Clinical trial results:
A Twelve-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study With Follow-Up Evaluating The Safety And Efficacy of Varenicline For Smoking Cessation in Healthy Adolescent Smokers

Summary

EudraCT number	2018-000761-37
Trial protocol	Outside EU/EEA
Global end of trial date	18 January 2018

Results information

Result version number	v1 (current)
This version publication date	29 July 2018
First version publication date	29 July 2018

Trial information

Trial identification

Sponsor protocol code	A3051073

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01312909
WHO universal trial number (UTN)	-
Other trial identifiers	CHANTIX: Alias Study Number

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy, safety, and tolerability of varenicline compared with placebo in adolescent smokers aged 12-19 years.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy:

Brief (up to 10 minutes of duration) age-appropriate smoking cessation counseling, in accordance with Public Health Service (PHS) guidelines was provided by a trained counselor at each clinic visit and at each telephone contact, starting with the baseline visit till end of the study.

Evidence for comparator: -

Actual start date of recruitment	26 April 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Georgia: 1
Country: Number of subjects enrolled	Korea, Republic of: 28
Country: Number of subjects enrolled	Russian Federation: 64
Country: Number of subjects enrolled	Taiwan: 25
Country: Number of subjects enrolled	United States: 187
Worldwide total number of subjects	312
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	234
Adults (18-64 years)	78
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study consisted of 3 phases: Screening (3 weeks before first dose of study drug); treatment (from Week 2 to Week 12 after a 2-week titration) and non-treatment follow-up (Week 13 through Week 52).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Varenicline High Dose

Arm description:

Subjects received 2 tablets of Varenicline 0.5 milligram (mg) (total dose 1 mg) orally, twice daily from Week 2 to Week 12 after a 2-week titration. Subjects with a body weight less than or equal to (<=) 55 kilograms (kg) had Varenicline dose reduced by half, and received one tablet of Varenicline 0.5 mg and one matching placebo tablet orally, twice daily from Week 2 to Week 12 after a 2-week titration.

Arm type	Experimental
Investigational medicinal product name	Varenicline
Investigational medicinal product code	CP-526,555
Other name	Chantix/Champix
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two tablets of Varenicline 0.5 milligram (mg) (total dose 1 mg) orally, twice daily

Arm title	Varenicline Low Dose

Arm description:

Subjects received one tablet of Varenicline 0.5 mg and one matching placebo tablet orally, twice daily from Week 2 to Week 12 after a 2-week titration. Subjects with a body weight <= 55 kg had Varenicline dose reduced by half and received one tablet of Varenicline 0.5 mg and one matching placebo tablet orally, in the morning and 2 tablets of matching placebo orally, in the evening from Week 2 to Week 12 after a 2-week titration.

Arm type	Experimental
Investigational medicinal product name	Varenicline
Investigational medicinal product code	CP-526,555
Other name	Chantix/Champix
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Varenicline 0.5 mg tablet orally, twice daily

Arm title	Placebo

Arm description:

Subjects received 2 tablets of placebo (matched to Varenicline) orally, twice daily from Week 2 to Week 12 after a 2-week titration.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two tablets of placebo (matched to Varenicline) orally, twice daily

Number of subjects in period 1	Varenicline High Dose	Varenicline Low Dose	Placebo
Started	109	103	100
Treated	108	100	99
Completed	67	67	53
Not completed	42	36	47
Consent withdrawn by subject	8	10	7
Entrance criteria not met	-	-	2
Randomized but not treated	1	3	1
Adverse event	1	-	3
Unspecified	9	6	11
Lost to follow-up	21	17	20
Protocol deviation	2	-	2
Insufficient clinical response	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Varenicline High Dose
Reporting group description:	
Subjects received 2 tablets of Varenicline 0.5 milligram (mg) (total dose 1 mg) orally, twice daily from Week 2 to Week 12 after a 2-week titration. Subjects with a body weight less than or equal to (<=) 55 kilograms (kg) had Varenicline dose reduced by half, and received one tablet of Varenicline 0.5 mg and one matching placebo tablet orally, twice daily from Week 2 to Week 12 after a 2-week titration.	
Reporting group title	Varenicline Low Dose
Reporting group description:	
Subjects received one tablet of Varenicline 0.5 mg and one matching placebo tablet orally, twice daily from Week 2 to Week 12 after a 2-week titration. Subjects with a body weight <= 55 kg had Varenicline dose reduced by half and received one tablet of Varenicline 0.5 mg and one matching placebo tablet orally, in the morning and 2 tablets of matching placebo orally, in the evening from Week 2 to Week 12 after a 2-week titration.	
Reporting group title	Placebo
Reporting group description:	
Subjects received 2 tablets of placebo (matched to Varenicline) orally, twice daily from Week 2 to Week 12 after a 2-week titration.	

Reporting group values	Varenicline High Dose	Varenicline Low Dose	Placebo
Number of subjects	109	103	100
Age categorical Units: Subjects			
Adolescents (12-17 years)	80	78	76
Adults (18-64 years)	29	25	24
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Here the data provided is for N=307 subjects of safety analysis set (subjects who took at least 1 dose of randomized study medication, including partial doses).			
Units: years			
arithmetic mean	16.0	16.0	15.8
standard deviation	± 2.0	± 1.7	± 1.8
Sex: Female, Male Units: Subjects			
Female	39	38	37
Male	70	65	63
Race/Ethnicity, Customized			
Here the data provided is for N=307 subjects of safety analysis set (subjects who took at least 1 dose of randomized study medication, including partial doses).			
Units: Subjects			
White|	81	73	74
Black|	9	9	5
Asian|	16	18	19
Other|	2	0	1
Unknown	1	3	1

Reporting group values	Total		
Number of subjects	312		

Age categorical Units: Subjects			
Adolescents (12-17 years)	234		
Adults (18-64 years)	78		
From 65-84 years	0		
85 years and over	0		
Age Continuous			
Here the data provided is for N=307 subjects of safety analysis set (subjects who took at least 1 dose of randomized study medication, including partial doses).			
Units: years arithmetic mean standard deviation	- -		
Sex: Female, Male Units: Subjects			
Female	114		
Male	198		
Race/Ethnicity, Customized			
Here the data provided is for N=307 subjects of safety analysis set (subjects who took at least 1 dose of randomized study medication, including partial doses).			
Units: Subjects			
White|	228		
Black|	23		
Asian|	53		
Other|	3		
Unknown	5		

End points

End points reporting groups

Reporting group title	Varenicline High Dose

Reporting group description:

Subjects received 2 tablets of Varenicline 0.5 milligram (mg) (total dose 1 mg) orally, twice daily from Week 2 to Week 12 after a 2-week titration. Subjects with a body weight less than or equal to (<=) 55 kilograms (kg) had Varenicline dose reduced by half, and received one tablet of Varenicline 0.5 mg and one matching placebo tablet orally, twice daily from Week 2 to Week 12 after a 2-week titration.

Reporting group title	Varenicline Low Dose

Reporting group description:

Subjects received one tablet of Varenicline 0.5 mg and one matching placebo tablet orally, twice daily from Week 2 to Week 12 after a 2-week titration. Subjects with a body weight <= 55 kg had Varenicline dose reduced by half and received one tablet of Varenicline 0.5 mg and one matching placebo tablet orally, in the morning and 2 tablets of matching placebo orally, in the evening from Week 2 to Week 12 after a 2-week titration.

Reporting group title	Placebo

Reporting group description:

Subjects received 2 tablets of placebo (matched to Varenicline) orally, twice daily from Week 2 to Week 12 after a 2-week titration.

Primary: 4-Week Continuous Abstinence Rate: Percentage of Subjects Who Remained Abstinent From Week 9 Through Week 12

End point title	4-Week Continuous Abstinence Rate: Percentage of Subjects Who Remained Abstinent From Week 9 Through Week 12

End point description:

The percentage of subjects who, at each visit from Week 9 through Week 12, reported no smoking and no use of other nicotine-containing products since the last study visit (on the Nicotine Use Inventory) and at each of these visits were confirmed to have quit based on urine cotinine less than 200 nanograms/milliliter (ng/mL). The full analysis set included all randomized subjects.

End point type	Primary

End point timeframe:

Week 9 through Week 12

End point values	Varenicline High Dose	Varenicline Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	103	100	
Units: percentage of subjects				
number (not applicable)	20.2	27.2	18.0	

Statistical analyses

Statistical analysis title	Varenicline High Dose Vs. Placebo

Statistical analysis description:

Odds ratios and p-values were obtained from a logistic regression model with terms treatment, age strata, body weight strata and pooled center.

Comparison groups	Varenicline High Dose v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6337 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	2.37

Notes:

[1] - Threshold for significance at 0.05 level.

Statistical analysis title	Varenicline Low Dose Vs. Placebo

Statistical analysis description:

Odds ratios and p-values were obtained from a logistic regression model with terms treatment, age strata, body weight strata and pooled center.

Comparison groups	Varenicline Low Dose v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1114 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	3.39

Notes:

[2] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects With 7-Day Point Prevalence of Smoking Abstinence at Weeks 12, 24 and 52

End point title	Percentage of Subjects With 7-Day Point Prevalence of Smoking Abstinence at Weeks 12, 24 and 52

End point description:

The percentage of subjects who reported no smoking and no use of other nicotine-containing products (treatment phase) or tobacco products (non-treatment phase) on the Nicotine Use Inventory in the 7 days prior to the study visits or telephone contacts at Week 12,24 and 52.The full analysis set included all randomized subjects.

End point type	Secondary

End point timeframe:

Weeks 12, 24 and 52

End point values	Varenicline High Dose	Varenicline Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	103	100	
Units: percentage of subjects				
number (not applicable)				
Week 12	31.2	37.9	23.0	
Week 24	31.2	35.9	23.0	
Week 52	28.4	35.0	20.0	

Statistical analyses

Statistical analysis title	Varenicline High Dose Vs. Placebo
Statistical analysis description:	
Week 12: Odds ratios and p-values were obtained from separate logistic regression models of treatment, pooled center, age strata and body weight strata.	
Comparison groups	Varenicline High Dose v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5793
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	2.38

Statistical analysis title	Varenicline Low Dose Vs. Placebo
Statistical analysis description:	
Week 12: Odds ratios and p-values were obtained from separate logistic regression models of treatment, pooled center, age strata and body weight strata.	
Comparison groups	Varenicline Low Dose v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0932
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	3.51

Statistical analysis title	Varenicline High Dose Vs. Placebo
Statistical analysis description:	
Week 24: Odds ratios and p-values were obtained from separate logistic regression models of treatment, pooled center, age strata and body weight strata.	
Comparison groups	Varenicline High Dose v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5647
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	2.5

Statistical analysis title	Varenicline Low Dose Vs. Placebo
Statistical analysis description:	
Week 24: Odds ratios and p-values were obtained from separate logistic regression models of treatment, pooled center, age strata and body weight strata.	
Comparison groups	Varenicline Low Dose v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2917
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	2.96

Statistical analysis title	Varenicline High Dose Vs. Placebo
Statistical analysis description:	
Week 52: Odds ratios and p-values were obtained from separate logistic regression models of treatment, pooled center, age strata and body weight strata.	
Comparison groups	Varenicline High Dose v Placebo

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5616
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	2.69

Statistical analysis title	Varenicline Low Dose Vs. Placebo
Statistical analysis description:	
Week 52: Odds ratios and p-values were obtained from separate logistic regression models of treatment, pooled center, age strata and body weight strata.	
Comparison groups	Varenicline Low Dose v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.13
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	3.78

Secondary: Change From Baseline in Daily Number of Cigarettes Smoked at Weeks 12, 24, and 52

End point title	Change From Baseline in Daily Number of Cigarettes Smoked at Weeks 12, 24, and 52
End point description:	
The reduction in the number of the cigarettes smoked was calculated by subtracting the reported average number of cigarettes smoked per day in the past 7 days at Weeks 12, 24 and 52 from the average number of cigarettes smoked per day in the past 7 days reported at the baseline visit. The full analysis set included all randomized subjects. The longitudinal model includes all subjects regardless of observed visits.	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 12, 24, and 52	

End point values	Varenicline High Dose	Varenicline Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	103	100	
Units: cigarettes smoked per day				
least squares mean (standard error)				
Change at Week 12|	-8.56 (± 0.43)	-8.20 (± 0.44)	-8.01 (± 0.46)	
Change at Week 24|	-6.93 (± 0.44)	-7.31 (± 0.45)	-6.59 (± 0.48)	
Change at Week 52|	-6.80 (± 0.45)	-7.74 (± 0.46)	-6.98 (± 0.48)	

Statistical analyses

Statistical analysis title	Varenicline High Dose Vs. Placebo

Statistical analysis description:

Week 12: Analysis was performed using longitudinal repeated measures model with the change from baseline average number of Cigarettes Smoked as the dependent variable, including terms treatment, visit, age strata, body weight strata, pooled center, baseline measure and treatment by visit interaction.

Comparison groups	Varenicline High Dose v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.354
Method	Longitudinal repeated measures model
Parameter estimate	Least square (LS) mean difference
Point estimate	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.69
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.58

Statistical analysis title	Varenicline Low Dose Vs. Placebo

Statistical analysis description:

Week 12: Analysis was performed using longitudinal repeated measures model with the change from baseline average number of Cigarettes Smoked as the dependent variable, including terms treatment, visit, age strata, body weight strata, pooled center, baseline measure and treatment by visit interaction.

Comparison groups	Varenicline Low Dose v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7574
Method	Longitudinal repeated measures model
Parameter estimate	LS mean difference
Point estimate	-0.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.35
upper limit	0.98
Variability estimate	Standard error of the mean
Dispersion value	0.59

Statistical analysis title	Varenicline High Dose Vs. Placebo

Statistical analysis description:

Week 24: Analysis was performed using longitudinal repeated measures model with the change from baseline average number of Cigarettes Smoked as the dependent variable, including terms treatment, visit, age strata, body weight strata, pooled center, baseline measure and treatment by visit interaction.

Comparison groups	Varenicline High Dose v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5676
Method	Longitudinal repeated measures model
Parameter estimate	LS mean difference
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.53
upper limit	0.84
Variability estimate	Standard error of the mean
Dispersion value	0.6

Statistical analysis title	Varenicline Low Dose Vs. Placebo

Statistical analysis description:

Week 24: Analysis was performed using longitudinal repeated measures model with the change from baseline average number of Cigarettes Smoked as the dependent variable, including terms treatment, visit, age strata, body weight strata, pooled center, baseline measure and treatment by visit interaction.

Comparison groups	Varenicline Low Dose v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2356
Method	Longitudinal repeated measures model
Parameter estimate	LS mean difference
Point estimate	-0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.92
upper limit	0.47

Variability estimate	Standard error of the mean
Dispersion value	0.61

Statistical analysis title	Varenicline High Dose Vs. Placebo

Statistical analysis description:

Week 52: Analysis was performed using longitudinal repeated measures model with the change from baseline average number of Cigarettes Smoked as the dependent variable, including terms treatment, visit, age strata, body weight strata, pooled center, baseline measure and treatment by visit interaction.

Comparison groups	Varenicline High Dose v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.773
Method	Longitudinal repeated measures model
Parameter estimate	LS mean difference
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	1.38
Variability estimate	Standard error of the mean
Dispersion value	0.62

Statistical analysis title	Varenicline Low Dose Vs. Placebo

Statistical analysis description:

Week 52: Analysis was performed using longitudinal repeated measures model with the change from baseline average number of Cigarettes Smoked as the dependent variable, including terms treatment, visit, age strata, body weight strata, pooled center, baseline measure and treatment by visit interaction.

Comparison groups	Varenicline Low Dose v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2166
Method	Longitudinal repeated measures model
Parameter estimate	LS mean difference
Point estimate	-0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.99
upper limit	0.45
Variability estimate	Standard error of the mean
Dispersion value	0.62

Secondary: Continuous Abstinence Rate: Percentage of Subjects Who Remained Abstinent From Week 9 Through Week 24 and Week 52

End point title	Continuous Abstinence Rate: Percentage of Subjects Who Remained Abstinent From Week 9 Through Week 24 and Week 52

End point description:

The percentage of subjects who, at each visit from Week 9 to 52 (inclusive), reported no smoking and no use of other nicotine-containing products (Weeks 9-12) or tobacco products (Weeks 13-52) since the last study visit/last contact (on the Nicotine Use Inventory) and at any of the study visits were confirmed to have quit based on urine cotinine less than 200 ng/mL. The full analysis set included all randomized subjects. The longitudinal model included all subjects regardless of observed visits.

End point type	Secondary

End point timeframe:

Week 9 through Week 24; Week 9 through Week 52

End point values	Varenicline High Dose	Varenicline Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	103	100	
Units: percentage of subjects				
number (not applicable)				
Week 9 through Week 24	10.1	24.3	13.0	
Week 9 through Week 52	8.3	20.4	9.0	

Statistical analyses

Statistical analysis title	Varenicline High Dose Vs. Placebo

Statistical analysis description:

Week 9 through Week 24: Odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment, pooled center, age strata and body weight strata.

Comparison groups	Varenicline High Dose v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6133
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.9

Statistical analysis title	Varenicline Low Dose Vs. Placebo

Statistical analysis description:

Week 9 through Week 24: Odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment, pooled center, age strata and body weight strata.

Comparison groups	Varenicline Low Dose v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0335
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	4.79

Statistical analysis title	Varenicline High Dose Vs. Placebo

Statistical analysis description:

Week 9 through Week 52: Odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment, pooled center, age strata and body weight strata.

Comparison groups	Varenicline High Dose v Placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9874
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	2.65

Statistical analysis title	Varenicline Low Dose Vs. Placebo

Statistical analysis description:

Week 9 through Week 52: Odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment, pooled center, age strata and body weight strata.

Comparison groups	Varenicline Low Dose v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0188
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.79

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	6.55

Secondary: Daily Number of Cigarettes Smoked at Baseline

End point title	Daily Number of Cigarettes Smoked at Baseline

End point description:

The average number of cigarettes smoked per day in the past 7 days reported at the baseline visit.

End point type	Secondary

End point timeframe:

Baseline

End point values	Varenicline High Dose	Varenicline Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	103	100	
Units: cigarettes smoked per day				
arithmetic mean (standard error)	10.68 (± 0.624)	9.56 (± 0.530)	9.57 (± 0.531)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Treatment-Emergent Adverse Events (AEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs)

End point description:

An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. A serious AE (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events between first dose of study drug and up to 30 days after last dose that were absent before treatment or that worsened relative to pretreatment state. AEs included both non-serious AEs and SAEs. The safety analysis set included all participants who took at least one dose of randomized study medication, including partial doses.

End point type	Other pre-specified

End point timeframe:

First dose up to last dose (up-to Week 12) plus 30 days

End point values	Varenicline High Dose	Varenicline Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	100	99	
Units: subjects	65	53	52	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Treatment Emergent Treatment-Related Adverse Events (AEs)

End point title	Number of Subjects With Treatment Emergent Treatment-Related Adverse Events (AEs)

End point description:

Treatment-related AE was any untoward medical occurrence attributed to study drug in a subject who received study drug.Treatment-emergent were events between first dose of study drug and up to 30 days after last dose that were absent before treatment or that worsened relative to pretreatment state.Relatedness to drug was assessed by the investigator(Yes/No). Subjects with multiple occurrences of an AE within a category were counted once within the category.An AE:any untoward medical occurrence attributed to study drug in a subject who received study drug. A serious AE (SAE):an AE resulting in any of the following outcomes or deemed significant for any other reason:death;initial or prolonged inpatient hospitalization;life-threatening experience;persistent or significant disability;congenital anomaly.AEs included both non-serious AEs and SAEs.The safety analysis set included all subjects who took at least one dose of randomized study medication,including partial doses.

End point type	Other pre-specified

End point timeframe:

First dose up to last dose (up-to Week 12) plus 30 days

End point values	Varenicline High Dose	Varenicline Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	100	99	
Units: subjects	46	28	27	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Treatment-Emergent Neuropsychiatric Adverse Event Elicited by Neuropsychiatric Adverse Event Interview (NAEI)

End point title	Number of Subjects With Treatment-Emergent Neuropsychiatric Adverse Event Elicited by Neuropsychiatric Adverse Event Interview (NAEI)

End point description:

An AE was any untoward medical occurrence attributed to study drug in a subject who received study drug. SAE: AE causing: death; initial/prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent/significant disability/incapacity; congenital anomaly. Treatment-emergent were events between first dose of study drug and up to 30 days after last dose that were

absent before treatment or that worsened relative to pretreatment state. Solicited AEs collected by semi-structured NAEI inquiring about AEs: depression, anxiety, delusions, hallucinations, paranoia, psychosis, mania, panic, agitation, dissociative states, feeling abnormal, hostility, aggression and homicidal ideation. If a subject had a positive response to any item on the NAEI, investigator determined if it met criteria AE criteria. The safety analysis set included all subjects who took at least one dose of randomized study medication, including partial doses.

End point type	Other pre-specified

End point timeframe:

First dose up to last dose (up-to Week 12) plus 30 days

End point values	Varenicline High Dose	Varenicline Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	100	99	
Units: subjects				
Neuropsychiatric AEs	18	11	12	
Neuropsychiatric SAEs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Categorical Scores on the Columbia Suicide Severity Rating Scale (C-SSRS)

End point title	Number of Subjects With Categorical Scores on the Columbia Suicide Severity Rating Scale (C-SSRS)

End point description:

The C-SSRS (mapped to Columbia Classification Algorithm of Suicide Assessment (C-CASA) categories);was an interview-based instrument to systematically assess suicidal ideation and suicidal behavior.C-SSRS assessed whether participant experienced any of the following:completed suicide;suicide attempt(response of "Yes" on "actual attempt");preparatory acts toward imminent suicidal behavior("Yes" on "preparatory acts or behavior","aborted attempt" or "interrupted attempt"),suicidal ideation("Yes" on "wish to be dead","non-specific (NS) active suicidal thoughts","active suicidal ideation with methods without intent to act or some intent to act,without specific plan or with specific plan and intent,any self-injurious behavior (IB) with no suicidal intent ("Yes"on "Has participant engaged in non-suicidal self-injurious behavior").Here,number of participants with positive response(response of "yes") to suicidal behavior or/and Ideation,any non-suicidal self-

End point type	Other pre-specified

End point timeframe:

Screening, Baseline, Week 1 up to Week 12 (treatment-emergent [TE]), thereafter up to Week 52 (last follow-up [FU])

End point values	Varenicline High Dose	Varenicline Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	100	99	
Units: subjects				
Screening:Suicidal Behavior or/and Ideation	2	3	2	

Screening:Suicidal Ideation	2	3	2	
Screening: Wish to be Dead	2	2	2	
Screening: Non-Specific Active Suicidal Thoughts	1	1	2	
Screen:Self InjuriousBehavior,no Suicidal Intent	3	3	2	
TE:Suicidal Behavior or/and Ideation(n=105,99,96)	1	0	1	
TE:Suicidal Ideation(n=105,99,96)	1	0	1	
TE: Wish to be Dead(n=105,99,96)	1	0	1	
TE: NS Active Suicidal Thoughts (n=105,99,96)	0	0	1	
TE:Self IB, no Suicidal Intent (n=105,99,96)	0	0	1	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Hospital Anxiety and Depression Scale (HADS) - Anxiety (HADS-A) Total Scores at Specified Time-points

End point title	Change From Baseline in Hospital Anxiety and Depression Scale (HADS) - Anxiety (HADS-A) Total Scores at Specified Time-points

End point description:

The HADS is a self-administered questionnaire measuring anxiety. Hospital Anxiety and Depression Scale Anxiety subscale (HADS-A) consisted of 7 items that were assessed on a scale of 0 = no anxiety to 3 = severe feeling of anxiety. Total HADS-A subscale score range from 0 = no anxiety to 21 = severe anxiety; higher scores indicated more severe anxiety. The safety analysis set included all subjects who took at least one dose of randomized study medication, including partial doses. Here, 'n' signifies subjects evaluable for this end point at specified time point.

End point type	Other pre-specified

End point timeframe:

Baseline, Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 20, 28, 36, 44, and 52

End point values	Varenicline High Dose	Varenicline Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	100	99	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=108,100,99)	2.4 (± 2.05)	1.9 (± 2.06)	2.3 (± 2.26)	
Change at Week 1 (n=104,99,94)	-0.6 (± 1.86)	-0.5 (± 1.53)	-0.3 (± 1.91)	
Change at Week 2 (n=102,97,89)	-1.1 (± 1.95)	-0.7 (± 1.90)	-0.5 (± 2.18)	
Change at Week 3 (n=101,91,87)	-1.2 (± 1.85)	-0.8 (± 1.96)	-1.0 (± 2.09)	
Change at Week 4 (n=95,88,87)	-1.5 (± 1.83)	-0.9 (± 2.31)	-0.9 (± 2.21)	
Change at Week 5 (n=92,86,81)	-1.3 (± 2.03)	-1.0 (± 2.12)	-1.2 (± 2.19)	
Change at Week 6 (n=90,84,75)	-1.5 (± 1.91)	-1.0 (± 2.25)	-1.2 (± 2.31)	
Change at Week 7 (n=88,79,73)	-1.6 (± 2.13)	-1.1 (± 2.41)	-1.2 (± 2.39)	
Change at Week 8 (n=88,81,74)	-1.5 (± 2.11)	-1.1 (± 2.20)	-1.3 (± 1.99)	

Change at Week 9 (n=86,77,69)	-1.4 (± 2.17)	-1.2 (± 2.35)	-1.1 (± 2.13)	
Change at Week 10 (n=81,80,70)	-1.4 (± 2.07)	-1.2 (± 2.44)	-1.1 (± 2.34)	
Change at Week 11 (n=83,80,67)	-1.4 (± 2.00)	-1.2 (± 2.23)	-1.3 (± 2.12)	
Change at Week 12 (n=82,77,65)	-1.4 (± 2.07)	-1.3 (± 2.31)	-1.2 (± 2.15)	
Change at Week 13 (n=84,76,65)	-1.5 (± 2.13)	-1.2 (± 2.17)	-1.2 (± 2.33)	
Change at Week 14 (n=79,76,62)	-1.4 (± 2.33)	-1.2 (± 2.53)	-1.2 (± 2.19)	
Change at Week 15 (n=76,74,62)	-1.7 (± 2.09)	-1.3 (± 2.43)	-1.0 (± 3.35)	
Change at Week 16 (n=76,74,61)	-1.6 (± 2.16)	-1.2 (± 2.44)	-1.1 (± 2.54)	
Change at Week 20 (n=78,72,60)	-1.5 (± 2.28)	-1.2 (± 2.31)	-1.3 (± 2.21)	
Change at Week 28 (n=72,69,56)	-1.5 (± 2.54)	-1.2 (± 2.46)	-1.2 (± 2.38)	
Change at Week 36 (n=72,67,53)	-1.4 (± 2.42)	-1.2 (± 2.51)	-1.3 (± 2.03)	
Change at Week 44 (n=70,66,53)	-1.8 (± 2.21)	-1.2 (± 2.34)	-1.0 (± 1.90)	
Change at Week 52 (n=67,67,53)	-1.6 (± 2.20)	-1.1 (± 2.39)	-1.5 (± 2.06)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Hospital Anxiety and Depression Scale (HADS) Scores - Depression Total Score at Specified Time-Points

End point title	Change From Baseline in Hospital Anxiety and Depression Scale (HADS) Scores - Depression Total Score at Specified Time-Points

End point description:

Hospital Anxiety and Depression Scale Depression subscale (HADS-D) consists of 7 items that were assessed on a scale of 0 = no depression to 3 = severe feeling of depression. Total HADS-D subscale score range from 0 = no depression to 21 = severe feeling of depression; higher scores indicated a greater intensity of depression. The safety analysis set included all subjects who took at least one dose of randomized study medication, including partial doses. Here, 'n' signifies subjects evaluable for this end point at specified time point.

End point type	Other pre-specified

End point timeframe:

Baseline, Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 20, 28, 36, 44, and 52

End point values	Varenicline High Dose	Varenicline Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	100	99	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=108,100,99)	1.5 (± 1.93)	1.4 (± 1.79)	1.4 (± 1.83)	
Change at Week 1 (n=104,99,94)	-0.4 (± 1.43)	-0.2 (± 1.18)	0.1 (± 1.61)	
Change at Week 2 (n=102,97,89)	-0.5 (± 1.57)	-0.2 (± 1.65)	-0.1 (± 1.80)	
Change at Week 3 (n=101,91,87)	-0.5 (± 1.39)	-0.3 (± 1.55)	-0.3 (± 1.79)	
Change at Week 4 (n=95,88,87)	-0.7 (± 1.39)	-0.3 (± 1.79)	-0.4 (± 2.00)	
Change at Week 5 (n=92,86,81)	-0.6 (± 1.66)	-0.3 (± 1.97)	-0.3 (± 1.88)	
Change at Week 6 (90,84,75)	-0.6 (± 1.85)	-0.4 (± 1.60)	-0.5 (± 1.83)	
Change at Week 7 (n=88,79,73)	-0.7 (± 1.52)	-0.5 (± 1.91)	-0.4 (± 2.13)	
Change at Week 8 (n=88,81,74)	-0.8 (± 1.87)	-0.5 (± 1.80)	-0.5 (± 1.80)	

Change at Week 9 (n=86,77,69)	-0.8 (± 1.63)	-0.5 (± 1.85)	-0.5 (± 2.30)	
Change at Week 10 (n=81,80,70)	-0.9 (± 1.67)	-0.7 (± 1.63)	-0.4 (± 2.77)	
Change at Week 11 (n=83,80,67)	-0.7 (± 1.53)	-0.9 (± 1.66)	-0.5 (± 2.11)	
Change at Week 12 (n=82,77,65)	-0.7 (± 1.79)	-0.7 (± 1.72)	-0.6 (± 2.11)	
Change at Week 13 (n=84,76,65)	-0.6 (± 2.16)	-0.7 (± 1.79)	-0.7 (± 1.95)	
Change at Week 14 (n=79,76,62)	-0.8 (± 1.96)	-0.6 (± 1.84)	-0.5 (± 2.22)	
Change at Week 15 (n=76,74,62)	-0.8 (± 1.83)	-0.8 (± 1.84)	-0.3 (± 3.26)	
Change at Week 16 (n=76,74,61)	-0.6 (± 2.09)	-0.6 (± 2.08)	-0.2 (± 2.79)	
Change at Week 20 (n=78,72,60)	-0.8 (± 1.71)	-0.8 (± 1.84)	-0.6 (± 2.24)	
Change at Week 28 (n=72,69,56)	-0.9 (± 1.63)	-0.8 (± 1.90)	-0.5 (± 2.40)	
Change at Week 36 (n=72,67,53)	-0.7 (± 2.19)	-0.8 (± 1.77)	-0.4 (± 2.40)	
Change at Week 44 (n=70,66,53)	-0.9 (± 1.93)	-0.9 (± 1.78)	-0.3 (± 2.44)	
Change at Week 52 (n=67,67,53)	-0.7 (± 1.81)	-0.8 (± 1.67)	-0.6 (± 2.02)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects with Laboratory Abnormalities

End point title	Number of Subjects with Laboratory Abnormalities

End point description:

Criteria for laboratory abnormalities: Lymphocytes Absolute (Abs), Lymphocytes percentage (%), Total Neutrophils (Abs), Neutrophils %: <0.8*LLN or >1.2*ULN; Basophils (Abs), Basophils %Eosinophils (Abs), Eosinophils %, Monocytes (Abs), Monocytes %:> 1.2*ULN; Total Bilirubin milligram per deciliter (mg/dl) >1.5*ULN; alanine aminotransferase: >3.0*ULN; Blood urea nitrogen, Creatinine: >1.3*ULN; Uric acid :> 1.2*ULN. The safety analysis set included all subjects who took at least one dose of randomized study medication, including partial doses. Here, 'Number of Subjects Analyzed'= subjects evaluable for this end point.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 12

End point values	Varenicline High Dose	Varenicline Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103	93	90	
Units: subjects	35	33	26	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Blood Pressure (BP) at Week 12

End point title	Change From Baseline in Blood Pressure (BP) at Week 12

End point description:

Measurement of BP included supine and sitting systolic BP, standing systolic BP, supine and sitting

diastolic BP and standing diastolic BP. Blood pressure was taken after subjects rested in a sitting position for 5 minutes. BP was recorded after subjects had been supine for approximately 5 minutes, and then orthostatic blood pressure was recorded immediately when the subject stood. The safety analysis set included all subjects who took at least one dose of randomized study medication, including partial doses. Here, 'Number of Subjects Analyzed= subjects evaluable for this end point.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12

End point values	Varenicline High Dose	Varenicline Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	77	59	
Units: millimeters of mercury (mmHg)				
median (full range (min-max))				
Supine Systolic BP:Baseline	115.0 (85 to 164)	114.0 (92 to 136)	109.0 (95 to 142)	
Supine Systolic BP:Change at Week 12	0.0 (-33 to 25)	0.0 (-32 to 31)	0.0 (-35 to 43)	
Sitting Systolic BP:Baseline	117.0 (90 to 148)	115.0 (95 to 139)	113.0 (95 to 135)	
Sitting Systolic BP:Change at Week 12	-1.0 (-24 to 31)	0.0 (-30 to 28)	2.0 (-28 to 28)	
Standing Systolic BP:Baseline	116.0 (88 to 157)	115.0 (92 to 155)	112.0 (90 to 136)	
Standing Systolic BP:Change at Week 12	0.0 (-30 to 40)	0.0 (-21 to 53)	3.0 (-18 to 47)	
Supine Diastolic BP:Baseline	69.0 (45 to 99)	66.0 (45 to 84)	65.0 (50 to 90)	
Supine Diastolic BP:Change at Week 12	0.0 (-26 to 17)	0.0 (-20 to 22)	0.0 (-35 to 21)	
Sitting Diastolic BP:Baseline	72.0 (50 to 94)	70.0 (38 to 92)	69.0 (47 to 87)	
Sitting Diastolic BP:Change at Week 12	0.0 (-20 to 28)	-1.0 (-35 to 23)	1.0 (-18 to 22)	
Standing Diastolic BP:Baseline	73.0 (57 to 106)	72.0 (55 to 99)	70.0 (50 to 92)	
Standing Diastolic BP:Change at Week 12	0.0 (-28 to 22)	-1.0 (-43 to 23)	2.0 (-21 to 20)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Pulse Rate at Week 12

End point title	Change From Baseline in Pulse Rate at Week 12

End point description:

Measurement of pulse rate included supine, sitting and standing pulse rate. Pulse rate was taken after subjects rested in a sitting position for 5 minutes. Pulse rate was recorded after subjects had been supine for approximately 5 minutes and then immediately upon standing. The safety analysis set included all subjects who took at least one dose of randomized study medication, including partial doses. Here, 'Number of Subjects Analyzed= subjects evaluable for this end point.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12

End point values	Varenicline High Dose	Varenicline Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	77	59	
Units: beats per minute (bpm)				
median (full range (min-max))				
Supine Pulse Rate:Baseline	75.0 (50 to 111)	72.0 (50 to 105)	72.0 (54 to 113)	
Supine Pulse Rate:Change at Week 12	0.0 (-32 to 44)	1.0 (-23 to 23)	3.0 (-30 to 29)	
Sitting Pulse Rate:Baseline	75.0 (58 to 118)	75.0 (48 to 113)	77.0 (58 to 115)	
Sitting Pulse Rate:Change at Week 12	-1.0 (-22 to 25)	0.0 (-33 to 30)	1.0 (-43 to 36)	
Standing Pulse Rate:Baseline	84.0 (61 to 139)	85.0 (61 to 119)	85.0 (63 to 122)	
Standing Pulse Rate:Change at Week 12	1.0 (-35 to 44)	-3.0 (-25 to 32)	-3.0 (-53 to 44)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose up to last dose (up-to Week 12) plus 30 days

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Varenicline High Dose

Reporting group description:

Subjects received 2 tablets of Varenicline 0.5 milligram (mg) (total dose 1 mg) orally, twice daily from Week 2 to Week 12 after a 2-week titration. Subjects with a body weight less than or equal to (<=) 55 kilograms (kg) had Varenicline dose reduced by half, and received one tablet of Varenicline 0.5 mg and one matching placebo tablet orally, twice daily from Week 2 to Week 12 after a 2-week titration.

Reporting group title	Varenicline Low Dose

Reporting group description:

Subjects received one tablet of Varenicline 0.5 mg and one matching placebo tablet orally, twice daily from Week 2 to Week 12 after a 2-week titration. Subjects with a body weight <= 55 kg had Varenicline dose reduced by half and received one tablet of Varenicline 0.5 mg and one matching placebo tablet orally, in the morning and 2 tablets of matching placebo orally, in the evening from Week 2 to Week 12 after a 2-week titration.

Reporting group title	Placebo

Reporting group description:

Subjects received 2 tablets of placebo (matched to Varenicline) orally, twice daily from Week 2 to Week 12 after a 2-week titration.

Serious adverse events	Varenicline High Dose	Varenicline Low Dose	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 108 (2.78%)	1 / 100 (1.00%)	1 / 99 (1.01%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			

subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Adjustment disorder with mixed disturbance of emotion and conduct			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingitis			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Varenicline High Dose	Varenicline Low Dose	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 108 (60.19%)	53 / 100 (53.00%)	51 / 99 (51.52%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Pregnancy, puerperium and perinatal conditions			
Pregnancy			

subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 108 (0.00%)	2 / 100 (2.00%)	0 / 99 (0.00%)
occurrences (all)	0	2	0
Chest pain			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Chills			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Drug withdrawal syndrome			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Energy increased			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Feeling jittery			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	2	0
Malaise			
subjects affected / exposed	1 / 108 (0.93%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	1	1	0
Pain			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	0 / 108 (0.00%)	2 / 100 (2.00%)	1 / 99 (1.01%)
occurrences (all)	0	2	1
Immune system disorders			

Multiple allergies			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	2 / 99 (2.02%)
occurrences (all)	0	0	2
Cough			
subjects affected / exposed	2 / 108 (1.85%)	2 / 100 (2.00%)	0 / 99 (0.00%)
occurrences (all)	2	2	0
Bronchial hyperreactivity			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Haemoptysis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	1 / 108 (0.93%)	1 / 100 (1.00%)	1 / 99 (1.01%)
occurrences (all)	1	1	1
Oropharyngeal pain			
subjects affected / exposed	1 / 108 (0.93%)	3 / 100 (3.00%)	0 / 99 (0.00%)
occurrences (all)	1	3	0
Pharyngeal oedema			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Respiratory disorder			
subjects affected / exposed	1 / 108 (0.93%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	1	1	0
Sinus congestion			

subjects affected / exposed	1 / 108 (0.93%)	1 / 100 (1.00%)	1 / 99 (1.01%)
occurrences (all)	1	1	3
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	8 / 108 (7.41%)	5 / 100 (5.00%)	4 / 99 (4.04%)
occurrences (all)	8	5	4
Adjustment disorder			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	6 / 108 (5.56%)	4 / 100 (4.00%)	7 / 99 (7.07%)
occurrences (all)	6	4	10
Agitation			
subjects affected / exposed	9 / 108 (8.33%)	5 / 100 (5.00%)	5 / 99 (5.05%)
occurrences (all)	11	5	5
Attention deficit/hyperactivity disorder			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Aversion			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Depressed mood			
subjects affected / exposed	0 / 108 (0.00%)	2 / 100 (2.00%)	0 / 99 (0.00%)
occurrences (all)	0	2	0
Depression			
subjects affected / exposed	3 / 108 (2.78%)	2 / 100 (2.00%)	3 / 99 (3.03%)
occurrences (all)	3	3	3
Dissociation			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Flat affect			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Grief reaction			

subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Hallucination			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	2 / 99 (2.02%)
occurrences (all)	1	0	2
Hostility			
subjects affected / exposed	7 / 108 (6.48%)	3 / 100 (3.00%)	4 / 99 (4.04%)
occurrences (all)	7	3	5
Insomnia			
subjects affected / exposed	2 / 108 (1.85%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	2	0	0
Irritability			
subjects affected / exposed	2 / 108 (1.85%)	3 / 100 (3.00%)	1 / 99 (1.01%)
occurrences (all)	2	3	1
Mania			
subjects affected / exposed	1 / 108 (0.93%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	1	1	0
Middle insomnia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Nightmare			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Restlessness			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Initial insomnia			
subjects affected / exposed	2 / 108 (1.85%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	2	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Blood pressure increased			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Blood pressure orthostatic decreased			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Body mass index increased			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	2 / 99 (2.02%)
occurrences (all)	0	0	2
White blood cell count decreased			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	2 / 108 (1.85%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	2	1	0
Fall			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Foot fracture			
subjects affected / exposed	1 / 108 (0.93%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	1	1	0
Joint injury			

subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Ligament injury			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Ligament rupture			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	2 / 108 (1.85%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	2	0	1
Procedural pain			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Road traffic accident			
subjects affected / exposed	0 / 108 (0.00%)	3 / 100 (3.00%)	1 / 99 (1.01%)
occurrences (all)	0	3	1
Skin abrasion			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Wrist fracture			
subjects affected / exposed	2 / 108 (1.85%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Disturbance in attention			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	6 / 108 (5.56%)	7 / 100 (7.00%)	3 / 99 (3.03%)
occurrences (all)	6	7	3
Dysgeusia			
subjects affected / exposed	1 / 108 (0.93%)	3 / 100 (3.00%)	2 / 99 (2.02%)
occurrences (all)	1	3	2

Headache			
subjects affected / exposed	14 / 108 (12.96%)	5 / 100 (5.00%)	8 / 99 (8.08%)
occurrences (all)	14	5	8
Hypoaesthesia			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Memory impairment			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Migraine			
subjects affected / exposed	2 / 108 (1.85%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	3	0	0
Sinus headache			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Sleep paralysis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	2 / 108 (1.85%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	2	0	1
Tension headache			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	2 / 99 (2.02%)
occurrences (all)	0	0	2
Tremor			
subjects affected / exposed	1 / 108 (0.93%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			

Hypoacusis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Deafness unilateral			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Otorrhoea			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	3 / 108 (2.78%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	3	0	1
Abdominal distension			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	1 / 108 (0.93%)	3 / 100 (3.00%)	1 / 99 (1.01%)
occurrences (all)	1	3	2
Abdominal pain upper			
subjects affected / exposed	2 / 108 (1.85%)	1 / 100 (1.00%)	2 / 99 (2.02%)
occurrences (all)	3	1	2
Diarrhoea			
subjects affected / exposed	2 / 108 (1.85%)	1 / 100 (1.00%)	3 / 99 (3.03%)
occurrences (all)	2	1	3
Gastric disorder			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Gastroduodenitis			
subjects affected / exposed	1 / 108 (0.93%)	1 / 100 (1.00%)	1 / 99 (1.01%)
occurrences (all)	1	1	1
Haematemesis			

subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia oral			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	26 / 108 (24.07%)	19 / 100 (19.00%)	12 / 99 (12.12%)
occurrences (all)	31	22	14
Odynophagia			
subjects affected / exposed	0 / 108 (0.00%)	2 / 100 (2.00%)	0 / 99 (0.00%)
occurrences (all)	0	2	0
Toothache			
subjects affected / exposed	0 / 108 (0.00%)	2 / 100 (2.00%)	1 / 99 (1.01%)
occurrences (all)	0	3	1
Vomiting			
subjects affected / exposed	14 / 108 (12.96%)	2 / 100 (2.00%)	2 / 99 (2.02%)
occurrences (all)	18	2	2
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 108 (0.93%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	1	1	0
Dermatitis allergic			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Dermatitis contact			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	2 / 99 (2.02%)
occurrences (all)	0	0	2

Rash maculo-papular			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Urinary hesitation			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 108 (0.93%)	2 / 100 (2.00%)	1 / 99 (1.01%)
occurrences (all)	1	2	1
Back pain			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Costochondritis			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	2 / 108 (1.85%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	2	0	0
Myalgia			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Neck pain			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0

Conjunctivitis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Folliculitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Furuncle			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	2 / 108 (1.85%)	0 / 100 (0.00%)	2 / 99 (2.02%)
occurrences (all)	2	0	3
Gastroenteritis viral			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal viral infection			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Gonorrhoea			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 108 (0.00%)	2 / 100 (2.00%)	0 / 99 (0.00%)
occurrences (all)	0	2	0
Laryngitis			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	4 / 108 (3.70%)	3 / 100 (3.00%)	5 / 99 (5.05%)
occurrences (all)	6	3	5
Pharyngitis			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Pharyngitis streptococcal			
subjects affected / exposed	1 / 108 (0.93%)	3 / 100 (3.00%)	0 / 99 (0.00%)
occurrences (all)	1	3	0

Respiratory tract infection			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	2 / 99 (2.02%)
occurrences (all)	0	0	2
Respiratory tract infection viral			
subjects affected / exposed	3 / 108 (2.78%)	0 / 100 (0.00%)	3 / 99 (3.03%)
occurrences (all)	4	0	4
Rhinitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Sinusitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	0	2	0
Tonsillitis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Tooth abscess			
subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	6 / 108 (5.56%)	5 / 100 (5.00%)	2 / 99 (2.02%)
occurrences (all)	6	5	2
Urinary tract infection			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	0 / 108 (0.00%)	1 / 100 (1.00%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Viral pharyngitis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 108 (0.93%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 108 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	0	0	1
Dehydration			
subjects affected / exposed	1 / 108 (0.93%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
Increased appetite			
subjects affected / exposed	2 / 108 (1.85%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences (all)	2	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2011	Inconsistency between AE reporting period criteria was modified to make timeframe be "informed consent through last visit". 24 week endpoints was added to make consistent with other protocols in program. Dosing instructions were clarified. Section 8.2 was changed to correct inconsistency between start of AE collection and AE reporting periods.
09 August 2011	Modified exclusion criteria to indicate that use of psychoactive or psychotropic drugs in the 6 months prior to screening had to be discussed with the sponsor, rather than be prohibited (in order to allow consideration of ADHD subjects on Ritalin or Adderall).
23 November 2011	Modified exclusion criteria to indicate that use of psychoactive or psychotropic drugs in the 6 months prior to screening had to be discussed with the sponsor, rather than be prohibited (in order to allow consideration of ADHD subjects on Ritalin or Adderall). Removed specification for use of the COT-One cotinine testing kit.
20 January 2012	Protocol Summary "Safety Assessments" section wording had been slightly modified to improve quality.
09 July 2012	In Section 8.3 drug dependency and drug abuse was added as examples of reportable Adverse events (AEs) and removed from signs and symptoms resulting from these. Medication errors were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported