



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | A3051123 |
|-----------------------|----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Pfizer, Inc. |
| Sponsor organisation address | 235 East 42nd Street, New York, NY, United States, 10017 |
| Public contact | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

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

Notes:

General information about the trial

Main objective of the trial:

Primary Safety Objectives:

1. To characterize the neuropsychiatric safety profiles of varenicline and bupropion by estimating the differences from placebo in the incidence of the primary neuropsychiatric

AE endpoint for subjects:

a. With a diagnosis of psychiatric disorder;

b. Without a diagnosis of psychiatric disorder.

2. To characterize the differences in the neuropsychiatric safety profiles of varenicline and bupropion as compared with placebo between these sub-populations (cohorts).

Efficacy: Abstinence from Smoking

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

Protection of trial subjects:

All parties will ensure protection of subject personal data and will not include participant names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

Subjects enrolled per age group

| | |
|---|------|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 7529 |
| From 65 to 84 years | 529 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Varenicline |

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|-----------|
| Arm title | Bupropion |
|------------------|-----------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|--|------------------------------------|
| Arm title | NRT patch |
| Arm description: | |
| Participants were randomized to 1 of the 3 active dosing groups that took active medication of either varenicline, bupropion, NRT in this triple-dummy design. Participants in this arm received NRT started active dosing the morning of the Week 1 visit and received a 21 mg transdermal patch per day x 7 weeks, followed by a 14 mg transdermal patch per day x 2 weeks, and then a 7 mg transdermal patch x 2 weeks for a total of 11 weeks of treatment. They also received placebo varenicline and bupropion, dosed in the same manner as active medication. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Nicotine replacement therapy patch |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Transdermal patch |
| Routes of administration | Transdermal use |

Dosage and administration details:

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

| | |
|---|---------------------------------------|
| Arm title | Placebo |
| Arm description: | |
| Participants received matching placebo for varenicline, bupropion, and NRT in this triple-dummy design, and followed the same titration and dosing schedule as for the active treatments noted above. | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet, Transdermal patch |
| Routes of administration | Oral use, Transdermal use |

Dosage and administration details:

Matching placebo for varenicline, bupropion and NRT

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

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

Baseline characteristics

Reporting groups

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

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

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

End points

End points reporting groups

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

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

| | |
|--|---|
| End point title | Occurrence of neuropsychiatric (NPS) adverse events (AE) - the primary study endpoint |
| End point description: | |
| The primary safety endpoint is the occurrence of at least one treatment emergent "severe" adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent "moderate" or "severe" adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints. | |
| End point type | Primary |
| End point timeframe: | |
| Treatment emergent is first dose date to last dose date (upto 12 weeks) plus 30 days | |

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

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|
| Statistical analysis description: | |
| The reduced (final) statistical model included treatment group, cohort and region, plus the 2-way interaction of treatment by cohort. Other interactions not included due to lack of significance. Region reduced to 2-level to address event sparseness issue. | |
| Comparison groups | Bupropion v Varenicline v NRT patch v Placebo |
| Number of subjects included in analysis | 8058 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0652 ^[1] |
| Method | Regression, Linear |

Notes:

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

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

| End point title | Estimated NPS AE rate (%), by cohort |
|--|--------------------------------------|
| End point description: | |
| The primary safety endpoint is the occurrence of at least one treatment emergent "severe" adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent "moderate" or "severe" adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints. | |
| End point type | Primary |
| End point timeframe: | |
| Treatment emergent is first dose date to last dose date (upto 12 weeks) plus 30 days | |

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

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

Statistical analyses

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

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

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

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

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

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

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

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

| | |
|--|---|
| End point title | Occurrence of the components of the NPS AE primary endpoint, non-psychiatric history cohort |
| End point description: | |
| <p>The safety endpoint is the occurrence of at least one treatment emergent "severe" adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent "moderate" or "severe" adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide. Each of these 16 components is reported below. The safety dataset included all participants who had received at least one partial dose of study medication (N=8058) and was used to analyze all safety endpoints.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Treatment emergent is first dose date to last dose date (upto 12 weeks) plus 30 days | |

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 24

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

Statistical analyses

Secondary: HADS Total Score, psychiatric history cohort

| | |
|-----------------|--|
| End point title | HADS Total Score, psychiatric history cohort |
|-----------------|--|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 24

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

Statistical analyses

No statistical analyses for this end point

Secondary: HADS Total Score (overall)

| | |
|-----------------|----------------------------|
| End point title | HADS Total Score (overall) |
|-----------------|----------------------------|

End point description:

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

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 24 | |

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 24

| End point values | Varenicline | Bupropion | NRT patch | Placebo |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 2016 | 2006 | 2022 | 2014 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 1 (N= 1986, 1974, 1986, 1982) | 94.2 | 93.2 | 94.6 | 95.1 |
| Week 2 (N= 1934, 1936, 1927, 1926) | 90.8 | 90.8 | 90.5 | 91.2 |
| Week 3 (N= 1880, 1892, 1880, 1863) | 88.3 | 89.8 | 88.7 | 87.9 |
| Week 4 (N= 1860, 1856, 1858, 1834) | 86.6 | 88 | 87.1 | 86.3 |
| Week 5 (N= 1828, 1816, 1822, 1802) | 85.7 | 86.5 | 85.5 | 85.4 |
| Week 6 (N= 1816, 1808, 1820, 1773) | 85.2 | 86.5 | 85.1 | 84.1 |
| Week 8 (N= 1758, 1756, 1755, 1738) | 82.4 | 83.6 | 82.8 | 81.9 |
| Week 10 (N= 1717, 1707, 1715, 1675) | 80.6 | 81.7 | 80.4 | 79.2 |
| Week 12 (N= 1558, 1572, 1540, 1492) | 72.9 | 75.1 | 72.2 | 71.3 |
| Week 13 (N= 1612, 1608, 1602, 1575) | 75.9 | 76.7 | 75.2 | 74.9 |
| Week 16 (N= 1586, 1606, 1568, 1541) | 74.2 | 76.7 | 73.9 | 73.4 |
| Week 20 (N= 1563, 1573, 1523, 1510) | 73.4 | 75 | 72.2 | 71.7 |
| Week 24 (N= 1533, 1515, 1499, 1497) | 71.8 | 72.3 | 71.1 | 71.1 |

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 9 through Week 12

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

Notes:

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

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

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

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

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|-------------------------|
| Statistical analysis description: | |
| The analysis was done using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction. Region reduced to 2-level for consistency with primary safety model. | |
| Comparison groups | Varenicline v Placebo |
| Number of subjects included in analysis | 2014 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 ^[6] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.2 |
| upper limit | 5 |

Notes:

[6] - No multiplicity adjustment.

| Statistical analysis title | Statistical Analysis 2 |
|---|-------------------------|
| Statistical analysis description: | |
| The analysis was done using a logistic regression with terms treatment, cohort, region, treatment by cohort interaction, and region by cohort interaction. Region reduced to 2-level for consistency with primary safety model. | |
| Comparison groups | Bupropion v Placebo |
| Number of subjects included in analysis | 2010 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 ^[7] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.26 |

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

Notes:

[7] - No multiplicity adjustment.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

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

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

Notes:

[8] - No multiplicity adjustment.

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 9 through Week 12

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

Notes:

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

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

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

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

Statistical analyses

| | |
|-----------------------------------|----------------------|
| Statistical analysis title | Stistical Analysis 1 |
|-----------------------------------|----------------------|

Statistical analysis description:

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

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

Notes:

[13] - No multiplicity adjustment.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

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

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

Notes:

[14] - No multiplicity adjustment.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

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

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

Notes:

[15] - No multiplicity adjustment.

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 9 through Week 12

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

Notes:

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

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

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

| | |
|-------------------|-----------------------|
| Comparison groups | Varenicline v Placebo |
|-------------------|-----------------------|

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

Notes:

[17] - No multiplicity adjustment.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

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

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

Notes:

[18] - No multiplicity adjustment.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

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

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

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

Notes:

[19] - No multiplicity adjustment.

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 9 through Week 24

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

Notes:

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

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

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

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

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

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

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

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

Notes:

[24] - No multiplicity adjustment.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

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

| | |
|---|--------------------------|
| Comparison groups | Bupropion v Placebo |
| Number of subjects included in analysis | 2010 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[25] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.54 |
| upper limit | 2.59 |

Notes:

[25] - No multiplicity adjustment.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

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

| | |
|---|--------------------------|
| Comparison groups | NRT patch v Placebo |
| Number of subjects included in analysis | 2022 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[26] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.96 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.51 |
| upper limit | 2.54 |

Notes:

[26] - No multiplicity adjustment.

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

psychiatric history cohort

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 9 through Week 24

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

Notes:

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

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

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

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

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

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

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

Notes:

[31] - No multiplicity adjustment.

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

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

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

Notes:

[32] - No multiplicity adjustment.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

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

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

Notes:

[33] - No multiplicity adjustment.

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 9 through Week 24

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

Notes:

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

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|--------------------------|
| Statistical analysis description: | |
| The analysis was done using a logistic regression with terms treatment and region. Region reduced to 2-level for consistency with primary safety model. | |
| Comparison groups | Varenicline v Placebo |
| Number of subjects included in analysis | 4030 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[35] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.28 |
| upper limit | 3.3 |

Notes:

[35] - No multiplicity adjustment.

| Statistical analysis title | Statistical Analysis 2 |
|---|--------------------------|
| Statistical analysis description: | |
| The analysis was done using a logistic regression with terms treatment and region. Region reduced to 2-level for consistency with primary safety model. | |
| Comparison groups | Bupropion v Placebo |
| Number of subjects included in analysis | 4020 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[36] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.56 |
| upper limit | 2.29 |

Notes:

[36] - No multiplicity adjustment.

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: | |
| The analysis was done using a logistic regression with terms treatment and region. Region reduced to 2-level for consistency with primary safety model. | |
| Comparison groups | NRT patch v Placebo |
| Number of subjects included in analysis | 4036 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[37] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.49 |
| upper limit | 2.19 |

Notes:

[37] - No multiplicity adjustment.

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 Weeks

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

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

Notes:

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 Weeks

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

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

Notes:

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

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: 7day point prevalence of abstinence (overall)

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 Weeks

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

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Varenicline |
|-----------------------|-------------|

Reporting group description:

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

| | |
|-----------------------|-----------|
| Reporting group title | Bupropion |
|-----------------------|-----------|

Reporting group description:

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

| | |
|-----------------------|-----------|
| Reporting group title | NRT patch |
|-----------------------|-----------|

Reporting group description:

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

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: