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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Chantix™/Varenicline Tartrate

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NCT NO.: 00143325

PROTOCOL NO.: A3051044

PROTOCOL TITLE: An Open-label, Multicenter Study With Follow-Up Evaluating the Safety and Efficacy of Varenicline Tartrate in Comparison to Transdermal Nicotine Patch for Smoking Cessation

Study Center(s): Subjects were enrolled in 4 study centers in Belgium, 6 in France, 4 in the Netherlands, 4 in the United Kingdom, and 6 in the United States.

Study Initiation and Completion Dates: 17 January 2005 to 28 June 2006

Phase of Development: Phase 3

Study Objective(s):

Primary: The primary objective of this study was to compare varenicline oral tablets to nicotine transdermal patches [NicoDerm CQ®Clear in the United States (US), NiQuitin CQ®Clear in the European Union (EU)] for smoking cessation after 12 weeks of varenicline treatment and a 10-week standard regimen of nicotine replacement therapy (NRT), using the 4-week Continuous Quit Rate (CQR) as the primary measure.

Secondary: Secondary objectives were to:

- Compare smoking cessation efficacy of 12 weeks of varenicline treatment and 10 weeks of nicotine transdermal patch (NRT) treatment through the non-treatment follow-up periods to the end of Week 52
- Compare varenicline to NRT for treatment effects on craving, withdrawal and reward
- Evaluate the safety of 12 weeks of varenicline treatment and 10 weeks of NRT treatment.

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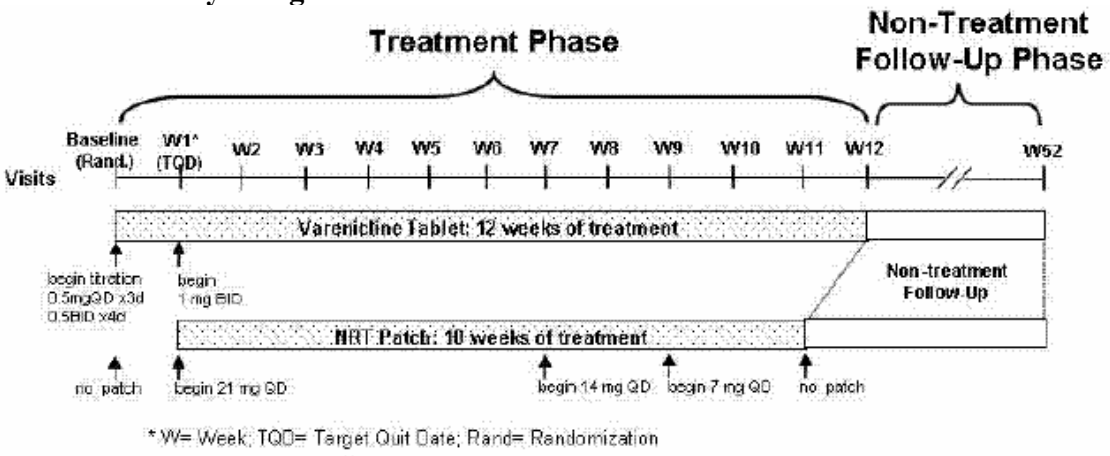
METHODS

Study Design:

This was a 52-week, open-label, randomized, multicenter clinical trial comparing the efficacy and safety of varenicline 1 mg BID with that of the NRT patch for smoking cessation. The duration of active treatment was 12 weeks for varenicline and a standard regimen of 10 weeks for NRT patch, followed by a non-treatment follow-up phase through Week 52. Details are shown in Figure S1. All visits were in an outpatient clinic setting. Visits occurred weekly during the treatment phase. During the follow-up phase, subjects returned for clinic visits at Weeks 13, 16, 24, 32, 40, 48, and 52 and received a telephone call at Weeks 14, 20, 28, 36, and 44. Efficacy was assessed at each clinic visit as well as during telephone contacts in the follow-up phase. Safety was assessed at each clinic visit during the treatment phase.

At the baseline visit, subjects were given an educational booklet on smoking cessation to review ("Clearing the Air: How to Quit Smoking...and Quit for Keeps," National Cancer Institute, Publication 95-1647). At baseline and each subsequent visit, subjects were provided up to 10 minutes of counseling, in accordance with the Agency for Healthcare Research and Quality (AHRQ) Guidelines (2000).

Figure S1 Study Design



* W= Week; TQD= Target Quit Date; Rand= Randomization

Number of Subjects (Planned and Analyzed):

Planned: The planned enrollment was 365 subjects in each of 2 treatment arms, for a total of 730 subjects.

Analyzed: A total of 757 smokers were randomized to the study and 746 (376 varenicline and 370 NRT) were treated and constituted the primary analysis population.

Diagnosis and Main Criteria for Inclusion:

Subjects were current cigarette smokers, male or female, between the ages of 18 and 75 years, inclusive, who were motivated to stop smoking. Subjects had to have smoked an

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average of at least 15 cigarettes per day during the past year. Females who were of childbearing potential were included if they were not pregnant or nursing, and a) were instructed and agreed to avoid pregnancy through 30 days after the last dose of study medication; b) had a negative serum pregnancy test (β-hCG) at Screening; and c) agreed to use birth control method(s).

Study Treatment:

Subjects were randomized to receive open-label varenicline 1 mg BID or transdermal patches (NRT):

- Varenicline 0.5 mg and 1.0 mg film-coated tablets
- NicoDerm CQ®Clear (US) / NiQuitin CQ®Clear (EU) (7, 14, and 21 mg patches)

Study drug administration is shown in Table S1.

Table S1 Treatment Administration

Study Group	Study Treatment Administration	Dosing Instruction
Varenicline	Baseline visit to Week 1 visit: one 0.5 mg tablet QD for 3 days in the evening starting at baseline followed by one 0.5 mg tablet BID (AM and PM) for 4 days Week 1 visit to Week 12 visit; one 1 mg tablet BID for 11 weeks	Drug was to be taken with 240 mL of water and subjects were advised to eat prior to taking drug. For BID regimens, there must have been at least 8 hours between morning and evening dose
Nicotine Transdermal Patch	Baseline visit to Week 1 visit: No treatment Week 1 visit to Week 7 visit; one 21 mg patch daily for 6 weeks Week 7 visit to Week 9 visit; one 14 mg patch daily for 2 weeks Week 9 visit to Week 11 visit; one 7 mg patch daily for 2 weeks	Subjects had to follow dosing instructions provided with commercial packaging

NRT= Nicotine replacement therapy

Efficacy Evaluations:

Primary: The primary efficacy evaluation was carbon monoxide (CO)-confirmed 4-week Continuous Quit Rate (CQR) for the last 4 weeks of treatment Weeks 9-12 for varenicline and Weeks 8-11 for NRT).

Secondary:

- Long Term Quit Rate
- Continuous Abstinence Rate

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- 7-day Point Prevalence of Abstinence
- 4-week Point Prevalence of Abstinence at Week 52
- Craving and withdrawal assessed by the Minnesota Nicotine Withdrawal Scale (MNWS)
- Reinforcing effects of smoking assessed by the Smoking Effects Inventory (SEI; only in subjects who had smoked since the previous assessment)

Safety Evaluations: Safety data, including blood pressure, pulse rate, weight, and adverse event (AE) information were collected at each clinic visit during the treatment phase of the study. Clinical laboratory testing was conducted and ECGs were administered at baseline and at Week 12 (or early termination). Blood pressure, pulse rate, and weight were collected at each clinic visit during the non-treatment follow-up phase.

Statistical Methods:

Efficacy: The All Subjects population was the primary population for the study and was defined as all subjects who took at least 1 dose (including partial doses) of randomized study medication.

All measures of abstinence were analyzed as binary data. Subjects were classified as responders or non-responders for each parameter and time point, and analyses were of responder rates (n responders/N treated). In the analyses of these parameters, subjects who withdrew from the study and therefore did not have data for subsequent visits were assumed to be smokers (nonresponders) for the remainder of the study, regardless of their smoking status at the last recorded visit.

Binary data were analyzed using logistic regression including treatment and center in the primary model. Hypothesis testing was carried out using the likelihood ratio chi-squared statistic at a significance level of 0.05. The treatment-by-center interaction was investigated in a separate model with interaction tested at the 0.05 significance level.

Results for the MNWS and the SEI were treated as continuous data. The data were summarized for each timepoint at which they were collected using descriptive statistics (eg, mean and standard error). Inferential analyses were conducted for the subscales of the MNWS and the SEI, comparing varenicline with NRT.

Safety:

For summarization of AEs, investigator terms for individual AEs were mapped to MedDRA Lowest Level Terms and summarized by Preferred Term and System Organ Class (SOC). Summary tables show the number and percentage of subjects in each treatment group who experienced each type of AE. Information on serious adverse events (SAEs) and discontinuations was also tabulated.

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RESULTS

Subject Disposition and Demography:

From a total of 24 centers, 757 smokers were randomized to the study (378 to varenicline and 379 to NRT). Among those subjects, 746 (376 varenicline and 370 NRT) were treated. Two subjects who had been assigned to varenicline and 9 subjects assigned to NRT did not take any study drug. Approximately, two-thirds of the subjects in each treatment group completed the 12-month study. Subject disposition is summarized in Table S2.

Table S2 Subject Disposition

	Varenicline		NRT	
	N	Percent	N	Percent
Number screened— 957				
Assigned to treatment	378		379	
Treated[a]	376	100.0	370	100.0
Completed Study[b]	247	65.7	230	62.2
Discontinued Study	129	34.3	140	37.8
During Treatment Phase	65	17.3	75	20.3
Adverse events	13	3.5	6	1.6
Lack of efficacy	0	0.0	8	2.2
Protocol deviations	1	0.3	2	0.5
Refusal to participate further	25	6.6	34	9.2
Lost to follow-up	22	5.9	18	4.9
Other[c]	4	1.1	7	1.9
During Nontreatment Follow-up Phase	64	17.0	65	17.6
Lack of efficacy	0	0.0	1	0.3
Protocol deviations	0	0.0	1	0.3
Refusal to participate further	22	5.9	19	5.1
Lost to follow-up	26	6.9	29	7.8
Other[d]	16	4.3	15	4.1

[a]Percentages based on number of subjects treated.
[b]Subjects could discontinue study medication but remain in the study.
[c]Other reasons (treatment phase): Varenicline— 2 subjects moved or went out of the city for an extended period, 2 varenicline subjects were no longer motivated; NRT— 4 subjects moved or went out of the city, 1 subject was no longer motivated, and 2 subjects continued to smoke cannabis or use codeine.
[d]Other reasons (nontreatment phase): Varenicline— 4 subjects moved, 3 subjects used a Nicoderm patch and/or bupropion HCL, 4 subjects had other commitments, 4 subjects were no longer motivated/started smoking again, 1 subject started another trial; NRT— 1 subject was housebound, 4 subjects moved or went out of the city, 3 subjects had other commitments, 6 subjects were no longer motivated, and 1 subject used bupropion.

Treatment groups were well balanced with respect to baseline demographic characteristics and smoking history. Overall, 49% were male and the majority (above 93%) was White. The average age was 43 years and ages ranged between 18 and 75 years. The average weights were 83 and 69 kg for males and females, respectively. Subjects smoked an average of 23 cigarettes per day over the previous month and had been smoking for an average of 26 years since an average age of 16 years. On the Fagerström Test for Nicotine Dependence, subjects scored on average 5.5 out of a possible 10 with 75% reporting smoking their first cigarette within 30 minutes of waking.

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Efficacy Results:

Primary: Primary efficacy results are shown in Table S3.

Table S3 CO-confirmed 4-week Continuous Quit Rate Over the Last 4 Weeks of Treatment

	CQR		Odds Ratio (95% CI)	p-value
	n/N	Percent	Varenicline vs NRT	Varenicline vs NRT
Varenicline[a]	210/376	55.9		
NRT[b]	160/370	43.2	1.70 (1.26 – 2.28)	0.0004

CI= Confidence interval, CQR= Continuous Quit Rate, NRT= Nicotine replacement therapy
[a]Week 9 through Week 12
[b]Week 8 through Week 11

Secondary: Secondary endpoints are shown in Tables S4 – S9.

Table S4 Long Term Quit Rate: Week 24 and Week 52

	LTQR		Odds Ratio (95% CI)	p-value
	n/N	Percent	Varenicline vs NRT patch	Varenicline vs NRT patch
Week 24				
Varenicline	150/376	39.9		
NRT	114/370	30.8	1.52 (1.12,2.07)	0.0076
Week 52				
Varenicline	111/376	29.5		
NRT	92/370	24.9	1.29 (0.92, 1.79)	0.1343

CI= Confidence interval, LTQR= Long Term Quit Rate, NRT= Nicotine replacement therapy

Table S5 Continuous Abstinence Rate, Last 4 Weeks of Treatment Through Week 52

	Continuous Abstinence Rate		Odds Ratio (95% CI)	p-value
	n/N	Percent	Varenicline vs NRT	Varenicline vs NRT
Varenicline[a]	98/376	26.1		
NRT[b]	75/370	20.3	1.40 (0.99 – 1.99)	0.0558

CI= Confidence interval, NRT= Nicotine replacement therapy
[a]From Week 9
[b]From Week 8

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Table S6 7-day Point Prevalence of Abstinence: EOT, Week 24 and Week 52

	7-day Point Prevalence		Odds Ratio (95% CI)	p-value
	n/N	Percent	Varenicline vs NRT	Varenicline vs NRT
EOT				
Varenicline	233/376	62.0		
NRT	174/370	47.0	1.71 (1.27, 2.30)	0.0004
Week 24				
Varenicline	145/376	38.6		
NRT	126/370	34.1	1.22 (0.90, 1.66)	0.1928
Week 52				
Varenicline	131/376	34.8		
NRT	116/370	31.4	1.18 (0.87, 1.62)	0.2854

CI= Confidence interval, EOT= End of treatment (Week 12 for the varenicline treatment group and Week 11 for the NRT treatment group), NRT= Nicotine replacement group

Table S7 4-week Point Prevalence of Abstinence at Week 52

	4-week Point Prevalence		Odds Ratio (95% CI)	p-value
	n/N	Percent	Varenicline vs NRT	Varenicline vs NRT
Varenicline	127/376	33.8		
NRT	108/370	29.2	1.26 (0.92, 1.72)	0.1567

CI= Confidence interval, NRT= Nicotine replacement therapy

Table S8 MNWS: Repeated-measures Analysis of Data for Week 1 Through Week 7

			Comparision vs NRT[a]			
	N	LSMean[b] (SE)	Difference (SE)	95% CI	p-value	Effect Size[c]
Varenicline						
Urge to smoke	367	1.35 (0.04)	-0.32 (0.06)	-0.44, -0.21	<0.0001	-0.37
Negative affect	369	0.63 (0.03)	-0.16 (0.04)	-0.24, -0.07	0.0003	-0.21
Restlessness	368	0.76 (0.04)	-0.20 (0.05)	-0.31, -0.10	0.0001	-0.21
Increased appetite	368	1.07 (0.04)	0.09 (0.06)	-0.02, 0.21	0.1163	0.12
Insomnia	368	0.70 (0.04)	-0.07 (0.05)	-0.17, 0.04	0.2073	-0.07
NRT						
Urge to smoke	366	1.67 (0.04)				
Negative affect	366	0.79 (0.03)				
Restlessness	366	0.96 (0.04)				
Increased appetite	364	0.97 (0.04)				
Insomnia	366	0.76 (0.04)				

[a]Inferential analyses were based on a repeated-measures model with factors: treatment group, baseline measure, center, visit, and treatment-by-visit interaction. Model estimated on the average effect and the p-value versus NRT was obtained by contrasting the average of Week 1 through Week 7.
[b]Higher score indicates greater intensity of symptoms.
[c]Effect size= LS mean treatment differences/pooled standard deviation at baseline (pooled by center).
CI= Confidence interval, LS= Least squares, MNWS= Minnesota Nicotine Withdrawal Scale, NRT= Nicotine replacement therapy, SE= Standard error

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Table S9 SEI— Repeated-measures Analysis of Data for Weeks 1 – 7

			Comparison vs NRT[a]			
	N	LSMean[b] (SE)	Difference (SE)	95% CI	p-value	Effect Size[c]
Varenicline						
Smoking satisfaction	361	2.73 (0.09)	-0.54 (0.12)	-0.77, -0.31	<0.0001	-0.43
Psychological reward	361	2.30 (0.07)	-0.32 (0.10)	-0.51, -0.13	0.0011	-0.26
Enjoyment of RTS	358	2.04 (0.08)	-0.39 (0.11)	-0.60, -0.17	0.0004	-0.25
Craving reduction	360	3.62 (0.10)	-0.52 (0.14)	-0.79, -0.24	0.0002	-0.32
Aversion	361	1.76 (0.07)	-0.07 (0.09)	-0.25, 0.11	0.4362	-0.08
NRT						
Smoking satisfaction	354	3.27 (0.08)				
Psychological reward	354	2.61 (0.07)				
Enjoyment of RTS	353	2.42 (0.08)				
Craving reduction	354	4.14 (0.10)				
Aversion	354	1.83 (0.06)				

[a]Inferential analyses were based on a repeated-measures model with factors: treatment group, baseline measure, center, visit, and treatment-by-visit interaction. Model estimates on the average effect and the p-values versus NRT were obtained by contrasting the average of Week 1 through Week 7.
[b]Higher scores indicate greater intensity of smoking effects; thus, higher scores are desirable for the aversion subscale and lower scores are desirable for the other 4 subscales.
[c]Effect size= LS mean treatment differences/pooled standard deviations at baseline (pooled by center)
CI= Confidence interval, LS= least squares, NRT= nicotine replacement therapy, RTS= Enjoy respiratory tract sensations, SEI= Smoking effects inventory

Safety Results:

The incidence of treatment-emergent, all-causality AEs was 84.8% for varenicline and 70.3% for NRT. The incidence of AEs considered related to study medication was higher in the varenicline group than in the NRT group (75.8% varenicline, 47.6% NRT). Frequent (those occurring in 5% or more of subjects) all causality AEs are shown in Table S10.

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Table S10 Most Frequent (≥ 5%) Adverse Events, All Causality[a]

SOC Adverse Event (MedDRA Preferred Term)	Varenicline N= 376		NRT N= 370	
	n	Percent	n	Percent
Gastrointestinal disorders	**221**	**58.8**	**79**	**21.4**
Nausea	140	37.2	36	9.7
Constipation	31	8.2	9	2.4
Vomiting	23	6.1	4	1.1
Diarrhea	22	5.9	10	2.7
Flatulence	22	5.9	5	1.4
Abdominal pain upper	21	5.6	4	1.1
Nervous system disorders	**140**	**37.2**	**63**	**17.0**
Headache	72	19.1	36	9.7
Dizziness	28	7.4	13	3.5
Psychiatric disorders	**136**	**36.2**	**116**	**31.4**
Insomnia	80	21.3	71	19.2
Abdominal dreams	44	11.7	31	8.4
Infections & infestations	**79**	**21.0**	**51**	**13.8**
Nasopharyngitis	16	5.3	11	3.0
General disorders	**57**	**15.2**	**61**	**16.5**
Fatigue	21	5.6	9	2.4
Respiratory, thoracic & mediastinal disorders	**45**	**12.0**	**38**	**10.3**
Musculoskeletal & connective tissue disorders	**41**	**10.9**	**52**	**14.1**
Skin & subcutaneous tissue disorders	**27**	**7.2**	**58**	**15.7**

[a]Occurring in ≥ 5% of subjects in either the varenicline or NRT treatment groups.
MedDRA= Medical Dictionary for Regulatory Activities, NRT= Nicotine replacement therapy, SOC= System organ class

The numbers of subjects permanently discontinuing treatment due to AEs were 30 (8.0%) and 16 (4.3%) in the varenicline and NRT groups, respectively. Frequent AEs (occurring in 3 or more subjects) that led to discontinuation are shown in Table S11.

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Table S11 Adverse Events Most Frequently (3 or More Subjects) Contributing to Discontinuation of Study Medication

SOC Adverse Event (MedDRA Preferred Term)[a, b]	Varenicline N= 376		NRT N= 370	
	n	Percent	n	Percent
Gastrointestinal disorders	**14**	**3.7**	**3**	**0.8**
Nausea	8	2.1	3	0.8
Nervous system disorders	**11**	**2.9**	**1**	**0.3**
Headache	3	0.8	1	0.3
Dizziness	4	1.1	0	0.0
Depression	4	1.1	1	0.3
Sleep disorders	**5**	**1.3**	**1**	**0.3**
Insomnia	3	0.8	1	0.3
General disorders & administration site conditions	**3**	**0.8**	**5**	**1.4**
Eye disorders	**3**	**0.8**	**0**	**0.0**
Skin & subcutaneous tissue disorders	**1**	**0.3**	**7**	**1.9**

[a]Includes events that led to discontinuation of study medication in 3 or more subjects in either treatment group.
[b]Treatment discontinuation in a given subject could be attributed to a single AE or to multiple events.
MedDRA= Medical Dictionary for Regulatory Activities, NRT= Nicotine replacement system, SOC= System organ class

Ten subjects experienced events meeting the predefined criteria for an SAE while receiving treatment or within 30 days of the last dose in this study: 2 subjects in the varenicline group and 8 subjects in the NRT group. An additional 3 subjects (2 in the varenicline group and 1 in the NRT group) experienced non-fatal SAEs during the non-treatment follow-up phase of the study. All SAEs are summarized in Table S12.

Table S12 Serious Adverse Events

Subject Number	SAE (Investigator Term)	Relationship to Study Drug[b]
During Treatment[s]		
Varenicline		
1	Constipation	Not related
1	Depression	Related
NRT		
1	Biliduct cancer, sepsis	Not related
1	Gastrointestinal bleed	Not related
1	Myocardial infarction	Not related
1	Saliva gland tumor	Not related
2	Chest pain	Not related
1	Inferior myocardial infarction	Not related
1	Worsening old knee traumatism	Not related
Post-therapy		
Varenicline		
1	Acute ethanol intoxication	Not related
1	Suicidal ideations	Related
NRT		
1	Abdominal cyst	Not related

[a]Serious AE occurred during treatment or within 30 days after the last dose.
[b]Investigator opinion: "related" includes possibly, probably, or definitely related.

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There were no deaths in the study.

Median changes in laboratory parameter values from Baseline to last observation were small and comparable among treatment groups. Median changes in blood pressure and pulse rate from Baseline to last observation (on treatment or within 7 days of last dose) and mean changes in blood pressure and pulse rate from Baseline to each weekly observation during Weeks 1–13 were small and indicated no differences among the treatment groups. The median change from Baseline to last observation (on treatment or within 7 days of last dose) in body weight was 1.82 kg for varenicline-treated subjects (N= 370) and 1.12 kg for subjects in the NRT treatment group (N= 362). No varenicline-treated subjects experienced QTc ≥ 480 msec however, 1 varenicline-treated subject experienced a QTc increase of ≥ 60 msec using the Bazett and Fridericia corrections. For this subject, the QTcB baseline value was 395 msec; baseline QTcF was 388 msec.

CONCLUSION(S):

This open-label, randomized, 12-week treatment study comparing varenicline 1 mg BID with a standard 10-week regimen of NRT patch for smoking cessation, with follow-up to Week 52, demonstrated that:

- Varenicline was significantly more efficacious than NRT patch for the primary endpoint of Continuous Quit Rate at the end of the treatment period (p= 0.0004), and showed a higher Continuous Abstinence rate through Week 52 (p= 0.0558).
- Varenicline reduced the urge to smoke, the negative affect and restlessness associated with withdrawal, and the smoking satisfaction, psychological reward, enjoyment of respiratory tract sensations, and craving reduction that can reinforce smoking behavior compared with NRT patch.
- There were no data suggestive of a safety concern.
- Varenicline was well tolerated and there were few treatment discontinuations for AEs. The AE most affecting varenicline tolerability was nausea, which was generally mild to moderate in intensity and infrequently resulted in treatment discontinuation.
- Overall, varenicline was superior to NRT patch for smoking cessation, was safe and well tolerated.

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