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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Varenicline

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

NATIONAL CLINICAL TRIAL NO.: NCT00717093

PROTOCOL NO.: A3051104

PROTOCOL TITLE: A Randomized, Multicenter Double-Blind Placebo-Controlled Study Evaluating the Efficacy of Varenicline in Cessation of Oral Smokeless Tobacco Use

Study Center(s): 16 Centers in Sweden and Norway

Study Initiation Date and Primary Completion or Completion Dates: 27 August 2008 to 15 July 2009

Phase of Development: 4

Study Objective(s): The primary objective of the study was to compare the efficacy of varenicline to placebo for cessation of use of smokeless tobacco assessed using the 4-week continuous quit rate (CQR) at the end of treatment (EOT) (Week 12).

The secondary objectives were:

- To compare varenicline with placebo for the continuous abstinence (CA) from smokeless tobacco from Weeks 9 through 26.
- To compare varenicline with placebo for the 7-day point prevalence (PP) of abstinence at the EOT (Week 12).
- To compare varenicline with placebo for the 7-day PP of abstinence at the end of study (Week 26).
- To compare varenicline with placebo for the long-term quit rate (LTQR) of smokeless tobacco from Weeks 9 through 26.
- To assess the safety and tolerability of varenicline compared with placebo, for 12 weeks of treatment in users of smokeless tobacco.

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METHODS

Study Design: This was a double-blind, randomized, multicenter, parallel-group design clinical trial, comparing varenicline with placebo for smokeless tobacco use cessation. Subjects received blinded study treatment of either varenicline or placebo for 12 weeks followed by a 14-week follow-up period.

Subjects randomized to varenicline were up-titrated to the full dose during the first week of treatment in the following manner: 0.5 mg once daily (OD) for 3 days, followed by 0.5 mg twice daily (BID) for 4 days, and then 1 mg BID for the following 11 weeks of the treatment period. Subjects randomized to placebo followed the same dosing regimen using matching placebo tablets.

Number of Subjects (Planned and Analyzed): A sample size of 432 subjects was planned and 432 subjects were enrolled.

Diagnosis and Main Criteria for Inclusion: Male or female daily smokeless tobacco users aged 18 years and older, who were motivated to stop use of all tobacco products were included.

Study Treatment: Subjects were randomized to varenicline or matching placebo tablets. Subjects randomized to varenicline were up-titrated during the first week of treatment in the following manner: 0.5 mg OD for 3 days followed by 0.5 mg BID for 4 days, and then 1 mg BID for the following 11 weeks of the treatment period. Subjects randomized to placebo followed the same dosing regimen using matching placebo tablets.

Varenicline tartrate was administered orally with water. During the first week of the study, tablets containing 0.5 mg Varenicline tartrate or matching placebo were administered. During the remaining 11 weeks of the study, tablets containing 1 mg varenicline tartrate or matching placebo were administered.

Efficacy Evaluations: The primary efficacy endpoint was the 4-week CQR rate using the Nicotine Use Inventory (NUI) which described smokeless tobacco use (eg, snus or any other forms of smokeless tobacco) during both the treatment and follow-up phases. The NUI was completed at visits in Weeks 9, 10, 11, 12, and 26.

Salivary cotinine tests were used to confirm the smokeless tobacco status of subjects. Subjects whose cotinine level was >15 ng/mL at any given time point were not classed as responders for the corresponding endpoints.

Salivary cotinine was carried out at screening (baseline) and at Weeks 9, 10, 11, 12, and 26.

Secondary Efficacy Endpoints:

The key secondary efficacy endpoint was CA from smokeless tobacco for Weeks 9 through 26 as measured by subject recall and confirmed by salivary cotinine.

Other secondary efficacy endpoints were:

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- The 7-day PP of abstinence at the EOT (Week 12) and end of study (Week 26)
- The LTQR of smokeless tobacco from Weeks 9 through 26.

Safety Evaluations: Safety evaluations included adverse event (AE) monitoring and, at screening only, the following were performed (samples were taken and stored at entry so that tests could be performed in the event of an AE): laboratory evaluations (blood biochemistry and hematology), a physical exam, and vital signs measurement (blood pressure and pulse rate). Weight was recorded at screening (baseline) and at Weeks 12 and 26. A urinalysis was also collected at screening (baseline).

Statistical Methods: The All Subjects population represents all subjects randomized into the study who received at least 1 dose of study treatment. The Completers Analysis set was the subset of the All Subjects population having at least 80% treatment compliance with study medication. The Safety Analysis set was the same as the All Subjects population.

The primary inference for the study was a comparison of the proportion of responders on varenicline and placebo based on the 4-week continuous quit rate assessed at the EOT (Weeks 9 to 12). This measure was obtained through reports of smokeless tobacco use and other nicotine use as captured on the NUI and confirmed using salivary cotinine (subjects with a cotinine level greater than 15 ng/mL at any given time point were not classified as responders for the corresponding endpoints). Missing salivary cotinine was imputed as negative (ie, not disqualifying the subject as a responder).

Subjects who discontinued the study were assumed to be non-responders for the remainder of the study. In computing the proportion of responders based on the 4-week CQR, those subjects were included in the denominator but not in the numerator.

The key secondary endpoint was continuous abstinence from smokeless tobacco (and all other nicotine containing products) for Weeks 9 through 26 as measured by subject recall and confirmed by salivary cotinine.

Other secondary endpoints were:

- The 7-day point prevalence of abstinence at the EOT (Week 12).
- The 7-day point prevalence of abstinence at the end of study (Week 26).
- The long term quit rate (LTQR) of smokeless tobacco (subjects who met the primary abstinence endpoint and did not use snus or any other nicotine containing product/s for more that 6 days in the follow-up period being assessed) from Weeks 9 through 26.

Logistic regression models were fitted to the primary endpoint and secondary endpoints and included treatment and centre as independent variables.

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Significance tests for the treatment comparison (varenicline compared with placebo) were performed at the 2-sided 0.05 level and the 95% confidence intervals (CIs) were two–sided. The difference between varenicline and placebo was estimated with a 95% CI around the odds ratio.

A step-down procedure for the key secondary endpoint was used to preserve the family-wise error rate. If no statistically significant treatment effect was found for the primary endpoint then statistical tests were not performed on the key secondary endpoint. If a statistically significant treatment effect was observed in the primary endpoint, then statistical tests on the key secondary endpoint were conducted. The comparison of varenicline and placebo for the key secondary endpoint was performed at the two-sided alpha level of 0.05 since the step-down procedure protects the family-wise error-rate.

All AEs were coded using the *Medical Dictionary for Regulatory Activities* (MedRA) and were listed by subject and summarized by treatment group. The incidence of treatment-emergent AEs was tabulated by treatment group and body system. The incidence of treatment-emergent AEs was displayed by severity and relationship to study medication. In addition, the incidence of AEs causing withdrawal and SAEs were tabulated. AE incidence tables include all events that are reported to have started after the start of study medication.

RESULTS

Subject Disposition and Demography: A total of 447 subjects were screened for participation in this study; 214 subjects were assigned to active treatment on varenicline; 218 subjects were assigned to the placebo group. One (1) patient was randomized but declined to participate prior to being assigned to study drug. A total of 213 subjects in the varenicline group and 218 subjects in the placebo group were treated. Of these subjects, 170 (79.8%) in the varenicline group and 170 (78.0%) in the placebo group, completed the study.

A total of 43 (20.2%) subjects in the varenicline group and 48 (22.0%) subjects in the placebo group discontinued the study. Higher percentages of subjects in both treatment groups discontinued for reasons not related to the study drug than for reasons related to the study drug. Of the subjects whose discontinuations were related to the study drug, the highest percentage of discontinuations in the varenicline group was related to an AE (7.5%); in the placebo group the highest percentage was due to lack of efficacy (6.0%). For discontinuations not related to the study drug, the highest percentage of discontinuations occurring in both the varenicline (5.6%) and placebo (8.7%) groups was subject unwillingness to continue with the study. A summary of subject disposition, as well as data sets analyzed, is provided in Table 1.

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Table 1. Subject Disposition

	Varenicline	Placebo
Number (%) of subjects		
Screened 447		
Assigned to study treatment	214	218
Treated	213	218
Completed study	170 (79.8)	170 (78.0)
Discontinued	43 (20.2)	48 (22.0)
Analyzed for efficacy		
All SubjectsS population [a]	213 (100.0)	218 (100.0)
Completers Analysis set [b]	159 (74.6)	152 (69.7)
Analyzed for safety		
Adverse events	213 (100.0)	218 (100.0)
Discontinuation related to study drug	19 (8.9)	19 (8.7)
Adverse events	16 (7.5)	6 (2.8)
Lack of efficacy	3 (1.4)	13 (6.0)
Discontinuation not related to study drug	24 (11.3)	29 (13.3)
Subject no longer willing to participate	12 (5.6)	19 (8.7)
Lost to follow-up	9 (4.2)	6 (2.8)
Adverse events	3 (1.4)	3 (1.4)
Other	0	1 (0.5)

[a] The All Subjects population represents all subjects randomized into the study who received at least 1 dose of study treatment. The All Subjects population was the analysis set used for both efficacy and adverse events and was the same as the Safety Analysis set.
[b] The Completers Analysis set was the subset of the All Subjects population having 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.

In both the varenicline and placebo group, the number of male subjects was higher than the number of female subjects. For both sexes, and in both groups, the greatest number of subjects was between 18 and 44 years of age, with a range of 18 to 80 years in the varenicline group and 18 to 74 years in the placebo group. All subjects, with the exception of 2 males in the varenicline group and 1 male in the placebo group, were white. In the varenicline group, the mean weight for females was slighter higher than the mean weight for females in the placebo group:72.1 kg versus 68.2 kg, but the mean weight for males was slightly higher in the placebo group than in the varenicline group: 87.8 kg versus 88.2 kg. Table 2 provides an overview of demography.

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Table 2. Demographic Characteristics – Safety Analysis Set

	Varenicline			Placebo		
	Male	Female	**Total**	Male	Female	**Total**
Number (%) of subjects	189	24	213	196	22	218
Age (years)						
< 18	0	0	0	0	0	0
18-44	103 (54.5)	14 (58.3)	117 (54.9)	101 (51.5)	14 (63.6)	115 (52.8)
45-64	78 (41.3)	10 (41.7)	88 (41.3)	85 (43.4)	8 (36.4)	93 (42.7)
≥ 65	8 (4.2)	0	8 (3.8)	10 (5.1)	0	10 (4.6)
Mean	44.2	41.2	43.9	44.5	38.4	43.9
SD	12.0	12.3	12.0	11.8	13.1	12.0
Range	18-80	22-64	18-80	18-74	18-63	18-74
Race						
White	187 (98.9)	24 (100)	211 (99.1)	195 (99.5)	22 (100.0)	217 (99.5)
Asian	2 (1.1)	0	2 (0.9)	0	0	0
Other	0	0	0	1 (0.5)	0	1 (0.5)
Weight (kg)						
Mean	87.8	72.1	86.0	88.2	68.2	86.3
SD	13.1	10.7	13.8	13.1	13.1	14.3
Range	60.8-132.1	54.0-98.0	54.0-132.1	60.2-134.5	55.0-117.1	55.0-134.5
N	188 (99.5)	24 (100)	212 (99.5)	193 (98.5)	21 (95.5)	214 (98.2)

SD = standard deviation

A similar number of subjects in both the varenicline and placebo groups reported having past or present medical history.

The mean total modified Fagerström score for the varenicline and placebo groups was similar, 7.5 and 7.6, respectively. Refer to Table 3 for an overview of summary statistics captured by the modified Fagerström test, and refer to Table 4 for answers to questions 3a and 3b.

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Table 3. Summary Statistics for Total Score of Modified Fagerström Test for Nicotine Dependence – Safety Analysis Set

Parameter	Varenicline N=213	Placebo N=218
Total Score:		
Mean (SD)	7.5 (1.6)	7.6 (1.7)
	n (%)	**n (%)**
Question 1:		
≥61 minutes	10 (4.7)	14 (6.4)
31-60 minutes	32 (15.0)	31 (14.2)
6-30 minutes	82 (38.5)	99 (45.4)
0-5 minutes	89 (41.8)	74 (33.9)
Question 2:		
8-12	89 (41.8)	87 (39.9)
≥13	124 (58.2)	131 (60.1)
Question 4:		
No	19 (8.9)	14 (6.4)
Yes	194 (91.1)	204 (93.6)
Question 5:		
No	69 (32.4)	65 (29.8)
Yes	144 (67.6)	153 (70.2)
Question 6:		
0-20 minutes	19 (8.9)	22 (10.1)
21-35 minutes	66 (31.0)	56 (25.7)
≥36 minutes	128 (60.1)	140 (64.2)
Question 7:		
No	70 (32.9)	64 (29.4)
Yes	143 (67.1)	154 (70.6)

Question 1: How soon after waking do you take your first smoke-free tobacco?
Question 2: How many times a day do you take smoke-free tobacco?
Question 4: Do you keep smoke-free tobacco in the mouth for most of the time?
Question 5: Do you intentionally swallow tobacco juices?
Question 6: How many minutes do you keep each smoke-free tobacco in the mouth?
Question 7: Do you use smoke-free tobacco if you are ill and in bed?
SD = standard deviation

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Table 4. Summary of Questions 3a and 3b of Modified Fagerström Test for Nicotine Dependence – Safety Analysis Set

Parameter	Varenicline N=213	Placebo N=218
	n (%)	n (%)
Question 3a:		
Loose	114 (53.52)	126 (57.8)
Bag	105 (49.3)	98 (44.95)
Question 3b:		
Small	13 (6.1)	11 (5.05)
Regular	135 (63.38)	139 (63.76)
Large	65 (30.52)	68 (31.19)

Question 3a: What type of smoke-free tobacco do you use?
Question 3b: What size smoke-free tobacco do you buy?

Efficacy Results: In the All Subjects population, the 4-week CQR at the EOT (Week 12) was significantly higher for subjects (59%) in the varenicline group versus subjects on placebo (39%) ($p<0.0001$). These results were supported by the Completers Analysis set. Table 5 provides a summary of results for the primary endpoint analysis.

Table 5. Summary of Primary Statistical Analysis: 4-Week CQR (Logistic Regression)

Treatment	N	Treatment Comparison: Varenicline versus Placebo			
		Observed Responder Rate, n (%)	Odds Ratio	95% CI for Odds Ratio	p-value
All-Subjects Population					
Varenicline	213	125 (58.69)	2.39	(1.59, 3.58)	<0.0001
Placebo	218	85 (38.99)			
Completers Analysis Set					
Varenicline	159	115 (72.33)	3.25	(1.92, 5.49)	<0.0001
Placebo	152	75 (49.34)			

Missing salivary cotinine values were imputed as negative.
Odds ratio and p-values were obtained from a logistic regression model including the main effects of treatment and center.
CI = confidence interval; CQR = continuous quit rate

At Week 9, 66% of subjects in the varenicline group versus 46% of subjects in the placebo group reported continuous abstinence from tobacco. There was a steady decline in the percentage of subjects with abstinence in both the varenicline group and placebo group starting at Week 10 and continuing to Week 26. At the Week 26 time point, 45% of subjects in the varenicline group and 33% of those in the placebo group reported continuous abstinence ($p=0.0118$). Refer to Table 6 for additional details related to CA.

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Table 6. Summary of Key Secondary Statistical Analysis: CA at Weeks 9 to 26 (Logistic Regression) – All Subjects Population

	Varenicline N=213	Placebo N=218
Week	**n (%)**	**n (%)**
Week 9	140 (65.73)	101 (46.33)
Week 10	135 (63.38)	96 (44.04)
Week 11	132 (61.97)	93 (42.66)
Week 12	125 (58.69)	85 (38.99)
Week 26:	95 (44.60)	73 (33.49)
Odds ratio (95% CI) versus placebo	1.70 (1.12, 2.58)	
p-value versus placebo	0.0118	

Missing salivary cotinine values were imputed as negative.
Odds ratio and p-value were obtained from a logistic regression model including the main effects of treatment and center.
CA = continuous abstinence; CI = confidence interval; NUI = Nicotine Use Inventory

For the 7-day PP of abstinence, the percentage of responders was significantly higher in the varenicline group than in the placebo group at Week 12 ($p<0.0001$). The difference at Week 26 (48% versus 40%, respectively) was not significant ($p=0.0919$). Refer to Table 7 for additional details.

Table 7. Summary of Secondary Statistical Analysis: 7-day PP for Abstinence at Weeks 12 and 26 – All Subjects Population

Treatment	N	Treatment Comparison: Varenicline versus Placebo			
		Observed Responder Rate, n (%)	Odds Ratio	95% CI for Odds Ratio	p-value
Week 12					
Varenicline	213	123 (57.75)	2.28	(1.52, 3.41)	<0.0001
Placebo	218	85 (38.99)			
Week 26					
Varenicline	213	102 (47.89)	1.42	(0.94, 2.13)	0.0919
Placebo	218	88 (40.37)			

Missing salivary cotinine was imputed as negative.
Odds ratio and p-value were obtained from a logistic regression model including the main effects of treatment and center.
CI = confidence interval; PP = point prevalence
[a]More subjects qualified for the CQR between weeks 9-12 than for the 7-day PP at Week 12 due to a pre-specified visit window algorithm and NUI missing data imputation rules

Subjects in the varenicline group (48%) had a significantly higher LTQR at Week 26 than subjects in the placebo group (36%), as shown in Table 8.

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Table 8. Summary of Secondary Statistical Analysis: LTQR (Logistic Regression) – All Subjects Population

Treatment	N	Treatment Comparison: Varenicline versus Placebo			
		Observed Responder Rate, n (%)	Odds Ratio	95% CI for Odds Ratio	p-value
Varenicline	213	102 (47.89)	1.77	(1.17, 2.67)	0.0063
Placebo	218	78 (35.78)			

Odds ratio and p-value were obtained from a logistic regression model including the main effects of treatment and center.
CI = confidence interval; CQR = continuous quit rate; LTQR = long term quit rate; NUI = nicotine use inventory

Safety Results: In total, 168 (78.9%) subjects in the varenicline group and 126 (58%) subjects in the placebo group experienced AEs during the study. Of these, 138 (64%) subjects in the varenicline group and 86 (40%) subjects in the placebo group had AEs that were related to study treatment. The number and percentage of subjects with AEs, SAEs, and severe AEs, and the number of subjects who were permanently discontinued from treatment or whose doses were reduced or temporarily discontinued due to AEs, are presented in Table 9

Table 9. Summary of Treatment-Emergent Adverse Events – Safety Analysis Set

	Varenicline N=213		Placebo N=218	
	All Causalities	Treatment -Related	All Causalities	Treatment-Related
Number of AEs	387	269	247	137
Number (%) of subjects:				
Subjects with AEs	168 (78.9)	138 (64.8)	126 (57.8)	86 (39.4)
Subjects with SAEs	2 (0.9)	1 (0.5)	3 (1.4)	0 (0)
Subjects with severe AEs	6 (2.8)	4 (1.9)	6 (2.8)	1 (0.5)
Subjects with dose reduced or temporary discontinuation due to AEs	17 (8.0)	12 (5.6)	12 (5.5)	7 (3.2)
Subjects permanently discontinued from treatment	25 (11.7)	20 (9.4)	18 (8.3)	15 (6.9)

Includes data up to 28 days (for SAEs) and 30 days (for AEs) after last dose of study drug.
Except for the number of AEs, subjects were counted only once per treatment in each row.
AE = adverse event, SAE = serious adverse event

In both the varenicline and placebo groups, the highest percentage of AEs (all causality) were reported in the system organ class (SOC) of gastrointestinal disorders, 51% for varenicline and 20% for placebo; followed by psychiatric disorders, nervous system disorders, general disorders and administration site conditions, and infections and infestations. A full listing of AEs (occurring in greater than 1% of subjects), by SOC and preferred term are displayed in Table 10.

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Table 10. Summary of Adverse Events Occurring in ≥1% of Subjects in Either Treatment Group (All Causalities) – Safety Analysis Set

System Organ Class Preferred term	Varenicline N=213 n (%)	Placebo N=218
Gastrointestinal disorders	**109 (51.2)**	**44 (20.2)**
Abdominal pain	4 (1.9)	1 (0.5)
Abdominal pain upper	11 (5.2)	5 (2.3)
Constipation	4 (1.9)	2 (0.9)
Diarrhea	10 (4.7)	11 (5.0)
Dry mouth	4 (1.9)	1 (0.5)
Dyspepsia	8 (3.8)	8 (3.7)
Flatulence	18 (8.5)	7 (3.2)
Nausea	74 (34.7)	14 (6.4)
Vomiting	6 (2.8)	2 (0.9)
General disorders and administration site conditions	**37 (17.4)**	**29 (13.3)**
Fatigue	22 (10.3)	15 (6.9)
Irritability	11 (5.2)	9 (4.1)
Pyrexia	3 (1.4)	4 (1.8)
Infections and infestations	**26 (12.2)**	**29 (13.3)**
Gastroenteritis	2 (0.9)	4 (1.8)
Influenza	7 (3.3)	7 (3.2)
Nasopharyngitis	12 (5.6)	8 (3.7)
Pneumonia	0	3 (1.4)
Sinusitis	3 (1.4)	1 (0.5)
Upper respiratory tract infection	0	3 (1.4)
Investigations	**4 (1.9)**	**1 (0.5)**
Weight increased	3 (1.4)	0
Metabolism and nutrition disorders	**8 (3.8)**	**3 (1.4)**
Increased appetite	4 (1.9)	1 (0.5)
Nervous system disorders	**34 (16.0)**	**32 (14.7)**
Disturbance in attention	1 (0.5)	5 (2.3)
Dizziness	4 (1.9)	6 (2.8)
Headache	22 (10.3)	20 (9.2)
Paresthesia	3 (1.4)	0
Psychiatric disorders	**58 (27.2)**	**42 (19.3)**
Abnormal dreams	17 (8.0)	3 (1.4)
Depressed mood	4 (1.9)	3 (1.4)
Depression	2 (0.9)	5 (2.3)
Insomnia	13 (6.1)	6 (2.8)
Nightmare	4 (1.9)	3 (1.4)
Restlessness	2 (0.9)	4 (1.8)
Sleep disorder	22 (10.3)	15 (6.9)
Skin and subcutaneous tissue disorders	**9 (4.2)**	**11 (5.0)**
Hyperhidrosis	1 (0.5)	6 (2.8)
Vascular disorders	**2 (0.9)**	**4 (1.8)**
Hypertension	2 (0.9)	3 (1.4)

Subjects were counted only once per treatment in each row. For the TESS algorithm any missing severities were imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity was summarized.
Missing baseline severities were imputed as mild.
Included data up to 30 days after last dose of study drug.
Medical Dictionary for Regulatory Activities (v12.0) coding applied

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Treatment-related treatment-emergent AEs occurring in >1% of subjects in either treatment group are displayed in Table 11.

Table 11. Summary of Treatment-Emergent Adverse Events Occurring in ≥1% of Subjects in Either Treatment Group (Treatment-Related) – Safety Analysis Set

System Organ Class Preferred term	Varenicline N=213 n (%)	Placebo N=218 n (%)
Gastrointestinal disorders	**101 (47.4)**	**35 (16.1)**
Abdominal pain	3 (1.4)	1 (0.5)
Abdominal pain upper	8 (3.8)	2 (0.9)
Constipation	3 (1.4)	2 (0.9)
Diarrhea	7 (3.3)	7 (3.2)
Dry mouth	3 (1.4)	1 (0.5)
Dyspepsia	6 (2.8)	7 (3.2)
Flatulence	18 (8.5)	7 (3.2)
Nausea	72 (33.8)	14 (6.4)
General disorders and administration site conditions	**26 (12.2)**	**23 (10.6)**
Fatigue	16 (7.5)	12 (5.5)
Irritability	9 (4.2)	7 (3.2)
Pyrexia	0	3 (1.4)
Investigations	**4 (1.9)**	**0**
Weight increased	3 (1.4)	0
Metabolism and nutrition disorders	**5 (2.3)**	**0**
Increased appetite	3 (1.4)	0
Nervous system disorders	**23 (10.8)**	**16 (7.3)**
Dizziness	3 (1.4)	5 (2.3)
Headache	14 (6.6)	10 (4.6)
Psychiatric disorders	**50 (23.5)**	**35 (16.1)**
Abnormal dreams	17 (8.0)	2 (0.9)
Depressed mood	3 (1.4)	2 (0.9)
Depression	1 (0.5)	5 (2.3)
Insomnia	11 (5.2)	5 (2.3)
Nightmare	3 (1.4)	3 (1.4)
Sleep disorder	17 (8.0)	13 (6.0)

Subjects were counted only once per treatment in each row. Table includes data up to 30 days after last dose of study drug.

Most treatment-emergent AEs were considered mild to moderate in intensity. For the varenicline and placebo groups combined, there were a total of 16 severe treatment-emergent AEs (8 treatment-related). Six (6) instances of severe treatment-related AEs were reported for the varenicline group as follows: dizziness, disturbance in sexual arousal, feeling cold, flatulence, nausea, and paresthesia. In the placebo group, 2 instances of severe treatment-related AEs were reported as follows: 1 severe instance each of abdominal pain and diarrhea.

Forty-three subjects were permanently discontinued from treatment: 25 in the varenicline group (20 treatment-related) and 18 in the placebo group (15 treatment-related). Refer to Table 12 for an overview of subject discontinuations due to AEs, as well as the severity, outcome, and overall relationship to treatment of AEs.

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Table 12. Permanent Discontinuations Due to Adverse Events - Safety Analysis Set

Page 1 of 2

Adverse Event(s)[a] Leading to Discontinuation of Treatment	Severity/Outcome	Causality
Varenicline		
vision blurred	moderate/resolved	study drug
bleeding poster operative	moderate/resolved	other- tonsillectomy
nausea[e]	moderate/ongoing	study drug
headache[e]	moderate/ongoing	study drug
diarrhea	moderate/resolved	study drug
nausea	mild/resolved	study drug
nausea	mild/resolved	study drug
nausea	mild/resolved	study drug
abdominal pain upper	moderate/resolved	study drug
pityriasis rosea	moderate/resolved	other-recurrent illness
naueea	mild/resolved	study drug
fatigue	moderate/resolved	study drug
nausea	moderate/resolved	study drug
sleep disorder	moderate/resolved	study drug
fatigue	moderate/resolved	study drug
depressed mood	moderate/resolved	other-nicotine withdrawal symptoms
abdominal pain	severe/ resolved	other-unknown
confusion[c]	moderate/ongoing	other-probably lack of sleep due to wife's psychiatric illness
abdominal pain	moderate/resolved	study drug
nausea	severe/ resolved	study drug
loss of consciousness[b]	moderate/resolved	study drug
irritability	moderate/resolved	study drug
nausea	moderate/resolved	study drug
personality disorder	mild/resolved	study drug
sleep disorder	moderate/resolved	study drug
nightmare	moderate/resolved	study drug
Placebo		
ankylosing spondylitis	moderate/resolved	other recurrent illness
fatigue	moderate/resolved	study drug
dizziness	mild/resolved	study drug
headache	moderate/resolved	study drug
sleep disorder	moderate/resolved	study drug
depression	mild/resolved	study drug
palpitations	moderate/resolved	study drug

All events were treatment-emergent
[a] *Medical Dictionary for Regulatory Activities* (v 12.0) preferred term
[b] Serious adverse event (according to investigator's assessment).
[c] See Errata.
[d] Subject still in study but not on study medication.
[e] Same subject.
[f] Same subject.

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Page 2 of 2 **(Placebo continued)**		
ankylosing spondylitis	moderate/resolved	other – recurrent illness
fatigue	moderate/resolved	study drug
hypertension	moderate/resolved	study drug
headache[f]	mild/resolved	other-nicotine withdrawal
sleep disorder [f]	moderate/resolved	study drug
sleep disorder	moderate/resolved	study drug
abdominal pain[d]	severe/ resolved	study drug
withdrawal due to nicotine abstinence	severe/ resolved	other-nicotine withdrawal
disturbance in attention	severe/ resolved	other-nicotine withdrawal
diarrhea	mild/resolved	study drug
sleep disorder	mild/resolved	study drug
depressed mood	mild/resolved	study drug
constipation	mild/resolved	study drug
insomnia	moderate/resolved	study drug

All events were treatment-emergent
[a] *Medical Dictionary for Regulatory Activities* (v 12.0) preferred term
[b] Serious adverse event (according to investigator's assessment).
[c] See Errata.
[d] Subject still in study but not on study medication.
[e] Same subject.
[f] Same subject.

Twenty-nine (29) subjects experienced dose reductions or temporary discontinuations due to AEs: 17 in the varenicline group (12 treatment-related) and 12 in the placebo group (7 treatment-related). Refer to Table 13 for additional details.

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Table 13. Dose Reductions and Temporary Discontinuations Due to Adverse Events - Safety Analysis Set

Adverse Event(s)[a] Leading to Discontinuation	Severity/Outcome	Action with Study Drug	Causality
Varenicline			
gastroenteritis viral[b]	moderate/resolved	stopped temporarily	other illness - virus infection
rash[b]	moderate/resolved	stopped temporarily	study drug
pyrexia	mild/resolved	reduced	other illness - virus infection
pyrexia	moderate/resolved	reduced	other illness - virus infection
back pain	moderate/resolved	stopped temporarily	other illness - unknown
nasopharyngitis	mild/resolved	stopped temporarily	other - virus
nausea	mild/resolved	stopped temporarily	study drug
abdominal pain upper	moderate/resolved	reduced	study drug
nausea[c]	moderate/resolved	reduced	study drug
headache[c]	moderate/resolved	reduced	study drug
mood altered[c]	mild/resolved	reduced	study drug
abnormal dreams	moderate/resolved	reduced	study drug
nausea	mild/resolved	reduced	study drug
abdominal pain upper[d]	mild/resolved	stopped temporarily	study drug
nausea[d]	moderate/resolved	stopped temporarily	study drug
fatigue	moderate/resolved	stopped temporarily	other-insomnia
nausea	mild/resolved	stopped temporarily	study drug
neuropathy peripheral	moderate/resolved	stopped temporarily	study drug
ejaculation disorder	moderate/resolved	stopped temporarily	study drug
abdominal pain upper	moderate/resolved	reduced	study drug
nausea	mild/resolved	reduced	study drug
Placebo			
gastroenteritis	mild/resolved	stopped temporarily	other illness - virus infection
diarrhea	mild/resolved	stopped temporarily	Illness - (gastroenteritis virus / bacteria
gastroenteritis viral[e]	mild/resolved	stopped temporarily	other illness-virus
influenza[e]	mild/resolved	stopped temporarily	other illness-virus
depression	moderate/resolved	stopped temporarily	study drug
depression	mild/resolved	stopped temporarily	study drug
constipation	mild/resolved	reduced	study drug
fatigue	mild/resolved	stopped temporarily	study drug
hyperhidrosis	mild/resolved	reduced	study drug
nausea	mild/resolved	reduced	study drug
frustration	moderate/resolved	stopped temporarily	other-nicotine withdrawal
depression	moderate/resolved	stopped temporarily	study drug
Influenza	moderate/resolved	stopped temporarily	other-viral infection

Medical Dictionary for Regulatory Activities (v12.0) coding applied.
[a] *Medical Dictionary for Regulatory Activities* (v 12.0) preferred term.
[b] Same subject.
[c] Same subject.
[d] Same subject.
[e] Same subject.

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Overall, 5 subjects experienced 6 SAEs: 2 subjects experienced 3 SAEs in the varenicline group and 3 subjects experienced 3 SAEs in the placebo group. In the placebo group, none of the SAEs were related to study drug treatment. One (1) subject developed colon cancer, 1 subject experienced an Achilles tendon rupture, and 1 subject experienced cardiac failure.

In the varenicline group, 1 subject experienced moderate post-operative hemorrhage that was unrelated to study drug, and 1 subject experienced 2 SAEs which were both considered related to study drug: a loss of consciousness and a traffic accident (which resulted from the loss of consciousness).

Among the All Subjects population, weight gain (>7%) was seen in 10.3% of subjects in the varenicline group and 11.5% of subjects on placebo. More subjects in the placebo group (25%) than the varenicline group (15%) who were responders on the 4-week CQR gained weight. A similar difference was observed between the varenicline and placebo groups for CA responders between Weeks 9 and 26; 27% of subjects on placebo experienced weight gain versus 17% on varenicline.

Categorical summaries of post-baseline weight are presented in Table 14, below.

Table 14. Categorical Summaries of Post-Baseline Weight – Safety Analysis Set

	Varenicline		Placebo	
Population **Criteria for Weight Change**	**N**	**n (%)**	**N**	**n (%)**
All-Subject Population				
Increase (weight >7%)	213	22 (10.3)	218	25 (11.5)
Decrease (weight ≤7%)	213	1 (0.5)	218	2 (0.9)
4-week CQR responders				
Increase (weight >7%)	125	19 (15.2)	85	21 (24.7)
Decrease (weight ≤7%)	125	0 (0.0)	85	2 (2.4)
CA at Weeks 9-26 responders				
Increase (weight >7%)	95	16 (16.8)	73	18 (24.7)
Decrease (weight ≤7%)	95	0 (0.0)	73	2 (2.7)

Increase/decrease from baseline, where baseline is defined as the measurement at screening.
CA = continuous abstinence; CQR = continuous quit rate

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CONCLUSION(S):

- The primary efficacy endpoint, the 4-week continuous quit rate at the EOT (Week 12), was significantly higher for the varenicline group than for the placebo group.

- For the key secondary endpoint (continuous abstinence from Weeks 9 to 26), there was a significantly higher percentage of responders in the varenicline group at Week 26 than in the placebo group. There was a steady decline in responders from Week 12 through Week 26.

- The responder rate for the 7-day PP of abstinence at Week 12 was significantly higher in the varenicline group than the placebo group. There was no significant difference at Week 26.

- The LTQR of smokeless tobacco at Week 26 was significantly higher for subjects in the varenicline group than subjects in the placebo group.

- There were no clinical safety concerns related to AEs. One (1) subject experienced 2 SAEs which were both considered related to study drug: a loss of consciousness and a traffic accident (which resulted from the loss of consciousness). There were no other treatment-related SAEs in this study.

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