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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00285012

PROTOCOL NO.: A3051054

PROTOCOL TITLE: A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial with 40-Week Follow-Up Evaluating the Safety and Efficacy of Varenicline Tartrate for Smoking Cessation in Patients with Mild-To-Moderate Chronic Obstructive Pulmonary Disease

Study Center(s): Subjects were randomized at 27 centers; 17 centers in the United States, 4 centers in France, 3 centers in Italy, and 3 centers in Spain.

Study Initiation and Completion Dates: 02 MAY 2006 to 30 APRIL 2009

Phase of Development: Phase 3b

Study Objective(s): The primary efficacy objective was a comparison of 12 weeks of treatment with varenicline 1 mg twice daily (BID) with placebo for smoking cessation efficacy in subjects with mild to moderate chronic obstructive pulmonary disease (COPD), and to evaluate continuous abstinence for 40 weeks after the treatment period.

The safety objective was to gather safety data in subjects with COPD for 12 weeks of treatment with varenicline l mg BID or placebo followed by 40 weeks of non-treatment follow-up.

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled, parallel group, multicenter, phase 3b study with a 12-week treatment period followed by a 40-week non-treatment period for a total study duration of 52 weeks. Approximately 500 subjects with mild to moderate COPD who were motivated to stop smoking were 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 each subject's smoking status was followed through the non-treatment period to Week 52. Smoking status was confirmed by end-expiratory exhaled carbon monoxide (exhaled CO) measurements (smoking was confirmed if CO >10 parts per million [ppm]).

All subjects 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 period. All subjects were instructed to quit smoking at midnight preceding the day of the Week 1 visit. Subjects were contacted by a telephone call 3 days after the target quit date (TQD+3) to be reminded of study participation and to receive support for the smoking cessation attempt. Subjects returned for clinic visits weekly from Weeks 2 through 12 during the treatment period. During the non-treatment follow-up, subjects returned for visits at Weeks 13, 16, 24, 32, 40, 48, and 52, and were contacted by phone at Weeks 14, 20, 28, 36, and 44.

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

Number of Subjects (Planned and Analyzed): It was planned to randomize 500 subjects to varenicline or placebo in a 1:1 ratio. Two hundred and fifty (250) subjects were assigned to varenicline treatment and 254 subjects to placebo treatment. Of these, 248 subjects and 251 subjects 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 35 years of age and older who had mild to moderate COPD (as defined by the 2003 Global Initiative for Chronic Obstructive Lung Diseases [GOLD] criteria), and who were 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 and a clinical diagnosis of COPD. Additionally, the subjects had to have at screening or within 30 days of the Screening visit a forced expiratory volume in 1 second (FEV_1) ≥50% of predicted normal value after the administration of a short-acting bronchodilator.

Study Treatment: Subjects were randomized to 1 of 2 treatment groups: varenicline 1 mg BID or placebo. Subjects randomized 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 received 1 mg BID for 11 weeks. During the non-treatment follow-up period from Week 13 to Week 52, 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: The Fagerström Test for Nicotine Dependence (FTND) was administered at the Screening visit to assess the level of dependency on nicotine. Efficacy data were collected at each study visit using the Nicotine Use Inventory (NUI) and exhaled CO measurements. NUI was also completed at all telephone contacts except the telephone contact occurring at TQD+3. In addition, spirometry data was collected at the Screening, Baseline, Weeks 12, 24, and 52 or Early Termination (ET_{12}, ET_{52}) visits. The number of cigarettes smoked daily was collected during the first 3 weeks of the study. The Clinical COPD Questionnaire (CCQ) which evaluates respiratory symptoms, functional and mental

states as they relate to the subject's clinical airway condition was administered at each study visit.

Pharmacogenomic 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.

Safety Evaluations: Safety was evaluated based on adverse events (AEs), vital signs, physical examination, body weight and height, electrocardiograms (ECGs), and laboratory test results including biochemical markers of inflammation.

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 subject population for intent-to treat (ITT) efficacy analyses in this study and was also the subject population for safety summaries and analyses. Analyses of the Evaluable Subjects group (all subjects who took at least 14 days of study medication in the first 21 days of the study) and Completers group (all subjects who had at least 80% treatment compliance) were intended to support the robustness of the conclusions made on the All Subjects population.

The primary inference of this study was to evaluate the hypothesis that varenicline is superior to placebo for the 4-week continuous quit rate (CQR) for Weeks 9 through 12. The primary efficacy endpoint was the CO-confirmed 4-week CQR for Weeks 9 through 12, inclusive, using the weekly reports of cigarette and nicotine use 'since the last visit'. The 2 key secondary efficacy endpoints were the continuous abstinence (CA) rate from Weeks 9 through 52 and long term quit rate (LTQR; defined as subjects who were considered responders in the assessment of the primary endpoint at the end of the 12-week treatment period and had no more than a total of 6 cumulative days of smoking during the 40-week non-treatment follow-up) at Week 52. Other secondary efficacy endpoints included CA rate from Weeks 9 through 24, LTQR through Week 24, 7-day point prevalence of smoking cessation at Weeks 12, 24, and 52, 4-week point prevalence of smoking cessation at Week 52, change from baseline in spirometry measurements at Weeks 12, 24, and 52, the CCQ total scores and domain scores at Weeks 12, 24, and 52 and the number of cigarettes smoked per day during the first 3 weeks of the treatment period.

Five hundred subjects randomized to varenicline or placebo in a 1:1 ratio provided at least 90% power to detect a difference in the primary endpoint between the varenicline and placebo groups, assuming a true placebo 4-week CQR of 0.18 and a varenicline response rate of at least 0.38 (odds ratio of at least 2.79). This sample size also provided at least 81% power to detect a difference in CA from Weeks 9 through 52 assuming a placebo response rate of 0.09 and a varenicline response rate of at least 0.18 (odds ratio of at least 2.21). It was assumed that the power to detect a treatment effect in LTQR at Week 52 was comparable to that for the CA through Week 52.

Descriptive statistics, such as mean, median, standard deviation (SD), and range for continuous variables, and counts and percentages for categorical variables were used to

summarize data. If required, the statistical methodology to be used for analyzing continuous data was the Analysis of Variance (ANOVA) model. The model to be used in the analysis had treatment group and investigative center as fixed effects. All statistical testing was two-sided and used a 0.05 level of significance. A closed testing procedure to preserve the type I error rate for the primary and key secondary endpoints was used. P-values were reported for other secondary analyses, provided the primary endpoint was met, with no adjustments for the analysis of multiple secondary endpoints.

The statistical methodology to be used for analyzing binary efficacy data was the logistic regression model including treatment group and investigative center as independent variables. The inferences were made from the logistic regression model including only the main effects of treatment and center, regardless of the significance of the treatment by center interaction. The treatment by center interactions were investigated with the interaction tested at the 0.05 significance level.

All subjects in the All Subjects population who had a safety measurement 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 and Data Sets Analyzed

Number (%) of subjects	Varenicline		Placebo	
Screened: 1010				
Assigned to study treatment	250		254	
Treated	248		251	
Completed treatment	207	(83.5)	193	(76.9)
Discontinued treatment[a]	41	(16.5)	58	(23.1)
Related to study drug	11	(4.4)	11	(4.4)
Adverse event	11	(4.4)	8	(3.2)
Lack of efficacy	0		3	(1.2)
Not related to study drug	30	(12.1)	47	(18.7)
Adverse event	1	(0.4)	6	(2.4)
Lost to follow up	10	(4.0)	10	(4.0)
Subject not willing to participate in study	13	(5.2)	25	(10.0)
Other	6	(2.4)	6	(2.4)
Completed study	176	(71.0)	157	(62.5)
Discontinued study[b]	72	(29.0)	94	(37.5)
Subject died[c]	2	(0.8)	1	(0.4)
Related to study drug	4	(1.6)	10	(4.0)
Adverse event	4	(1.6)	7	(2.8)
Lack of efficacy	0		3	(1.2)
Not related to study drug	66	(26.6)	83	(33.1)
Adverse event	1	(0.4)	4	(1.6)
Lost to follow up	29	(11.7)	31	(12.4)
Subject not willing to participate in study	31	(12.5)	43	(17.1)
Other	5	(2.0)	5	(2.0)
Analyzed for efficacy				
All subjects	248	(100.0)	251	(100.0)
Evaluable subjects	239	(96.4)	240	(95.6)
Completer subjects	210	(84.7)	196	(78.1)
Analyzed for safety				
Adverse events	248	(100.0)	251	(100.0)
Laboratory data[d]	222	(89.5)	211	(84.1)

[a] Subjects could discontinue from treatment and remain in the study.
[b] Discontinuations from the study could occur during the treatment period or during the post-therapy follow-up period.
[c] Deaths occurred in the non-treatment period and were not assessed as related to study drug.
[d] Laboratory data were analyzed for those subjects who had at least 1 non-missing post-baseline laboratory value.

The majority of subjects in the varenicline and placebo groups were male (varenicline: 155 subjects [62.5%]; placebo: 156 subjects [62.2%]) and white (varenicline: 203 subjects [81.9%]; placebo: 211 subjects [84.1%]). The mean age for the varenicline and placebo groups was 57.2 years (range 35 to 83 years) and 57.1 years (34 to 77 years), respectively. Treatment groups were well balanced with respect to baseline weight, body mass index (BMI), height, spirometry variables, reversibility of airflow obsruction, and smoking history.

Efficacy Results: An overview of the primary and selected secondary endpoints is given in Table 2.

Statistical significance in favor of varenicline treatment was reached for the primary and both key secondary endpoints (all p <0.0001). The CA rate from Week 9 to Week 24 and the LTQR at Week 24 were also statistically significantly higher in the varenicline group than in the placebo group (both p <0.0001).

Table 2. Overview of Primary and Selected Secondary Efficacy Evaluations (All Subjects)

Endpoint	Varenicline N=248 n (%)	Placebo N=251 n (%)	Odds Ratio (95% CI) versus placebo	p-value
4-week CQR Weeks 9 to 12	105 (42.34)	22 (8.76)	8.40 (4.99, 14.14)	<0.0001
CA				
Week 24	64 (25.81)	18 (7.17)	4.88 (2.75, 8.65)	<0.0001
Week 52	46 (18.55)	14 (5.58)	4.04 (2.13, 7.67)	<0.0001
LTQR				
Week 24	70 (28.23)	19 (7.57)	5.17 (2.96, 9.02)	<0.0001
Week 52	53 (21.37)	17 (6.77)	3.92 (2.18, 7.07)	<0.0001

CA = continuous abstinence, CI = confidence interval, CQR = continuous quit rate, LTQR =long term quit rate, N = number of subjects in respective treatment group, n (QCR) = 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 >10ppm at any of these visits, n (CA) = number of subjects who at each contact from Week 9 through the given time point, 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 >10ppm (if assessed at a clinic visit), n (LTQR) = number of subjects who were responders for the primary endpoint and who had no more than 6 days of smoking from Week 12 through the given visit.

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: p <0.0001, Week 24: p <0.0001, Week 52: p = 0.0008), the 4-week point prevalence of abstinence at Week 52 (p = 0.0002).

Statistical significance in favor of varenicline treatment was also achieved for post-bronchodilator FEV_1 at Week 12 (last-observation-carried-forward [LOCF] analysis: absolute values p = 0.007; percent of predicted: p = 0.001; observed cases analysis: absolute values p = 0.013; percent of predicted: p = 0.003). At Weeks 24 and 52, there were no statistically significant differences between the 2 treatment groups for post-bronchodilator FEV_1 in either LOCF or observed cases analyses. There was no statistically significant difference between the 2 treatment groups at any time point for post-bronchodilator FEV_1/FVC.

For the respiratory symptom score and the total score of the CCQ, the change from baseline was statistically significantly higher in the varenicline group compared with the placebo group at Weeks 12 and 52 (respiratory symptom score: p = 0.002 and p = 0.016, respectively; total score: p = 0.033 and p = 0.023, respectively). The difference between the treatment groups in respiratory symptom score and the total score at Week 24 and the differences in the functional state and mental state scores at any time point were not statistically significant. In

both the varenicline and placebo groups, the decrease in mean number of cigarettes smoked per day to Day 21 and per day by week to Week 12 was comparable.

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

Safety Results: Non-serious AEs were collected from the time that the subject provided informed consent through Week 13 (1 week following last dose of study drug); the collection period of serious AEs (SAEs) was 28 days following last dose of study drug. The lag period for data inclusion was 30 days.

Treatment-emergent AEs reported by ≥2 subjects in any treatment group are summarized in Table 3**.**

Table 3. Treatment Emergent All Causality AEs Reported by ≥2% of Subjects in Any Treatment Group (All Subjects)

	Varenicline (N = 248)		Placebo (N = 251)	
Number of subjects evaluable for AEs	248		251	
AE (MedDRA v12.0 Preferred Term)	**Number (%) of subjects**			
Nausea	67	(27.0)	20	(8.0)
Abnormal dreams	27	(10.9)	7	(2.8)
Upper respiratory tract infection	24	(9.7)	21	(8.4)
Insomnia	24	(9.7)	15	(6.0)
Headache	20	(8.1)	20	(8.0)
Flatulence	18	(7.3)	13	(5.2)
Vomiting	16	(6.5)	6	(2.4)
Constipation	12	(4.8)	6	(2.4)
Dry mouth	12	(4.8)	4	(1.6)
Bronchitis	11	(4.4)	11	(4.4)
Fatigue	11	(4.4)	2	(0.8)
Weight increased	11	(4.4)	2	(0.8)
Nasopharyngitis	10	(4.0)	12	(4.8)
Dyspepsia	9	(3.6)	1	(0.4)
Cough	9	(3.6)	7	(2.8)
Back pain	8	(3.2)	5	(2.0)
Diarrhoea	7	(2.8)	9	(3.6)
Gastrooesophageal reflux disease	7	(2.8)	5	(2.0)
Abdominal pain	7	(2.8)	2	(0.8)
Dysgeusia	7	(2.8)	6	(2.4)
Chronic obstructive pulmonary disease	7	(2.8)	4	(1.6)
Sinusitis	7	(2.8)	5	(2.0)
Anxiety	6	(2.4)	7	(2.8)
Depression	6	(2.4)	5	(2.0)
Irritability	6	(2.4)	4	(1.6)
Rhinitis	6	(2.4)	3	(1.2)
Oropharyngeal pain	6	(2.4)	3	(1.2)
Abdominal pain upper	6	(2.4)	0	
Gastroenteritis	5	(2.0)	3	(1.2)
Influenza	5	(2.0)	3	(1.2)
Dyspnoea	5	(2.0)	2	(0.8)
Nasal congestion	5	(2.0)	2	(0.8)
Nightmare	5	(2.0)	1	(0.4)
Decreased appetite	5	(2.0)	0	
Dizziness	4	(1.6)	7	(2.8)
Arthralgia	3	(1.2)	6	(2.4)
Pain in extremity	2	(0.8)	5	(2.0)
Total number of preferred term events	**604**		**408**	

AEs are sorted in descending order by frequency in the varenicline treatment group.
Includes data up to 30 days after last dose of study drug.
If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence was taken. Subjects were counted only once per treatment in each row.
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects in respective treatment group.

Discontinuations from treatment due to AEs are listed in Table 4.

Table 4. Discontinuations Due to Adverse Events[a]

Discontinuations from Treatment and from Study				
MedDRA v12.0 preferred term	**Onset (Day)[b]**	**Outcome**	**Causality**	**SAE**
Varenicline				
Nausea	4	Resolved	Study drug	No
Nausea	12	Resolved	Study drug	No
Upper respiratory tract infection	2	Resolved	Other	No
Nausea	29	Resolved	Study drug	No
Vomiting	18	Resolved	Study drug	No
Placebo				
Vertigo	1	Resolved	Study drug	No
Muscle spasms	12	Resolved	Study drug	No
Musculoskeletal pain	49	Unknown	Other	Yes
Tremor	20	Still present	Study drug	No
Suicidal ideation	43	Resolved	Study drug	No
Lung neoplasm malignant	14	Still present	Disease under study	Yes
Acute myocardial infarction	38	Resolved	Other	Yes
Anger	50	Unknown	Study drug	No
Depressive symptom	50	Still present	Study drug	No
Depression	9	Still present	Other	No
Adjustment disorder	44	Still present	Study drug	No
Dizziness	5	Resolved	Study drug	No
Discontinuations from Treatment yet Remained in the Study				
MedDRA v12.0 preferred term	**Onset (Day)[b]**	**Outcome**	**Causality**	**SAE**
Varenicline				
Vomiting	67	Resolved	Study drug	No
Anxiety	55	Resolved	Study drug	No
Abdominal pain	56	Resolved	Study drug	No
Nausea	11	Resolved	Study drug	No
Nausea	8	Resolved	Study drug	No
Placebo				
Depression	32	Still present	Other	No
Nausea	17	Resolved	Study drug	No

[a] There are differences between source tables for Discontinuations from Study, Discontinuations from Treatment, Discontinuations from Treatment due to AEs, and Treatment-Emergent AEs in the number of subjects who permanently discontinued due to an AE because different pages of the case report form are used as source for these tables.
[b] Day relative to start of study treatment. First day of study treatment = Day 1.
MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event

One subject in the varenicline group died due to cardiac arrest at Day 99 (2 weeks after the last dose of study drug). It was not assessed as related to the study drug.

Additionally, 1 death occurred in each treatment group (road traffic accident at Day 168 in the varenicline group, amyotrophic lateral sclerosis at Day 397 in the placebo group) in the post-treatment phase that were not assessed as treatment related.

All other non-fatal SAEs during the treatment phase and the 28-day post-treatment reporting period, as well as those reported more than 28 days after the last treatment dose, are summarized in Table 5.

Table 5. Non-Fatal Serious Adverse Events

MedDRA v12.0 preferred term	Onset (Day)[a]	Outcome	Causality
Varenicline			
Acute myocardial infarction	39	Resolved	Unrelated
Vocal cord polyp	-5	Resolved	Unrelated
Hyperkeratosis	27	Resolved	Unrelated
Back pain	37	Resolved	Unrelated
Angina pectoris	4	Resolved	Unrelated
Cerebrovascular accident	37	Resolved	Unrelated
Cellulitis	55	Resolved	Unrelated
SAEs reported >28 days post last dose[b]			
Left ventricular dysfunction	151	Resolved	Unrelated
Aortic valve stenosis	155	Resolved	Unrelated
COPD	237	Resolved	Unrelated
Chest pain	292	Resolved	Unrelated
Laryngeal cancer	169	Resolved	Unrelated
Placebo			
Bronchitis	5	Resolved	Unrelated
Cerebrovascular accident[c]	27	Resolved	Unrelated
Cholelithiasis	7	Resolved	Unrelated
Lung neoplasm malignant	70	Resolved	Unrelated
Pneumonia	23	Resolved	Unrelated
Musculoskeletal pain	49	Unknown	Unrelated
Lung neoplasm malignant	12[d]	Not recovered	Unrelated
Acute myocardial infarction	38	Resolved	Unrelated
Appendicitis	40	Resolved	Unrelated
COPD	88	Resolved	Unrelated
Chest pain	84	Resolved	Unrelated
Anxiety	84	Resolved	Unrelated
SAEs reported >28 days post last dose[b]			
COPD	223	Resolved	Unrelated
Pneumonia	303	Resolved	Unrelated
Palpitations	358	Resolved	Unrelated
Chest pain	358	Resolved	Unrelated

[a] Day relative to start of study treatment. First day of study treatment = Day 1.
[b] Reported after the 28 day reporting period for SAEs.
[c] Ischaemic stroke in study database.
[d] Onset at Day 14 in study database.
COPD = chronic obstructive pulmonary disease, 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.

CONCLUSIONS: This 12-week study comparing varenicline 1 mg BID with placebo for smoking cessation in subjects with mild and moderate COPD with a 40-week follow-up period demonstrated that:

- Varenicline treatment was efficacious for smoking cessation in subjects with mild-to-moderate COPD. 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) and key secondary endpoints reflecting long-term abstinence (CA rate Weeks 9 to 52 and LTQR at Week 52). Varenicline treatment also achieved statistically significantly higher abstinence rates as evidenced by the parameters 7-day point prevalence of abstinence at Weeks 12, 24 and 52 and the 4-week point prevalence of abstinence at Week 52. After 12 weeks of treatment with varenicline, statistically significant differences in favor of varenicline were obtained for the respiratory symptom score and the total score of the CCQ, and for post-bronchodilator FEV_1 at Week 12 (although the study was not powered to assess changes in CCQ or FEV_1).

- 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 deaths and the SAEs were not assessed as treatment related.