Clinical trial results:
A PHASE 4, NON-TREATMENT FOLLOW-UP FOR CARDIAC ASSESSMENTS FOLLOWING USE OF SMOKING CESSATION TREATMENTS IN SUBJECTS WITH AND WITHOUT A HISTORY OF PSYCHIATRIC DISORDERS.

Summary

EudraCT number	2011-005513-37
Trial protocol	DE ES FI BG DK SK
Global end of trial date	10 July 2015

Results information

Result version number	v1 (current)
This version publication date	24 July 2016
First version publication date	24 July 2016

Trial information

Trial identification

Sponsor protocol code	A3051148

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01574703
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 East 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 18007181021, 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	10 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 July 2015
Global end of trial reached?	Yes
Global end of trial date	10 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the cardiovascular safety assessment in Study 2010-022914-15 and continuing into Study 2011-005513-37 was to characterize the cardiovascular safety profiles of varenicline and bupropion compared to placebo.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002). A signed and dated informed consent was required before any screening procedures were done. The study investigators explained the nature, purpose, and risks of the study to each participant. Each participant was informed that he/she could withdraw from the study at any time and for any reason. Each participant was given sufficient time to consider the implications of the study before deciding whether to participate. Participants who chose to participate signed an informed consent document.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 134
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Brazil: 12
Country: Number of subjects enrolled	Bulgaria: 352
Country: Number of subjects enrolled	Canada: 153
Country: Number of subjects enrolled	Denmark: 54
Country: Number of subjects enrolled	Finland: 349
Country: Number of subjects enrolled	Germany: 377
Country: Number of subjects enrolled	Mexico: 157
Country: Number of subjects enrolled	New Zealand: 105
Country: Number of subjects enrolled	Russian Federation: 106
Country: Number of subjects enrolled	Slovakia: 179
Country: Number of subjects enrolled	South Africa: 213
Country: Number of subjects enrolled	Spain: 134

Country: Number of subjects enrolled	United States: 2241
Country: Number of subjects enrolled	Chile: 16
Worldwide total number of subjects	4595
EEA total number of subjects	1445

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)	4220
From 65 to 84 years	375
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 6293 participants who completed the parent study 2010-022914-15 as per protocol, a total of 4595 participants enrolled into this study 2011-005513-37 from 132 centers in 16 countries.

Pre-assignment

Screening details:

This is a non-treatment extension study of parent study 2010-022914-15.No study drug was provided in the extension phase. However,cardiovascular events that occurred during parent study 2010-022914-15 when participants received varenicline(N=2016), bupropion(N=2006),NRT(N=2022),or placebo(N=2014)in a triple-dummy design were analyzed in this study.

Period 1

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

Blinding implementation details:

Randomization took place during the parent study.The blinding in effect during the parent study 2010-022914-15 remained in place during this Study 2011-005513-37.

Arms

Are arms mutually exclusive?	Yes
Arm title	Varenicline

Arm description:

This was the non-treatment extension study of parent study 2010-022914-15. No study drug was provided during this extension phase. However, Cardiovascular events that occurred during parent study 2010-022914-15 when participants received varenicline in a triple-dummy design were analyzed as part of this study.

Arm type	Experimental
Investigational medicinal product name	Varenicline
Investigational medicinal product code	CP-526,555
Other name	Champix
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

This was the non-treatment extension study of parent study 2010-022914-15. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received varenicline in a triple-dummy design were analyzed as part of this study.

Arm title	Bupropion

Arm description:

This was the non-treatment extension study of parent study 2010-022914-15. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received bupropion in a triple-dummy design were analyzed as part of this study.

Arm type	Experimental
Investigational medicinal product name	Bupropion
Investigational medicinal product code	
Other name	Zyban Bupropion hydrochloride
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

This was the non-treatment extension study of parent study 2010-022914-15. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received bupropion in a triple-dummy design were analyzed as part of this study.

Arm title	Nicotine Replacement Therapy (NRT) patch

Arm description:

This was the non-treatment extension study of parent study NCT01456936. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received NRT patch in a triple-dummy design were analyzed as part of this study.

Arm type	Experimental
Investigational medicinal product name	NRT patch
Investigational medicinal product code	Transdermal nicotine Patch (NRT)
Other name	Nicotine
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

This was the non-treatment extension study of parent study NCT01456936. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received NRT patch in a triple-dummy design were analyzed as part of this study.

Arm title	Placebo

Arm description:

This was the non-treatment extension study of parent study 2010-022914-15. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received placebo in a triple-dummy design were analyzed as part of this study.

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

Dosage and administration details:

This was the non-treatment extension study of parent study 2010-022914-15. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received placebo in a triple-dummy design were analyzed as part of this study.

Number of subjects in period 1	Varenicline	Bupropion	Nicotine Replacement Therapy (NRT) patch
Started	1192	1166	1116
Completed	1067	1054	1011
Not completed	125	112	105
Unspecified Reason	27	15	20
Consent withdrawn by subject	53	52	36
Adverse Event	-	2	1
Death	2	1	1

Lost to follow-up	43	41	46
Met Withdrawal Criteria	-	1	1
Protocol deviation	-	-	-

Number of subjects in period 1	Placebo
Started	1121
Completed	1007
Not completed	114
Unspecified Reason	16
Consent withdrawn by subject	61
Adverse Event	1
Death	-
Lost to follow-up	35
Met Withdrawal Criteria	-
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Varenicline
Reporting group description:	
This was the non-treatment extension study of parent study 2010-022914-15. No study drug was provided during this extension phase. However, Cardiovascular events that occurred during parent study 2010-022914-15 when participants received varenicline in a triple-dummy design were analyzed as part of this study.	
Reporting group title	Bupropion
Reporting group description:	
This was the non-treatment extension study of parent study 2010-022914-15. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received bupropion in a triple-dummy design were analyzed as part of this study.	
Reporting group title	Nicotine Replacement Therapy (NRT) patch
Reporting group description:	
This was the non-treatment extension study of parent study NCT01456936. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received NRT patch in a triple-dummy design were analyzed as part of this study.	
Reporting group title	Placebo
Reporting group description:	
This was the non-treatment extension study of parent study 2010-022914-15. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received placebo in a triple-dummy design were analyzed as part of this study.	

Reporting group values	Varenicline	Bupropion	Nicotine Replacement Therapy (NRT) patch
Number of subjects	1192	1166	1116
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)	1093	1064	1018
From 65-84 years	99	102	98
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	48.1	47.7	48.3
standard deviation	± 12.2	± 12.5	± 11.9
Gender, Male/Female Units: Participants			
Female	659	648	623
Male	533	518	493

Reporting group values	Placebo	Total	
Number of subjects	1121	4595	
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)	1045	4220	
From 65-84 years	76	375	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	47.5		
standard deviation	± 12.2	-	
Gender, Male/Female Units: Participants			
Female	621	2551	
Male	500	2044	

Subject analysis sets

Subject analysis set title	Varenicline
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety analysis set is defined as all participants that receive at least one partial dose of study drug during the parent study (i.e., the Safety analysis set for 2010-022914-15).

Subject analysis set title	Bupropion
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety analysis set is defined as all participants that receive at least one partial dose of study drug during the parent study (i.e., the Safety analysis set for 2010-022914-15).

Subject analysis set title	NRT patch
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety analysis set is defined as all participants that receive at least one partial dose of study drug during the parent study (i.e., the Safety analysis set for 2010-022914-15).

Subject analysis set title	Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety analysis set is defined as all participants that receive at least one partial dose of study drug during the parent study (i.e., the Safety analysis set for 2010-022914-15).

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	46.3	46.9
standard deviation	± 12.4	± 12.6	± 12.2
Gender, Male/Female			
Units: Participants			
Female	1114	1114	1139
Male	902	892	883

Reporting group values	Placebo		
Number of subjects	2014		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	1899		
From 65-84 years	115		
85 years and over	0		
Age Continuous			
Units: Years			
arithmetic mean	46.4		
standard deviation	± 12.1		
Gender, Male/Female			
Units: Participants			
Female	1138		
Male	876		

End points

End points reporting groups

Reporting group title	Varenicline

Reporting group description:

This was the non-treatment extension study of parent study 2010-022914-15. No study drug was provided during this extension phase. However, Cardiovascular events that occurred during parent study 2010-022914-15 when participants received varenicline in a triple-dummy design were analyzed as part of this study.

Reporting group title	Bupropion

Reporting group description:

This was the non-treatment extension study of parent study 2010-022914-15. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received bupropion in a triple-dummy design were analyzed as part of this study.

Reporting group title	Nicotine Replacement Therapy (NRT) patch

Reporting group description:

This was the non-treatment extension study of parent study NCT01456936. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received NRT patch in a triple-dummy design were analyzed as part of this study.

Reporting group title	Placebo

Reporting group description:

This was the non-treatment extension study of parent study 2010-022914-15. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received placebo in a triple-dummy design were analyzed as part of this study.

Subject analysis set title	Varenicline
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety analysis set is defined as all participants that receive at least one partial dose of study drug during the parent study (i.e., the Safety analysis set for 2010-022914-15).

Subject analysis set title	Bupropion
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety analysis set is defined as all participants that receive at least one partial dose of study drug during the parent study (i.e., the Safety analysis set for 2010-022914-15).

Subject analysis set title	NRT patch
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety analysis set is defined as all participants that receive at least one partial dose of study drug during the parent study (i.e., the Safety analysis set for 2010-022914-15).

Subject analysis set title	Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety analysis set is defined as all participants that receive at least one partial dose of study drug during the parent study (i.e., the Safety analysis set for 2010-022914-15).

Primary: Time to occurrence of major adverse cardiovascular event (MACE) during treatment period (up to date of last dose of study drug) in study 2010-022914-15.

End point title	Time to occurrence of major adverse cardiovascular event (MACE) during treatment period (up to date of last dose of study drug) in study 2010-022914-15.

End point description:

This is an adjudicated endpoint. MACE is defined as a cardiovascular death, a non-fatal myocardial infarction or a non-fatal stroke evaluated during the treatment phase (up to date of last dose of study

drug). The measure type mentioned in the outcome data table is Hazard Ratio relative to Placebo. The term Baseline visit refers to the Baseline (Week 0) visit of the parent study 2010-022914-15. The safety population included all participants who received at least one dose of study drug in 2010-022914-15 parent study.

End point type	Primary

End point timeframe:

Baseline to last dose of study drug.

End point values	Varenicline	Bupropion	NRT patch	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2016	2006	2022	
Units: Unitless				
number (confidence interval 95%)	0.29 (0.05 to 1.68)	0.5 (0.1 to 2.5)	0.29 (0.05 to 1.7)	

Statistical analyses

Statistical analysis title	Statistical analysis for overall treatment groups
Comparison groups	Varenicline v Bupropion v NRT patch
Number of subjects included in analysis	6044
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37 [1]
Method	Logrank

Notes:

[1] - P-value for the treatment effect from the Log-Rank test stratified by Cohort.

Secondary: Time to MACE up to date of last dose of study drug plus 30 days follow-up in study 2010-022914-15.

End point title	Time to MACE up to date of last dose of study drug plus 30 days follow-up in study 2010-022914-15.

End point description:

This is an adjudicated endpoint. MACE is defined as a cardiovascular death, a non-fatal myocardial infarction or a non-fatal stroke evaluated during the treatment phase (up to date of last dose of study drug) plus 30 days follow-up. The measure type mentioned in the outcome data table is Hazard Ratio relative to Placebo. The safety analysis set is defined as all participants that received at least one partial dose of study drug during the parent study 2010-022914-15.

End point type	Secondary

End point timeframe:

Baseline to last dose of study drug plus 30 days.

End point values	Varenicline	Bupropion	NRT patch	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2016	2006	2022	
Units: Unitless				
number (confidence interval 95%)	0.29 (0.05 to 1.7)	0.51 (0.1 to 2.51)	0.5 (0.1 to 2.48)	

Statistical analyses

Statistical analysis title	Statistical analysis for overall treatment groups
Comparison groups	Varenicline v Bupropion v NRT patch
Number of subjects included in analysis	6044
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.53 [2]
Method	Logrank

Notes:

[2] - P-value for the treatment effect from the Log-Rank test stratified by Cohort.

Secondary: Time to MACE until the end of study 2011-005513-37.

End point title	Time to MACE until the end of study 2011-005513-37.

End point description:

This is an adjudicated endpoint. MACE is defined as a cardiovascular death, a non-fatal myocardial infarction or a non-fatal stroke evaluated during the treatment phase (up to date of last dose of study drug). The measure type mentioned in the outcome data table is Hazard Ratio relative to Placebo. The safety analysis set is defined as all participants that received at least one partial dose of study drug during the parent study 2010-022914-15.

End point type	Secondary

End point timeframe:

Baseline until end of study (end of study is defined as last visit in study 2011-005513-37, or in study 2010-022914-15 for those participants not enrolled into study 2011-005513-37).

End point values	Varenicline	Bupropion	NRT patch	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2016	2006	2022	
Units: Unitless				
number (confidence interval 95%)	0.39 (0.12 to 1.27)	1.09 (0.42 to 2.83)	0.75 (0.26 to 2.13)	

Statistical analyses

Statistical analysis title	Statistical analysis for overall treatment groups
Comparison groups	Varenicline v Bupropion v NRT patch

Number of subjects included in analysis	6044
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34 [3]
Method	Logrank

Notes:

[3] - P-value for the treatment effect from the Log-Rank test stratified by Cohort.

Secondary: Incidence of MACE assessed during treatment period (up to date of last dose of study drug) in study 2010-022914-15.

End point title	Incidence of MACE assessed during treatment period (up to date of last dose of study drug) in study 2010-022914-15.

End point description:

This is an adjudicated endpoint. MACE is defined as a cardiovascular death, a non-fatal myocardial infarction or a non-fatal stroke evaluated during the treatment phase (up to date of last dose of study drug). The safety analysis set is defined as all participants that received at least one partial dose of study drug during the parent study 2010-022914-15.

End point type	Secondary

End point timeframe:

Baseline to last dose of study drug.

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2016	2006	2022	2014
Units: percentage of participants				
number (not applicable)	0.05	0.1	0.05	0.2

Statistical analyses

Statistical analysis title	Statistical analysis b/w Varenicline and Bupropion
Comparison groups	Varenicline v Bupropion
Number of subjects included in analysis	4022
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8375 [4]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.22
upper limit	4.23

Notes:

[4] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Varenicline and NRT
Comparison groups	Varenicline v NRT patch
Number of subjects included in analysis	4038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.978 [5]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	5.05

Notes:

[5] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Varenicline and Placebo
Comparison groups	Varenicline v Placebo
Number of subjects included in analysis	4030
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6142 [6]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.54
upper limit	3.27

Notes:

[6] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Bupropion and NRT
Comparison groups	Bupropion v NRT patch
Number of subjects included in analysis	4028
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8602 [7]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.28
upper limit	5.13

Notes:

[7] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Bupropion and Placebo
Comparison groups	Bupropion v Placebo
Number of subjects included in analysis	4020
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7217 [8]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.15
upper limit	2.88

Notes:

[8] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w NRT patch and Placebo
Comparison groups	NRT patch v Placebo
Number of subjects included in analysis	4036
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6322 [9]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.41
upper limit	3.28

Notes:

[9] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Secondary: Incidence of MACE+ assessed during treatment period (up to date of last dose of study drug) in study 2010-022914-15.

End point title	Incidence of MACE+ assessed during treatment period (up to date of last dose of study drug) in study 2010-022914-15.

End point description:

This is an adjudicated endpoint. MACE+ is defined as any MACE or a new onset or worsening peripheral vascular disease (PVD) requiring intervention, a need for coronary revascularization, or hospitalization for unstable angina. The safety analysis set is defined as all participants that received at least one partial dose of study drug during the parent study 2010-022914-15.

End point type	Secondary

End point timeframe:

Baseline to last dose of study drug.

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2016	2006	2022	2014
Units: percentage of participants				
number (not applicable)	0.25	0.2	0.1	0.25

Statistical analyses

Statistical analysis title	Statistical analysis b/w Varenicline and Bupropion
Comparison groups	Varenicline v Bupropion
Number of subjects included in analysis	4022
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9687 [10]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.48
upper limit	3.34

Notes:

[10] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Varenicline and NRT
Comparison groups	Varenicline v NRT patch
Number of subjects included in analysis	4038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7905 [11]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.58
upper limit	4.7

Notes:

[11] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Varenicline and Placebo

Comparison groups	Varenicline v Placebo
Number of subjects included in analysis	4030
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8962 [12]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.36
upper limit	2.94

Notes:

[12] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Bupropion and NRT
Comparison groups	Bupropion v NRT patch
Number of subjects included in analysis	4028
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7767 [13]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.72
upper limit	4.98

Notes:

[13] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Bupropion and Placebo
Comparison groups	Bupropion v Placebo
Number of subjects included in analysis	4020
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.926 [14]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.13
upper limit	2.85

Notes:

[14] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w NRT and Placebo
Comparison groups	NRT patch v Placebo
Number of subjects included in analysis	4036
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7113 [15]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.85
upper limit	3.31

Notes:

[15] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Secondary: Incidence of MACE assessed up to date of last dose of study drug plus 30 days follow-up in study 2010-022914-15.

End point title	Incidence of MACE assessed up to date of last dose of study drug plus 30 days follow-up in study 2010-022914-15.

End point description:

This is an adjudicated endpoint. MACE is defined as a cardiovascular death, a non-fatal myocardial infarction or a non-fatal stroke evaluated during the treatment phase (up to date of last dose of study drug) plus 30 days follow-up. The safety analysis set is defined as all participants that received at least one partial dose of study drug during the parent study 2010-022914-15.

End point type	Secondary

End point timeframe:

Baseline to last dose of study drug plus 30 days follow-up.

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2016	2006	2022	2014
Units: percentage of participants				
number (not applicable)	0.05	0.1	0.1	0.2

Statistical analyses

Statistical analysis title	Statistical analysis b/w Varenicline and Bupropion
Comparison groups	Varenicline v Bupropion

Number of subjects included in analysis	4022
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8117 [16]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.27
upper limit	4.13

Notes:

[16] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Varenicline and NRT
Comparison groups	Varenicline v NRT patch
Number of subjects included in analysis	4038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7303 [17]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.21
upper limit	3.65

Notes:

[17] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Varenicline and Placebo
Comparison groups	Varenicline v Placebo
Number of subjects included in analysis	4030
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5946 [18]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	3.21

Notes:

[18] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Bupropion and NRT
Comparison groups	Bupropion v NRT patch
Number of subjects included in analysis	4028
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92 [19]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.27
upper limit	3.85

Notes:

[19] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Bupropion and Placebo
Comparison groups	Bupropion v Placebo
Number of subjects included in analysis	4020
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7236 [20]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.09
upper limit	2.84

Notes:

[20] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w NRT patch and Placebo
Comparison groups	NRT patch v Placebo
Number of subjects included in analysis	4036
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8201 [21]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.42

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.01
upper limit	3.17

Notes:

[21] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Secondary: Incidence of MACE+ assessed up to date of last dose of study drug plus 30 days follow-up in study 2010-022914-15.

End point title	Incidence of MACE+ assessed up to date of last dose of study drug plus 30 days follow-up in study 2010-022914-15.

End point description:

This is an adjudicated endpoint. MACE+ is defined as any MACE or a new onset or worsening PVD requiring intervention, a need for coronary revascularization, or hospitalization for unstable angina. The safety analysis set is defined as all participants that received at least one partial dose of study drug during the parent study 2010-022914-15.

End point type	Secondary

End point timeframe:

Baseline to last dose of study drug plus 30 days follow-up.

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2016	2006	2022	2014
Units: percentage of participants				
number (not applicable)	0.25	0.2	0.15	0.35

Statistical analyses

Statistical analysis title	Statistical analysis b/w Varenicline and Bupropion
Comparison groups	Varenicline v Bupropion
Number of subjects included in analysis	4022
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8932 [22]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.22
upper limit	2.81

Notes:

[22] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Varenicline and NRT
Comparison groups	Varenicline v NRT patch
Number of subjects included in analysis	4038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8747 [23]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.09
upper limit	2.63

Notes:

[23] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Varenicline and Placebo
Comparison groups	Varenicline v Placebo
Number of subjects included in analysis	4030
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.671 [24]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.35
upper limit	2.15

Notes:

[24] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Bupropion and NRT
Comparison groups	Bupropion v NRT patch
Number of subjects included in analysis	4028
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9886 [25]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.32
upper limit	3.27

Notes:

[25] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Bupropion and Placebo
Comparison groups	Bupropion v Placebo
Number of subjects included in analysis	4020
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7631 [26]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.92
upper limit	2.14

Notes:

[26] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w NRT patch and Placebo
Comparison groups	NRT patch v Placebo
Number of subjects included in analysis	4036
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8022 [27]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.23
upper limit	2.5

Notes:

[27] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Secondary: Incidence of MACE assessed until end of study 2011-005513-37.

End point title	Incidence of MACE assessed until end of study 2011-005513-37.

End point description:

This is an adjudicated endpoint. MACE is defined as a cardiovascular death, a non-fatal myocardial infarction or a non-fatal stroke evaluated until end of study. The safety analysis set is defined as all participants that received at least one partial dose of study drug during the parent study 2010-022914-

15.

End point type	Secondary

End point timeframe:

Baseline until end of study (end of study is defined as last visit in study 2011-005513-37, or in study 2010-022914-15 for those participants not enrolled into study 2011-005513-37).

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2016	2006	2022	2014
Units: percentage of participants				
number (not applicable)	0.15	0.45	0.3	0.4

Statistical analyses

Statistical analysis title	Statistical analysis b/w Varenicline and Bupropion
Comparison groups	Varenicline v Bupropion
Number of subjects included in analysis	4022
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6441 [28]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.78
upper limit	2.96

Notes:

[28] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Varenicline and NRT
Comparison groups	Varenicline v NRT patch
Number of subjects included in analysis	4038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7327 [29]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.63
upper limit	3.26

Notes:

[29] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Varenicline and Placebo
Comparison groups	Varenicline v Placebo
Number of subjects included in analysis	4030
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6109 [30]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	2.82

Notes:

[30] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Bupropion and NRT
Comparison groups	Bupropion v NRT patch
Number of subjects included in analysis	4028
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8707 [31]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.48
upper limit	2.93

Notes:

[31] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Bupropion and Placebo
Comparison groups	Bupropion v Placebo
Number of subjects included in analysis	4020
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9531 [32]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.63
upper limit	2.48

Notes:

[32] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w NRT patch and Placebo
Comparison groups	NRT patch v Placebo
Number of subjects included in analysis	4036
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8262 [33]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.99
upper limit	2.39

Notes:

[33] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Secondary: Incidence of MACE+ assessed until end of study 2011-005513-37.

End point title	Incidence of MACE+ assessed until end of study 2011-005513-37.

End point description:

This is an adjudicated endpoint. MACE+ is defined as any MACE or a new onset or worsening PVD requiring intervention, a need for coronary revascularization, or hospitalization for unstable angina. The safety analysis set is defined as all participants that received at least one partial dose of study drug during the parent study 2010-022914-15.

End point type	Secondary

End point timeframe:

Baseline until end of study (end of study is defined as last visit in study 2011-005513-37, or in study 2010-022914-15 for those participants not enrolled into study 2011-005513-37).

End point values	Varenicline	Bupropion	NRT patch	Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2016	2006	2022	2014
Units: percentage of participants				
number (not applicable)	0.5	0.75	0.49	0.6

Statistical analyses

Statistical analysis title	Statistical analysis b/w Varenicline and Bupropion
Comparison groups	Varenicline v Bupropion
Number of subjects included in analysis	4022
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6105 [34]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.65
upper limit	2.01

Notes:

[34] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Varenicline and NRT
Comparison groups	Varenicline v NRT patch
Number of subjects included in analysis	4038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7895 [35]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.65
upper limit	2.01

Notes:

[35] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Varenicline and Placebo
Comparison groups	Varenicline v Placebo
Number of subjects included in analysis	4030
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6804 [36]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.75
upper limit	1.8

Notes:

[36] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Bupropion and NRT
Comparison groups	Bupropion v NRT patch
Number of subjects included in analysis	4028
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8127 [37]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.95
upper limit	2.49

Notes:

[37] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w Bupropion and Placebo
Comparison groups	Bupropion v Placebo
Number of subjects included in analysis	4020
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9218 [38]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.04
upper limit	2.25

Notes:

[38] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Statistical analysis title	Statistical analysis b/w NRT patch and Placebo
Comparison groups	NRT patch v Placebo
Number of subjects included in analysis	4036
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8841 [39]
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.32
upper limit	2

Notes:

[39] - P-values are for the risk differences of pairwise comparisons based on the logistic regression model with terms Baseline Cardiovascular Risk, treatment, cohort, region, and treatment by cohort interaction.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected at the Week 24 visit of study 2010-022914-15 until the end of study (i.e. Week 52 or date of discontinuation, as applicable).

Adverse event reporting additional description:

The Safety analysis set was defined as all participants that received at least one partial dose of study drug during the parent study (i.e., the safety analysis set for 2010-022914-15).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Varenicline

Reporting group description:

This was the non-treatment extension study of parent study 2010-022914-15. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received varenicline in a triple-dummy design were analyzed as part of this study.

Reporting group title	Bupropion

Reporting group description:

This was the non-treatment extension study of parent study 2010-022914-15. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received bupropion in a triple-dummy design were analyzed as part of this study.

Reporting group title	NRT patch

Reporting group description:

This was the non-treatment extension study of parent study NCT01456936. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received NRT patch in a triple-dummy design were analyzed as part of this study.

Reporting group title	Placebo

Reporting group description:

This was the non-treatment extension study of parent study 2010-022914-15. No study drug was provided during this extension phase. However, cardiovascular events that occurred during parent study 2010-022914-15 when participants received placebo in a triple-dummy design were analyzed as part of this study.

Serious adverse events	Varenicline	Bupropion	NRT patch
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 1192 (2.85%)	39 / 1166 (3.34%)	43 / 1116 (3.85%)
number of deaths (all causes)	2	1	1
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			

subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Anogenital warts			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Breast neoplasm			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Colon cancer			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Gastric cancer			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Hepatosplenic T-cell lymphoma			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Lung neoplasm malignant			

subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma stage II			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Non-small cell lung cancer			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Ovarian cancer			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Aortic stenosis			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iliac artery occlusion			

subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Drug detoxification			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 1192 (0.08%)	1 / 1166 (0.09%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Premature baby			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Drug withdrawal syndrome			

subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Asthma			
subjects affected / exposed	1 / 1192 (0.08%)	1 / 1166 (0.09%)	2 / 1116 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Pleurisy			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Pulmonary embolism			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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 failure			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Adjustment disorder with depressed mood			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar disorder			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Completed suicide			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Depressed mood			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	2 / 1192 (0.17%)	1 / 1166 (0.09%)	0 / 1116 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 1192 (0.00%)	2 / 1166 (0.17%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Schizophrenia, paranoid type			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Suicidal ideation			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Femoral neck fracture			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Joint dislocation			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Ligament rupture			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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

Ligament sprain			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Multiple injuries			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Periorbital haemorrhage			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Postoperative ileus			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Stab wound			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Sternal fracture			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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

Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 1192 (0.00%)	4 / 1166 (0.34%)	2 / 1116 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Angina unstable			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Aortic valve incompetence			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	2 / 1116 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Coronary artery disease			
subjects affected / exposed	2 / 1192 (0.17%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			

subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Mitral valve incompetence			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Carotid artery stenosis			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Cerebral infarction			

subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Morton’s neuralgia			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Syncope			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 1192 (0.00%)	2 / 1166 (0.17%)	0 / 1116 (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
Eye disorders			
Chalazion			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Endocrine ophthalmopathy			

subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Colitis			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
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	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal stenosis			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Duodenal ulcer perforation			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Enteritis			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Haemorrhoids			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia strangulated			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Pancreatitis			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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 perforation			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Cholecystitis acute			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder disorder			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	2 / 1116 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis alcoholic			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Urinary bladder polyp			

subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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

Rotator cuff syndrome			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Spinal osteoarthritis			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Cellulitis			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Diarrhoea infectious			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Diverticulitis			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Erysipelas			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Gastroenteritis viral			

subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Haemorrhagic fever with renal syndrome			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Meningitis viral			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Necrotising fasciitis			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Perirectal abscess			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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
Pharyngitis streptococcal			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Pneumonia			
subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	3 / 1116 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	1 / 1192 (0.08%)	1 / 1166 (0.09%)	0 / 1116 (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
Pyelonephritis			

subjects affected / exposed	1 / 1192 (0.08%)	0 / 1166 (0.00%)	0 / 1116 (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
Sinusitis			
subjects affected / exposed	0 / 1192 (0.00%)	1 / 1166 (0.09%)	0 / 1116 (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
Staphylococcal infection			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	1 / 1116 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 1192 (0.00%)	0 / 1166 (0.00%)	0 / 1116 (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

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 1121 (3.66%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			

subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anogenital warts			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bladder cancer			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast neoplasm			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric cancer			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatosplenic T-cell lymphoma			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			

subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung adenocarcinoma stage II				
subjects affected / exposed	1 / 1121 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Non-small cell lung cancer				
subjects affected / exposed	1 / 1121 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian cancer				
subjects affected / exposed	1 / 1121 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine leiomyoma				
subjects affected / exposed	1 / 1121 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aortic aneurysm				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic stenosis				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Embolism				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Iliac artery occlusion				

subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral artery stenosis			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Drug detoxification			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	2 / 1121 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Premature baby			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug withdrawal syndrome			

subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleurisy			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Respiratory failure				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Adjustment disorder with depressed mood				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bipolar disorder				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Completed suicide				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depressed mood				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Major depression				
subjects affected / exposed	2 / 1121 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Schizophrenia				
subjects affected / exposed	2 / 1121 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Schizophrenia, paranoid type				
subjects affected / exposed	1 / 1121 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Hepatic enzyme increased				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Contusion				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	1 / 1121 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament rupture				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Ligament sprain			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple injuries			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Periorbital haemorrhage			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative ileus			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stab wound			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sternal fracture			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ulna fracture			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 1121 (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 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aortic valve incompetence			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arrhythmia			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	2 / 1121 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery occlusion			

subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic cardiomyopathy				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mitral valve incompetence				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 1121 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stress cardiomyopathy				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Aphasia				
subjects affected / exposed	1 / 1121 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carotid artery stenosis				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				

subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Morton’s neuralgia				
subjects affected / exposed	1 / 1121 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 1121 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	1 / 1121 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Chalazion				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocrine ophthalmopathy				

subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulum			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Duodenal stenosis			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer perforation			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis			

subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematochezia			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Impaired gastric emptying			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia strangulated			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal perforation			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gallbladder disorder			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis alcoholic			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary bladder polyp			

subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bursitis			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc degeneration			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Rotator cuff syndrome			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal osteoarthritis			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 1121 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea infectious			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 1121 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			

subjects affected / exposed	1 / 1121 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic fever with renal syndrome				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningitis viral				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Necrotising fasciitis				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Perirectal abscess				
subjects affected / exposed	1 / 1121 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis streptococcal				
subjects affected / exposed	0 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 1121 (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 / 1121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				

subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Kidney infection			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 1121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 1121 (0.09%)		
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	165 / 1192 (13.84%)	160 / 1166 (13.72%)	116 / 1116 (10.39%)
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	103 / 1192 (8.64%)	78 / 1166 (6.69%)	69 / 1116 (6.18%)
occurrences (all)	123	81	83

Upper respiratory tract infection			
subjects affected / exposed	63 / 1192 (5.29%)	84 / 1166 (7.20%)	48 / 1116 (4.30%)
occurrences (all)	75	104	53

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	143 / 1121 (12.76%)		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	81 / 1121 (7.23%)		
occurrences (all)	97		
Upper respiratory tract infection			
subjects affected / exposed	63 / 1121 (5.62%)		
occurrences (all)	65		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 November 2011	In Amendment 1, the following changes were included; updated the study protocol template from the non interventional template to the interventional template because local regulations in some countries where the study was to be conducted considered certain study procedures an intervention (eg, blood draws). The contents of the protocol were minimally changed to include language applicable to interventional studies.
05 June 2012	In Amendment 2, incorporated changes based on feedback from the US FDA and to match the most recent protocol template and Pfizer SOPs. The following sections were updated: Vital signs (PR and BP) were added to all clinic visits; Section 6 (Study Procedures) was updated to include additional vital signs at every clinic visit; Section 6.2.1 (Clinic Visits) was updated to add a definition of a visit window; Section 6.3 (Subject Withdrawal) was updated to include information that all subjects would be followed until final visit unless they withdrew consent; Section 7.1 (Physical Examination, Vital Signs and Electrocardiogram) was updated to include vital signs at every clinic visit; Section 7.5 (Cardiovascular Events of Interest) was 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 would be identified, reviewed, and adjudicated; Section 8 updated various Adverse Event sections to match the most recent protocol template and Pfizer SOPs; Section 9.2 Efficacy Analysis was changed to Exploratory Efficacy Analyses. This was updated to provide clarification to these exploratory statistical analyses; and Section 15 Publication of Study Results updated to match the most recent protocol template and Pfizer SOPs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27116918