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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00691483

PROTOCOL NO.: A3051095

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

Study Center(s): 33 in 14 countries (Argentina [1], Brazil [1], Canada [2], China [3], Czech Republic [2], France [1], Germany [2], Hungary [2], Italy [1], Republic of Korea [2], Mexico [1], Taiwan [2], United Kingdom [1], United States (US) [12])

Study Initiation Date and Primary Completion or Completion Dates:
22 September 2008 to 10 December 2009

Phase of Development: Phase 4

Study Objective(s): The primary efficacy objective of this protocol was to compare 12 weeks of treatment with varenicline 1 mg twice daily (BID) to placebo for smoking cessation in the setting of a subject self-selected quit date (before Week 5 visit), and to evaluate continuous abstinence (CA) from smoking for 12 weeks after the treatment period.

Additional secondary objectives were to compare treatments for urge to smoke, smoking satisfaction, and the psychological reward over time in subjects in the US by analyses of the results from the Minnesota Nicotine Withdrawal Scale (MNWS) and the Modified Cigarette Evaluation Questionnaire (mCEQ), respectively.

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

METHODS

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

cessation. The study consisted of a 12-week treatment phase followed by a 12-week non-treatment phase for a total study duration of 24 weeks. Approximately 652 subjects (at least 489 varenicline and 163 placebo) were to be randomized in a 3:1 ratio to receive either varenicline (1-week titration followed by 11 weeks of 1 mg BID treatment) or placebo. Blinded study medication was discontinued at the Week 12 visit and was followed by a non-treatment period to Week 24. Subjects were to self-select a quit date to occur between Day 8 (the date of dose escalation to 1 mg BID) and the Week 5 visit day. The Week 1 visit occurred at the end of the first week of treatment. Subjects were to return for clinic visits at Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 during the treatment period. During the non-treatment follow-up, subjects were to return for visits at Weeks 13, 16, 20 and 24, and were contacted by phone at Weeks 14, 18 and 22. Each subject received brief smoking cessation counseling, consistent with the Agency for Healthcare Research and Quality (AHRQ) guidelines or similar local guidelines at each clinic visit and at each telephone contact starting with the baseline visit. At the baseline visit, subjects also received an educational booklet about smoking cessation.

Number of Subjects (Planned and Analyzed): It was planned to randomize at least 652 subjects to varenicline or placebo in a 3:1 ratio. Four hundred and ninety three (493) subjects were assigned to varenicline and 166 to placebo. Of these, 486 and 165 were treated with at least 1 dose of varenicline and placebo, respectively.

Diagnosis and Main Criteria for Inclusion: Subjects were eligible for enrollment into the study if they were current cigarette smokers between 18 and 75 years of age and motivated to stop smoking. Subjects had to have smoked an average of at least 10 cigarettes per day during the past year and during the month prior to the screening visit, with no continuous period of abstinence greater than 3 months in the past year. In addition, subjects were not to have had serious or unstable disease within the past 6 months.

Study Treatment: Subjects were randomized to receive either blinded varenicline or placebo. Subjects randomized to varenicline were titrated to the full dose during the first week in the following manner: 0.5 mg once daily (QD) x 3 days followed by 0.5 mg BID x 4 days, and then 1 mg BID for 11 weeks. During the non-treatment follow-up period from Week 13 to Week 24, subjects did not receive study medication. Tablets (blinded varenicline or placebo) were supplied in bottles containing sufficient tablets for 1 week. Varenicline was supplied as 0.5 mg tablets for the first week and 1.0 mg tablets for the remaining 11 weeks of the study treatment period.

Efficacy Evaluations: Efficacy data were collected using the Nicotine Use Inventory (NUI) and exhaled CO measurements. NUI was also completed at all telephone contacts. Data on quitting plans and quit attempts (defined as quitting smoking for at least a few hours with the conviction to quit permanently) occurring during the first 5 weeks of the study were also collected using the Plan and Quit Questionnaire. The MNWS was used to assess craving and nicotine withdrawal symptoms. The rewarding effects associated with smoking were measured with the mCEQ. The MNWS and the mCEQ were administered at the baseline visit and weekly through Week 12 to subjects enrolled in US centers only.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: This study included the collection of a single blood sample for de-identified pharmacogenomic studies. Participation in this component of the study was voluntary and required a separate informed consent. Pharmacogenomic analyses were described in a separate protocol and were not part of this study report.

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

Statistical Methods: The All Subjects population was defined as all subjects who received at least 1 dose, including partial doses, of randomized study medication. The All Subjects population was the primary population for efficacy and safety analyses in this study. Analyses of the Evaluable Subjects population (all subjects who took at least 14 days of study medication in the first 21 days of the study), Completers population (all subjects who had at least 80% treatment compliance), and intention-to-treat (ITT) population (all randomized subjects) were intended to support the robustness of the conclusions made on the All Subjects population.

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, when used in a setting where subjects are given some discretion regarding setting their own quit date. The primary efficacy endpoint was the CO-confirmed 4-week CQR for Weeks 9 through 12, inclusive. The key secondary efficacy endpoint was the continuous abstinence rate (CAR) from Weeks 9 through 24.

Other secondary efficacy endpoints included CO-confirmed and non-CO-confirmed long term quit rate (LTQR) from Weeks 9 through 24, 7-day point prevalence of smoking cessation at Weeks 12 and 24, 4-week point prevalence of smoking cessation at Week 24, non-CO-confirmed 4-week CQR for Weeks 9 through 12, and endpoints related to plans for or times of smoking quit attempts. Patient-reported outcomes (PRO) endpoints included data from the MNWS and the mCEQ with focus on the Urge-to-Smoke item of the MNWS (baseline and weekly through Week 12) and the Smoking Satisfaction and Psychological Reward domains of the mCEQ (baseline and weekly through Week 12).

A planned sample size of 652 subjects randomized to varenicline or placebo in a 3:1 ratio (489 varenicline and 163 placebo) was to provide at least 90% power to detect a difference in the primary endpoint between the varenicline and placebo groups, assuming a true Weeks 9 to 12 CAR of 0.24 and 0.46 for placebo and varenicline, respectively (odds ratio [OR] of at least 2.67). This sample size also provided at least 90% power to detect a difference between varenicline and placebo in the secondary endpoint Weeks 9 to 24 CAR, assuming a true Weeks 9 to 24 CAR of 0.18 and 0.31 for placebo and varenicline, respectively (OR of at least 2.10).

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

For the time-to-event endpoint, statistical inference was based on the Kaplan-Meier method with treatment groups as strata. For continuous PRO endpoints, statistical inference was based on a linear repeated measures model with covariates in harmony with those used to control the analysis of the primary endpoint.

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

An additional sensitivity analysis was performed on the primary and key secondary analyses to assess the impact of excluding 18 subjects with unreliable data who were randomized at investigational center 1032.

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

RESULTS

Subject Disposition and Demography: Subject disposition and data sets are summarized in Table 1. Subjects were encouraged to remain in the study if they discontinued treatment in order to provide data for smoking status and other outcomes. Table 1 consequently provides 2 separate presentations on subject disposition, 1 representing treatment and 1 representing study.

Table 1. Subject Disposition

Number (%) of subjects	Varenicline	Placebo
Screened: 831		
Assigned to study treatment	493	166
Treated	486	165
Completed study	425 (87.4)	141 (85.5)
Discontinued study	61 (12.6)	24 (14.5)
Completed study treatment period	442 (90.9)	142 (86.1)
Discontinued study in treatment period	44 (9.1)	23 (13.9)
Completed treatment	425 (87.4)	131 (79.4)
Discontinued treatment [a]	61 (12.6)	34 (20.6)
Related to study drug	24 (4.9)	14 (8.5)
Adverse event	23 (4.7)	11 (6.7)
Lack of efficacy	1 (0.2)	3 (1.8)
Not related to study drug	37 (7.6)	20 (12.1)
Adverse event	1 (0.2)	2 (1.2)
Lost to follow up	9 (1.9)	10 (6.1)
Subject no longer willing to participate in study	18 (3.7)	6 (3.6)
Other	9 (1.9)	2 (1.2)
Discontinued treatment, but stayed in study [b]	17 (3.5)	11 (6.7)
Completed follow-up period	0	10 (6.1)
Discontinued study in follow-up period	17 (3.5)	1 (0.6)
Not related to study drug	17 (3.5)	1 (0.6)
Lost to follow up	8 (1.6)	0
Subject no longer willing to participate in study	7 (1.4)	1 (0.6)
Other	2 (0.4)	0

[a] Discontinuations from the study could occur during the treatment period or during the post-therapy follow-up period, i.e. subjects discontinuing treatment were not necessarily also discontinuing the study.
[b] Subjects could discontinue from treatment and remain in the study.

Most of the subjects in either treatment group (60%) were male. The mean age for the varenicline group was 43.9 years and ranged from 18 to 75 years. The mean age of the placebo group was 43.2 years and ranged from 18 to 72 years. The average body mass indices (BMIs) were 26.2 kg/m^2 and 26.7 kg/m^2 for the varenicline and placebo groups, respectively. The distribution of races was similar in both treatment groups, with subjects in both groups being mostly White.

A summary of data sets analyzed is provided in Table 2.

Table 2. Data Sets Analyzed

Number (%) of subjects	Varenicline N = 493	Placebo N = 166
Analyzed for efficacy [a]		
All Subjects [b]	486 (98.6)	165 (99.4)
Evaluable Subjects [c]	468 (94.9)	160 (96.4)
Completer Subjects [d]	425 (86.2)	130 (78.3)
ITT (All Randomized Subjects) [e]	493 (100.0)	166 (100.0)
Analyzed for safety [f]		
Adverse events [g]	486 (100.0)	165 (100.0)
Laboratory data [h]	444 (91.4)	144 (87.3)

ITT = intent-to-treat, N = number of subjects in the respective treatment group.
[a] Percentages based on ITT population.
[b] The All Subjects population was defined as all subjects who received at least 1 dose of study drug. This was the primary efficacy analysis population.
[c] The Evaluable Subjects group was defined to be a subset of the All Subjects population, who took at least 14 days of study drug in the first 21 days of the study.
[d] The Completers population group was defined as the subset of the All Subjects population, who had at least 80% treatment compliance.
[e] The ITT population was defined as all randomized subjects.
[f] Percentages based on All Subjects population.
[g] Adverse events were analyzed for the All Subjects population (see footnote b).
[h] Laboratory data were analyzed for all subjects who had at least 1 postbaseline laboratory value.

Efficacy Results: An overview of the primary and the key secondary endpoint is given in Table 3.

Analyses of smoking cessation rates for the All Subjects population showed that varenicline was more efficacious than placebo in all measures of abstinence, both at the end of the 12-week treatment period and during the non-treatment follow-up through Week 24. Statistical significance in favor of varenicline treatment was reached for the primary and the key secondary endpoints (all $p < 0.0001$).

Table 3. Overview of Primary and Key Secondary Efficacy Endpoints (All Subjects Population)

Endpoint	Varenicline N = 486 n (%)	Placebo N = 165 n (%)	Odds Ratio[#] (95% CI) versus placebo	p-value[#]
4-week CQR Weeks 9 to 12	262 (53.9)	32 (19.4)	6.03 (3.80, 9.56)	<0.0001
CA Week 9 to Week 24	171 (35.2)	21 (12.7)	4.45 (2.62, 7.55)	<0.0001

[#] Odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment and pooled center.

CA = continuous abstinence, CI = confidence interval, CO = carbon monoxide, CQR = continuous quit rate, N = number of subjects in respective treatment group, ppm = parts per million.

n (CQR) = the 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 (on the Nicotine Use Inventory) and who did not have CO >10 ppm at any of these visits;

n (CA) = number of subjects who at each contact from Weeks 9 to 24, reported no smoking and no use of other nicotine-containing products (treatment phase) or tobacco products (non-treatment phase) since the last study contact (on the Nicotine Use Inventory) and who did not have CO >10 ppm at the clinic visit.

The LTQR at Week 24 was also statistically significantly higher in the varenicline group than in the placebo group (OR: 4.91 (95% confidence interval [CI] 2.96, 8.13), p <0.0001). Other results for abstinence endpoints were consistent with the results above. Significantly greater abstinence rates for the varenicline group were observed for the 7-day point prevalence of abstinence at all time points (Week 12: OR 5.66 (95% CI 3.66, 8.75), p <0.0001, Week 24: OR: 4.12 (95% CI 2.58, 6.58), p <0.0001), and for the 4-week point prevalence of abstinence at Week 24 (4.14 (95% CI 2.58, 6.67), p <0.0001).

Subjects in the varenicline group made their first quit attempt statistically significantly earlier (p = 0.0074) compared with subjects in the placebo group, with the median 17 days versus 24 days, respectively. Two hundred and forty five (245) (50.4%) subjects in the varenicline group made a first quit attempt during Week 1 and Week 2 compared with 62 (37.6%) subjects in the placebo group.

At all weekly time points from Week 1 through Week 12, MNWS scores for Urge to Smoke and mCEQ scores for Satisfaction were lower for varenicline than for placebo, but only marginally lower for mCEQ Psychological Reward.

Pharmacogenomic Results: Pharmacogenomic analyses were described in a separate protocol and were not part of this study.

Safety Results: Treatment-emergent AEs reported by ≥2% of subjects in any treatment group are summarized below in Table 4.

Table 4. Treatment-Emergent Adverse Events Reported by ≥2% of Subjects in Any Treatment Group (All Causalities) (All Subjects Population)

	Varenicline N = 486	Placebo N = 165
System Organ Class AE Preferred Term (MedDRA v12.1)	**Number (%) of subjects**	
Cardiac disorders	**18 (3.7)**	**0**
Ear and labyrinth disorders	**3 (0.6)**	**4 (2.4)**
Gastrointestinal disorders	**200 (41.2)**	**32 (19.4)**
Toothache	6 (1.2)	6 (3.6)
Constipation	23 (4.7)	5 (3.0)
Diarrhea	11 (2.3)	3 (1.8)
Abdominal pain	6 (1.2)	4 (2.4)
Abdominal pain upper	14 (2.9)	0
Dyspepsia	13 (2.7)	2 (1.2)
Nausea	142 (29.2)	15 (9.1)
Vomiting	19 (3.9)	1 (0.6)
Dry mouth	18 (3.7)	3 (1.8)
General disorders and administration site conditions	**57 (11.7)**	**17 (10.3)**
Fatigue	23 (4.7)	3 (1.8)
Irritability	14 (2.9)	6 (3.6)
Infections and infestations	**119 (24.5)**	**39 (23.6)**
Bronchitis	12 (2.5)	1 (0.6)
Nasopharyngitis	34 (7.0)	14 (8.5)
Rhinitis	7 (1.4)	4 (2.4)
Sinusitis	8 (1.6)	4 (2.4)
Upper respiratory tract infection	13 (2.7)	4 (2.4)
Influenza	19 (3.9)	6 (3.6)
Injury, poisoning and procedural complications	**18 (3.7)**	**10 (6.1)**
Investigations	**26 (5.3)**	**8 (4.8)**
Weight increased	17 (3.5)	3 (1.8)
Metabolism and nutrition disorders	**23 (4.7)**	**6 (3.6)**
Increased appetite	11 (2.3)	5 (3.0)
Musculoskeletal and connective tissue disorders	**45 (9.3)**	**14 (8.5)**
Arthralgia	6 (1.2)	4 (2.4)
Back pain	15 (3.1)	4 (2.4)
Nervous system disorders	**95 (19.5)**	**35 (21.2)**
Headache	55 (11.3)	20 (12.1)
Disturbance in attention	11 (2.3)	6 (3.6)
Dizziness	8 (1.6)	8 (4.8)
Somnolence	11 (2.3)	2 (1.2)
Psychiatric disorders	**137 (28.2)**	**27 (16.4)**
Anxiety	4 (0.8)	5 (3.0)
Depressed mood	5 (1.0)	5 (3.0)
Depression	4 (0.8)	5 (3.0)
Abnormal dreams	61 (12.6)	5 (3.0)
Insomnia	43 (8.8)	6 (3.6)
Sleep disorder	20 (4.1)	6 (3.6)

(continued)

Table 4 continued: Treatment-Emergent Adverse Events Reported by ≥2% of Subjects in Any Treatment Group (All Causalities) (All Subjects Population)

	Varenicline N = 486	Placebo N = 165
System Organ Class AE Preferred Term (MedDRA v12.1)	**Number (%) of subjects**	
Reproductive system and breast disorders	**10 (2.1)**	**3 (1.8)**
Respiratory, thoracic and mediastinal disorders	**38 (7.8)**	**8 (4.8)**
Cough	14 (2.9)	5 (3.0)
Skin and subcutaneous tissue disorders	**24 (4.9)**	**7 (4.2)**
Vascular disorders	**16 (3.3)**	**4 (2.4)**

Subjects are only counted once per treatment in each row.
Includes data up to 30 days after last dose of study drug.
Note: Two additional adverse events occurred in the varenicline group (common cold and headache) which are not documented in the clinical database.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects in respective treatment group.

Sleep disorders and disturbances were the most frequently reported psychiatric disorders for both varenicline and placebo treated subjects, followed by anxiety disorders and symptoms and depressed mood disorders and disturbances. Suicidal and self-injurious behaviour (suicidal ideation) was documented as AE for 1 subject (0.2%) in the varenicline group and 2 subjects (1.2%) in the placebo group.

A change in PHQ-9 depression severity from any at baseline to an increased severity at any postbaseline visit was only reported for 1 subject (0.6 %) in the placebo group (from mild to moderate depression). Shifts from no depression at baseline to a postbaseline assessment of mild depression occurred in 54 subjects [11.1%] in the varenicline group and 25 subjects [15.2%] in the placebo group; shifts from none at baseline to moderate or moderately severe depression were reported for 8 (1.6%) and 3 (0.6%)varenicline subjects, respectively, and 3 (1.8%) and 0 placebo subjects. No allocation to the depression category severe occurred at any study visit for either treatment group.

Subjects who permanently discontinued treatment due to AEs are listed in Table 5.

Table 5. Discontinuations Due to Adverse Events

Discontinuations from Treatment and from Study

MedDRA v12.1 preferred term	Onset (Day)[a]	Outcome	Causality	SAE
Varenicline				
Amnesia	5	Resolved	Study drug	No
Aggression	7	Resolved	Study drug	No
Major depression	23	Still present	Study drug	No
Irritability	2	Resolved	Study drug	No
Irritability	15	Resolved	Study drug	No
Abdominal pain upper	7	Resolved	Study drug	No
Rash	22	Resolved	Study drug	No
Depression	28	Resolved	Study drug	No
Nausea	8	Resolved	Study drug	No
Syncope	6	Resolved	Study drug	Yes
Nausea	1	Resolved	Study drug	No
Abnormal dreams	18	Resolved	Study drug	No
Vulvovaginal dryness	17	Resolved	Study drug	No
Lower limb fracture	20	Resolved	Other – fracture left leg	No
Placebo				
Suicidal ideation	11	Resolved	Study drug	Yes
Depression	16	Resolved	Study drug	No
Depression	26	Resolved	Study drug	No
Headache	10	Unknown	Other illness	No
Depressed mood	15	Resolved	Study drug	No
Somnolence	28	Still present	Study drug	No

Discontinuations from Treatment

MedDRA v12.1 preferred term	Onset (Day)[a]	Outcome	Causality	SAE
Varenicline				
Headache	12	Resolved	Study drug	No
Vomiting	4	Resolved	Study drug	No
Insomnia	19	Resolved	Study drug	No
Dyspepsia	14	Resolved	Study drug	No
Nausea	9	Resolved	Study drug	No
Insomnia	36	Resolved	Study drug	No
Irritability	21	Resolved	Study drug	No
Nausea	8	Resolved	Study drug	No
Nightmare	25	Resolved	Study drug	No
Nausea	74	Resolved	Study drug	No
Placebo				
Disturbance in attention	14	Resolved	Study drug	No
Disturbance in attention	14	Resolved	Study drug	No
Migraine	15	Resolved	Study drug	No
Intervertebral disc protrusion	22	Resolved	Other illness – herniated lumbar disc	No
Depressed mood	5	Resolved	Study drug	No
Anxiety	36	Resolved	Study drug	No
Obsessive compulsive disorder	35	Resolved	Study drug	No

[a] Day relative to start of study treatment. First day of study treatment = Day 1.
MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event.

There were no deaths in this study.

All SAEs during the treatment phase and reported during the 28 day post-treatment collection period are summarized in Table 6.

Table 6. Serious Adverse Events

MedDRA v12.1 preferred term	Onset (Day)[a]	Day of last dose[b]	Outcome	Causality[c]
Varenicline				
Intervertebral disc protrusion	21	84	Resolved	Unrelated
Carotid artery stenosis	43	85	Resolved	Unrelated
Colonic obstruction[d]	133	84	Resolved	Unrelated
Pneumonia[d]	141	84	Resolved	Unrelated
Syncope	6	7	Resolved	Related[e]
Atrial flutter[d]	147	83	Resolved	Unrelated
Peripheral arterial occlusive disease[f]	111	82	Resolved	Unrelated
Intervertebral disc protrusion	18	85	Resolved	Unrelated
Calculus ureteric	97	81	Resolved	Unrelated
Pyelocaliectasis	97	81	Resolved	Unrelated
Ureteric obstruction	100	81	Resolved	Unrelated
Prostate cancer[d]	155	83	Resolving	Unrelated
Placebo				
Suicidal ideation	11	13	Resolved	Unrelated[g]
Gastrointestinal haemorrhage[d]	140	84	Resolved	Unrelated
Thyroid cancer[d]	73	21	Resolved	Unrelated

[a] Day relative to start of study treatment. First day of study treatment = Day 1.
[b] Based on Administration Schedule.
[c] Causality according to investigator.
[d] Reported after the 28 day collection period for SAEs and included in study database. Since the event occurred after the 28 day reporting period and was considered unrelated to the investigational product, it was classified as 'invalid' in the safety database.
[e] The sponsor concluded that the syncope was not related to varenicline treatment and that the presence of risk factors like smoking, diabetes and a predisposing condition of coronary artery disease had played a contributory role to the syncope.
[f] This event was included in the summary of treatment-emergent SAEs (occurrence 29 days post dose) that was based on the study database.
[g] This SAE was recorded as related to study drug in statistical outputs based on the clinical database. In statistical outputs based on the safety database, the event was assessed as unrelated according to follow-up information received from the investigator.
MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event.

The results from laboratory, body weight, vital signs, ECG, and physical examination did not raise any safety concerns.

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

- Varenicline treatment compared to placebo treatment resulted in statistically significantly higher abstinence rates as measured by the primary efficacy endpoint CO-confirmed 4-week CQR. Varenicline treatment also achieved statistically significantly higher abstinence rates as evidenced by the parameters CAR Weeks 9 to 24, LTQR at Week 24,

7-day point prevalence of abstinence at Weeks 12 and 24, and the 4-week point prevalence of abstinence at Week 24. Varenicline statistically significantly reduced the Urge to Smoke based on the MNWS and the Satisfaction from Smoking based on the mCEQ, when compared to placebo.

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