Clinical trial results:
A PHASE 4, RANDOMIZED, DOUBLE BLIND, ACTIVE AND PLACEBO CONTROLLED, MULTICENTER STUDY EVALUATING THE NEUROPSYCHIATRIC SAFETY AND EFFICACY OF 12 WEEKS VARENICLINE TARTRATE 1 MG BID AND BUPROPION HYDROCHLORIDE 150 MG BID FOR SMOKING CESSATION IN SUBJECTS WITH AND WITHOUT A HISTORY OF PSYCHIATRIC DISORDERS

Summary

EudraCT number	2010-022914-15
Trial protocol	ES DE DK FI BG SK
Global end of trial date	13 January 2015

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	A3051123

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01456936
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 East 42nd Street, New York, NY, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc.,, +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc.,, +1 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 January 2015
Global end of trial reached?	Yes
Global end of trial date	13 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Safety Objectives:
1. To characterize the neuropsychiatric safety profiles of varenicline and bupropion by estimating the differences from placebo in the incidence of the primary neuropsychiatric
AE endpoint for subjects:
a. With a diagnosis of psychiatric disorder;
b. Without a diagnosis of psychiatric disorder.
2. To characterize the differences in the neuropsychiatric safety profiles of varenicline and bupropion as compared with placebo between these sub-populations (cohorts).

Efficacy: Abstinence from Smoking
Main Efficacy Objective: To compare smoking abstinence rates of varenicline and bupropion relative to placebo for the last 4 weeks of treatment and continuously through Week 24, as measured by CO-confirmed continuous abstinence rate (CAR) CAR9-12 and CAR9-24, respectively, separately for subjects with and without a diagnosis of psychiatric disorder.

Protection of trial subjects:

All parties will ensure protection of subject personal data and will not include partcipant names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.
The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety, Regulatory reason
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 329
Country: Number of subjects enrolled	Australia: 55
Country: Number of subjects enrolled	Brazil: 21
Country: Number of subjects enrolled	Bulgaria: 490
Country: Number of subjects enrolled	Canada: 277
Country: Number of subjects enrolled	Chile: 17
Country: Number of subjects enrolled	Denmark: 113

Country: Number of subjects enrolled	Finland: 501
Country: Number of subjects enrolled	Germany: 876
Country: Number of subjects enrolled	Mexico: 187
Country: Number of subjects enrolled	New Zealand: 125
Country: Number of subjects enrolled	Russian Federation: 126
Country: Number of subjects enrolled	Slovakia: 202
Country: Number of subjects enrolled	South Africa: 295
Country: Number of subjects enrolled	Spain: 237
Country: Number of subjects enrolled	United States: 4207
Worldwide total number of subjects	8058
EEA total number of subjects	2419

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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	7529
From 65 to 84 years	529
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 11,186 participants were screened for participation in the study, of which 3042 participants were considered to be screen failures, leaving 8144 participants eligible for study participation (efficacy population). 86 participants (1.1%) did not receive study drug. A total of 8058 participants received study drug (safety population).

Pre-assignment

Screening details:

Participants were classified into 2 cohorts: participants without diagnosis of psychiatric disorder and participants with a stable diagnosis of psychiatric disorder confirmed by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID) 4th edition conducted at screening.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Varenicline

Arm description:

Participants were randomized to 1 of the 3 active dosing groups that took active medication of either varenicline, bupropion, Nicotine Replacement Therapy (NRT) in this triple-dummy design. Participants in this arm received varenicline titrated to the full dose during the first week in the following manner: 0.5 mg daily once (QD) x 3 days, 0.5 mg twice daily (BID) x 4 days, then 1 mg BID for 11 weeks. They also received placebo bupropion and NRT patch, dosed in the same manner as the active medication.

Arm type	Experimental
Investigational medicinal product name	Varenicline tartrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The titration had two steps: 0.5 mg once daily for 3 days, 0.5 mg twice daily for 4 days and 1 mg twice daily for 11 weeks.

Arm title	Bupropion

Arm description:

Participants were randomized to 1 of the 3 active dosing groups that took active medication of either varenicline, bupropion, NRT in this triple-dummy design. Participants in this arm received bupropion 150 mg QD x 3 days and taken 150 mg BID for the remainder of the treatment period (11 weeks and 4 days). They also received placebo varenicline and NRT patch, dosed in the same manner as the active medication.

Arm type	Experimental
Investigational medicinal product name	Buproprion hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg daily once for 3 days and 150 mg twice daily for remainder of treatment period.

Arm title	NRT patch

Arm description:

Participants were randomized to 1 of the 3 active dosing groups that took active medication of either varenicline, bupropion, NRT in this triple-dummy design. Participants in this arm received NRT started active dosing the morning of the Week 1 visit and received a 21 mg transdermal patch per day x 7 weeks, followed by a 14 mg transdermal patch per day x 2 weeks, and then a 7 mg transdermal patch x 2 weeks for a total of 11 weeks of treatment. They also received placebo varenicline and bupropion, dosed in the same manner as active medication.

Arm type	Active comparator
Investigational medicinal product name	Nicotine replacement therapy patch
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

1 mg daily once for 3 days, 1 mg daily twice for 4 days, 21 mg per day for 7 weeks, 14 mg per day for 2 weeks and 7 mg for 2 weeks for a toal of 11 weeks of treatment

Arm title	Placebo

Arm description:

Participants received matching placebo for varenicline, bupropion, and NRT in this triple-dummy design, and followed the same titration and dosing schedule as for the active treatments noted above.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Transdermal patch
Routes of administration	Oral use, Transdermal use

Dosage and administration details:

Matching placebo for varenicline, buproprion and NRT

Number of subjects in period 1	Varenicline	Bupropion	NRT patch
Started	2016	2006	2022
Completed	1598	1586	1557
Not completed	418	420	465
Adverse event, serious fatal	-	3	1
Adverse event (study drug unrelated)	9	7	9
No longer meets eligibility criteria	4	8	6
Pregnancy	1	-	-
Medication error	-	1	-
Other reason	41	30	36
No longer willing to participate	195	218	224
Adverse event (study drug)	25	21	26
Lost to follow-up	135	126	144
Insufficient clinical response	4	4	14
Protocol deviation	4	2	5

Number of subjects in period 1	Placebo
Started	2014
Completed	1552
Not completed	462
Adverse event, serious fatal	3
Adverse event (study drug unrelated)	9
No longer meets eligibility criteria	5
Pregnancy	1
Medication error	1
Other reason	33
No longer willing to participate	248
Adverse event (study drug)	17
Lost to follow-up	127
Insufficient clinical response	13
Protocol deviation	5

Baseline characteristics

Reporting groups	
Reporting group title	Varenicline
Reporting group description:	
Participants were randomized to 1 of the 3 active dosing groups that took active medication of either varenicline, bupropion, Nicotine Replacement Therapy (NRT) in this triple-dummy design. Participants in this arm received varenicline titrated to the full dose during the first week in the following manner: 0.5 mg daily once (QD) x 3 days, 0.5 mg twice daily (BID) x 4 days, then 1 mg BID for 11 weeks. They also received placebo bupropion and NRT patch, dosed in the same manner as the active medication.	
Reporting group title	Bupropion
Reporting group description:	
Participants were randomized to 1 of the 3 active dosing groups that took active medication of either varenicline, bupropion, NRT in this triple-dummy design. Participants in this arm received bupropion 150 mg QD x 3 days and taken 150 mg BID for the remainder of the treatment period (11 weeks and 4 days). They also received placebo varenicline and NRT patch, dosed in the same manner as the active medication.	
Reporting group title	NRT patch
Reporting group description:	
Participants were randomized to 1 of the 3 active dosing groups that took active medication of either varenicline, bupropion, NRT in this triple-dummy design. Participants in this arm received NRT started active dosing the morning of the Week 1 visit and received a 21 mg transdermal patch per day x 7 weeks, followed by a 14 mg transdermal patch per day x 2 weeks, and then a 7 mg transdermal patch x 2 weeks for a total of 11 weeks of treatment. They also received placebo varenicline and bupropion, dosed in the same manner as active medication.	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo for varenicline, bupropion, and NRT in this triple-dummy design, and followed the same titration and dosing schedule as for the active treatments noted above.	

Reporting group values	Varenicline	Bupropion	NRT patch
Number of subjects	2016	2006	2022
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1884	1859	1887
From 65-84 years	132	147	135
85 years and over	0	0	0
Age Continuous | Units: years			
arithmetic mean	46.5	46.35	46.85
standard deviation	± 12.4	± 12.6	± 12.15
Gender, Male/Female Units: Participants			
Female	1114	1116	1141
Male	902	890	881

Reporting group values	Placebo	Total	
Number of subjects	2014	8058	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1899	7529	
From 65-84 years	115	529	
85 years and over	0	0	
Age Continuous | Units: years			
arithmetic mean	46.4		
standard deviation	± 12.15	-	
Gender, Male/Female Units: Participants			
Female	1138	4509	
Male	876	3549	

End points

End points reporting groups

Reporting group title	Varenicline

Reporting group description:

Participants were randomized to 1 of the 3 active dosing groups that took active medication of either varenicline, bupropion, Nicotine Replacement Therapy (NRT) in this triple-dummy design. Participants in this arm received varenicline titrated to the full dose during the first week in the following manner: 0.5 mg daily once (QD) x 3 days, 0.5 mg twice daily (BID) x 4 days, then 1 mg BID for 11 weeks. They also received placebo bupropion and NRT patch, dosed in the same manner as the active medication.

Reporting group title	Bupropion

Reporting group description:

Participants were randomized to 1 of the 3 active dosing groups that took active medication of either varenicline, bupropion, NRT in this triple-dummy design. Participants in this arm received bupropion 150 mg QD x 3 days and taken 150 mg BID for the remainder of the treatment period (11 weeks and 4 days). They also received placebo varenicline and NRT patch, dosed in the same manner as the active medication.

Reporting group title	NRT patch

Reporting group description:

Participants were randomized to 1 of the 3 active dosing groups that took active medication of either varenicline, bupropion, NRT in this triple-dummy design. Participants in this arm received NRT started active dosing the morning of the Week 1 visit and received a 21 mg transdermal patch per day x 7 weeks, followed by a 14 mg transdermal patch per day x 2 weeks, and then a 7 mg transdermal patch x 2 weeks for a total of 11 weeks of treatment. They also received placebo varenicline and bupropion, dosed in the same manner as active medication.

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo for varenicline, bupropion, and NRT in this triple-dummy design, and followed the same titration and dosing schedule as for the active treatments noted above.

Primary: Occurrence of neuropsychiatric (NPS) adverse events (AE) - the primary study endpoint

End point title	Occurrence of neuropsychiatric (NPS) adverse events (AE) - the primary study endpoint

End point description:

The primary safety endpoint is the occurrence of at least one treatment emergent “severe” adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent “moderate” or “severe” adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.

End point type	Primary

End point timeframe:

Treatment emergent is first dose date to last dose date (upto 12 weeks) plus 30 days

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2016	2006	2022	2014
Units: percentage of participants				
number (not applicable)				
Non-psychiatric cohort (N= 990, 989, 1006, 999)	1.3	2.2	2.5	2.4
Psychiatric cohort (N= 1026, 1017, 1016, 1015)	6.5	6.7	5.2	4.9
Overall (N= 2016, 2006, 2022, 2014)	4	4.5	3.9	3.7

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The reduced (final) statistical model included treatment group, cohort and region, plus the 2-way interaction of treatment by cohort. Other interactions not included due to lack of significance. Region reduced to 2-level to address event sparseness issue.

Comparison groups	Bupropion v Varenicline v NRT patch v Placebo
Number of subjects included in analysis	8058
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0652 [1]
Method	Regression, Linear

Notes:

[1] - For the reduced model at 10% level (typical for interaction assessment due to inherently poor power), there was a significant interaction between treatment and cohort. No multiplicity adjustments were utilized.

Primary: Estimated NPS AE rate (%), by cohort

End point title	Estimated NPS AE rate (%), by cohort

End point description:

The primary safety endpoint is the occurrence of at least one treatment emergent "severe" adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent "moderate" or "severe" adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.

End point type	Primary

End point timeframe:

Treatment emergent is first dose date to last dose date (upto 12 weeks) plus 30 days

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2016	2006	2022	2014
Units: Units on scale				
least squares mean (confidence interval 100%)				

Non-psychiatric cohort (N=3984)	1.25 (0.6 to 1.9)	2.44 (1.52 to 3.36)	2.31 (1.37 to 3.25)	2.52 (1.58 to 3.46)
Psychiatric cohort (N= 4074)	6.42 (4.91 to 7.93)	6.62 (5.09 to 8.15)	5.2 (3.84 to 6.56)	4.83 (3.51 to 6.16)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Non-psychiatric cohort	
Comparison groups	Varenicline v Placebo
Number of subjects included in analysis	4030
Analysis specification	Pre-specified
Analysis type	
Method	Regression, Linear
Parameter estimate	Risk difference (RD)
Point estimate	-1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	-0.15

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Non-psychiatric	
Comparison groups	Bupropion v Placebo
Number of subjects included in analysis	4020
Analysis specification	Pre-specified
Analysis type	
Method	Regression, Linear
Parameter estimate	Risk difference (RD)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.37
upper limit	1.21

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Non-psychiatric cohort	
Comparison groups	NRT patch v Placebo

Number of subjects included in analysis	4036
Analysis specification	Pre-specified
Analysis type	
Method	Regression, Linear
Parameter estimate	Risk difference (RD)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.54
upper limit	1.12

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Psychiatric cohort	
Comparison groups	Varenicline v Placebo
Number of subjects included in analysis	4030
Analysis specification	Pre-specified
Analysis type	
Method	Regression, Linear
Parameter estimate	Risk difference (RD)
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	3.59

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Psychiatric cohort	
Comparison groups	Bupropion v Placebo
Number of subjects included in analysis	4020
Analysis specification	Pre-specified
Analysis type	
Method	Regression, Linear
Parameter estimate	Risk difference (RD)
Point estimate	1.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	3.81

Statistical analysis title	Statistical Analysis 6
Statistical analysis description: Psychiatric cohort	
Comparison groups	NRT patch v Placebo
Number of subjects included in analysis	4036
Analysis specification	Pre-specified
Analysis type	
Method	Regression, Linear
Parameter estimate	Risk difference (RD)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.53
upper limit	2.26

Secondary: Occurrence of the components of the NPS AE primary endpoint, non-psychiatric history cohort

End point title	Occurrence of the components of the NPS AE primary endpoint, non-psychiatric history cohort

End point description:

The safety endpoint is the occurrence of at least one treatment emergent "severe" adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent "moderate" or "severe" adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide. Each of these 16 components is reported below. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.

End point type	Secondary

End point timeframe:

Treatment emergent is first dose date to last dose date (upto 12 weeks) plus 30 days

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	990	989	1006	999
Units: participants				
Anxiety (severe)	0	1	0	3
Depression (severe)	1	0	0	0
Feeling abnormal (severe only)	0	0	0	0
Hostility (severe)	0	1	1	0
Agitation (moderate and severe)	10	11	19	11
Aggression (moderate and severe)	3	3	2	3
Delusions (moderate and severe)	0	0	1	0
Hallucinations (moderate and severe)	1	0	0	0
Mania (moderate and severe)	0	1	2	2
Panic (moderate and severe)	0	4	1	3
Paranoia (moderate and severe)	0	1	0	0
Psychosis (moderate and severe)	0	0	1	0

Homicidal ideation (moderate and severe)	0	0	1	0
Suicidal behavior (moderate and severe)	0	1	1	0
Suicidal ideation (moderate and severe)	0	1	2	3
Suicide (moderate and severe)	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of the components of the NPS AE primary endpoint, psychiatric history cohort

End point title	Occurrence of the components of the NPS AE primary endpoint, psychiatric history cohort

End point description:

The safety endpoint is the occurrence of at least one treatment emergent "severe" adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent "moderate" or "severe" adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide. Each of these 16 components is reported below. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.

End point type	Secondary

End point timeframe:

Treatment emergent is first dose date to last dose date (upto 12 weeks) plus 30 days

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1026	1017	1016	1015
Units: participants				
Anxiety (severe)	5	4	6	2
Depression (severe)	6	4	7	6
Feeling abnormal (severe only)	0	1	0	0
Hostility (severe)	0	0	0	0
Agitation (moderate and severe)	25	29	21	22
Aggression (moderate and severe)	14	9	7	8
Delusions (moderate and severe)	1	1	1	0
Hallucinations (moderate and severe)	5	4	2	2
Mania (moderate and severe)	7	9	3	6
Panic (moderate and severe)	7	16	13	7
Paranoia (moderate and severe)	1	0	0	2
Psychosis (moderate and severe)	4	2	3	1
Homicidal ideation (moderate and severe)	0	0	0	0
Suicidal behavior (moderate and severe)	1	1	0	1
Suicidal ideation (moderate and severe)	5	2	3	2
Suicide (moderate and severe)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of the components of NPS AE Primary Endpoint (Overall)

End point title	Occurrence of the components of NPS AE Primary Endpoint (Overall)

End point description:

The NPS AE composite results (as previously described) are for the two cohorts combined and are presented below. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.

End point type	Secondary

End point timeframe:

Treatment emergent is first dose date to last dose date (upto 12 weeks) plus 30 days

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2016	2006	2022	2014
Units: participants				
Anxiety	5	5	6	5
Depression	7	4	7	6
Feeling Abnormal	0	1	1	0
Hostility	0	1	1	0
Agitation	35	40	40	33
Aggression	17	12	9	11
Delusions	1	1	2	0
Hallucination	6	4	2	2
Mania	7	10	5	8
Panic Disorder	7	20	14	10
Paranoia	1	1	0	2
Psychosis	4	2	4	1
Homicidal Ideation	0	0	1	0
Suicidal Behavior	1	2	1	1
Suicidal Ideation	5	3	5	5
Suicide	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of severe-only NPS AEs in the primary endpoint, by cohort

End point title	Occurrence of severe-only NPS AEs in the primary endpoint, by cohort

End point description:

The primary safety endpoint is the occurrence of at least one treatment emergent "severe" adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent "moderate" or "severe" adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.

End point type	Secondary

End point timeframe:

Treatment emergent is first dose date to last dose date (upto 12 weeks) plus 30 days

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2016	2006	2022	2014
Units: percentage of participants				
number (not applicable)				
Non-psychiatric cohort (N= 990, 989, 1006, 999)	0.1	0.4	0.3	0.5
Psychiatric cohort (N= 1026, 1017, 1016, 1015)	1.4	1.4	1.4	1.3
Overall (N= 2016, 2006, 2022, 2014)	0.7	0.9	0.8	0.9

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of the components of the observed severe-only NPS AE primary endpoint, non-psychiatric history cohort

End point title	Occurrence of the components of the observed severe-only NPS AE primary endpoint, non-psychiatric history cohort

End point description:

The safety endpoint is the occurrence of at least one treatment emergent "severe" adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent "moderate" or "severe" adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide. Only those events rated as severe are reported; this excludes any moderate events in the primary NPS AE endpoint. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.

End point type	Secondary

End point timeframe:

Treatment emergent is first dose date to last dose date (upto 12 weeks) plus 30 days

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	990	989	1006	999
Units: participants				
Anxiety	0	1	0	3
Depression	1	0	0	0
Feeling abnormal	0	0	0	0
Hostility	0	1	1	0
Agitation	0	0	2	0
Aggression	1	1	0	0
Delusions	0	0	0	0
Hallucinations	0	0	0	0
Mania	0	0	0	0
Panic	0	1	1	1
Paranoia	0	0	0	0
Psychosis	0	0	0	0
Homicidal ideation	0	0	0	0
Suicidal behavior	0	1	0	0
Suicidal ideation	0	0	0	1
Suicide	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of the components of the observed severe-only NPS AE primary endpoint, psychiatric history cohort

End point title	Occurrence of the components of the observed severe-only NPS AE primary endpoint, psychiatric history cohort

End point description:

The safety endpoint is the occurrence of at least one treatment emergent “severe” adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent “moderate” or “severe” adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide. Only those events rated as severe are reported; this excludes any moderate events in the primary NPS AE endpoint. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.

End point type	Secondary

End point timeframe:

Treatment emergent is first dose date to last dose date (upto 12 weeks) plus 30 days

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1026	1017	1016	1015
Units: Participants				
Anxiety	5	4	6	2
Depression	6	4	7	6
Feeling abnormal	0	1	0	0

Hostility	0	0	0	0
Agitation	1	1	4	2
Aggression	1	1	0	1
Delusions	0	0	0	0
Hallucinations	0	1	0	0
Mania	2	1	0	0
Panic	0	1	0	1
Paranoia	0	0	0	0
Psychosis	0	1	1	0
Homicidal ideation	0	0	0	0
Suicidal behavior	1	1	0	1
Suicidal ideation	1	0	1	0
Suicide	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of the components of severe-only NPS AE endpoint (overall)

End point title	Occurrence of the components of severe-only NPS AE endpoint (overall)

End point description:

The NPS AE endpoint was the occurrence of at least 1 treatment-emergent "severe" AE of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least 1 treatment-emergent "severe" AE of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.

End point type	Secondary

End point timeframe:

Treatment emergent is first dose date to last dose date (upto 12 weeks) plus 30 days

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2016	2006	2022	2014
Units: participants				
Anxiety	5	5	6	5
Depression	7	4	7	6
Feeling Abnormal	0	1	0	0
Hostility	0	1	1	0
Agitation	1	1	6	2
Aggression	2	2	0	1
Delusions	0	1	0	0
Hallucination	0	1	0	0
Mania	2	1	0	0
Panic Disorder	0	2	1	2
Paranoia	1	1	0	2
Psychosis	4	2	4	1

Suicidal Behavior	1	2	0	1
Suicidal Ideation	1	0	1	0
Suicide	0	0	0	1
Homicidal Ideation	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Hospital Anxiety and Depression Scale (HADS) Total Score, non-psychiatric history cohort

End point title	Hospital Anxiety and Depression Scale (HADS) Total Score, non-psychiatric history cohort

End point description:

The HADS is a subject self-reporting scale completed in person at clinic visits at Baseline and Weeks 1 through 6, 8, 10, 12, 13, 16, 20, and 24. It contains 14 individual item responses ranging in increasing severity from 0 (normal) to 3 (most severe) for a total range of 0 to 42. Of the 14 items, 7 assess anxiety and 7 assess depression, providing 2 subscales with ranges of 0 to 21. For each subscale, 0 to 7 is considered normal, while 15 to 21 represents severe symptoms.The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	990	989	1006	999
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 1 (N= 984, 972, 989, 992)	3.26 (± 3.92)	3.58 (± 4.25)	3.06 (± 3.87)	3.38 (± 4.2)
Week 2 (N= 961, 954, 963, 970)	2.91 (± 3.86)	3.07 (± 3.96)	2.84 (± 3.85)	3.2 (± 4.25)
Week 3 (N= 935, 930, 936, 941)	2.61 (± 3.85)	2.64 (± 3.82)	2.63 (± 3.93)	2.77 (± 3.94)
Week 4 (N= 923, 916, 934, 923)	2.4 (± 3.66)	2.36 (± 3.57)	2.46 (± 3.8)	2.77 (± 4.21)
Week 5 (N= 911, 897, 906, 902)	2.29 (± 3.51)	2.24 (± 3.52)	2.32 (± 3.86)	2.48 (± 3.92)
Week 6 (N= 899, 893, 909, 897)	2.23 (± 3.56)	2.18 (± 3.57)	2.4 (± 3.87)	2.48 (± 3.97)
Week 8 (N= 868, 861, 877, 877)	2.17 (± 3.6)	2.16 (± 3.7)	2.28 (± 3.6)	2.64 (± 4.29)
Week 10 (N= 853, 844, 852, 846)	2.29 (± 3.89)	1.96 (± 3.24)	2.33 (± 3.8)	2.57 (± 4.41)
Week 12 (N= 772, 768, 750, 742)	2.07 (± 3.48)	1.83 (± 3.21)	2.01 (± 3.51)	2.46 (± 4.1)
Week 13 (N= 797, 796, 789, 807)	2.11 (± 3.74)	1.85 (± 3.22)	2.01 (± 3.47)	2.38 (± 4.27)
Week 16 (N= 784, 797, 775, 789)	2.05 (± 3.47)	1.9 (± 3.43)	2.09 (± 3.61)	2.34 (± 3.98)
Week 20 (N= 771, 785, 762, 772)	2.1 (± 3.54)	1.93 (± 3.36)	1.97 (± 3.53)	2.31 (± 4.15)
Week 24 (N= 758, 748, 737, 758)	2.01 (± 3.49)	1.87 (± 3.47)	2.01 (± 3.45)	2.25 (± 4.04)

Statistical analyses

No statistical analyses for this end point

Secondary: HADS Total Score, psychiatric history cohort

End point title	HADS Total Score, psychiatric history cohort

End point description:

The HADS is a subject self-reporting scale completed in person at clinic visits at Baseline and Weeks 1 through 6, 8, 10, 12, 13, 16, 20, and 24. It contains 14 individual item responses ranging in increasing severity from 0 (normal) to 3 (most severe) for a total range of 0 to 42. Of the 14 items, 7 assess anxiety and 7 assess depression, providing 2 subscales with ranges of 0 to 21. For each subscale, 0 to 7 is considered normal, while 15 to 21 represents severe symptoms. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1026	1017	1016	1015
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 1 (N= 1026, 1017, 1015, 1015)	6.76 (± 6.14)	7.58 (± 6.87)	6.82 (± 6.33)	6.7 (± 5.94)
Week 2 (N= 1005, 1004, 996, 995)	6.42 (± 6.36)	6.99 (± 6.47)	6.64 (± 6.55)	6.42 (± 6.17)
Week 3 (N= 947, 961, 945, 926)	5.99 (± 6.21)	6.51 (± 6.39)	6.3 (± 6.55)	6.02 (± 6.1)
Week 4 (N= 935, 938, 929, 908)	5.87 (± 6.39)	6.36 (± 6.55)	6.16 (± 6.51)	6.04 (± 6.31)
Week 5 (N= 918, 918, 914, 895)	5.58 (± 6.32)	6.03 (± 6.41)	5.82 (± 6.44)	5.8 (± 6.31)
Week 6 (N= 917, 914, 912, 874)	5.39 (± 6.14)	5.87 (± 6.41)	5.62 (± 6.22)	5.75 (± 6.26)
Week 8 (N= 887, 893, 878, 859)	5.43 (± 6.24)	5.96 (± 6.68)	5.63 (± 6.36)	5.63 (± 6.26)
Week 10 (N= 864, 865, 864, 823)	5.38 (± 6.35)	5.72 (± 6.5)	5.64 (± 6.3)	5.55 (± 6.38)
Week 12 (N= 790, 803, 798, 749)	5.17 (± 6.09)	5.66 (± 6.63)	5.44 (± 6.3)	5.42 (± 6.13)
Week 13 (N= 813, 812, 814, 763)	5.06 (± 6.11)	5.44 (± 6.54)	5.36 (± 6.2)	5.09 (± 5.96)
Week 16 (N= 795, 805, 791, 748)	5.26 (± 6.35)	5.62 (± 6.68)	5.44 (± 6.34)	5.37 (± 6.38)
Week 20 (N= 784, 784, 763, 737)	5.17 (± 6.02)	5.54 (± 6.44)	5.46 (± 6.18)	5.26 (± 6.22)
Week 24 (N= 770, 764, 758, 729)	5.21 (± 6.27)	5.69 (± 6.64)	5.57 (± 6.32)	5.04 (± 5.97)

Statistical analyses

No statistical analyses for this end point

Secondary: HADS Total Score (overall)

End point title	HADS Total Score (overall)

End point description:

The HADS is a subject self-reporting scale completed in person at clinic visits at Baseline and Weeks 1 through 6, 8, 10, 12, 13, 16, 20, and 24. It contains 14 individual item responses ranging in increasing severity from 0 (normal) to 3 (most severe) for a total range of 0 to 42. Of the 14 items, 7 assess anxiety and 7 assess depression, providing 2 subscales with ranges of 0 to 21. For each subscale, 0 to 7 is considered normal, while 15 to 21 represents severe symptoms. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2016	2006	2022	2014
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 1 (N= 1989, 1976, 1985, 1987)	5.03 (± 5.45)	5.61 (± 6.07)	4.95 (± 5.58)	5.05 (± 5.41)
Week 2 (N= 1938, 1937, 1931, 1929)	4.68 (± 5.55)	5.06 (± 5.73)	4.74 (± 5.7)	4.8 (± 5.53)
Week 3 (N= 1882, 1891, 1881, 1867)	4.31 (± 5.44)	4.6 (± 5.63)	4.48 (± 5.71)	4.38 (± 5.37)
Week 4 (N= 1858, 1854, 1863, 1831)	4.15 (± 5.5)	4.39 (± 5.65)	4.31 (± 5.64)	4.39 (± 5.6)
Week 5 (N= 1829, 1815, 1820, 1797)	3.94 (± 5.37)	4.16 (± 5.52)	4.08 (± 5.59)	4.14 (± 5.51)
Week 6 (N= 1816, 1807, 1821, 1771)	3.82 (± 5.27)	4.05 (± 5.52)	4.01 (± 5.42)	4.09 (± 5.48)
Week 8 (N= 1755, 1754, 1755, 1736)	3.82 (± 5.36)	4.1 (± 5.75)	3.96 (± 5.43)	4.12 (± 5.56)
Week 10 (N= 1717, 1709, 1716, 1669)	3.85 (± 5.49)	3.86 (± 5.48)	4 (± 5.47)	4.04 (± 5.67)
Week 12 (N= 1562, 1571, 1548, 1491)	3.64 (± 5.21)	3.79 (± 5.58)	3.78 (± 5.42)	3.95 (± 5.42)
Week 13 (N= 1610, 1608, 1603, 1570)	3.6 (± 5.29)	3.66 (± 5.47)	3.71 (± 5.32)	3.7 (± 5.34)
Week 16 (N= 1579, 1602, 1566, 1537)	3.67 (± 5.37)	3.77 (± 5.63)	3.78 (± 5.44)	3.82 (± 5.5)
Week 20 (N= 1555, 1569, 1525, 1509)	3.65 (± 5.18)	3.73 (± 5.44)	3.72 (± 5.33)	3.75 (± 5.47)
Week 24 (N= 1528, 1512, 1495, 1487)	3.62 (± 5.33)	3.8 (± 5.64)	3.82 (± 5.41)	3.62 (± 5.27)

Statistical analyses

No statistical analyses for this end point

Secondary: Positive responses for suicidal behavior and/or ideation by Columbia Suicide Severity Rating Scale (CSSRS) - non-psychiatric history cohort

End point title	Positive responses for suicidal behavior and/or ideation by Columbia Suicide Severity Rating Scale (CSSRS) - non-psychiatric history cohort

End point description:

The C-SSRS is a semi-structured interview designed to evaluate an individual's degree of suicidal ideation, preparatory acts or behavior to actual attempt, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent". Answers at screening are for lifetime history. Answers for all other visits are since last visit. The scale is also used to record any completed suicides. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.

End point type	Secondary

End point timeframe:

Lifetime, Baseline and Treatment-Emergent is first dose date to last dose date (up to 12 weeks) plus 30 days.

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	990	989	1006	999
Units: participants with positive responses				
Suicidal Behavior (Screening lifetime)	6	9	7	6
Suicidal Ideation (Screening lifetime)	48	43	50	49
Suicidal Behavior (Baseline)	0	0	0	0
Suicidal Ideation (Baseline)	0	1	0	1
Suicidal Behavior (treatment emergent 12 weeks)	0	0	1	1
Suicidal Ideation (treatment emergent 12 weeks)	7	4	3	6

Statistical analyses

No statistical analyses for this end point

Secondary: Positive responses for suicidal behavior and/or ideation by Columbia Suicide Severity Rating Scale (CSSRS) - psychiatric history cohort

End point title	Positive responses for suicidal behavior and/or ideation by Columbia Suicide Severity Rating Scale (CSSRS) - psychiatric history cohort

End point description:

The C-SSRS is a semi-structured interview designed to evaluate an individual's degree of suicidal ideation, preparatory acts or behavior to actual attempt, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent". Answers at screening are for lifetime history. Answers for all other visits are since last visit. The scale is also used to record any completed suicides. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.

End point type	Secondary

End point timeframe:

Lifetime, Baseline and Treatment-Emergent is first dose date to last dose date (up to 12 weeks) plus 30 days.

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1026	1017	1016	1015
Units: participants with positive responses				
Suicidal Behavior (Screening lifetime)	137	143	111	123
Suicidal Ideation (Screening lifetime)	338	357	333	349
Suicidal Behavior (Baseline)	0	0	0	1
Suicidal Ideation (Baseline)	6	5	2	3
Suicidal Behavior (treatment emergent 12 weeks)	0	1	0	2
Suicidal Ideation (treatment emergent 12 weeks)	27	15	20	25

Statistical analyses

No statistical analyses for this end point

Secondary: Positive responses for suicidal behavior and/or ideation by Columbia Suicide Severity Rating Scale (CSSRS) - overall

End point title	Positive responses for suicidal behavior and/or ideation by Columbia Suicide Severity Rating Scale (CSSRS) - overall

End point description:

The C-SSRS is a semi-structured interview designed to evaluate an individual's degree of suicidal ideation, preparatory acts or behavior to actual attempt, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent". Answers at screening are for lifetime history. Answers for all other visits are since last visit. The scale is also used to record any completed suicides. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.

End point type	Secondary

End point timeframe:

Lifetime, Baseline and Treatment-Emergent is first dose date to last dose date (up to 12 weeks) plus 30 days.

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2016	2006	2022	2014
Units: participants with positive responses				
Suicidal Behavior (Screening lifetime)	143	152	118	129
Suicidal Ideation (Screening lifetime)	386	400	383	398
Suicidal Behavior (Baseline)	0	0	0	1
Suicidal Ideation (Baseline)	6	6	2	4
Suicidal Behavior (treatment emergent 12 weeks)	0	1	1	3
Suicidal Ideation (treatment emergent 12 weeks)	34	19	23	31

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression of Improvement (CGII), "No Change" rating by visit

End point title	Clinical Global Impression of Improvement (CGII), "No Change" rating by visit

End point description:

The CGI-I is a clinician rated instrument that measures change in participant's psychiatric condition (or lack thereof in the stratum without psychiatric disorders) on a 7 point scale ranging from 1 (very much improved) to 7 (very much worse), with 4 = no change. The ratings were applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as "normal, not at all ill" on the CGI-S at baseline and assuming no psychiatric symptoms emerge during the trial, would be rated as "no change" on the CGI-I at follow-up visits). For those participants with a psychiatric diagnosis, the clinician should rate the severity of the mental illness with respect to the clinician's experience with the psychiatric population to which the participant belongs. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2016	2006	2022	2014
Units: percentage of participants				
number (not applicable)				
Week 1 (N= 1986, 1974, 1986, 1982)	94.2	93.2	94.6	95.1
Week 2 (N= 1934, 1936, 1927, 1926)	90.8	90.8	90.5	91.2
Week 3 (N= 1880, 1892, 1880, 1863)	88.3	89.8	88.7	87.9
Week 4 (N= 1860, 1856, 1858, 1834)	86.6	88	87.1	86.3
Week 5 (N= 1828, 1816, 1822, 1802)	85.7	86.5	85.5	85.4
Week 6 (N= 1816, 1808, 1820, 1773)	85.2	86.5	85.1	84.1
Week 8 (N= 1758, 1756, 1755, 1738)	82.4	83.6	82.8	81.9
Week 10 (N= 1717, 1707, 1715, 1675)	80.6	81.7	80.4	79.2
Week 12 (N= 1558, 1572, 1540, 1492)	72.9	75.1	72.2	71.3
Week 13 (N= 1612, 16081602, 1575)	75.9	76.7	75.2	74.9
Week 16 (N= 1586, 1606, 1568, 1541)	74.2	76.7	73.9	73.4
Week 20 (N= 1563, 1573, 1523, 1510)	73.4	75	72.2	71.7
Week 24 (N= 1533, 1515, 1499, 1497)	71.8	72.3	71.1	71.1

Statistical analyses

No statistical analyses for this end point

Secondary: COconfirmed continuous abstinence for Weeks 9 through 12, non-psychiatric history cohort

End point title	COconfirmed continuous abstinence for Weeks 9 through 12, non-psychiatric history cohort

End point description:

A responder to this endpoint requires the answer “no” to both questions 1 and 2 on the Nicotine Use Inventory at every visit from Week 9 to Week 12 (inclusive). The efficacy population included all randomized participants (N=8144) and was used to analyze all efficacy endpoints.

End point type	Secondary

End point timeframe:

Week 9 through Week 12

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1005[2]	1001[3]	1013[4]	1009[5]
Units: percentage of participants				
number (not applicable)	38	26.1	26.4	13.7

Notes:

[2] - The number of participants analyzed here is based on efficacy population (N=8144).

[3] - The number of participants analyzed here is based on efficacy population (N=8144).

[4] - The number of participants analyzed here is based on efficacy population (N=8144).

[5] - The number of participants analyzed here is based on efficacy population (N=8144).

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	Varenicline v Placebo
Number of subjects included in analysis	2014
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.2
upper limit	5

Notes:

[6] - No multiplicity adjustment.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	Bupropion v Placebo
Number of subjects included in analysis	2010
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	2.85

Notes:

[7] - No multiplicity adjustment.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	NRT patch v Placebo
Number of subjects included in analysis	2022
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.83
upper limit	2.9

Notes:

[8] - No multiplicity adjustment.

Secondary: COconfirmed continuous abstinence for Weeks 9 through 12, psychiatric history cohort

End point title	COconfirmed continuous abstinence for Weeks 9 through 12, psychiatric history cohort

End point description:

A responder to this endpoint requires the answer “no” to both questions 1 and 2 on the Nicotine Use Inventory at every visit from Week 9 to Week 12 (inclusive). The efficacy population included all randomized participants (N=8144) and was used to analyze all efficacy endpoints.

End point type	Secondary

End point timeframe:

Week 9 through Week 12

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1032[9]	1033[10]	1025[11]	1026[12]
Units: percentage of participants				
number (not applicable)	29.2	19.3	20.4	11.4

Notes:

[9] - The number of participants analyzed here is based on efficacy population (N=8144).

[10] - The number of participants analyzed here is based on efficacy population (N=8144).

[11] - The number of participants analyzed here is based on efficacy population (N=8144).

[12] - The number of participants analyzed here is based on efficacy population (N=8144).

Statistical analyses

Statistical analysis title	Stistical Analysis 1

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	Varenicline v Placebo
Number of subjects included in analysis	2058
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [13]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.56
upper limit	4.11

Notes:

[13] - No multiplicity adjustment.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	Bupropion v Placebo
Number of subjects included in analysis	2059
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.46
upper limit	2.39

Notes:

[14] - No multiplicity adjustment.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	NRT patch v Placebo
Number of subjects included in analysis	2051
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [15]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.56
upper limit	2.55

Notes:

[15] - No multiplicity adjustment.

Secondary: COconfirmed continuous abstinence for Weeks 9 through 12 (overall)

End point title	COconfirmed continuous abstinence for Weeks 9 through 12 (overall)

End point description:

A responder to this endpoint requires the answer "no" to both questions 1 and 2 on the Nicotine Use Inventory at every visit from Week 9 to Week 12 (inclusive). The efficacy population included all randomized participants (N=8144) and was used to analyze all efficacy endpoints.

End point type	Secondary

End point timeframe:

Week 9 through Week 12

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2016	2006[16]	2022	2014
Units: Percentage of participants				
number (not applicable)	33.5	22.6	23.4	12.5

Notes:

[16] - The number of participants analyzed here is based on efficacy population (N=8144).

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment and region. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	Varenicline v Placebo

Number of subjects included in analysis	4030
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.07
upper limit	4.24

Notes:

[17] - No multiplicity adjustment.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment and region. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	Bupropion v Placebo
Number of subjects included in analysis	4020
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.75
upper limit	2.45

Notes:

[18] - No multiplicity adjustment.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment and region. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	NRT patch v Placebo
Number of subjects included in analysis	4036
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.82
upper limit	2.54

Notes:

[19] - No multiplicity adjustment.

Secondary: CO-confirmed continuous abstinence from Week 9 through Week 24, non-psychiatric history cohort

End point title	CO-confirmed continuous abstinence from Week 9 through Week 24, non-psychiatric history cohort

End point description:

A responder to this endpoint requires the answer "no" to both questions 1 and 2 on the Nicotine Use Inventory at every visit from Week 9 to Week 24 (inclusive). The efficacy population included all randomized participants (N=8144) and was used to analyze all efficacy endpoints.

End point type	Secondary

End point timeframe:

Week 9 through Week 24

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1005[20]	1001[21]	1013[22]	1009[23]
Units: percentage of participants				
number (not applicable)	25.5	18.8	18.5	10.5

Notes:

[20] - The number of participants analyzed here is based on efficacy population (N=8144).

[21] - The number of participants analyzed here is based on efficacy population (N=8144).

[22] - The number of participants analyzed here is based on efficacy population (N=8144).

[23] - The number of participants analyzed here is based on efficacy population (N=8144).

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	Varenicline v Placebo
Number of subjects included in analysis	2014
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [24]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.99

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.33
upper limit	3.83

Notes:

[24] - No multiplicity adjustment.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	Bupropion v Placebo
Number of subjects included in analysis	2010
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [25]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.54
upper limit	2.59

Notes:

[25] - No multiplicity adjustment.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	NRT patch v Placebo
Number of subjects included in analysis	2022
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [26]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.51
upper limit	2.54

Notes:

[26] - No multiplicity adjustment.

Secondary: CO-confirmed continuous abstinence from Week 9 through Week 24,

psychiatric history cohort	
End point title	CO-confirmed continuous abstinence from Week 9 through Week 24, psychiatric history cohort

End point description:

A responder to this endpoint requires the answer "no" to both questions 1 and 2 on the Nicotine Use Inventory at every visit from Week 9 to Week 24 (inclusive). The efficacy population included all randomized participants (N=8144) and was used to analyze all efficacy endpoints.

End point type	Secondary

End point timeframe:

Week 9 through Week 24

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1032[27]	1033[28]	1025[29]	1026[30]
Units: percentage of participants				
number (not applicable)	18.3	13.7	13	8.3

Notes:

[27] - The number of participants analyzed here is based on efficacy population (N=8144).

[28] - The number of participants analyzed here is based on efficacy population (N=8144).

[29] - The number of participants analyzed here is based on efficacy population (N=8144).

[30] - The number of participants analyzed here is based on efficacy population (N=8144).

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	Varenicline v Placebo
Number of subjects included in analysis	2058
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [31]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	3.29

Notes:

[31] - No multiplicity adjustment.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	Bupropion v Placebo
Number of subjects included in analysis	2059
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [32]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.33
upper limit	2.36

Notes:

[32] - No multiplicity adjustment.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	NRT patch v Placebo
Number of subjects included in analysis	2051
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [33]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.24
upper limit	2.2

Notes:

[33] - No multiplicity adjustment.

Secondary: CO-confirmed continuous abstinence from Week 9 through Week 24 (overall)

End point title	CO-confirmed continuous abstinence from Week 9 through Week 24 (overall)

End point description:

A responder to this endpoint requires the answer "no" to both questions 1 and 2 on the Nicotine Use Inventory at every visit from Week 9 to Week 24 (inclusive). The efficacy population included all randomized participants (N=8144) and was used to analyze all efficacy endpoints.

End point type	Secondary

End point timeframe:

Week 9 through Week 24

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2016	2006	2022	2014[34]
Units: percentage of participants				
number (not applicable)	21.8	16.2	15.7	9.4

Notes:

[34] - The number of participants analyzed here is based on efficacy population (N=8144).

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment and region. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	Varenicline v Placebo
Number of subjects included in analysis	4030
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [35]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.28
upper limit	3.3

Notes:

[35] - No multiplicity adjustment.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment and region. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	Bupropion v Placebo
Number of subjects included in analysis	4020
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [36]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.56
upper limit	2.29

Notes:

[36] - No multiplicity adjustment.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

The analysis was done using a logistic regression with terms treatment and region. Region reduced to 2-level for consistency with primary safety model.

Comparison groups	NRT patch v Placebo
Number of subjects included in analysis	4036
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [37]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.49
upper limit	2.19

Notes:

[37] - No multiplicity adjustment.

Secondary: 7day point prevalence of abstinence, non-psychiatric history cohort

End point title	7day point prevalence of abstinence, non-psychiatric history cohort

End point description:

A responder to this endpoint requires the answer "no" to both questions 3 and 6 on the Nicotine Use Inventory (NUI) at that specific visit. NUI Question 3 (Baseline through Week 24): Has the participant smoked any cigarettes (even a puff) in the last 7 days? NUI Question 6 (Baseline through Week 12): Has the participant used any other nicotine containing products in the last 7 days? NUI Question 6 (Week 13 through Week 24): Has the participant used any other tobacco products in the last 7 days? The efficacy population included all randomized participants (N=8144) and was used to analyze all efficacy endpoints.

End point type	Secondary

End point timeframe:

24 Weeks

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1005[38]	1001[39]	1013[40]	1009[41]
Units: percentage of participants				
number (not applicable)				
Week 1	1.7	1	1.2	1.5
Week 2	20.9	21.3	15.5	11.4
Week 3	30	26.6	22.1	13.6
Week 4	34.3	27.7	25.9	14.5
Week 5	38.4	29.8	27.8	14.9
Week 6	41	31.4	30.4	15.9
Week 7	44.4	35.2	35.1	19.2
Week 8	42.3	31	31.4	16.7
Week 9	47.1	34.9	34.8	19
Week 10	42.4	31	31.1	16.9

Week 11	46.6	34.1	34.9	20.8
Week 12	44.4	30.5	30.4	17.8
Week 13	41.1	30.7	29.9	17.2
Week 14	44.5	33.5	32	20.4
Week 15	43.8	33.2	32.4	21.3
Week 16	37.2	28.5	28.1	18.2
Week 17	40.7	31.9	31.4	20.1
Week 18	40.9	31.3	31.7	20.8
Week 19	39.9	31.2	31.2	20.8
Week 20	35.1	27.5	26.3	18.2
Week 21	38.1	30.3	29.3	20.1
Week 22	38.7	29.9	29	20.3
Week 23	37.6	30.6	28.3	20.3
Week 24	33.6	26	27	17.4

Notes:

[38] - The number of participants analyzed here is based on efficacy population (N=8144).

[39] - The number of participants analyzed here is based on efficacy population (N=8144).

[40] - The number of participants analyzed here is based on efficacy population (N=8144).

[41] - The number of participants analyzed here is based on efficacy population (N=8144).

Statistical analyses

No statistical analyses for this end point

Secondary: 7day point prevalence of abstinence, psychiatric history cohort

End point title	7day point prevalence of abstinence, psychiatric history cohort

End point description:

A responder to this endpoint requires the answer "no" to both questions 3 and 6 on the Nicotine Use Inventory (NUI) at that specific visit. NUI Question 3 (Baseline through Week 24): Has the participant smoked any cigarettes (even a puff) in the last 7 days? NUI Question 6 (Baseline through Week 12): Has the participant used any other nicotine containing products in the last 7 days? NUI Question 6 (Week 13 through Week 24): Has the participant used any other tobacco products in the last 7 days? The efficacy population included all randomized participants (N=8144) and was used to analyze all efficacy endpoints.

End point type	Secondary

End point timeframe:

24 Weeks

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1032[42]	1033[43]	1025[44]	1026[45]
Units: percentage of participants				
number (not applicable)				
Week 1	1	1.2	0.7	0.5
Week 2	16.8	14.6	13	9.2
Week 3	22.7	18.1	17.9	10.7
Week 4	26.6	21.3	21.1	11.8
Week 5	28.5	21.8	22.4	12.4
Week 6	30.8	22.7	23.3	13.4
Week 7	34.8	25.4	27.5	16.6

Week 8	32.7	22.1	24.6	15
Week 9	36.2	26	29.4	17.2
Week 10	35.1	24.3	25	14
Week 11	38.6	27.4	29.4	17.2
Week 12	35	23.9	24.9	14.2
Week 13	32.7	22.6	24	14.8
Week 14	34.7	25	26.8	17.8
Week 15	33.4	25.3	26	18.3
Week 16	29.1	21.9	21.8	13.9
Week 17	32.3	24	24.8	17.4
Week 18	31.7	24.5	24.7	18.2
Week 19	31.6	24.7	25.1	17.6
Week 20	26.6	20.4	25.1	17.6
Week 21	29.7	23.2	23.7	17.5
Week 22	29.1	22.9	23.6	16.5
Week 23	28.5	23.5	22.2	16.4
Week 24	26.1	20.4	20.1	14

Notes:

[42] - The number of participants analyzed here is based on efficacy population (N=8144).

[43] - The number of participants analyzed here is based on efficacy population (N=8144).

[44] - The number of participants analyzed here is based on efficacy population (N=8144).

[45] - The number of participants analyzed here is based on efficacy population (N=8144).

Statistical analyses

No statistical analyses for this end point

Secondary: 7day point prevalence of abstinence (overall)

End point title	7day point prevalence of abstinence (overall)

End point description:

A responder to this endpoint requires the answer "no" to both questions 3 and 6 on the Nicotine Use Inventory (NUI) at that specific visit. NUI Question 3 (Baseline through Week 24): Has the participant smoked any cigarettes (even a puff) in the last 7 days? NUI Question 6 (Baseline through Week 12): Has the participant used any other nicotine containing products in the last 7 days? NUI Question 6 (Week 13 through Week 24): Has the participant used any other tobacco products in the last 7 days? The efficacy population included all randomized participants (N=8144) and was used to analyze all efficacy endpoints.

End point type	Secondary

End point timeframe:

24 Weeks

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2016	2006[46]	2022	2014
Units: percentage of participants				
number (not applicable)				
Week 1	1.3	1.1	0.9	1
Week 2	18.8	17.9	14.2	10.3
Week 3	26.3	22.3	20	12.1
Week 4	30.4	24.4	23.5	13.1

Week 5	33.4	25.7	25.1	13.6
Week 6	35.8	26.9	26.8	14.6
Week 7	39.5	30.2	31.3	17.9
Week 8	37.4	26.5	28	15.9
Week 9	41.6	30.4	32.1	18.1
Week 10	38.7	27.6	28	15.5
Week 11	42.5	30.7	32.1	18.8
Week 12	39.6	27.1	27.6	16
Week 13	36.8	26.5	26.9	16
Week 14	39.5	29.2	29.4	19.1
Week 15	38.5	29.2	29.2	19.8
Week 16	33.1	25.1	24.9	16.1
Week 17	36.4	27.9	28.1	18.8
Week 18	36.2	27.8	28.2	19.5
Week 19	35.7	27.9	28.1	19.2
Week 20	30.8	23.9	23.7	16.3
Week 21	33.9	26.7	26.5	18.8
Week 22	33.8	26.4	26.3	18.4
Week 23	33	27	25.3	18.3
Week 24	29.8	23.2	23.6	15.7

Notes:

[46] - The number of participants analyzed here is based on efficacy population (N=8144).

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline throughout the study period (16 weeks). Treatment emergent is first dose date to last dose date (up to 12 weeks) plus 30 days.

Adverse event reporting additional description:

Adverse events (AEs) were reported from the time the informed consent was signed throughout the study including 30 days after the last dose of study medication. In addition to the standard collection of volunteered and observed AEs, neuropsychiatric AEs of interest were solicited using the Neuropsychiatric Adverse Event Interview (NAEI).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Varenicline

Reporting group description:

Participants were randomized to 1 of the 3 active dosing groups that took active medication of either varenicline, bupropion, NRT in this triple-dummy design. Participants in this arm received varenicline titrated to the full dose during the first week in the following manner: 0.5 mg QD x 3 days, 0.5 mg BID x 4 days, then 1 mg BID for 11 weeks. They also received placebo bupropion and NRT patch, dosed in the same manner as the active medication.

Reporting group title	Bupropion

Reporting group description:

Participants were randomized to 1 of the 3 active dosing groups that took active medication of either varenicline, bupropion, NRT in this triple-dummy design. Participants in this arm received bupropion 150 mg QD x 3 days and taken 150 mg BID for the remainder of the treatment period (11 weeks and 4 days). They also received placebo varenicline and NRT patch, dosed in the same manner as the active medication.

Reporting group title	NRT patch

Reporting group description:

Participants were randomized to 1 of the 3 active dosing groups that took active medication of either varenicline, bupropion, NRT in this triple-dummy design. Participants in this arm received NRT started active dosing the morning of the Week 1 visit and received a 21 mg transdermal patch per day x 7 weeks, followed by a 14 mg transdermal patch per day x 2 weeks, and then a 7 mg transdermal patch x 2 weeks for a total of 11 weeks of treatment. They also received placebo varenicline and bupropion, dosed in the same manner as active medication.

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo for varenicline, bupropion, and NRT in this triple-dummy design, and followed the same titration and dosing schedule as for the active treatments noted above.

Serious adverse events	Varenicline	Bupropion	NRT patch
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 2016 (1.93%)	48 / 2006 (2.39%)	45 / 2022 (2.23%)
number of deaths (all causes)	0	3	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			

subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobular breast carcinoma in situ			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Prostate cancer			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal cell carcinoma			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Transitional cell carcinoma			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			

subjects affected / exposed	2 / 2016 (0.10%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	2 / 2022 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			

subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Hypertension			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Vascular rupture			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Surgical and medical procedures			
Female sterilisation			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee operation			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Therapy change			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ectopic pregnancy			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	4 / 2022 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernia			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 2016 (0.00%)	2 / 2006 (0.10%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Bartholin’s cyst			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Menorrhagia			

subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 2016 (0.10%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinitis allergic			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Depression			
subjects affected / exposed	1 / 2016 (0.05%)	1 / 2006 (0.05%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Suicidal ideation			
subjects affected / exposed	2 / 2016 (0.10%)	1 / 2006 (0.05%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 2016 (0.00%)	2 / 2006 (0.10%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aggression			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol withdrawal syndrome			
subjects affected / exposed	1 / 2016 (0.05%)	1 / 2006 (0.05%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcoholism			
subjects affected / exposed	0 / 2016 (0.00%)	3 / 2006 (0.15%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	2 / 2022 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety disorder			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Bipolar I disorder			
subjects affected / exposed	1 / 2016 (0.05%)	2 / 2006 (0.10%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar II disorder			

subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Borderline personality disorder			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emotional disorder			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Hallucination, auditory			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Intentional self-injury			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Mental disorder			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Schizoaffective disorder			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Sleep disorder			

subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Suicidal behaviour			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Electrocardiogram abnormal			
subjects affected / exposed	1 / 2016 (0.05%)	1 / 2006 (0.05%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure increased			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Liver function test abnormal			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Burns third degree			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fall			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Road traffic accident			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Spinal fracture			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
skull fracture			

subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Foot fracture			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Joint dislocation			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Ligament rupture			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Lumbar vertebral fracture			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	4 / 2022 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			

subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cornoary artery disease			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Myocardial infarction			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Cardiac failure congestive			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular disorder			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Coronary artery occlusion			

subjects affected / exposed	2 / 2016 (0.10%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	1 / 2016 (0.05%)	1 / 2006 (0.05%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Migraine			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Syncope			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial aneurysm			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Seizure			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Ulcerative keratitis			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous detachment			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Gastritis			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Oesophagitis			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Pancreatitis			

subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	2 / 2022 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Cholelithiasis			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 2016 (0.00%)	2 / 2006 (0.10%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis atopic			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Psoriasis			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Thyrotoxic crisis			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Cervical spinal stenosis			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fistula			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Intervertebral disc degeneration			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Pain in extremity			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Muscular weakness			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Bronchitis			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	2 / 2022 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Post procedural infection			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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

Pyelonephritis			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Wound infection			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes			

subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	2 / 2016 (0.10%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	0 / 2022 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 2016 (0.05%)	0 / 2006 (0.00%)	0 / 2022 (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
Hypokalaemia			
subjects affected / exposed	0 / 2016 (0.00%)	0 / 2006 (0.00%)	1 / 2022 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 2016 (0.00%)	1 / 2006 (0.05%)	0 / 2022 (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

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 2014 (2.04%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lobular breast carcinoma in situ			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal cell carcinoma			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transitional cell carcinoma			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma of colon			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Breast cancer			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral artery stenosis			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aortic aneurysm			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma			

subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular rupture			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Female sterilisation			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Knee operation			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Therapy change			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Ectopic pregnancy				
subjects affected / exposed	0 / 2014 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	2 / 2014 (0.10%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hernia				
subjects affected / exposed	0 / 2014 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	1 / 2014 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 2014 (0.05%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Drug hypersensitivity				
subjects affected / exposed	0 / 2014 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Bartholin’s cyst				
subjects affected / exposed	0 / 2014 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Menorrhagia				

subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 2014 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Rhinitis allergic			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Panic attack			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Suicidal ideation			
subjects affected / exposed	3 / 2014 (0.15%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aggression			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alcoholism			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anxiety			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anxiety disorder			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bipolar I disorder			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bipolar II disorder			

subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Borderline personality disorder			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Completed suicide			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Emotional disorder			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hallucination, auditory			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intentional self-injury			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mental disorder			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Schizoaffective disorder			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sleep disorder			

subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal behaviour			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Electrocardiogram abnormal			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood pressure increased			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver function test abnormal			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Burns third degree			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Fall			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laceration			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal fracture			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
skull fracture			

subjects affected / exposed	0 / 2014 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Foot fracture				
subjects affected / exposed	0 / 2014 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hand fracture				
subjects affected / exposed	0 / 2014 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	0 / 2014 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament rupture				
subjects affected / exposed	0 / 2014 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar vertebral fracture				
subjects affected / exposed	0 / 2014 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	1 / 2014 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 2014 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				

subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cornoary artery disease			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute coronary syndrome			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arrhythmia			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	2 / 2014 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiovascular disorder			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery occlusion			

subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Palpitations			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intracranial aneurysm			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Ulcerative keratitis			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vitreous detachment			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulum			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			

subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dermatitis atopic			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psoriasis			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Thyrotoxic crisis			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervical spinal stenosis			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fistula			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc degeneration			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abscess			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Parotitis			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural infection			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pyelonephritis			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal abscess			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth abscess			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oral herpes			

subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	2 / 2014 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 2014 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 2014 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Varenicline	Bupropion	NRT patch
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1158 / 2016 (57.44%)	1033 / 2006 (51.50%)	1003 / 2022 (49.60%)
Nervous system disorders			
Headache			
subjects affected / exposed	245 / 2016 (12.15%)	186 / 2006 (9.27%)	233 / 2022 (11.52%)
occurrences (all)	307	241	280
General disorders and administration site conditions			
Application site pruritus			
subjects affected / exposed	22 / 2016 (1.09%)	12 / 2006 (0.60%)	109 / 2022 (5.39%)
occurrences (all)	24	12	113
Fatigue			
subjects affected / exposed	124 / 2016 (6.15%)	57 / 2006 (2.84%)	75 / 2022 (3.71%)
occurrences (all)	129	60	83
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	66 / 2016 (3.27%)	146 / 2006 (7.28%)	59 / 2022 (2.92%)
occurrences (all)	68	155	59
Nausea			
subjects affected / exposed	511 / 2016 (25.35%)	201 / 2006 (10.02%)	199 / 2022 (9.84%)
occurrences (all)	596	221	221
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	201 / 2016 (9.97%)	131 / 2006 (6.53%)	251 / 2022 (12.41%)
occurrences (all)	209	137	265
Anxiety			
subjects affected / exposed	132 / 2016 (6.55%)	169 / 2006 (8.42%)	137 / 2022 (6.78%)
occurrences (all)	158	200	161
Insomnia			
subjects affected / exposed	189 / 2016 (9.38%)	245 / 2006 (12.21%)	195 / 2022 (9.64%)
occurrences (all)	206	261	213
Irritability			
subjects affected / exposed	82 / 2016 (4.07%)	71 / 2006 (3.54%)	108 / 2022 (5.34%)
occurrences (all)	95	77	115
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	174 / 2016 (8.63%)	156 / 2006 (7.78%)	126 / 2022 (6.23%)
occurrences (all)	197	171	160
Upper respiratory tract infection			
subjects affected / exposed	109 / 2016 (5.41%)	104 / 2006 (5.18%)	97 / 2022 (4.80%)
occurrences (all)	116	117	108

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	884 / 2014 (43.89%)		
Nervous system disorders			
Headache			
subjects affected / exposed	199 / 2014 (9.88%)		
occurrences (all)	246		
General disorders and administration site conditions			
Application site pruritus			
subjects affected / exposed	16 / 2014 (0.79%)		
occurrences (all)	16		
Fatigue			
subjects affected / exposed	83 / 2014 (4.12%)		
occurrences (all)	88		
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	64 / 2014 (3.18%)		
occurrences (all)	65		
Nausea			
subjects affected / exposed	137 / 2014 (6.80%)		
occurrences (all)	147		
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	92 / 2014 (4.57%)		
occurrences (all)	97		
Anxiety			
subjects affected / exposed	120 / 2014 (5.96%)		
occurrences (all)	141		
Insomnia			

subjects affected / exposed	139 / 2014 (6.90%)		
occurrences (all)	152		
Irritability			
subjects affected / exposed	104 / 2014 (5.16%)		
occurrences (all)	108		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	135 / 2014 (6.70%)		
occurrences (all)	154		
Upper respiratory tract infection			
subjects affected / exposed	115 / 2014 (5.71%)		
occurrences (all)	124		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2010	The protocol was amended to incorporate changes requested by the Food and Drug Adminstration (FDA), to clarify certain protocol aspects, and to correct inconsistencies/typographical errors. The changes requested by FDA were to use a different guidance for suicide risk, clarifying the primary focus of suicide risk assessment was the presence or absence of current significant suicidality.
28 June 2011	The protocol was amended to incorporate changes requested by the FDA and the European Medical Agency (EMA). In addition, bupropion was added to the title, objectives, and endpoints as an active comparator. The amendment also incorporated changes to the NAEI based on the outcome of the pilot study in a similar subject population. In addition, the amendment provided updates to be in compliance with Pfizer SOPs, clarified certain protocol aspects, and corrected inconsistencies/typographical errors.
04 October 2011	The protocol was amended to include detailed cardiovascular (CV) medical history, collection of CV events of interest during the study, and a Cardiovascular Event Adjudication Committee. The protocol was also updated to be consistent with updated SOP CT 02 in regards to Section 15.1, Communication of Results to Pfizer.
10 October 2011	The protocol was amended to incorporate changes requested by the EMA for the countries of Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Slovakia, and Spain. Participants with Bipolar I and II disorders were to be excluded from the study. The medical health professional was defined as a psychiatrist only.
30 May 2012	The protocol was amended to incorporate changes based on feedback from the FDA and regulatory agencies in the European Union (EU). Vital signs (pulse rate and blood pressure) were added to all clinic visits. ECG was added to Week 12 and Early Termination (ET) before the Week 12 visit. Section 4.2 Exclusion Criterion #22 was added to exclude participants with skin conditions that could hinder the use of NRT placement. Section 6 (Study Procedures) is updated to include additional vital signs at every clinic visit and ECG at Week 12 or ET12. Section 6.4 (Subject Withdrawal) is updated to include information for Off Treatment in Study (OTIS) participants and all participants were followed until final visit unless they withdrew consent. Section 7.1.1.2 (Physical Examination, Vital Signs and ECG) updated to include vital signs at every clinic visit and ECG as Week 12 or ET12. Section 7.1.15 (Cardiovascular Events of Interest) is changed from: Hospitalization for angina pectoris or chest pain to: Hospitalization for unstable angina. Also wording was added to further clarify how events of interest are identified, reviewed and adjudicated.
07 November 2012	The protocol was amended to incorporate changes based on the updated bupropion Company Core Data Sheet dated 18 Sep 2012. Study Period and Nontreatment Follow up Period Pregnancy testing was added to visits at Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, and 16. Partcipant withdrawal added "Study drug will be discontinued immediately for any female partcipant who becomes pregnant during the treatment period of the study. Laboratory section (7.1.14) was updated to include the additional pregnancy testing at clinic visits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

After database lock and unblinding, one additional participant in the NRT arm of psychiatric cohort was found who had a primary endpoint event (moderate suicidal ideation) which required hospitalization; this event is not included in any analyses.

Notes: