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GENERIC DRUG NAME / COMPOUND NUMBER: Varenicline tartrate / CP-526,555

PROTOCOL NO.: A3051122

PROTOCOL TITLE: A Phase 4 12-Week, Double-Blind, Placebo-Controlled, Multicenter Study Evaluating the Safety and Efficacy of Varenicline Tartrate (CP-526,555) 1 mg BID for Smoking Cessation in Subjects With Depression

Study Centers: Thirty-eight centers took part in the study and enrolled subjects; 15 in the United States, 5 in Hungary, 4 each in the Russian Federation and Spain, 3 each in Germany and Romania and 2 each in Bosnia and Herzegovina and Croatia.

Study Initiation and Final Completion Dates: 25 March 2010 to 13 June 2012

Phase of Development: Phase 4

Study Objectives:

Primary Objective:

- Compare 12 weeks of varenicline treatment to placebo for end of treatment smoking cessation efficacy in smokers with depression.

Secondary Objectives:

- Compare 12 weeks of varenicline to placebo for long-term smoking abstinence through Week 52 in smokers with depression;
- Summarize safety and tolerability data, including effects on psychiatric rating scales, for 12 weeks of treatment with either varenicline or placebo.

METHODS

Study Design: This was a double-blind, placebo-controlled, randomized, multicenter clinical study designed to assess the efficacy and safety of 1 mg varenicline twice daily (BID) in comparison to placebo for smoking cessation in smokers who had past or present major depressive disorder (MDD). The duration of treatment was 12 weeks followed by a nontreatment follow-up phase of 40 weeks. All clinic visits were in an outpatient clinic setting. Telephone contacts were also used during the nontreatment phase.

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

Screening Phase: The Screening period was approximately 7 to 10 days (which allowed for 7 additional days as necessary for the return and evaluation of Screening results).

Treatment Phase: Randomized subjects entered the 12-week, placebo-controlled treatment period with weekly clinic visits for efficacy and safety assessments and smoking cessation counseling. For the active treatment group, varenicline dosing began with a 1-week titration followed by 11 weeks of 1 mg BID. All subjects set a target quit date (TQD) to coincide with the Week 1 visit. The Week 1 visit occurred at the end of the first week of the Treatment phase. It was the day that those randomized to the varenicline group began 1 mg BID. Smoking cessation counseling of up to 10 minutes in duration was provided at each clinic visit beginning at Baseline.

Nontreatment Phase: Blinded study medication was discontinued at the Week 12 visit, and subjects were to continue into the nontreatment follow-up phase. Subjects who did not complete 12 weeks of treatment were still eligible to continue into this phase provided that they complied with the nontreatment phase procedures. All efforts were to be made to keep the subjects in the study. Clinic visits were to occur at Weeks 13, 16, 24, 32, 40, and 52. Subjects were to be contacted by telephone at Weeks 14, 20, 28, 36, 44, and 48. During the nontreatment phase, smoking cessation counseling of up to 10 minutes in duration was provided at each visit and telephone contact.

The primary purpose of the nontreatment follow-up phase was to assess the long-term smoking abstinence. In addition, during this phase, subjects were monitored for suicidal ideation and behavior (SIB) adverse events (AEs) and recurrence of any major depressive episode. The schedule of activities for the Screening and Treatment phases is presented in Table 1. The nontreatment follow-up phase schedule is presented in Table 2.

Table 1. Schedule of Activities

Procedure	Screen	BL	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[a] 12
Informed consent[b]	X														
Medical history	X														
Smoking history	X														
Fagerstrom test	X														
Electrocardiogram	X														
Blood chemistry	X														
CBC	X														
Pregnancy test[c] (urine)	X	X													
Molecular profiling samples[d]	X														
Height	X														
Weight	X	X												X	X
Physical examination	X	X												X	X
Vital signs (heart rate, BP)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SCID	X														
SBQ-R	X														
MADRS		X	X	X	X	X	X	X	X	X	X	X	X	X	X
HAM-A		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
BIS-11	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-I			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
Exhaled CO	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neuropsychiatric AEs interview		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drugs		X	X	X	X	X	X	X	X	X	X	X	X		
Target quit day			X												
Dosing record			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
Nondrug treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine drug screen[e]	X	X													
Counseling (≤10 min)		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1. Schedule of Activities

Procedure	Screen	BL	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[a] 12

AE = adverse event; BIS-11 = Barratt Impulsiveness Scale; BL = Baseline; BP = blood pressure; CBC = complete blood count; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; CO = carbon monoxide; C-SSRS = Columbia Suicide Severity Rating Scale; ET = early termination; HAM-A = Hamilton Anxiety Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; SBQ-R = Suicide Behaviors Questionnaire-Revised; SCID = Structured Clinical Interview for DSM Disorders; Wk = week.

a. If ET was before the Week 12 visit.
b. Was signed prior to any protocol procedures being performed.
c. All females unless surgically sterilized or at least 2 years postmenopausal.
d. Optional.
e. Could have been performed at other visits at the investigator's discretion.

Table 2. Nontreatment Follow-Up Phase (Clinic Visits and Telephone Contacts)

Procedure	Wk 13 C	Wk 14 T	Wk 16 C	Wk 20 T	Wk 24 C	Wk 28 T	Wk 32 C	Wk 36 T	Wk 40 C	Wk 44 T	Wk 48 T	Wk 52 C	ET 52[a] C
Vital signs (heart rate, BP)	X		X		X		X		X			X	X
Nicotine use inventory	X	X	X	X	X	X	X	X	X	X	X	X	X
Exhaled carbon monoxide	X		X		X		X		X			X	X
Concomitant medications[b]	X		X		X[b]		X[b]		X[b]			X[b]	X[b]
Nondrug treatment	X		X		X		X		X			X	X
Counseling (≤10 min)	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs	X		X										
Neuropsychiatric AEs interview	X		X										
MADRS	X		X										
HAM-A	X		X										
C-SSRS	X		X		X		X		X			X	X
BIS-11	X		X										
CGI-S	X		X		X		X		X			X	X
CGI-I	X		X		X		X		X			X	X

AE = adverse event; BIS-11 = Barratt Impulsiveness Scale; BP = blood pressure; C = clinic visit; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ET = early termination; HAM-A = Hamilton Anxiety Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; T = telephone visit; Wk = week.

a. If ET was after Week 12 and before Week 52.

b. Smoking cessation–related and depression-related medications only.

Number of Subjects (Planned and Analyzed): Approximately 250 subjects were planned to be randomized in each of the 2 treatment groups, for a total of approximately 500 subjects randomized across the study centers. A total of 646 subjects (21 in Bosnia and Herzegovina, 23 in Croatia, 62 in Germany, 57 in Hungary, 24 in Romania, 64 in Russian Federation, 39 in Spain, 356 in United States) were screened and 525 subjects were randomized into the study (256 to varenicline and 269 to placebo) and analyzed as the safety analysis set. A total of 138 subjects discontinued treatment (55 from varenicline and 83 from placebo).

Diagnosis and Main Criteria for Inclusion: The study included male or female cigarette smokers, aged 18-75 years, motivated to stop smoking and considered suitable for a smoking cessation attempt. Subjects had to have smoked an average of at least 10 cigarettes per day during the past year and over the past month, and an exhaled carbon monoxide (CO) >10 ppm at Screening. A current or past diagnosis of MDD without psychotic features, either single or recurrent, using Diagnostic and Statistic Manual of Mental Disorders, Fourth Edition, Text Revision (DSM IV TR) based on clinical assessment and confirmed by Structured Clinical Interview for DSM Disorders (SCID) and at least one of the following: 1) on stable antidepressant treatment for MDD (stable dose for at least 2 months); 2) major depressive episode, using DSM IV TR, in the past 2 years successfully treated.

Exclusion Criteria: Subjects having current or past diagnosis of dementia, schizophrenia, schizoaffective disorder, or other psychotic disorder, bipolar I disorder, bipolar II disorder; subjects with antisocial, schizotypal, or any other personality disorder severe enough to compromise the subject's ability to comply with the study requirements and subject on current use of either bupropion or nortryptiline were excluded.

Study Treatment: Placebo and varenicline tartrate 0.5 mg were provided as film-coated tablets supplied in bottles containing a sufficient amount of tablets for 10 days. New bottles were dispensed at each clinic visit. Study drug administration began with a titration period. Treatment began from the Week 1 drug supply on the evening of the Baseline visit day. For the first 3 days of the Week 1 dosing period, subjects took one 0.5 mg tablet per day in the evening. For the next 4 days, this dose increased to two 0.5 mg tablets per day, with 1 additional tablet in the morning and 1 in the evening. On study Day 8, which coincided with the Week 1 visit, subjects were directed to increase their dose by taking 1 additional 0.5 mg tablet in the morning (total of two 0.5 mg tablets in the morning) and by taking 1 additional tablet in the evening (total of two 0.5 mg tablets in the evening). Subjects continued at that dose for the duration of the active phase of the study.

Efficacy and Safety Endpoints:

Primary Efficacy Endpoint:

The 4-week Continuous Quit Rate (CQR) for Weeks 9 through 12.

Secondary endpoints:

- Continuous Abstinence rate (CAR) from Week 9 through Week 52.
- CAR from Week 9 through Week 24.

- 7-day point prevalence of abstinence at Weeks 12, 24, and 52.
- 4-week point prevalence of abstinence at Week 52.

Safety Endpoints:

- AEs (including solicited neuropsychiatric adverse events).
- Psychiatric rating scales.
    - Clinical Global Impression of Improvement (CGI-I).
    - Clinical Global Impression of Severity (CGI-S).
    - Hamilton Anxiety Scale (HAM-A).
    - Montgomery-Asberg Depression Rating Scale (MADRS).
    - Columbia Suicide-Severity Rating Scale (C-SSRS).
    - Barratt Impulsiveness Scale (BIS-11).
    - Physical examination and vital signs.
    - Laboratory measures.

Safety Evaluations: All AEs observed, reported, or solicited were recorded up to and including Week 16. In addition to spontaneously reported AEs, active solicitation of neuropsychiatric (NPS) AEs of special interest was conducted using the Neuropsychiatric Adverse Event Interview (NAEI). During follow-up visits, the NAEI, in conjunction with volunteered AEs, was used to prospectively monitor worsening of existing NPS symptoms and treatment-emergent NPS symptoms. If a subject could have a positive response to any item on the NAEI, an investigator was to determine whether this met criteria as an AE.

Sitting blood pressure (BP) and pulse were measured at all clinic visits. Laboratory measures and a 12-lead electrocardiogram (ECG) was obtained at Screening (Table 1).

Statistical Methods: The primary efficacy analysis population was defined as all subjects who took at least 1 dose of randomized study medication (All Subjects population). The Full analysis set (FAS) was defined as all subjects who were randomized to a treatment regardless of dosing. The safety analysis set was defined as all subjects who received at least 1 dose of study medication. The Completer Subjects population was defined as a subset of the All Subjects set in which subjects 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 trial treatment. Subjects who discontinued the study were assumed to be smokers from the time point of discontinuation through the end of the study. In computing responder rates, subjects who discontinued the study were included in the denominator but not in the numerator, regardless of their last smoking status evaluation. Responders were defined as subjects who:

- Answered “no” to the question, “smoked cigarettes since last visit;” and

- Answered “no” to the question, “used other nicotine since last visit.”

The primary efficacy analysis was the analysis of the 4-week CO-confirmed CQR from Week 9 through Week 12 of treatment for varenicline compared with placebo. Subjects were assessed as responders for CO-confirmed CQR using the weekly reports of cigarette and nicotine use “since the last visit” in the Nicotine use inventory (NUI) for Weeks 9 through 12, inclusive. The 4-week CO-confirmed CQR was analyzed using the logistic regression model.

CAR from Week 9 through Weeks 24 and 52 was assessed using the reports of cigarette and nicotine use from the NUI for Weeks 9 through 24, inclusive and Weeks 9 through 52, inclusive for the respective periods. Responders were defined as subjects who:

- Answered “no” to the question, “smoked cigarettes since the last study visit” for Weeks 9 through 12.

- Answered “no” to the question, “smoked cigarettes since the last contact” for Weeks 13 through 24 and for Weeks 13 through 52.

- Answered “no” to the question, “used other nicotine since the last study visit” for Weeks 9 through 12.

- Answered “no” to the question, “used tobacco products since the last contact” for Weeks 13 through 24 and for Weeks 13 through 52.

The 7-day point prevalence of abstinence rate was assessed using the NUI at Weeks 12, 24, and 52.

Responders were defined as subjects who:

- Answered “no” to the question, “smoked cigarettes in last seven days.”

- Answered “no” to the question, “used other nicotine in last seven days.”

The 4-week point-prevalence of smoking abstinence at Week 52 was summarized by treatment group and visit using descriptive statistics.

Responders were defined as subjects who:

- Answered “no” to the question, “smoked cigarettes in last 4 weeks.”

- Answered “no” to the question, “used tobacco products in last 4 weeks.”

Additionally, a subject was not considered a responder if the expired CO >10 ppm at any given time point being assessed. In the case of a missed visit(s) during evaluation period, a subject was considered a responder if that subject responded that he/she did not smoke or use nicotine products “since the last visit” at the visit after the missing visit(s).Missing CO measurements were imputed as negative (ie, not disqualifying the subject as a responder).

No attempt was made to impute missing data from the NUI. The CAR at Weeks 24 and 52 and the 7-day point prevalence of abstinence at Weeks 12, 24, and 52 were summarized by treatment group and visit using descriptive statistics. Observed rates and associated 95% CIs were displayed graphically. All endpoints were analyzed using the logistic regression model.

RESULTS

Subject Disposition and Demography: A total of 646 subjects were screened and 525 subjects were randomized into the study, all of whom took at least 1 dose of study medication and comprise the All Subjects analysis set and the FAS. A total of 387 subjects (201 subjects treated with varenicline and 186 subjects treated with placebo) completed treatment, and 354 subjects (175 subjects treated with varenicline and 179 subjects treated with placebo) completed the study. The discontinuations from treatment were higher in the placebo group than in the varenicline group (30.9% versus 21.5%). The most notable difference was among subjects who discontinued treatment for "other" reasons, such as relocation and lack of time or transportation (5.9% of subjects treated with varenicline and 10.0% of subjects treated with placebo). Discontinuations from treatment and from the study due to AEs were similar across treatment groups. A total of 171 subjects withdrew from the study, with "no longer willing to participate" and "other" as the most common reasons. A summary of the subject disposition and subject analyzed is provided in Table 3. Demographic characteristics are summarized in Table 4.

Table 3. Subject Disposition and Subjects Analyzed

Number (%) of Subjects	Varenicline	Placebo
Randomized and treated	256	269
Completed treatment	201 (78.5)	186 (69.1)
Discontinued treatment	55 (21.5)	83 (30.9)
Relation to study drug not defined	39 (15.2)	62 (23.0)
Does not meet entrance criteria	0	1 (0.4)
Lost to follow-up	5 (2.0)	7 (2.6)
No longer willing to participate in study	16 (6.3)	22 (8.2)
Other	15 (5.9)	27 (10.0)
Protocol violation	3 (1.2)	5 (1.9)
Related to study drug	13 (5.1)	15 (5.6)
Adverse event	13 (5.1)	15 (5.6)
Not related to study drug	3 (1.2)	6 (2.2)
Adverse event	3 (1.2)	6 (2.2)
Completed study	175 (68.4)	179 (66.5)
Discontinued study	81 (31.6)	90 (33.5)
Subject died	2 (0.8)	0
Relation to study drug not defined	73 (28.5)	85 (31.6)
Does not meet entrance criteria	0	1 (0.4)
Lost to follow-up	12 (4.7)	13 (4.8)
No longer willing to participate in study	31 (12.1)	33 (12.3)
Other	24 (9.4)	32 (11.9)
Protocol violation	6 (2.3)	6 (2.2)
Related to study drug	4 (1.6)	3 (1.1)
Adverse event	4 (1.6)	3 (1.1)
Not related to study drug	2 (0.8)	2 (0.7)
Adverse event	2 (0.8)	2 (0.7)
Analyzed for efficacy		
Full analysis set	256 (100.0)	269 (100.0)
All subjects analysis set	256 (100.0)	269 (100.0)
Completer subjects analysis set	207 (80.9)	197 (73.2)
Analyzed for safety		
Adverse events	256 (100.0)	269 (100.0)
Safety analysis set	256 (100.0)	269 (100.0)

Table 4. Demographic Characteristics – Safety Analysis Set

Number (%) of Subjects	Varenicline (N=256)	Placebo (N=269)
Sex		
Male	97 (37.9)	99 (36.8)
Female	159 (62.1)	170 (63.2)
Age (years)		
Mean (SD)	45.4 (10.9)	47.1 (10.8)
Range	19-73	20-73
Race (%)		
White	228 (89.1)	237 (88.1)
Black	26 (10.2)	25 (9.3)
Asian	0	1 (0.4)
Other	2 (0.8)	6 (2.2)
Body mass index (kg/m^2)		
Mean (SD)	26.8 (4.6)	27.3 (5.0)
Range	17.3-38.0	17.9-38.1

The safety analysis set is defined as all subjects who received at least 1 dose of study medication.
Body mass index is defined as weight/(height times .01)^2.
N = number of safety subjects; SD = standard deviation.

Efficacy Results: The CO-confirmed 4-week CQR for the All Subjects analysis set is presented in Table 5**.** At Week 12, treatment with varenicline resulted in a clinically and statistically significantly higher CO-confirmed 4-week CQR compared to placebo (35.9% versus 15.6%, respectively, p<0.0001).

Table 5. Carbon Monoxide-Confirmed 4-Week Continuous Quit Rate – All Subjects Analysis Set

Week	Varenicline (N=256)	Placebo (N=269)	Odds Ratio (95% CI) Versus Placebo	p-Value Versus Placebo
Week 12: n (%)	92 (35.9)	42 (15.6)	3.35 (2.16, 5.21)	<0.0001

The All Subjects analysis set was defined as all subjects who were randomized and took at least 1 dose of randomized study medication.
Odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment, pooled center, and cohort.
CI = confidence interval; N = number of subjects in the All Subjects analysis set; n = number of subjects who, at each visit from Week 9 through 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 carbon monoxide >10 ppm at any of these visits.

The key secondary endpoint, the CAR for All Subjects analysis set is presented in Table 6 for Week 24 and 52. At Week 52, treatment with varenicline resulted in higher CAR than treatment with placebo, and this difference was statistically significant (p = 0.0011). At Week 24, treatment with varenicline resulted in higher CAR than treatment with placebo, and this difference was statistically significant (p = 0.0001).

Table 6. Continuous Abstinence Rate at Weeks 24 and 52 - All Subjects Set

Week	Varenicline (N=256)	Placebo (N=269)	Odds Ratio (95% CI) Versus Placebo	p-Value Versus Placebo
Week 24: n (%)	64 (25.0)	33 (12.3)	2.53 (1.56, 4.10)	0.0001
Week 52: n (%)	52 (20.3)	28 (10.4)	2.36 (1.40, 3.98)	0.0011

The All Subjects analysis set was defined as all subjects who were randomized and took at least 1 dose of randomized study medication.
Odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment, pooled center, and cohort.
CI = confidence interval; N = number of subjects in the All Subjects analysis set; n = number of subjects who, at each visit from Week 9 through 52 (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 carbon monoxide >10 ppm at any of these visits.

The 7-day point prevalence of abstinence for the All Subjects analysis set is presented in Table 7. At Weeks 12, 24, and 52, treatment with varenicline was statistically significantly higher than placebo for the 7-day point prevalence of abstinence.

Table 7. Carbon Monoxide-Confirmed 7-Day Point Prevalence of Abstinence – All Subjects Analysis Set

Week	Varenicline (N = 256)	Placebo (N = 269)	Odds Ratio (95% CI) Versus Placebo	p-Value Versus Placebo
Week 12: n (%)	118 (46.1)	54 (20.1)	3.82 (2.53, 5.78)	<0.0001
Week 24: n (%)	80 (31.3)	49 (18.2)	2.16 (1.40, 3.33)	0.0004
Week 52: n (%)	73 (28.5)	47 (17.5)	1.98 (1.28, 3.08)	0.0020

The All Subjects analysis set was defined as all subjects who were randomized and took at least 1 dose of randomized study medication.
Odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment, pooled center, and cohort.
CI = confidence interval; N = number of subjects in the All Subjects analysis set; n = number of subjects who, at the given visit or telephone contact, 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 carbon monoxide >10 ppm on that day (if measured).

The CO-confirmed 4-week point prevalence of abstinence at Week 52 is presented for the All Subjects analysis set in Table 8. At Week 52, treatment with varenicline was statistically significantly higher than placebo for the CO-confirmed 4-week point prevalence of abstinence ($p = 0.0027$).

Table 8. Carbon Monoxide-Confirmed 4-Week Point Prevalence of Abstinence at Week 52 – All Subjects Analysis Set

	Varenicline (N=256)	Placebo (N=269)	Odds Ratio (95% CI) Versus Placebo	p-Value Versus Placebo
Week 52: n (%)	70 (27.3)	45 (16.7)	1.97 (1.26, 3.08)	0.0027

The All Subjects analysis set was defined as all subjects who were randomized and took at least 1 dose of randomized study medication.
Odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment, pooled center, and cohort.
CI = confidence interval; N = number of subjects in the All Subjects analysis set; n = number of subjects who, at the Week 52 visit, reported no smoking and no use of other tobacco products in the last 4 weeks and who did not have carbon monoxide >10 ppm at the visit.

Safety Results: A summary of treatment-emergent AEs (TEAEs) is presented in Table 9.

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

	Varenicline (N=256)	Placebo (N=269)
Subjects evaluable for AEs	256	269
Number of AEs	736 (461)	598 (326)
Subjects with AEs	185 (150)	180 (126)
Subjects with SAEs	7 (2)	7 (1)
Subjects with severe AEs	12 (6)	9 (1)
Subjects discontinued due to AEs	16 (13)	21 (15)
Subjects with dose reduced or temporary discontinuation due to AEs	22 (19)	10 (8)

AEs in this table include serious and non-serious AEs.
The safety analysis set was defined as all subjects who received at least 1 dose of study medication.
Includes data up to 30 days after last dose of study treatment.
Except for the number of AEs, subjects are counted only once per treatment in each row.
SAEs were evaluated according to the Investigator's assessment.
MedDRA version 15.0 coding applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects evaluable for AEs; SAE = serious adverse event.

A summary of non-serious TEAEs (All Causalities) experienced by ≥5% of subjects for either treatment, are presented in Table 10.

Table 10. Non-serious Treatment-Emergent Adverse Events in ≥5% of subjects by treatment group, All Causalities – Safety Analysis Set

System Organ Class and MedDRA Preferred Term	Varenicline n (%)	Placebo n (%)
Number (%) of subjects evaluable for adverse events	256	269
Number (%) of subjects with adverse events	158 (61.7)	126 (46.8)
Gastrointestinal Disorders	99 (38.7)	54 (20.1)
Constipation	15 (5.9)	9 (3.3)
Diarrhoea	16 (6.3)	12 (4.5)
Dry mouth	17 (6.6)	14 (5.2)
Nausea	69 (27.0)	28 (10.4)
Vomiting	13 (5.1)	9 (3.3)
General Disorders and Administration Site Conditions	28 (10.9)	22 (8.2)
Irritability	28 (10.9)	22 (8.2)
Infections and Infestations	29 (11.3)	26 (9.7)
Nasopharyngitis	14 (5.5)	13 (4.8)
Upper respiratory tract infection	15 (5.9)	13 (4.8)
Investigations	14 (5.5)	5 (1.9)
Weight increased	14 (5.5)	5 (1.9)
Nervous System Disorders	43 (16.8)	30 (11.2)
Headache	43 (16.8)	30 (11.2)
Psychiatric Disorders	78 (30.5)	65 (24.2)
Abnormal dreams	29 (11.3)	22 (8.2)
Agitation	17 (6.6)	10 (3.7)
Anxiety	18 (7.0)	25 (9.3)
Depression	17 (6.6)	13 (4.8)
Insomnia	28 (10.9)	13 (4.8)

Subjects are only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (v15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities

The incidence of treatment-emergent psychiatric AEs experienced by ≥2% of subjects in either treatment group is summarized in Table 11.

Table 11. Treatment-Emergent Psychiatric Adverse Events by ≥2% Subjects, All Causalities – Safety Analysis Set

System Organ Class MedDRA Preferred Term	Varenicline (N=256) Solicited and Volunteered n (%)	Placebo (N=269) Solicited and Volunteered n (%)
Psychiatric disorders	103 (40.2)	93 (34.6)
Abnormal dreams	29 (11.3)	22 (8.2)
Insomnia	28 (10.9)	13 (4.8)
Anxiety	18 (7.0)	25 (9.3)
Depression	17 (6.6)	13 (4.8)
Agitation	17 (6.6)	11 (4.1)
Tension	9 (3.5)	8 (3.0)
Depressed mood	7 (2.7)	10 (3.7)
Sleep disorder	7 (2.7)	4 (1.5)
Restlessness	5 (2.0)	5 (1.9)
Hostility	5 (2.0)	1 (0.4)

AE/SAE results are not separated in this table.
The safety analysis set was defined as all subjects who received at least 1 dose of study medication.
Subjects were counted only once per treatment for each row.
Includes data up to 30 days after last dose of study treatment.
MedDRA (version 15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects who received the treatment; n = number of subjects with an adverse event while on study treatment.

Treatment-related AEs:

The treatment-emergent, treatment-related AEs by ≥2% subjects are presented in Table 12.

Table 12. Treatment-Emergent Treatment Related Adverse Events by ≥2% Subjects - Safety Analysis Set

Adverse Events by SOC/ Preferred Term	Varenicline (N=256) n (%)	Placebo (N=269) n (%)
Gastrointestinal Disorders	98 (38.3)	48 (17.8)
Constipation	14 (5.5)	7 (2.6)
Diarrhoea	12 (4.7)	6 (2.2)
Abdominal pain upper	7 (2.7)	5 (1.9)
Dyspepsia	6 (2.3)	4 (1.5)
Flatulence	8 (3.1)	4 (1.5)
Nausea	63 (24.6)	20 (7.4)
Vomiting	8 (3.1)	7 (2.6)
Dry mouth	16 (6.3)	13 (4.8)
General Disorders and Administration Site Conditions	33 (12.9)	24 (8.9)
Fatigue	5 (2.0)	6 (2.2)
Irritability	21 (8.2)	14 (5.2)
Infections and infestations	10 (3.9)	10 (3.7)
Nasopharyngitis	6 (2.3)	6 (2.2)
Investigations	7 (2.7)	2 (0.7)
Weight increased	5 (2.0)	0
Metabolism and Nutrition Disorders	9 (3.5)	8 (3.0)
Decreased appetite	7 (2.7)	5 (1.9)
Nervous System Disorders	55 (21.5)	51 (19.0)
Headache	32 (12.5)	20 (7.4)
Dizziness	9 (3.5)	12 (4.5)
Dysgeusia	3 (1.2)	11 (4.1)
Somnolence	7 (2.7)	3 (1.1)
Psychiatric Disorders	80 (31.3)	68 (25.3)
Agitation	9 (3.5)	5 (1.9)
Anxiety	11 (4.3)	12 (4.5)
Depressed mood	6 (2.3)	7 (2.6)
Depression	10 (3.9)	8 (3.0)
Abnormal dreams	28 (10.9)	22 (8.2)
Insomnia	18 (7.0)	8 (3.0)
Sleep disorder	6 (2.3)	3 (1.1)

AE/SAE results are not separated out. The safety analysis set was defined as all subjects who received at least 1 dose of study medication.
Subjects were counted only once per treatment for each row.
Includes data up to 30 days after last dose of study treatment.
Number of adverse events (subjects) contributing to this table with missing information about solicited/volunteered classification: 0 (0).
MedDRA (v15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects who received the treatment; n = number of subjects with an adverse event while on study treatment; SOC = system organ class.

Serious adverse events (SAEs): The number of subjects with nonfatal SAEs was similar for both treatments (8 subjects treated with varenicline and 7 subjects treated with placebo). The majority of the SAEs were considered unrelated to the treatment and eventually resolved. Three SAEs were considered to be treatment related. Eight SAEs were post-therapy emergent. SAEs are presented in Table 13.

Withdrawals due to AEs: Permanent discontinuations from treatment due to AEs are presented in Table 14.

Table 13. Serious Adverse Events

Subject Number	Sex/ Age[a] (years)	MedDRA Preferred Term[b]	Therapy Stop Day[c]	Event Onset Day[d]	Event Stop Day[e]	Causality[f]	Clinical Outcome
Varenicline							
1	F/30	Palpitations	72	81	N/A	Related	Not recovered/Not resolved
2	M/56	Overdose	81	303	310	Unrelated	Recovered/Resolved
3	F/56	Nephrolithiasis	85	39	65	Unrelated	Recovered/Resolved
4	F/69	Autoimmune hepatitis	42	28	57	Related	Recovered/Resolved
5	F/42	Ligament laxity	84	101	102	Unrelated	Recovered/Resolved
6	F/58	Acute abdomen	85	54	72	Unrelated	Recovered/Resolved
		Haemodynamic instability	85	58	63	Unrelated	Recovered/Resolved
		Psychotic disorder	85	58	63	Unrelated	Recovered/Resolved
7	F/44	Intervertebral disc protrusion	93	65	76	Unrelated	Recovered/Resolved
8	M/58	Depression	14	13	91	Unrelated	Recovered/Resolved
		Suicidal ideation	14	13	91	Unrelated	Recovered/Resolved
Placebo							
1	M/64	Intentional self-injury	73	73	93	Related	Recovered/Resolved
2	M/52	Chest pain	86	92	110	Unrelated	Recovered/Resolved
		Depression suicidal	86	98	115	Unrelated	Recovered/Resolved
		Agitation	86	332	346	Unrelated	Recovered/Resolved
3	M/59	Agitation	63	69	441	Unrelated	Recovered/Resolved
4	F/47	Chronic obstructive pulmonary disease	87	38	42	Unrelated	Recovered/Resolved
		Bronchitis	87	38	42	Unrelated	Recovered/Resolved
5	M/55	Device dislocation	43	50	59	Unrelated	Recovered/Resolved
		Device related infection	43	43	59	Unrelated	Recovered/Resolved
6	F/48	Fractured coccyx	85	11	104	Unrelated	Recovered/Resolved
		Fall	85	11	11	Unrelated	Recovered/Resolved
7	M/43	Depression	88	63	N/A	Unrelated	Not recovered/Not resolved

N/A = not available or not applicable; OC = Oracle Clinical; SAE = serious adverse event; SDW = safety data warehouse.

a. Age at date of SAE onset.
b. Medical Dictionary for Regulatory Activities (MedDRA version 15.0) coding applied.
c. Therapy stop day is calculated as OC last active therapy date minus OC first active therapy date plus 1.
d. Onset study day is calculated as SDW onset date minus OC first active therapy date plus 1.
e. Event stop day is calculated as SDW SAE stop date minus OC first active therapy date plus 1.
f. Causality according to investigator's assessment.

Table 14. Permanent Discontinuations From Treatment Due to Adverse Events – Safety Analysis Set

Subject Number	Sex/Age[a] (years)	AE Study Start Day[b]	AE Study Stop Day[b]	AE Preferred Term[c]	Severity/Outcome	Causality	SAE[d]
Varenicline							
1	F/46	28	64	Depression	Moderate/resolved	Study drug	No
2	F/30	65	81	Palpitations	Mild/resolved	Study drug	No
3	F/60	5	11	Arthralgia	Moderate/resolved	Study drug	No
4	F/48	6	7	Pharyngeal oedema	Moderate/resolved	Study drug	No
5	F/62	38	43	Agitation	Moderate/resolved	Study drug	No
6	F/69	28	73	Autoimmune hepatitis	Severe/resolved	Study drug	Yes
7	F/54	11	27	Depressive symptom	Moderate/resolved	Study drug	No
8	F/24	57	62	Depression	Moderate/resolved	Study drug	No
9	F/30	10	40	Depression	Moderate/resolved	Disease under study	No
10	F/42	66	[>72]	Mania	Moderate/still present	Study drug	No
11	F/31	40	51	Depression	Moderate/resolved	Study drug	No
12	M/48	17	21	Agitation	Mild/resolved	Study drug	No
13	F/57	4	5	Malaise	Moderate/resolved	Study drug	No
14	F/57	54	72	Acute abdomen	Severe/resolved	Other illness	Yes
15	M/38	13	33	Depression	Severe/resolved	Study drug	No
16	M/58	13	91	Depression suicidal	Severe/resolved	Other-chronic marriage conflict worsened towards divorce	Yes
Placebo							
17	M/64	73	93	Intentional self-injury	Moderate/resolved	Study drug	Yes
18	F/42	72	72	Self-injurious ideation	Moderate/resolved	Other – most likely underlying personality traits	No
19	F/53	11	19	Anxiety	Moderate/resolved	Other – patient no longer wants to take meds due to anxiety about potential side effects of medications	No
20	F/38	9	12	Depression	Moderate/resolved	Study drug	No
21	F/27	32	34	Anxiety	Moderate/resolved	Study drug	No
22	F/65	30	39	Suicidal ideation	Mild/resolved	Study drug	No
23	F/60	18	26	Mania	Moderate/resolved	Study drug	No
24	M/53	61	70	Urticaria	Mild/resolved	Study drug	No
25	M/28	45	[>390]	Attention deficit hyperactivity disorder	Mild/still present	Other illness	No
26	M/59	4	8	Insomnia	Moderate/resolved	Study drug	No
27	F/52	4	15	Disturbance in attention	Moderate/resolved	Study drug	No

Table 14. Permanent Discontinuations From Treatment Due to Adverse Events – Safety Analysis Set

Subject Number	Sex/Age[a] (years)	AE Study Start Day[b]	AE Study Stop Day[b]	AE Preferred Term[c]	Severity/Outcome	Causality	SAE[d]
28	F/44	21	65	Depression	Moderate/resolved	Study drug	No
29	F/59	21	45	Hypnagogic hallucination	Moderate/resolved	Study drug	No
30	F/41	38	[>38]	Blood pressure increased	Moderate/still present	Other illness – hypertension	No
31	M/59	21	[>21]	Depression	Moderate/still present	Disease under study	No
32	M/55	43	58	Device related infection	Severe/resolved	Other – previous injury	Yes
33	F/42	55	64	Depressed mood	Moderate/resolved	Study drug	No
34	F/53	48	66	Depressed mood	Moderate/resolved	Study drug	No
35	F/54	13	52	Pelvic pain	Moderate/resolved	Study drug	No
36	M/36	63	117	Depressed mood	Moderate/resolved	Study drug	No
37	F/60	10	46	Depressed mood	Moderate/resolved	Study drug	No

[] Values in brackets are imputed from incomplete dates and times.
All AEs were treatment emergent.
The safety analysis set was defined as all subjects who have received at least 1 dose of study medication.
AE = adverse event; F = female; M = male; SAE = serious adverse event.
a. Age at screening.
b. Day relative to Start Day and Stop Day of each treatment period. First day of each treatment period = Day 1.
c. Medical Dictionary for Regulatory Activities (MedDRA version 15.0) coding applied.
d. SAE according to investigator's assessment.

Deaths: Two subjects died post-therapy, both from the varenicline treatment group. Neither death was related to the study treatment. There were no deaths reported in the placebo treatment group.

Psychiatric rating scales: The MADRS mean change from Baseline was similar in both treatment groups. The MADRS mean change from Baseline decreased for both treatment groups, which is indicative of improvement in depressive symptoms. The HAM-A mean change from Baseline was similar in both treatment groups and decreased (improved) during the study. Baseline CGI-S score distribution was comparable between the 2 treatment groups, and no subjects were rated as severely or extremely ill. The majority of subjects in either treatment group showed no change from Baseline either at the end of treatment (Week 12) or at Weeks 24 and 52. The CGI-I mean score was similar in both treatment groups and improved (lower values) during the study. For the observed BIS-11 scores, the mean change from Baseline over the course of the study was minimal in both groups with treatment group mean differences from Baseline ranging from -0.6 to 0.6 over the course of 16 weeks. In C-SSRS, a similar proportion of subjects in both treatment groups reported lifetime history of suicidal behavior and/or ideation, 34.4% for varenicline and 33.1% for placebo. There were no differences in the proportion of subjects with past history of suicide attempts (7.4 % varenicline versus 7.8% placebo). The incidence of suicidal ideation and or behavior measured by C-SSRS was low and similar between both treatment groups during the treatment (6.0% versus 7.5%) and the nontreatment phases (6.2% versus 5.8%).

CONCLUSIONS:

This study met its primary endpoint of comparing the CO-confirmed CQR for Weeks 9 through 12 between varenicline and placebo. Subjects in the varenicline group had a higher likelihood of quitting at the end of the treatment period (CO-confirmed CQR at Weeks 9 through 12: 35.9% varenicline treatment group versus 15.6% placebo treatment group, odds ratio 3.35 [95% CI: 2.16, 5.21]), and the difference was maintained at Week 52 (CAR Weeks 9 through 52: 20.3% varenicline treatment group versus 10.4% placebo treatment group, odds ratio 2.36 [95% CI: 1.40, 3.98]).

The MADRS and HAM-A showed nominal improvement during the study, which was similar in both treatment groups. The majority of subjects showed no changes in the CGI-S scores, and overall, no clinically significant patterns in shifts were noted. Changes from Baseline, as measured by CGI-I, were also similar for both treatment groups. The mean changes from Baseline for BIS-11 were minimal for both treatment groups.

The incidence of suicidal ideation and or behavior measured by C-SSRS was low and similar between both treatment groups during the treatment (6.0% versus 7.5%) and the nontreatment phases (6.2% versus 5.8%).

The most frequently reported AEs were in the system organ classes of gastrointestinal, psychiatric, and nervous system disorders. A higher percentage of subjects in the active treatment group experienced nausea, headache, and abnormal dreams than did subjects in the placebo group: 27.0% versus 10.4% (nausea), 16.8% versus 11.2% (headache), and 11.3% versus 8.2% (abnormal dreams). The most frequently reported NPS AEs, excluding sleep

disorders, were anxiety (7.0% varenicline versus 9.3% placebo), depression (6.6% varenicline versus 4.8% placebo), agitation (6.6% varenicline versus 4.1% placebo), tension (3.5% varenicline versus 3.0% placebo), and depressed mood (2.7% varenicline versus 3.7% placebo).