in each treatment group and there were no differences between treatment groups in the numbers or types of cardiovascular events.

Table 10. Selected Treatment-Emergent All Causality Adverse Events in Cardiac Disorders, Nervous System Disorders, and Vascular Disorders System Organ Classes (All Subjects)

System Organ Class Adverse Event (MedDRA v11.0 Preferred Term)	Varenicline (N=353) n (%)		Placebo (N=350) n (%)	
Cardiac Disorders				
Acute coronary syndrome	0		1	(0.3)
Acute myocardial infarction	2[a]	(0.6)	1	(0.3)
Angina pectoris	13[b]	(3.7)	7	(2.0)
Angina unstable	2	(0.6)	0	
Arrhythmia	1[a]	(0.3)	0	
Atrial fibrillation	2	(0.6)	2 a	(0.6)
Bundle branch block left	1	(0.3)	0	
Cardiac failure	1[a]	(0.3)	1	(0.3)
Cardiac failure congestive	0		1[a]	(0.3)
Cardiogenic shock	0		1[a]	(0.3)
Cardiovascular disorder	1	(0.3)	2	(0.6)
Coronary artery disease	1	(0.3)	0	
Myocardial infarction	1[a]	(0.3)	1	(0.3)
Palpitations	2	(0.6)	4[a]	(1.1)
Tachycardia	1	(0.3)	0	
Ventricular tachycardia	0		1	(0.3)
Nervous System Disorders				
Cerebrovascular accident	2[a]	(0.6)	0	
Syncope	1	(0.3)	1	(0.3)
Transient ischemic attack	0		1	(0.3)
Vascular Disorders				
Aortic arteriosclerosis	1	(0.3)	0	
Arteriosclerosis	3[a]	(0.8)	0	
Circulatory collapse	0		1	(0.3)
Femoral artery occlusion	1	(0.3)	0	
Hematoma	0		2	(0.6)
Hot flush	2	(0.6)	2	(0.6)
Hypertension	5[a]	(1.4)	9	(2.6)
Hypotension	2	(0.6)	2	(0.6)
Intermittent claudication	1	(0.3)	1	(0.3)
Ischemia	1	(0.3)	0	
Orthostatic hypotension	1	(0.3)	2	(0.6)
Peripheral vascular disorder	1	(0.3)	0	
Thrombosis	1	(0.3)	0	
Varicose vein	1	(0.3)	0	

Includes data up to 30 days after the last dose of study drug.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects with specified adverse event; v = version.
a. Led to treatment discontinuation in 1 subject.
b. Led to treatment discontinuation in 2 subjects.

Adjudicated Cardiovascular Events: A summary of cardiovascular events, both as defined by the Investigator and as defined by the adjudication committee is provided in Table 11.

In general, there was a low incidence of cardiovascular events in each treatment group (26 [7.4% varenicline and 23 [6.6% placebo]) and there were no differences between

treatment groups in the numbers or types of cardiovascular events. More cardiovascular events were reported by the Investigator than considered a cardiovascular event by the adjudication committee. The most common cardiovascular event submitted to the adjudication committee was hospitalization for angina pectoris (12 [3.4%] varenicline and 9 [2.6%] placebo according to the Investigator and 8 [2.3%] varenicline and 8 [2.3%] placebo according to the adjudication committee).

Table 11. Summary of Cardiovascular Events (All Subjects)

	Varenicline (N=353) n (%)		Placebo (N=350) n (%)	
Number (%) of Subjects Having At Least 1 CV Event	**26 (7.4)**		**23 (6.6)**	
Summary by Type of Event	**Investigator**	**Adjudicated**	**Investigator**	**Adjudicated**
Nonfatal myocardial infarction	9 (2.5)	7 (2.0)	3 (0.9)	3 (0.9)
Need for coronary revascularization	8 (2.3)	8 (2.3)	3 (0.9)	3 (0.9)
Hospitalization for angina pectoris	12 (3.4)	8 (2.3)	9 (2.6)	8 (2.3)
Hospitalization for congestive heart failure	2 (0.6)	0	2 (0.6)	2 (0.6)
Nonfatal stroke	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)
Transient ischemic attack	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
New diagnosis of PVD or admission for a procedure for the treatment of PVD	7 (2.0)	5 (1.4)	3 (0.9)	3 (0.9)
CV death	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)
Noncardiovascular death	1 (0.3)	1 (0.3)	3 (0.9)	3 (0.9)

Subjects with multiple CV events of the same type are counted only once per each row.
CV = cardiovascular; N = number of subjects; PVD = peripheral vascular disease; n = number of subjects with specified CV event.

Serious Adverse Events: A listing of treatment-related SAEs is provided in Table 12. Seven subjects had a treatment-related SAE during the study (4 [1.1%] varenicline and 3 [0.9%] placebo subjects). Four of the treatment-related SAEs in 3 subjects led to permanent discontinuation, including myocardial infarction (varenicline), cerebrovascular accident (varenicline), and atrial fibrillation and cardiac failure congestive (placebo).

Table 12. Treatment-Related Serious Adverse Events

Treatment / Serial No.	Adverse Event (MedDRA Preferred Term)	Day of Onset	Causality	Clinical Outcome
Varenicline				
1	Chest pain	36	Study drug	Recovered
2	Myocardial infarction[a]	1	Study drug	Recovered
3	Gingival bleeding	39	Study drug	Recovered
	Gingival recession	NA	Study drug	Recovered with sequelae
	Periodontal destruction	NA	Study drug	Recovered with sequelae
4	Cerebrovascular accident[a]	4	Study drug	Recovered with sequelae
Placebo				
1	Atrial fibrillation[a]	8	Study drug	Not recovered
	Cardiac failure congestive[a]	8	Study drug	Not recovered
2	Chest pain	51	Study drug	Recovered
3	Acute coronary syndrome	48	Study drug	Recovered

Days are relative to the day of starting study treatment (Day 1).
MedDRA = Medical Dictionary for Regulatory Activities; NA = not available
a. Led to permanent discontinuation from the study.

Permanent Discontinuations Due to Adverse Events: A summary of discontinuations from the study due to AEs is provided in Table 13. Few subjects discontinued due to an AE (8 varenicline and 5 placebo). All were considered related to study drug, except for 1 discontinuation due to AE in 1 varenicline subject (who discontinued due to fatigue) and 1 discontinuation due to AE in 1 placebo subject (who discontinued due to treatment-related malaise and treatment-unrelated emphysema).

Table 13. Permanent Discontinuations From Study Due to Adverse Events (All Subjects)

Treatment / Serial No.	Adverse Event (MedDRA Preferred Term)	Outcome
Varenicline		
1	Fatigue[a]	Resolved
2	Depressed mood	Resolved
3	Sluggishness, headache, abnormal dreams	Resolved
4	Chest pain[b], back pain[b], dyspnea[b], hyperhydrosis[b]	Resolved
5	Chest pain	Resolved
6	Headache	Resolved
7	Nausea	Unknown
8	Constipation, dysgeusia	Resolved
Placebo		
1	Diarrhea, nausea, vomiting, chest pain, disturbance in attention, headache	Resolved
2	Vision blurred, nausea, irritability, disturbance in attention, anxiety	Resolved
3	Rash	Still present at last follow-up
4	Vision blurred	Resolved
5	Malaise, emphysema[a]	Still present at last follow-up

MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event.
a. Not considered treatment related.
b. Considered a SAE.

Temporary Discontinuations Due to Adverse Events: More varenicline than placebo treated subjects required dose reductions or temporary discontinuations of study drug due to AEs. A total of 47 (13.3%) varenicline and 16 (4.6%) placebo subjects required dose reductions or temporary discontinuations of study drug due to AEs. Most AEs resolved after dose reduction or temporary discontinuation of study drug.

Deaths: A summary of deaths reported in the study is included in Table 14. A total of 7 subjects died during the study (2 [0.6%] varenicline and 5 [1.4%] placebo). None of the deaths were considered related to study treatment.

Table 14. Treatment Emergent Deaths

Treatment / Serial No.	Adverse Event (MedDRA Preferred Term)	Day of Death	Causality
Varenicline			
1	Myocardial infarction	239	Other illness
2	Pancreatic cancer	301	Other illness
Placebo			
1	Septic shock	116	Other
2	Diabetic coma, hypovolemia, pneumonia	36	Other illness
3	Acute myocardial infarction, cardiogenic shock, renal failure acute, and gastrointestinal hemorrhage	115	Other illness
4	Transitional cell carcinoma	361	Other illness
5	Acute myocardial infarction	162	Disease under study

MedDRA = Medical Dictionary for Regulatory Activities.

Overall, the frequency of clinically significant laboratory test abnormalities was low and similar between the treatment groups. Median changes in laboratory parameter values from Baseline to last observation were small and comparable between treatment groups.

Mean changes from Baseline to Week 12 and Week 52 were similar between varenicline and placebo treatment groups for vital sign and ECG data.

The mean change from Baseline to Week 12 and Week 52 for waist circumference was greater in the varenicline than the placebo group (mean change from Baseline to Week 12 was 1.3 cm for varenicline and 0.3 cm for placebo; mean change from Baseline to Week 52 was 1.8 cm for varenicline and 1.0 cm for placebo).

The mean changes in body weight in the varenicline and placebo groups from Baseline were 1.9 kg and 1.1 kg, respectively, to Week 12 and were 2.3 kg and 1.3 kg, respectively, to Week 52.

CONCLUSIONS: This 12-week treatment study that compared varenicline 1 mg BID with placebo for smoking cessation in subjects with cardiovascular disease, with follow-up at Week 52 demonstrated that:

- Varenicline is efficacious for smoking cessation both at the end of the treatment period and after long-term follow-up to Week 52, with statistical significance compared with placebo for all endpoints.

- There are no data suggestive of a safety concern in this population of subjects with cardiovascular disease.

- Varenicline is well tolerated and there were few treatment discontinuations for AEs, few deaths, and few treatment-related SAEs. The AE most affecting tolerability was nausea, which was generally mild to moderate in intensity and infrequently resulted in treatment discontinuation.

Overall, varenicline can be safely used and is well tolerated and efficacious for smoking cessation in subjects with cardiovascular disease.